Journal of Opioid Management™

A medical journal for proper and adequate use

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Editor-in-Chief, Robert E. Enck, MD

Professor of Medicine, Assistant Division Chief for Clinical Activities, Division of Medical Oncology, Thomas Jefferson University, Philadelphia, Pennsylvania.

Editorial Review Board

IN MEMORIAM

Michael J. Fox, MD

It is with great sadness that we announce the passing of Dr. Michael J. Fox. His guidance to us in the founding of this publication was exceptional and without precedent.

Dr. Fox held many positions, culminating in Senior Vice President at Smith Kline, Astra Zeneca, and Alkermes Pharmaceutical companies. As such, he was responsible for the ushering through development and FDA approval of nine medications.

His final corporate position was President and COO of Penwest Pharmaceuticals. He continued as Healthcare Advisors, Inc., a company he founded, which helped bring a number of new pharmaceuticals to market. He will be sorely missed.

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Call for manuscripts

Editorial Policy

The mission of the ***Journal of Opioid Management*** is to educate and promote, through scientifically rigorous research, the adequate and safe use of opioids in the treatment of pain as well as the legal and regulatory issues surrounding abuse, addiction, and prescription practices (both over- and under-prescribing). Original articles, case studies, literature reviews, editorials, and letters to the editor concerning all aspects of opioid management will be considered for publication. All submissions, excluding editorials and letters to the editor, are subject to peer review by the editorial board prior to acceptance.

Manuscript Submission

Electronic manuscript submission is preferred. Attach articles in MS Word, WordPerfect, or rich text (.rtf) format to the journal email address at *jom@pnpco.com.* If submitting via regular mail, please supply your article on a 3-1/2 inch IBM-PC format floppy disk in MS Word 6.0 or greater, WordPerfect, or rich text format (.rtf). Manuscripts and all correspondence should be addressed to the Managing Editor, Journal of Opioid Management, 470 Boston Post Road, Weston, MA 02493. Submit one paper copy of the manuscript, typed and double-spaced, with the floppy disk. As a general guideline, text should be 1,500 to 2,500 words (seven to 12 pages for a research paper, three to five manuscript pages for editorials or book reviews).

Manuscript Format

The cover page should indicate the article's title, the full name, highest pertinent academic degrees, institutional affiliations, and current address of each author, contact information for the author handling all correspondence, telephone number, fax number, and, if the manuscript was orally presented at a meeting, the name of the organization, place, and date it was read. The first use of an uncommon abbreviation should be preceded by the full name. Brief definitions of key terms may be appended to the manuscript and can be presented in parentheses after the term within the article. With the exception of forum articles, book reviews, or letters to the editor, manuscripts should include the following five sections: Abstract, Introduction, Methods, Results, and Discussion. Subheads should be inserted at suitable levels. Style should conform to "Uniform Requirements for Manuscripts Submitted to Biomedical Journals" (available online at *http://www.icmje.org).*

Figures & Tables

The ***Journal*** welcomes illustrations, charts, and photographs to accompany articles. Figures should be titled and numbered consecutively according to the citation in the text. Information presented in figures and tables should be explained in the text. If data have been published previously, an appropriate reference should be included.

Short, descriptive legends should be provided on a separate page. Legends for figures previously published should include a complete reference to the original publication, with the copyright designation. Copies of the publisher's and author's permission to use the figure must be provided. Photographs should include legends and should be numbered consecutively according to the citation in the text and labeled on the back. Tables, photos, and figures must be submitted in the following formats: TIFF, JPEG, or EPS.

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Manuscripts are received with the understanding that they are submitted solely to ***Journal of Opioid Management*** and that, apart from abstracts, none of the material contained in the manuscript has been published previously or is under consideration for publication elsewhere. Authors should secure all necessary clearances and approvals prior to submission.

Journal of Opioid Management is a refereed journal. All manuscripts are generally subject to review by at least two members of the editorial advisory board who are noted experts in the appropriate subject area. The ***Journal*** reserves the right to make editorial revisions prior to publication.

All manuscripts are acknowledged immediately, and every effort will be made to advise contributors of the status of their submissions within 60 days.

References

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Journal articles—

1. Mudd P, Smith JG, Allen AZ, et al.: High ideals and hard cases: The evolution of opioid therapy for cancer pain. *Hastings Cent Rep*. 1982; 12(2):11-14.

Books—

1. Bayles SP (ed.): *Nutritional Supplements and Interactions with Analgesics*. Boston: GK Hall & Co., 1978.

Book chapters—

1. Martin RJ, Post SG: Introducing alternative prescribing strategies. In Smith J, Howard RP, and Donaldson P (eds.): *The Oncology Management Handbook*. Madison, WI: Clearwater Press, 1998, pp. 310-334.

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Health Care Financing Administration: HCFA Statistics at a glance. Available at: www.hcfa/gov/stats/stahili.htm. Accessed December 27, 2002.

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Style should conform to "Uniform Requirements for Manuscripts Submitted to Biomedical Journals" prepared by the International Committee of Medical Journal Editors and published in *Ann Intern Med* 1997; 126: 36-47, and available on the web at *http:www.acponline.org/journals/annals/01jan97/unifreqr.htm.*

The ***Journal*** expects authors to disclose any commercial or financial associations that might pose a conflict of interest in connection with the submitted article. All funding sources supporting the work should be acknowledged on the title page.

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DR. WILLIAM HURWITZ SENTENCED TO 25 YEARS FOR PRESCRIPTION PRACTICES

Dr. William Hurwitz was sentenced to 25 years in federal prison in an Alexandria, Virginia courtroom on April 14, 2005. Dr. Hurwitz was previously convicted in December of running a drug conspiracy out of his office and trafficking narcotics, which resulted in the death of one patient and serious injury to two others. In addition to these charges, Dr. Hurwitz was accused of lying during his previous testimony and ignoring repeated warnings regarding his prescription practices.

The prosecutors accused Dr. Hurwitz of prescribing excessive amounts of dangerous drugs to addicts and others, even though he was aware of patients abusing the drugs and/or selling them for profit on the black market. In one instance, he issued a 1,600-pill-per-day prescription. The one death in this case came as the result of an overdose of morphine from a "massive prescription," according to the patient's daughter.

Arguments for Dr. Hurwitz's defense included testimony from patients whom had found relief through his prescriptions. Support for Dr. Hurwitz also came from patient advocacy groups, with the urging that a conviction would make other doctors afraid to issue adequate prescriptions for patients with legitimate pain concerns. The prosecutors maintained that although Dr. Hurwitz's practices were effective for some, the remaining facts showing his ignorance of prescription abuse and endangerment of his patients warranted punishment regardless.

Jurors convicted Dr. Hurwitz on 50 counts of a 62-count indictment, which included conspiracy to distribute controlled substances. He was acquitted on nine of these counts, and the jury deadlocked on the remaining three. This case is part of an ongoing investigation within a broader federal one by the Drug Enforcement Agency into doctors, pharmacists, and patients suspected of selling potent narcotics, fueling the epidemic in the Appalachia area. (Source: *The Washington Post*, April 15, 2005.)

MORPHINE PLUS GABAPENTIN BETTER FOR NEUROPATHIC PAIN

According to a study in the March 31, 2005, issue of the *New England Journal of Medicine*, combined administration of morphine and gabapentin produces better analgesia for neuropathic pain, rather than the use of either drug alone. In a double-blind, four-period crossover trial, 57 patients were randomized to receive placebo (lorazepam), sustained-release morphine, gabapentin, or a combination of gabapentin and morphine. Doses were administered orally, and the trial lasted five weeks. Forty-one patients completed the study.

The primary outcome was mean daily pain intensity in patients receiving a maximal tolerated dose, which was rated on a scale of 1 to 10 (with the higher numbers indicating more severe pain). The secondary outcome measures were pain ratings on the Short Form McGill Pain Questionnaire, adverse effects, maximal tolerated doses, mood, and quality of life.

Study results show that mean daily pain at a maximal tolerated dose (on a scale of 1 to 10) was 5.72 at baseline, 4.49 with placebo, 4.15 with gabapentin alone, 3.70 with morphine alone, and 3.06 with gabapentin plus morphine ($p < 0.05$ for the combination versus placebo, gabapentin, and morphine). The most frequently noted side effects were constipation, sedation, and dry mouth.

Study limitations include partial blinding, in that approximately one-third of the participants guessed they were receiving an active drug while receiving the placebo. This may have decreased the difference between treatment with gabapentin or placebo, according to the authors. They also recommend further research on other analgesic combinations with their respective single agents. (Source: *Medscape News*, March 30, 2005.)

OPIOID HIGHLIGHTS FROM THE 21ST ANNUAL MEETING OF THE AMERICAN ACADEMY OF PAIN MEDICINE

The 21st Annual Meeting of the American Academy of Pain Medicine (AAPM) was held February 23-37, 2005, in Palm Springs, California. Among the many topics discussed at the meeting, opioids continued to be a point of concern for those in attendance.

An important distinction in the definitions of abuse and addiction was made by Dr. Scott Fishman, who stated that addiction is a psychological disorder independent of the substance, whereas abuse is an aberrant use of a substance. Because addiction is usually associated with a strong family history, an assessment of addiction should include a thorough evaluation for obsessive use and use despite known harm (e.g., physical, economic, family/friends) to differentiate from signs of abuse, which are often more subtle. Dr. Fishman also touched on the legal issues of prescribing opioids and noted that the practitioner must treat each patient appropriately, through thorough assessment and constant reassessment, with documentation of quality of life, function, and benefits for each case.

Dr. Howard Heit focused on issues of misuse and diversion of opioids, and emphasized that a controlled substance agreement should be used to define the constructs for what a practitioner will and will not do in providing care. Patients should be motivated to reach treatment goals and have a stable behavioral profile. Although previous addiction does not give an absolute contraindication for opioid treatment, it does reinforce the need for a program that maintains previous addiction recovery, according to Dr. Heit. He provided the following list of guidelines for the prescription of opioids:

1. Ask the patient to sign an agreement setting clear rules and expectations.

2. Set the dose of medications at the appropriate level to treat the condition and titrate as necessary. Get feedback from the patient.

3. Give enough medication, plus rescue doses.

4. Ask the patient to bring any remaining drug doses to the next meeting in the original bottles. (This provides information on pharmacies used and other prescribing physicians.)

5. Monitor lost or stolen prescriptions.

6. Obtain random urine screens. Know what drugs laboratory screens can actually identify.

7. Use adjuvant analgesics as necessary.

8. Document all your thoughts in the chart.

9. See the patient as frequently as needed.

10. Work with significant others.

11. Know how to withdraw the patient from the medication(s).

12. Know the pharmacology of the drugs used.

13. Adequately treat acute pain to prevent the development of chronic pain.

(Source: *Medscape News*, April 5, 2005.)

NO CLASS ACTION FOR OXYCONTIN CASE

A New York judge in late January said a personal injury lawsuit against the makers of OxyContin that alleges addiction and other harm from the pain medication cannot go forward as a class-action case.

Justice Stephen J. Maltese, in the Supreme Court of the State of New York for Richmond County, said the case does not meet the criteria of a class action because addiction is an individual injury, and not a common one.

"[This case presents] important individual issues, and to lump all of those issues together would be inappropriate for all of the parties involved," Maltese wrote.

This case marks the ninth written opinion in a state or federal court that has rejected a request for class-action status in the various lawsuits that patients and/or their families have filed against manufacturer Purdue Pharma, LP over the past four years. (Source: American Medical News, February 21, 2005.)

CALENDAR

American Alliance of Cancer Pain Initiatives
16th Annual Meeting
Exploring New Gateways to Pain Management
June 9-11, 2005
Adam's Mark Hotel
St. Louis, Missouri

For registration information, contact:
Lorre Kolb
American Alliance of Cancer Pain Initiatives
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Madison, WI 53706.
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E-mail: *ljkolb@wisc.edu*
Web site: *http://www.aacpi.wisc.edu/16_mtg05.htm*

International Symposium on
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First Croatian Congress of
Regional Anesthesia and Analgesia
June 16-19, 2005
Hotel Excelsior
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Harvard Medical School and
Beth Israel Deaconess Medical Center
Principles and Practice of Pain Medicine
June 22-26, 2005
Fairmont Copley Plaza Hotel
Boston, Massachusetts

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International Association for the Study of Pain (IASP)
11th World Congress on Pain
August 21-26, 2005
Sydney Convention and Exhibition Centre
Sydney, Australia

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The Hong Kong College of Anaesthesiologists and
The Society of Anaesthetists of Hong Kong
East Meets West in Pain Medicine:
New Horizons in Anaesthesia
(an official satellite meeting of the
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August 27-28, 2005
Hong Kong Convention and Exhibition Centre
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American Academy of Pain Management
16th Annual Clinical Meeting
September 22-25, 2005
Manchester Grand Hyatt
San Diego, California

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LETTER TO THE EDITOR

Dear Dr. Enck:

As usual, I'm behind in my journal reading, so am just getting to your editorial. I saw that you're going to deal with double effect—always a good idea. My concern about it is that many of the clinicians with whom I have worked rely on double effect inappropriately. That is, they make the same errors that you mention in your editorial (misunderstanding tolerance and the need for increased doses based on pain levels, etc). Subsequently, if a patient dies, they blame it on double effect rather than on advanced cancer, multi-organ system failure, or whatever the underlying condition, not understanding that death is, in fact, a respiratory depressant.

I hope the *Journal of Opioid Management* takes these factors into consideration when it addresses double effect.

Congratulations on the new journal,

Mimi Mahon, PhD, FAAN
Senior Fellow
University of Pennsylvania Center for Bioethics
Philadelphia, Pennsylvania.

Editor's note: The answer is yes, and thank you for your letter.

Robert E. Enck, MD
Editor-in-Chief

Call for Letters to the Editor

The *Journal of Opioid Management* will consider for publication letters on subjects related to opioid therapy and pain management.

Letters responding to specific articles previously published in the *Journal* are especially welcome and encouraged. To ensure their timely publication, submit them as soon after the issue's distribution date as possible.

All letters should be typewritten and double-spaced; references should be limited to five whenever possible.

Please include your full name, job title, facility name, and address with all letters.

You may send your letter by mail, fax, or e-mail to:

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GUEST EDITORIAL

Does the opioid-sparing effect of NSAIDs benefit the patient in the postoperative period?

Alexander Ng, MBChB, MD, FRCA
Justiaan Swanevelder, MBChB, MMed(Anaes), FCA(SA), FRCA

Nonsteroidal anti-inflammatory drugs (NSAIDs) have been shown to reduce pain intensity[1] and improve patient satisfaction after surgery.[2] They work by inhibition of cyclo-oxygenase (COX) enzymes that catalyse the production of prostaglandins.[3] Nonselective NSAIDs (e.g., diclofenac[4] and piroxicam[5]) inhibit COX-1 and COX-2 enzymes, whereas selective NSAIDs (e.g., rofecoxib[6]) inhibit only COX-2 enzymes.

In randomized controlled trials (RCTs), it has been shown that pain relief after administration of NSAIDs is associated with a significant reduction in opioid consumption.[1] The expectation, therefore, is that there should be a concomitant improvement in opioid-related effects such as nausea, vomiting, sedation, and gastrointestinal ileus. Obviation of these factors is necessary to facilitate convalescence in the recovery period.

In some RCTs, patients who received NSAIDs experienced significantly less postoperative nausea and vomiting than those who had opioids. For instance, in a quantitative systematic review of use of NSAIDs after tonsillectomy, the relative risk [RR, 95 percent confidence interval (CI)], for postoperative nausea and vomiting in favor of NSAIDs compared with opioids was 0.73 (range, 0.63 to 0.85).[7] In another systematic review of patients undergoing abdominal, orthopedic, dental, and gynecological procedures, it was shown that morphine 10 mg intramuscular, but not ketorolac 10 to 30 mg intramuscular, is associated with an increased relative risk of postoperative nausea and vomiting compared with placebo.[8]

Furthermore, sedation is a dose-dependent effect of opioids and may be minimized by NSAIDs. For instance, in an RCT of pain relief after abdominal hysterectomy, total sedation score was significantly lower in patients receiving rectal diclofenac 75 mg bd than placebo.[1] This difference was attributable to the significantly lower opioid consumption in the treatment group compared with placebo.

Opioid administration is also associated with delayed gastric emptying and gastrointestinal ileus.[9] It is likely that NSAIDs may minimize these effects by reducing opioid consumption. To test this hypothesis, formal methods (e.g., radio-opaque markers, measurement of gastric emptying, and assessment of intestinal motility) would have to be used.[10]

Despite minimizing opioid-related effects, NSAIDs are associated with adverse effects themselves. They may impair renal function[11] and precipitate bronchospasm in susceptible patients. Furthermore, nonselective NSAIDs are associated with gastric irritation[12] and hemorrhage,[13] which restrict their use.

In recent years, selective NSAIDs or COX-2 inhibitors have been introduced and have been shown to be opioid sparing.[14] Compared with nonselective NSAIDs, they are associated with a reduced risk of gastric irritation,[12] bleeding after surgery,[15,16] and of possible delay in fracture healing.[17] Despite these advantages, however, it would seem that selective NSAIDs are linked to an increased risk of cardiovascular events, in particular myocardial infarction. Evidence on this issue first came to light in the year 2000, from the findings of the Vioxx Gastrointestinal Outcomes Research (VIGOR) study, in which the relative risk of myocardial infarction in patients with rheumatoid arthritis was significantly higher when they received rofecoxib compared with naproxen, a nonselective NSAID.[18] Subsequently, in a retrospective study, Ray[19] showed that this effect may be dose dependent. In a comparison of nonusers and celecoxib users, the RR (95 percent CI) of a serious cardiovascular event was 1.93 (range, 1.09 to 3.43) and 2.20 (range, 1.17 to 4.10), respectively, in patients taking rofecoxib in doses exceeding 25 mg.[19] This finding has been confirmed by a meta-analysis of 63 reports including 18 RCTs[20] in which the RR (95 percent CI) of a cardiovascular event was 2.83 (range, 1.24 to 6.43) and 1.37 (range, 0.52 to 3.61) in patients receiving rofecoxib 50 mg and 25 mg, respectively, when compared with control.

In September 2004, rofecoxib was withdrawn from the market. This decision came after analysis of the results of the Adenomatous Polyp Prevention on Vioxx (APROVe) RCT, which was designed to evaluate the effect of rofecoxib on recurrence of polyps in patients with a history

of colorectal adenoma.[21] Over a three-year period, there was an increased relative risk of myocardial infarction and stroke in patients taking rofecoxib 25 mg compared with placebo. There has been much criticism of the regulating bodies and manufacturer for not withdrawing rofecoxib sooner.[22] Indeed, in the cumulative meta-analysis of publications from 1997 to 2001, it would appear that the risk of cardiovascular events compared with control became significantly higher in the year 2000.[20]

The important question is whether the cardiovascular events associated with rofecoxib are specific to itself, or whether they may be generalized to other COX-2 inhibitors (e.g., celecoxib and valdecoxib). Celecoxib has been investigated extensively. In a case-control study, it would appear that these cardiovascular events are associated with rofecoxib but not with celecoxib. The odds ratio (95 percent CI) of myocardial infarction in patients receiving rofecoxib versus celecoxib was 2.72 (range, 1.24 to 5.95).[23] Similarly, in another case-control study, the odds ratio (95 percent CI) of myocardial infarction and sudden cardiac death in patients who had rofecoxib versus celecoxib was 1.59 (range, 1.10 to 2.32).[24] This elevated risk appears to occur during the first 90 days of exposure, but not thereafter.[25] Despite these reassuring results, a five-year RCT, the Adenoma Prevention with Celecoxib (APC) study, has been stopped by the National Institutes of Health.[26] In comparison with placebo, a daily dose of celecoxib 400 mg and 800 mg over an average of 33 months was associated with a hazard ratio (95 percent CI) of a major cardiovascular event of 2.5 (range, 1.0 to 6.4) and 3.4 (range, 1.4 to 8.5), respectively.[27,28]

In addition, adverse events have been associated with the consumption of valdecoxib and its prodrug, parecoxib, after cardiac surgery. In comparison with placebo, the risk ratio (95 percent CI) of cardiovascular events in patients receiving a combination of parecoxib and valdecoxib for 10 days postoperatively was 3.7 (range, 1.0 to 13.5).[29] In another RCT, this combination for 14 days after coronary revascularization was associated with a significantly higher incidence of sternal wound infections but not adverse cardiovascular events.[30]

Over the past year, many precautionary measures have been taken. In December 2004, the National Institutes of Health suspended another study, the Alzheimer's Disease Anti-Inflammatory Prevention Trial (ADAPT), in which celecoxib 200 mg bd, naproxen 220 mg bd, and placebo were evaluated.[31] Furthermore, after discussion with the European Medicines Agency, Pfizer announced in February 2005 that it would be revising safety information on celecoxib, valdecoxib, and parecoxib. These drugs are now contraindicated in patients with ischemic heart disease, cerebrovascular disease, and New York Heart Association II to IV congestive heart failure. In addition, it has been declared that valdecoxib and parecoxib should not be used for treatment of pain after coronary artery bypass surgery.[32]

In the postoperative period, the clinician would need to weigh the risks and benefits of nonselective NSAIDs and COX-2 inhibitors. Both analgesic adjuncts are associated with similar reductions in opioid consumption and pain intensity. Despite these benefits, both groups of drugs are contraindicated in patients with asthma and renal failure. Although COX-2 inhibitors may be useful after tonsillectomy in healthy patients when there is a propensity to hemorrhage, they are contraindicated after coronary revascularization, when the probability of a serious cardiovascular thrombotic event is high.[33] The opioid-sparing effects of nonselective NSAIDs and COX-2 inhibitors have not come without risk, and we await further safety data on COX-2 inhibitors to clarify whether some of them may continue to be administered postoperatively. Currently, it would seem that opioids remain a reasonable choice for management of moderate to severe pain intensity in the postoperative period.

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Extended-release lipid-foam encapsulated epidural morphine: Clinical efficacy and safety precautions

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INTRODUCTION

New developments in opioid analgesic delivery systems have centered around extending the release rate. One of the new delivery mechanisms, extended-release lipid-foam encapsulated epidural morphine, DepoDur (Endo Pharmaceuticals, Inc., Chadds Ford, PA), extends the release rate compared to standard 5-mg epidural morphine.[1] Most patients will require supplement opioids during the 48-hour interval after single-injection epidural DepoDur. The sustained-release lipid-foam encapsulated morphine formulation (Figure 1), EREM, is indicated for acute postoperative pain. It is administered as a single one-time dose in the lumbar epidural space for 48 hours' duration. From a theoretical point of view, extending the duration of release, intuitively, would control pain with less opportunity for periods of subtherapeutic levels as compared to intermittent dosing. The extended-release mechanism would also seem to lower the potential for adverse medication reactions compared to potentially excessive amounts of opioids during intermittent therapy. The clinical studies to date do show better pain control, but adverse drug reactions are not lower and may be slightly higher.[2,3] Furthermore, special precautions should be considered when administering extended-release lipid-foam encapsulated epidural morphine.

CLINICAL EFFICACY

The recommended dosing for major orthopedic surgery of lower extremities is 15 mg. For lower abdominal or pelvic surgery the recommended dose is 10 to 15 mg. Some patients may benefit from a 20-mg dose; however, the incidence of respiratory events was dose-related in clinical trials.[1,4]

Pain control

A randomized, multicenter, double-blind parallel-group study evaluated the pain intensity after 10- and 15-mg DepoDur as compared to epidural morphine 5 mg in 75 patients undergoing elective cesarean section.[2] The pain intensity scores were significantly lower in the DepoDur groups.

In another randomized, phase III trial comparing 10- and 15-mg DepoDur (as well as higher doses) with standard epidural morphine 5 mg in patients undergoing lower abdominal surgery, intravenous (IV) fentanyl patient-controlled analgesia (PCA) was available for rescue dosing. In this study, the pain intensity (based on AUC) at rest was significantly lower in the 15-mg DepoDur group ($p < 0.05$) but not the 10-mg DepoDur group.[3]

Supplemental opioids

Although DepoDur has demonstrated better pain control, supplement rescue opioids will be required in most patients during the 48-hour dosing interval. A randomized, multicenter, double-blind parallel-group study evaluated the efficacy of single epidural DepoDur doses of 5 (not a recommended dose), 10, and 15 mg compared to epidural morphine 5 mg in 75 patients undergoing elective cesarean section.[2] Most patients (96 percent) received supplemental analgesics during the 48-hour study period. The opioid use in the 0 to 48 hour period was less in the DepoDur group ($p < 0.05$); the 10-mg DepoDur group required a mean of 25 mg of supplement morphine equivalent (SME) compared to a mean of 47 mg SME in the control morphine group. There were no significant differences among treatment groups in the proportion of patients who received no supplemental analgesics.

Another randomized phase III trial compared 10- and 15-mg DepoDur (as well as higher doses) with standard epidural morphine 5 mg in patients undergoing lower abdominal surgery. IV fentanyl PCA was available for rescue analgesia. In this study, the amount of 48-hour mean rescue IV fentanyl PCA was significantly lower in the 15-mg DepoDur group but not the 10-mg DepoDur group.[3]

Adverse events

A randomized, multicenter, double-blind parallel-group

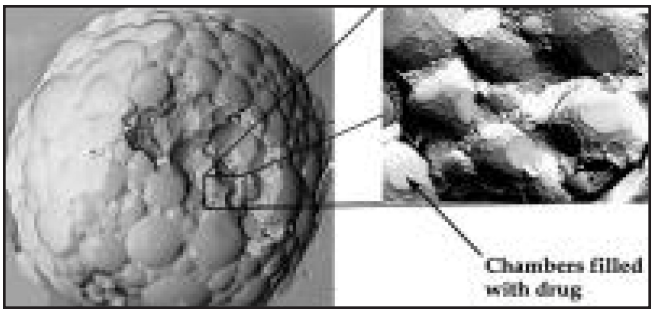

Figure 1. Electron micrograph of DepoFoam particles.

study evaluated the pain intensity after 10- and 15-mg DepoDur compared to epidural morphine 5 mg in 75 patients undergoing elective cesarean section.[2] See Table 1 for adverse reaction rates.

In the other phase III trial previously described, which compared 10- and 15-mg DepoDur (as well as higher doses) with standard epidural morphine 5 mg in patients undergoing lower abdominal surgery, pruritus and urinary retention were significantly higher in the DepoDur group.[3]

PRECAUTIONS

There are several inherent precautions required with sustained-release lipid-foam encapsulated morphine.

Protection from freezing

DepoFoam consists of lipid-based particles containing discrete water-filled chambers dispersed through the lipid matrix. Freezing DepoDur may destroy the slow-release mechanism.

Refrigeration storage

DepoDur is stored in a refrigerated temperature range of 2° to 8° C (36° to 46° F), but may be held at 15° to 30°C (59° to 86°F) for up to seven days in the intact, unopened vial.

Physicochemical interaction

It is important that DepoDur not be administered within 15 minutes of a local anesthetic such as lidocaine. Concomitant administration results in an increase in the rate of system morphine delivery.

Administration

The vial should be gently inverted and not vigorously shaken. An inline filter should not be used.

Awareness

One of the postoperative concerns is identification of a patient who has received sustained-release lipid-foam encapsulated morphine. As compared to standard epidural therapy, DepoDur requires no infusion device to enhance awareness after administration. Therefore, a special monitoring protocol should be established to ensure that members of the staff are aware that the patient has been given a medication with ongoing effects for 48 hours. In several case reports, fentanyl transdermal patches, which also have an extended release, have been overlooked and/or created associated adverse events owing to lack of awareness.[5]

Proper monitoring

Patients getting DepoDur may be inadvertently regarded by staff as needing less monitoring than patients with indwelling epidural catheters and IV PCA infusions.[6] Studies in patients who have sleep apnea are needed before DepoDur can be administered in this group of patients.

SUMMARY

DepoDur is a unique delivery system that has a Food and Drug Administration–approved recommended dose of 15 mg for orthopedic lower extremity surgery and a 10- to 15-mg dose for lower abdominal or pelvic surgery. Some patients may benefit from a 20-mg dose, but the incidence of serious adverse respiratory events has been dose related in clinical trials. For cesarean section, the recommended dose is 10 mg. Most patients will require supplemental analgesics during the 48 hours post surgical

Table 1. Adverse reaction rates in DepoDur versus morphine[2]

	Morphine 5 mg	DepoDur 10 mg	DepoDur 15 mg
Pruritus	28%	33%	67%
Nausea	39%	50%	50%
Vomiting	22%	11%	33%
Constipation	6%	17%	6%

procedure as well as routine monitoring similar to present continuous epidural monitoring procedures. The unique delivery system requires additional safety and storage precautions. The clinical studies to date do not show DepoDur administration to have any lower adverse reaction profile compared to standard epidural morphine.[2,3]

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ORIGINAL ARTICLE

Fluctuating QTc interval in an asymptomatic patient treated with methadone for chronic pain

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ABSTRACT

Prolongation of the QT interval associated with ventricular arrhythmias has been the most common cause of the restriction or withdrawal of drugs from the market in the past 10 years. Methadone, a synthetic opioid that is increasingly used for the management of chronic pain, has recently been implicated in the development of the prolonged QT syndrome. We present a case report of a patient who developed a prolonged QT while being treated with oral methadone for a chronic pain syndrome. Of particular interest in this patient is the fluctuation of the QT interval at a stable dose of methadone, suggesting that a single normal electrocardiogram (ECG) does not guarantee that the patient is not at risk of ventricular arrhythmias. After reviewing the current literature, we suggest that there is no dose of methadone that may be considered to be completely safe. Other risk factors for prolonged QT interval such as underlying cardiac abnormalities, electrolyte disturbances, and concurrent medications should be sought, and all patients should be monitored with serial ECGs even when methadone doses remain stable.

Key words: methadone, prolonged QT interval, chronic pain syndrome, electrocardiogram

INTRODUCTION

The prolongation of the QT interval associated with polymorphic ventricular tachycardia or the potentially fatal arrhythmia torsade de pointes has been the most common cause of the restriction or withdrawal of drugs from the market in the past 10 years.[1] Methadone is a synthetic opioid that is being increasingly used as an effective and inexpensive therapy for chronic pain.[2] Several recently published case series have implicated high-dose methadone in the development of the prolonged QT syndrome and torsade de pointes.[3-5] This effect is mediated through blockage of the ionic current through cardiac potassium channels composed of subunits expressed by the human ether-a-go-go (HERG) gene.[1] A "rate-corrected" QTc interval of > 500 msec is generally accepted as predictive of an increased risk for torsade de pointes.[4] A linear correlation between the log-dose of methadone and QTc interval was shown in a series of patients receiving intravenous methadone for chronic cancer pain.[6] The absolute daily dose at which QTc interval prolongation was seen varied widely between patients, however, depending in part on concurrent pharmacotherapy. No clear definition has yet emerged in the literature regarding what defines a high daily dose of methadone; estimates vary from > 60 mg per day[3] to 275 to 500 mg per day.[5] We present a case report of QTc fluctuation in an asymptomatic patient treated with 180 mg per day oral methadone for a chronic neuropathic pain syndrome.

CASE DISCUSSION

The patient, a 50-year-old woman, presented to a chronic pain clinic with a 20-year history of right knee pain. She had undergone several orthopedic procedures, which had left her with continual right knee and calf pain, as well as bilateral hip pain. The patient had been diagnosed with complex regional pain syndrome type I due to the presence of typical signs and symptoms including pain, allodynia, and trophic changes in the right limb. Before her presentation to our clinic, she had been treated for four years with epidural sympathetic blocks and intravenous lidocaine, which had provided moderate pain relief. Her medications on presentation included slow-release morphine 75 mg tid, oxycocet tablets for breakthrough pain (four to six per day), and gabapentin 1,200 mg qid. Her medical history was significant for osteoarthritis and migraines. There was no history of cardiac disease. Because she complained of inadequate pain relief on long-acting morphine, she was started on methadone, which was gradually titrated to 20 mg tid, or 60 mg per 24 hours. A preoperative electrocardiogram (ECG) performed after eight months of

Table 1. Drugs that interfere with methadone metabolism	
CYP3A4 inducers (decrease levels/effects)	**CYP3A4 inhibitors (increase levels/effects)**
Aminoglutethimide	Azole antifungals
Carbamazepine	Ciprofloxacin
Phenobarbitol	Clarithromycin
Phenytoin	Diclofenac
Rifamycins	Doxycycline
Nafcillin	Erythromycin
Nevirapine	Isoniazid
	Nefazodone
	Nicardipine
	Propofol
	Protease inhibitors
	Quinidine
	Verapamil
	Selective serotonin reuptake inhibitors

methadone treatment at this dose did not display a prolonged QTc. She was referred for a trial of spinal cord stimulation, which failed. Subsequently, her methadone dose was titrated upward over a period of five months to 80 mg tid, or 240 mg per 24 hours. Her other medications remained unchanged.

Because of recent reports in the literature suggesting the risk of QT prolongation in patients on high-dose methadone, the patient underwent a surveillance ECG. The QTc interval (as calculated by the Bazett formula: QTc interval = QT interval/vR-R interval) was found to be 569 msec. Laboratory investigations, including serum electrolytes, magnesium, and calcium, were normal. The patient's dose of methadone was reduced to 60 mg tid, or 180 mg per 24 hours. An ECG performed after three months at this dose showed normalization of the QTc to 407 msec. Despite the fact that the patient remained on a stable dose of methadone, further ECGs showed her QTc interval to be widely variable. Six weeks later, a third ECG, with no change of medication, showed the interval had lengthened to 567 msec. Due to poor pain control, the patient requested that her methadone dose be maintained despite the risk of arrhythmia. A fourth ECG performed three weeks later showed the QTc had again normalized.

DISCUSSION

The ability of methadone to prolong the QT interval, especially during upward titration of the drug, has been demonstrated in several case series.[3-6] None of the reports that we found during our search of the literature examined changes in the QT interval over time in patients on a maintenance dose of methadone. The potential for fluctuation of the QT interval in this situation is therefore unknown. The case we present suggests that there may be significant variation of the QT interval under conditions of stable dosing. This is particularly relevant in the chronic pain population as these patients may be maintained on methadone for long periods of time.

In a study of 17 patients who developed torsade de pointes on high-dose methadone, Krantz et al., using multiple linear regression analysis, found that only the daily methadone dose was predictive of the QTc interval.[4] The average daily dose of methadone in these patients was 397 ± 283 mg. The duration of methadone therapy ranged from less than one month to greater than one year. The authors note that the methadone dose of six patients had been increased just before the development of cardiac arrhythmias.[3] This suggests that upward titration of the dosage may represent a period of increased risk for prolongation of the QT interval.

Further supporting the claim that methadone treatment may place patients at risk for cardiac arrhythmias, a study of 190 patients receiving intravenous methadone for cancer pain demonstrated a dose-dependent relationship between methadone log-dose and QTc prolongation.[6] In this study, there was not a particular dose below which QTc prolongation was not seen. The authors therefore suggested that no dose of intravenous methadone could be considered safe, and that all patients undergoing this therapy should receive prospective ECG monitoring. A confounding factor in this study was that the intravenous methadone was formulated with chlorobutanol, an additive that also prolongs the QTc.

Table 2. Drugs that may prolong the QT interval				
Antiarrhythmic drugs	**Antimicrobial drugs**	**Antihistamines**	**Psychotropic drugs**	**Other drugs**
Quinidine	Erythromycin, azithromycin	Terfenidine	Thioridazine	Vasodilators—prenylamine
Procainamide	Clarithromycin	Astemizole	Phenothiazines	Diurectics—via electrolyte change
Diisopyramide	Trimethoprim-sulfamethoxazole		Butyrophenones	Motility drugs—cisapride, domperidone
Amiodarone	Pentamidine		Tricyclic or tetracyclic antidepressants	Droperidol
Sotalol	Some fluoroquinolones		Haloperidol	Probucol
Ibutilide	Other—spiramycin, chloroquine, halofantrine, mefloquin		Selective serotonin reuptake inhibitors	Cocaine
Bepridil			Risperdone	Terodiline
			Methadone	Papaverine
				Chloral hydrate
				Arsenic trioxide
				Cesium chloride

The duration of methadone therapy before ECG changes was not stated, although it was likely of short duration given that the drug was used in the context of patient-controlled analgesia (PCA) in an inpatient setting. Certainly, the daily dose of methadone for these patients could have been quite variable because it was being administered by PCA.

In contrast to these reports, two recent papers challenge the risk posed to patients by methadone use. Cruciani et al. studied 104 patients on more than 200 mg daily of oral methadone for chronic pain and narcotic addiction.[7] They found that 33 percent developed QTc prolongation, but none over 500 msec. Risk factors for lengthening of the QTc interval were male gender and duration of therapy less than 12 months. The authors concluded that, although methadone does increase the QTc interval, it does not increase the risk of torsade de pointes. A similar conclusion was reached by Martell et al.[8] In a letter to the editor published in the *Annals of Internal Medicine*, they reviewed the ECGs of 132 patients that were performed two months after initiation of methadone maintenance treatment for heroin addiction. The patients were on a stable methadone dose at the time of the ECG. The authors found that none of the patients experienced a QTc interval increase greater than 400 msec, and none had a QTc interval greater than 500 msec. Taken together, these articles suggest that there is less of a risk of QT prolongation when patients are on a stable maintenance dose of methadone.

Fluctuations in the effect of methadone on the QT interval may owe partially to the substantial variation in metabolism of the drug. Inturrisi et al. found that the interindividual variation in elimination half-life and clearance of methadone from the blood was fourfold and fivefold, respectively.[9] Methadone is metabolized in the liver by the type I cytochrome P450 (CYP450) group of enzymes. The CYP3A4 enzyme is the main CYP450 subtype enzyme mediating N-demethylation of methadone. The activity of this enzyme can vary by as much as 50-fold in the adult population, explaining some of the unpredictability in methadone's metabolism, effects, and side effects.[10] This enzyme is also subject to induction and inhibition by a large number of other drugs (Table 1). Of particular concern in patients taking methadone

are the inhibitors of CYP3A4, which increase the drug's bioavailability and may lead to overdose.[10]

The risk of prolonged QTc and the development of torsade de pointes should be carefully considered in chronic pain patients on methadone. Assessment of risk factors should be performed before prescribing the drug, and a baseline ECG is necessary to establish any underlying conduction abnormalities. Clinicians prescribing methadone should maintain a high index of suspicion, especially if patients are on multiple drugs that may prolong the QTc (Table 2), or if new drugs are added to their regimen. Further studies are required to explore the relationship between methadone dose and risk of QTc prolongation. Hayes et al. recently suggested that an ECG, serum electrolytes, and magnesium should be ordered on all patients taking oral methadone in doses exceeding 240 mg per day.[11] The recently released College of Physicians and Surgeons of Ontario (CPSO) consensus guidelines on the use of methadone for chronic pain advise a surveillance ECG in patients receiving doses greater than 200 mg per day.[12] However, our patient displayed a clinically significant prolongation of the QTc interval at a total daily dose of 180 mg per day of methadone. Several reports indicate that a particular danger period for the development of cardiac arrhythmias is during upward titration of the drug.[3] This case report demonstrates that the QTc interval may be variable even at a stable dose of methadone. We suggest that ECG monitoring should be conducted regularly to rule out prolonged QTc in patients on long-term methadone, as a single ECG is not sufficient to dismiss this risk. Conversely, a prolonged QTc found during surveillance may normalize as levels of methadone stabilize over time. Prolongation of the QT interval to > 500 msec should prompt a reevaluation of the risks and benefits of methadone treatment, consideration of alternatives, and a search for additional predisposing factors such as hypokalemia or other drugs. In addition, we follow the CPSO guidelines, which recommend a cardiology consult for all patients found to have a prolonged QTc interval.[12]

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ORIGINAL ARTICLE

The effect of tramadol or clonidine added to intraperitoneal bupivacaine on postoperative pain in total abdominal hysterectomy

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ABSTRACT

Recent studies suggest that intraperitoneal application of local anesthetics is useful in abdominal surgery. Tramadol and clonidine have specific effects on peripheral nerves when used alone. We aimed to evaluate the effects of intraperitoneal application of bupivacaine and the combinations of bupivacaine plus tramadol and bupivacaine plus clonidine on postoperative pain in total abdominal hysterectomy.

After standard anesthetic procedure during closure of the abdomen, Group 1 (n = 20) was given 20 mL bupivacaine 0.5 percent, Group 2 (n = 20) was given 20 mL bupivacaine 0.5 percent plus 100 mg tramadol, and Group 3 (n = 20) was given 20 mL bupivacaine 0.5 percent plus 1 μg per kg clonidine, all into the peritoneal cavity. Postoperative pain was evaluated with the visual analog scale (VAS) at 30 minutes, and two, four, six, 12, and 24 hours after extubation. While patients were supine and seated, mean arterial pressure (MAP), heart rate (HR), and peripheral oxygen saturation (SpO_2) values were noted. When VAS scores were 4 to 7, 0.5 mg per kg of meperidine was given intramuscularly (IM); above 7, 1 mg per kg of meperidine was given IM; and when VAS scores were 2 to 4, 500 mg acetaminophen was given orally. For evaluating quality of analgesia, rescue analgesic dose, analgesia time, and side effects were noted.

The groups were similar in respect to SpO_2; however, when Group 1 was compared to Groups 2 and 3 at 30 minutes, and two, four, and six hours, MAP and HR measurements were found to be significantly higher ($p < 0.05$). VAS values in sitting and supine positions at 30 minutes and two hours were significantly lower in Group 2 ($p < 0.05$) when compared to Group 1. VAS values for Group 3 at 30 minutes, and two and four hours in the supine position, and at 30 minutes and two hours in the sitting position, were found to be significantly lower than those in Group 1 ($p < 0.05$). There were no significant differences between Groups 2 and 3.

The mean dosage of meperidine used was 76.7 ± 10.5 mg in Group 1, 63.9 ± 8.4 mg in Group 2, and 70 ± 5.2 mg in Group 3. When Group 1 was compared to Group 2, there were significant differences found ($p < 0.05$). First analgesic requirement time was found to be 30 (range, 30 to 30) minutes in Group 1, 120 (range, 30 to 240) minutes in Group 2, and 110 (range, 30 to 240) minutes in Group 3. There were significant differences found when Groups 2 and 3 were compared to Group 1 ($p < 0.05$).

We concluded that the combinations of bupivacaine plus tramadol and bupivacaine plus clonidine administered intraperitoneally in total abdominal hysterectomy operations provide more effective analgesia than bupivacaine alone during the early postoperative period.

Key words: postoperative analgesia, intraperitoneal administration, bupivacaine, tramadol, clonidine

INTRODUCTION

Postoperative pain is among the major problems encountered in surgical patients. When pain occurs, the patient finds it difficult to perform respiratory exercises and normal activities.[1] In the treatment of pain occurring after a surgical procedure, the goals should be to eliminate or reduce any discomfort that might be experienced by the patient, to facilitate the recovery process, and to avoid any side effects that might occur as a result of the treatment.

In 1991, Narchi et al. suggested intraperitoneal administration of local anesthetics after laparoscopy. When they administered the local anesthetic agents lidocaine and bupivacaine intraperitoneally, they found a reduction in

Table 1. Demographic data of patients and duration of operation (mean ± SD)			
	Group 1 (n = 20)	**Group 2 (n = 20)**	**Group 3 (n = 20)**
Age (years)	53.6 ± 12.7	51.8 ± 12.6	52.7 ± 9.3
Weight (kg)	74.8 ± 10.6	75.8 ± 9.6	73.9 ± 12.7
Duration of operation (min)	111 ± 19.6	112.6 ± 17.8	115 ± 11.76
No statistically significant differences were found between the groups ($p > 0.05$).			

postoperative pain as compared to the control group.[2-4] In contrast, some other investigators have found that intraperitoneal administration of bupivacaine or morphine is not an effective method.[5-7]

Tramadol is a weak opioid, selective for the μ receptors.[8] Recent studies suggest that tramadol may have specific local anesthetic properties on peripheral nerves when used alone.[9-11] As a result of these findings, the investigators thought that addition of tramadol to local anesthetic would be effective.

Clonidine has depressant properties on the C-fiber action potential and produces tonic and phasic inhibition of nerve conduction in vitro.[12] As an adjunct, clonidine showed an enhancing effect on lidocaine-induced inhibition of C-fiber action potential.[13]

In our study, we aimed to evaluate how bupivacaine, a combination of bupivacaine plus tramadol, and a combination of bupivacaine plus clonidine, affected postoperative pain, analgesic consumption, and vital signs when administered intraperitoneally in total abdominal hysterectomy operations.

MATERIALS AND METHODS

After approval granted by the Hospital Ethical Committee, our study was conducted on 60 patients who were scheduled for total abdominal hysterectomy with an American Society of Anaesthesiologists (ASA) status of ASA I or ASA II, and who had no history of allergy to local anesthetic and opioid agents. Exclusion criteria were known allergy or contraindications to anesthetics or any drug used, asthma, renal insufficiency, cardiac disease, relative hypovolemia or such as from dehydration, and history of allergy to local anesthetic and opioid agents.

The patients were randomized to three groups of 20 each. The study design was randomized and double-blinded. Identical syringes containing each drug were prepared by an anesthesiology assistant not involved in the study according to the randomization list that was generated. As premedication, midazolam 0.15 mg per kg and atropine 0.01 mg per kg were administered intramuscularly (IM) 45 minutes before the surgical procedure. Anesthesia was induced by administering thiopental sodium 5 mg per kg intravenously (IV) and was maintained by 50 percent O_2, 50 percent N_2O, and 1 to 1.5 percent isoflurane after intubation had been achieved with atracurium 0.5 mg per kg. After the induction of anesthesia, all patients were administered an IV injection of fentanyl 2 μg per kg and 8 mg IV ondansetron for postoperative nausea or vomiting. Muscle relaxation was maintained by IV administration of atracurium 0.2 mg per kg. No other opioid analgesics were used during the operation. The 20 patients assigned to Group 1 received 20 mL of bupivacaine 0.5 percent; the 20 patients assigned to Group 2 received 20 mL of bupivacaine 0.5 percent plus tramadol 100 mg; and the remaining 20 patients assigned to Group 3 received 20 mL of bupivacaine 0.5 percent plus clonidine 1 μg per kg, all administered to the peritoneal cavity. MAP, SpO_2, and HR values were recorded 30 minutes after extubation and at two, four, six, 12, and 24 hours.

Assessment of postoperative pain when lying down and on movement (by putting the patient in a sitting position) was made on the basis of the visual analog scale (VAS), where 0 = "no pain" and 10 = "worst pain imaginable." VAS measurements were taken 30 minutes after extubation and at two, four, six, 12, and 24 hours. Patients who had a postoperative pain score of 4 to 7 were administered IM meperidine 0.5 mg per kg. Those who had a postoperative pain score of 7 or higher were administered IM meperidine 1 mg per kg. Total amounts of meperidine administered to each group were recorded. Patients who had a postoperative pain score of 2 to 4 were given oral acetaminophen 500 mg, and total amounts of acetaminophen received by each group were recorded. These measurements were recorded by an anesthesiology resident who did not know which medication was administered. Measurements in all patients were performed by the same person.

In our study, pain scores were used to determine analgesic effectiveness. To get information on the quality of analgesia, additional analgesics needed by each group within 24 hours and time to analgesic need were determined. Analgesic need was regarded as the time elapsed between the administration of the study agent and the administration of an additional analgesic.

Nausea and vomiting were assessed on a 4-point scale (0 = no nausea/vomiting; 1 = nausea alone; 2 = moderate vomiting; 3 = severe vomiting). Degree of sedation was measured on a 3-point scale (0 = alert; 1 = drowsy but arousable to voice; 2 = very drowsy, arousable to shaking). These assessments were recorded 30 minutes after extubation and at two, four, six, 12, and 24 hours.

Table 2. Visual analog scale (VAS) scores of pain at rest and in motion						
Time	VAS - supine position			VAS - sitting position		
	Group 1	Group 2	Group 3	Group 1	Group 2	Group 3
30 minutes	7 (6 – 10)	2 (1 – 5)*	5 (0 – 6)*	8 (7 – 10)	3 (2 – 6)*	6 (1 – 8)*
2 hours	7 (0 – 8)	3 (1 – 7)*	4 (2 – 7)*	8 (1 – 8)	4 (2 – 5)*	6 (3 – 8)*
4 hours	5 (2 – 9)	4 (2 – 5)	3 (1 – 7)*	6 (3 – 10)	5 (2 – 6)	4 (2 – 8)
6 hours	4 (1 – 7)	2 (1 – 4)	3 (1 – 6)	4 (2 – 8)	3 (2 – 5)	4 (2 – 7)
12 hours	2 (2 – 5)	2 (1 – 3)	2 (1 – 4)	3 (2 – 5)	3 (1 – 4)	3 (1 – 4)
24 hours	1 (1 – 3)	1 (0 – 2)	1 (0 – 3)	2 (2 – 3)	2 (2 – 3)	3 (1 – 4)
Values are median, range appears in parentheses. n = 20 for each group. *p < 0.05 when compared to Group 1.						

STATISTICAL ANALYSIS

Prestudy power analysis determined a sample size of 20 patients per group as having an 80 percent chance (ß = 0.20) for detecting a 34-mg difference in rescue meperidine requirements during the first 24 hours after surgery at the 95 percent confidence interval limitations (ß = 0.05).[14]

The Mann-Whitney U test was used to analyze the demographic data related to the patients. MAP, HR, SpO_2, and postoperative meperidine and acetaminophen administration data were analyzed using the One-Way ANOVA test. The Tamhane posthoc test was applied to determine the significance of differences in means because of nonhomogeneous variance of groups. VAS and the first analgesic requirement time were analyzed by using the Kruskal-Wallis test. If a significant result was obtained, the Bonferroni posthoc test was performed for multiple comparisons. The Chi-square (Fisher's exact) test was used for evaluating adverse events. These values were represented as the arithmetic mean and standard deviation (mean ± SD). Levels of significance were determined as $p < 0.05$ for significant difference.

RESULTS

Table I shows the demographic characteristics of the patients. No statistically significant differences were found between the groups ($p > 0.05$).

VAS values in Groups 1 and 2 were compared while the patients were in sitting and supine positions; it was determined that at 30 minutes and two hours the pain scores were significantly lower in Group 2 ($p < 0.05$). Pain scores measured with patients in the supine position in Groups 1 and 3 at 30 minutes, two hours, and four hours, and at 30 minutes and two hours with patients in the sitting position were found to be significantly lower in Group 3 ($p < 0.05$). There was no significant difference when Groups 2 and 3 were compared (Table 2).

The mean dosage of meperidine used was 76.7 ± 10.5 mg in Group 1, 63.9 ± 8.4 mg in Group 2, and 70 ± 5.2 mg in Group 3. When Group 1 was compared to Group 2, there were statistically significant differences found ($p < 0.05$). There were no statistically significant differences between other groups. Acetaminophen use was 500 mg in Groups 1, 2, and 3, with no difference between the groups ($p > 0.05$).

First analgesic requirement time was found to be 30 minutes (range, 30 to 30) in Group 1, 120 minutes (range, 30 to 240) in Group 2, and 110 minutes (range, 30 to 240) in Group 3. When Group 1 was compared to Groups 2 and 3, there were significant differences found ($p < 0.05$). When Groups 2 and 3 were compared, there were no statistically significant differences.

When the groups were compared for MAP, HR, and SpO_2 values during the postoperative period, no significant differences were found for SpO_2 ($p > 0.05$). Comparison of MAP and HR measurements in Group 1 to those of Groups 2 and 3 at 30 minutes, two hours, four hours, and six hours, however, found them to be significantly high ($p < 0.001$). When Groups 2 and 3 were compared, there were no statistically significant differences ($p > 0.05$) (Table 3).

One patient in Group 1, two patients in Group 2, and one patient in Group 3 experienced postoperative nausea rated 1 in severity and requiring no treatment. No statistically significant differences were found ($p > 0.05$). No sedation was seen in all patients.

DISCUSSION

In our study, we demonstrated that the combinations

Table 3. Changes of mean arterial pressure, heart rate, and peripheral oxygen saturation (mean ± SD)

Time	MAP			HR			SpO_2		
	Group 1	Group 2	Group 3	Group 1	Group 2	Group 3	Group 1	Group 2	Group 3
30 minutes	107 ± 7.7	81.8 ± 7.3*	82.6 ± 9.9*	102 ± 6.7	76.8 ± 4.3*	77.6 ± 8.9*	98.6 ± 0.48	98.6 ± 0.5	98.7 ± 0.48
2 hours	103.2 ± 5.1	85.4 ± 7.0	82.1 ± 4.3*	98.2 ± 5.2	80.4 ± 6.0*	77.1 ± 5.3*	98.5 ± 0.5	98.6 ± 0.5	98.6 ± 0.4
4 hours	95.2 ± 8.9	86.2 ± 4.6*	81.5 ± 9.8*	90.2 ± 3.9	81.2 ± 4.6*	76.5 ± 6.8*	98.6 ± 0.5	98.8 ± 0.5	98.6 ± 0.5
6 hours	97.4 ± 6.2	82.1 ± 6.1*	83.9 ± 5.6*	92.4 ± 4.2	77.1 ± 6.1*	78.4 ± 3.6*	98.5 ± 0.5	98.8 ± 0.6	98.5 ± 0.5
12 hours	88.2 ± 4.0	89.6 ± 7.1	88.6 ± 5.5	80.2 ± 4.07	79.6 ± 6.1	78.6 ± 5.7	98.7 ± 0.5	98.8 ± 0.7	98.6 ± 0.5
24 hours	89.7 ± 3.5	90.1 ± 4.3	88.6 ± 6.7	81.7 ± 3.5	79.1 ± 4.3	78.6 ± 4.9	98.8 ± 0.4	98.8 ± 0.6	98.8 ± 0.4

MAP (mmHg), mean arterial pressure; HR (beats/minute), heart rate; SpO_2 (percent), peripheral oxygen saturation. n = 20 for each group. * $p < 0.05$ when compared to Group 1.

of bupivacaine plus tramadol and bupivacaine plus clonidine, administered intraperitoneally in total hysterectomy operations, provide more effective analgesia than bupivacaine alone during the early postoperative period.

Tramadol has a dual mechanism of action, also blocking the reuptake of the norepinephrine and 5-hydroxy-tryptamine at the α2-adrenergic receptor level.[15,16] The pretreatment with α-adrenoreceptor antagonists yohimbine and idazoxan caused a significant reduction of tramadol's antinociceptive effect.[17] As a result, tramadol has a profile of action similar to that of clonidine, which inhibits the release of norepinephrine from prejunctional α2-adrenoreceptors in the periphery.[18] In view of this hypothesis, we compared the effect of addition of tramadol and clonidine to local anesthetic in our study. During our literature search, we did not find any study of intraperitoneal local anesthetics and intraperitoneal opioids administered to patients who underwent an open lower abdominal operation, which would be considered similar to our study. Kapral et al. obtained a prolongation of the motor blockade of the brachial plexus with 100 mg tramadol added to mepivacaine.[10] Acalovschi et al. found that 100 mg tramadol provided a shorter onset time of sensory block in intravenous regional anesthesia.[16] In our study, we used a similar dose of 100 mg tramadol.

In different studies, addition of clonidine to local anesthetic was investigated. Culebras et al. determined that addition of 150 μg clonidine to local anesthetic did not prolong the interscalene block,[19] whereas other investigations in regional anesthesia determined that addition of clonidine improved the effects of local anesthetics.[20-23] Singelyn et al.[20] added 30 μg clonidine to mepivacaine in a brachial plexus block, Bernard et al.[21] added 0.5 μg per kg clonidine to lidocaine in a brachial plexus block, Tschernko et al.[22] added 2 μg per kg clonidine to bupivacaine in an intercostal nerve block, and Joshi et al.[23] added 1 μg per kg clonidine to intra-articular bupivacaine—all of these improved analgesia of the local anesthetics. In our study, we used a similar dose of clonidine at 1 μg per kg.

Ali et al. administered 20 mL of bupivacaine 0.5 percent and 20 mL of lidocaine 2 percent together with epinephrine intraperitoneally to patients undergoing total abdominal hysterectomy,[24] and Williamson et al. administered a total amount of 200 mg of lidocaine in 50 mL saline intraperitoneally together with adrenaline to patients undergoing total abdominal hysterectomy.[25] When both groups of investigators evaluated the need for analgesia during the postoperative period and compared the use of morphine with the control group, they concluded that intraperitoneal administration of local anesthetics had no effect. We found similar results to Ali et al. in that 20 mL of bupivacaine 0.5 percent had no postoperative

analgesic effect alone in patients undergoing total abdominal hysterectomy. Bupivacaine was selected because it is the most widely used local anesthetic in our country.

Pang et al. injected 25 mg tramadol IM and demonstrated that it has local anesthetic effect.[9] Clonidine has also been reported to depress nerve action potentials, especially in C fibers, by a mechanism independent of the stimulation of α2-adrenergic receptors.[12,13] This mechanism accounts for strengthening of the local anesthetic block achieved by perineal administration of the drug. Finally, α2-adrenergic receptors located at nerve endings may play a role in the analgesic effect of the drug by preventing norepinephrine release.[26,27] In another study, results revealed that clonidine and, much more potently, dexmedetomidine inhibit peristalsis of the guinea pig ileum. The inhibition is caused by interaction with α2-adrenoceptors and, in the case of clonidine, also involves activation of small conductance Ca^{2+}-activated potassium channels and endogenous opioidergic pathways.[28] In our study, we considered that tramadol (a low-potency opioid) and clonidine (an α2 agonist), with their local anesthetic effect, would increase the effect of bupivacaine and delay the onset of the pain, while also reducing its severity. Systemic absorption may have played a role, but it has been demonstrated that local intraperitoneal bupivacaine and intraperitoneal meperidine were better than the combination of intraperitoneal bupivacaine and IM meperidine for postoperative analgesia in patients undergoing laparoscopic tubal ligation, demonstrating a local effect.[29]

The most frequent side effect of tramadol is nausea and vomiting; hemodynamic and respiratory depression are rarely seen.[30,31] The most common side effect of clonidine is hypotension, and there are studies on clonidine's transmission to the heart, which causes dangerous rhythm defects.[32,33] We did not see side effects other than nausea in our study groups; this may be because of our having used prophylactic ondansetron.

The most important complication of intraperitoneal local anesthetic application is IV injection. With sudden increase of systemic absorption, toxic symptoms can be seen. Intraperitoneally administered opioids cause constipation and ileus by affecting μ receptors in the gastrointestinal tract. Incidence of infection is rare because of widespread antimicrobial action of local anesthetics.[34]

Pain increases sympathetic activity, which causes tachycardia, an increase in peripheral vascular resistance, and, related to this, an increase in the workload of the heart.[35] Comparing Group 1 to Groups 2 and 3, the increase in MAP and HR is associated with increase in sympathetic activity.

We conclude that the combinations of bupivacaine plus tramadol and bupivacaine plus clonidine administered intraperitoneally in total hysterectomy operations provide more effective analgesia than bupivacaine alone during the early postoperative period.

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ORIGINAL ARTICLE

Morphine analgesia in cancer pain: Role of the glucuronides

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ABSTRACT

Preclinical data and limited studies in humans have suggested that morphine-6-glucuronide (M6G) has analgesic activity and morphine-3-glucuronide (M3G), contributes adversely to the therapeutic effect of morphine. This open point-prevalence study in 103 patients on oral morphine for cancer-related pain investigated the correlations between morphine doses, metabolites, and the degree of pain relief or toxicity. Morphine, M6G, and M3G were assayed by high-performance liquid chromatography on a single blood sample taken between two and four hours after dose. Pain, analgesia, and toxicity were recorded on numerical and visual analog scales. Patients received a median dose of 60 (range, 10 to 620) mg per day morphine, for a median of 4.1 weeks (range, 0.2 to 46.0 weeks). M3G:M6G ratios fell within a narrow range, with a median value of 4.39 (interquartile range, 3.78 to 6.96; range, 2.18 to 14.95). There were no significant correlations between M3G:M6G and morphine dose, or any measure of analgesia. The correlation between plasma concentration and pain score (i.e., better analgesia) was stronger for M6G ($r = 0.308$, $p < 0.01$) than morphine ($r = 0.197$, $p = 0.05$). These data suggest that M6G contributes significantly to the analgesic potency of oral morphine. No evidence was found for differences in M3G:M6G ratios contributing to analgesia or toxicity.

Key words: morphine, cancer pain, glucuronides, analgesia

INTRODUCTION

Morphine remains a mainstay of treatment for patients with severe cancer-related pain.[1] Although the recommendation is to titrate dose against effect, either analgesia or toxicity, this is empirical advice, and attempts to predict effective doses or respond to inadequate plasma concentrations of analgesics have generally proved fruitless.[2]

Oral morphine undergoes extensive presystemic glucuronidation, predominantly in the liver, to morphine-3-glucuronide (M3G) (80 percent) and morphine-6-glucuronide (M6G) (15 percent), with morphine contributing less than 5 percent of the total area under the concentration time curve (AUC).[3] In animal models, M6G gives potent and long-lasting analgesia.[4,5] Initially, M6G was thought to be present in only small amounts in humans, as in the rat.[6] However, the development of a new and specific high-performance liquid chromatography (HPLC) method revealed that M6G was present in higher concentrations than morphine after administration of intravenous (IV) morphine from one hour onward. Indeed, after oral morphine, M6G was found in considerably larger amounts at all time points, consistent with first-pass metabolism.[3,7] The first suggestion of M6G activity in humans was the observation of protracted narcosis in patients with renal failure who metabolize morphine yet retain the glucuronides.[8] M6G's actions have recently been confirmed in human studies, demonstrating that IV M6G is more potent than morphine with fewer side effects, producing little nausea or sedation and significantly less respiratory depression.[9-13]

Experiments in μ-opioid receptor gene knockout mice suggest that M6G acts predominantly through this receptor.[14] M6G has significantly greater analgesic potency than morphine,[4,12] such that some authors have claimed that it contributes up to 85 percent of the analgesic efficacy of morphine.[15,16] Others have argued that the effects of M6G may only be apparent with chronic dosing because of poor penetration to the central nervous system.[17] Modeling of effect-site concentrations of M6G suggests that after multiple oral doses of morphine, M6G might reach concentrations two times greater than that of morphine in the brain.[18]

Although M3G has no analgesic activity, it has been suggested that it may functionally antagonize the effects of morphine in rats.[19,20] Furthermore, other investigators have claimed that abnormal metabolite ratios may explain

4	3	2	1	0
No pain	Slight pain	Moderate pain	Severe pain	Very severe pain

Figure 1. Pain score.

the variation in the analgesic potency of morphine,[21] and that morphine tolerance may owe to accumulation of M3G over time.[22] These results have not been consistently reproduced in preclinical studies and there has been skepticism about this apparent activity.[23,24] There is an obvious analogy, however, to the accumulation of the neurostimulatory metabolite of meperidine; normeperidine,[25] hyperalgesia, and myoclonus have been attributed to M3G[26], and worse pain relief and increased toxicity has been reported to result from a disproportionately high M3G concentration.[22]

In this point-prevalence study, we sought to quantify the influence of plasma concentrations and ratios of morphine and its principal glucuronide metabolites on the analgesic and unwanted effects of oral morphine and to investigate the incidence of paradoxical pain and/or abnormally raised M3G:M6G ratios.

MATERIALS AND METHODS

The study was approved by the Royal Hospitals Trust Research Ethics Committee and was undertaken in the Department of Medical Oncology at St. Bartholomew's Hospital.

Patients

Patients with chronic severe pain related to cancer and receiving oral morphine were eligible for the study and gave informed consent. Patients were in- or outpatients within the Solid Tumour Division of the Department of Medical Oncology. Patients with neuropathic pain, typically much less responsive to opiates, were not excluded. Patients deemed at the multidisciplinary meeting to be "imminently dying" were excluded.

Assessment

A single 6-mL blood sample was drawn into a lithium heparin tube between two and four hours after taking oral morphine. This interval was chosen to avoid the first hour in which the glucuronide:morphine ratios are changing.[3] After centrifugation the plasma was separated and stored at -40°C until analysis. Plasma morphine, M3G, and M6G were quantitated by reversed-phase ion-paired high-performance liquid chromatography.[27] Information about patients' pain, analgesia, and limited demographic details were recorded on a proforma from data acquired at interview by one of the investigators (RTP) or a research nurse. Further data were abstracted from the patients' notes and drug chart. Serum creatinine, bilirubin, alkaline phosphatase, and aspartate transaminase were recorded as measures of renal and hepatic function. The normal laboratory ranges were creatinine 79 to 118 μmol per L in men and 58 to 93 μmol per L in women, bilirubin < 17 μmol per L, AST < 39 IU per L, and ALP < 117 IU per L.

At the time of taking the blood sample, the patient was asked to assess the degree of pain and pain relief using validated pain assessment scales (Figures 1 and 2) and a visual analog scale (VAS).[28] It was made clear that this was to be an impression of their overall experience of pain, at that time, on morphine and the scales were scored so that higher values represented better pain relief or less pain (Figures 1 and 2). Patients were also asked about the character of the pain and how this had changed in the two weeks prior. The subjective experience of side effects was reported without a formal grading system.

Statistical analysis

The intention was to enroll at least 100 patients into the study to reliably determine the population estimates and variability in the relative plasma ratios and amounts of M3G, M6G, and morphine. As very few studies have shown any correlation between analgesia and plasma concentrations, no accurate estimate of sample size could be undertaken. The data were checked for normality of distribution and rank correlation performed, taking $r > 0.200$ and $p < 0.05$ as significant. Subset analysis was performed using the Mann-Whitney test with $p < 0.05$ considered significant. Stepwise regression analysis was used to determine the influence of organ function on analgesia, measured plasma concentration, and concentration ratios.

RESULTS

Demographics

One hundred and three patients were studied, 50 men

My pain has:

5 ( ) been completely relieved
4 ( ) been almost completely relieved
3 ( ) eased moderately
2 ( ) eased only slightly
1 ( ) not changed at all
0 ( ) become more intense

Figure 2. Pain relief.

Table 1. Summary of mean (± SD and range) dose and ratio data		
	Value	
	Plasma concentration (nmol per L)	Ratio
M3G	1,379 (± 1,662; 36 to 12,530)	
M6G	266 (± 296; 8 to 2,048)	
Morphine	59 (± 67; 2 to 424)	
M6G + morphine	333 (± 332; 19 to 2,130)	
M3G:morphine		33.0 (± 31.1; 2.8 to 80.3)
M3G:M6G		5.6 (± 2.2; 2.2 to 15.0)
M6G:morphine		6.5 (± 6.6; 0.6 to 47.4)
M3G, morphine-3-glucuronide; M6G, morphine-6-glucuronide; SD, standard deviation.		

and 53 women, with a median age of 57 (range, 22 to 88) years and weight of 65 (range, 36 to 104) kg. The most common cancers were colorectal (22 patients), non–small-cell lung cancer (10), breast cancer (10), adenocarcinoma of unknown primary (nine), small-cell lung cancer (six), and pancreatic cancer (six).

Median serum creatinine was 80 (range, 40 to 1,740) µmol per L, and was above the upper limit of normal in 10 patients. Cockcroft-Gault estimation of glomerular filtration rate (GFR) gave a median GFR of 71 (range, 4 to 140) mL per min.[29] Plasma creatinine correlated with M3G:morphine ($r = 0.518$, $p < 0.001$) and M6G:morphine ratios ($r = 0.681$, $p < 0.001$). Liver function tests were abnormal in 20 patients in whom the median values for bilirubin, alkaline phosphatase, and aspartate transaminase were 14 (range, 4 to 411), 482 (range, 173 to 2,871), and 62 (range, 10 to 196) µmol per L respectively. No association was found between liver impairment and analgesia, side effects, or plasma ratios and concentrations.

Patients were taking oral morphine at a median dose of 60 (range, 10 to 620) mg per day; a mean dose of 106 (± 121) mg. Eighty-five patients were taking MST® (Morphine Slow-Release Tablets, NAPP Laboratories, Cambridge, United Kingdom) bid, and the remainder were taking morphine solution. Patients had been on morphine for a median of 4.1 (range, two days to 46 weeks) weeks; a mean of 8.5 (± 10.9) weeks. Twenty-five patients had been on morphine for less than two weeks. The blood was collected within one hour of the last dose of morphine in four patients. Dose correlated with the length of time on morphine ($r = 0.40$, $p < 0.01$).

Seventy-five patients (74 percent) were taking coanalgesics. Forty-seven (46 percent) were on nonsteroidal anti-inflammatory agents (NSAIDs), 13 (13 percent) on benzodiazepines, 11 (11 percent) on tricyclic antidepressants, and four (4 percent) on anticonvulsants. Patients on NSAIDs may have had more side effects ($r = 0.266$, $p = 0.06$), and the prescription of antiepileptics ($r = 0.23$, $p = 0.07$), but not antidepressants ($r = 0.08$), was associated with poorer pain relief. Use of tricyclics was associated with a slightly higher plasma morphine concentration, although the association did not achieve statistical significance ($r = 0.19$). The dose of morphine taken by patients receiving tricyclic antidepressants [160 (± 151) mg per 24 hours] appeared to be greater than for those not taking tricyclic antidepressants [98 (± 115) mg per 24 hours].

Plasma concentrations and ratios

Mean plasma concentrations and ratios are summarized in Table 1, and these values for ranges of daily doses are presented in Table 2. The frequency distribution of plasma concentrations of morphine + M6G is plotted in Figure 3. M6G was more highly correlated with M6G + morphine ($r = 0.98$, $p = 0.001$) than was morphine ($r = 0.57$, $p < 0.05$), reflecting the fact that M6G contributes more to the total AUC. Plasma M3G and M6G were tightly correlated ($r = 0.94$, $p < 0.001$) as were the M3G:morphine and M6G:morphine ratios ($r = 0.91$, $p < 0.001$). Dose correlated with plasma concentrations of M3G ($r = 0.30$, $p < 0.01$), M6G ($r = 0.36$, $p < 0.01$), morphine ($r = 0.40$, $p < 0.01$) and M6G + morphine ($r = 0.39$, $p < 0.01$) (Figure 4), but not with any of the ratios. The 62-fold dose range was associated with a 212-fold range for morphine, a 348-fold range for M3G, and a 256-fold range for M6G plasma concentrations.

M3G:M6G ratios were not normally or log-normally distributed. The mean (± standard deviation) M3G:M6G ratio was 5.60 (± 2.24) (Figure 5). The median value was 4.39, with the values spanning a seven-fold range of 2.18 to 14.95. The interquartile range was 3.78 to 6.96. There was no correlation between M3G:M6G ratio and duration of treatment ($p = 0.65$).

Table 2. Summary of mean (± SD) plasma concentrations (nmol per L) and ratio data for different dose levels				
	Dose (mg) per 24 h			
	0 to 50	51 to 100	101 to 200	201 to 620
n	40	30	14	15
M3G	908 (± 2,013)	1,211 (± 778)	1,811 (± 1,238)	2,710 (± 1,800)
M6G	175 (± 356)	233 (± 149)	311 (± 176)	550 (± 302)
Morphine	28 (± 26)	63 (± 55)	73 (± 74)	117 (± 111)
M3G:M6G	5.7 (± 2.3)	5.8 (± 2.7)	6.0 (± 1.8)	4.9 (± 1.6)
M3G:morphine	36.6 (± 39.3)	28.8 (± 23.7)	34.9 (± 17.9)	34.3 (± 35.1)
M6G:morphine	7.3 (± 8.8)	5.5 (± 4.9)	5.7 (± 2.6)	7.5 (± 6.5)
M3G, morphine-3-glucuronide; M6G, morphine-6-glucuronide; SD, standard deviation.				

Efficacy and toxicity

Patients appeared to accurately report their symptoms using the scales, with only one patient recording severe pain and good pain relief. Eighty-six patients (83 percent) had moderate or better pain relief, and of this group 74 percent [64 of the total group (62 percent)] had almost complete or complete pain relief. The two measures of pain, pain score and VAS, were well correlated with $r = 0.81$ ($p < 0.001$). Pain relief (PR) score correlated with pain score ($r = 0.59$, $p = 0.001$) and VAS ($r = 0.51$, $p = 0.001$). Mean pain score was 3.58 (± 1.16), between "slight" (3) and "no" (4) pain. The only measure of analgesia to correlate with any plasma concentration was the pain score, which correlated only with M6G ($r = 0.21$, $p = 0.03$) (not shown graphically), but not morphine ($r = 0.03$) or M3G ($r = 0.16$), while M6G + morphine approached significance ($r = 0.19$, $p = 0.06$). For further analysis, the data were divided into two subsets: greater than and less than the median. In subset analysis, comparing greater than and less than the median, higher values of M6G + morphine were significantly associated with pain score ($p = 0.017$) as was comparison of the highest with the lowest quartile ($p = 0.032$). In the same analysis, plasma M6G was highly significantly associated with pain score ($p = 0.008$); however, there was no association with plasma morphine concentrations ($p = 0.32$). Stepwise regression analysis failed to find any significant association between pain score and any pharmacokinetic parameter.

Seventeen patients (17 percent) had poor pain control as defined by a PR score of 2 (minimal PR) or less. Eleven patients (11 percent) had particularly severe toxicity, and only five (5 percent) of the patients had poor efficacy and excess toxicity. In this latter group, the mean M3G:M6G ratio was 4.02 (± 2.37), not significantly different from the mean M3G:M6G ratio for the 43 patients with good analgesia (pain score 3 or 4 and PR 4 or 5) and no excess toxicity of 5.62 (± 2.32) ($p = 0.498$). No atypical toxicity was reported. No myoclonus was observed. Only three patients, all with normal renal function, had significant mental obtundation.

Two patients at the time of this study had pain that appeared to be worsening because (as opposed to in spite) of morphine, referred to as paradoxical pain.[21] One had an M3G:M6G ratio of 8.17, having been on morphine for three weeks and on a dose of 180 mg per day. He had small-cell lung cancer and rapidly deteriorated and died three days after giving blood for the study. The second had an M3G:M6G ratio of 14.83, having been stabilized on 60 mg per day for a long period for celiac-plexus pain. Both of these patients had abnormal liver function tests. The other patient who had a high M3G:M6G (14.95) (Figure 5), had undetectable amounts of morphine and low concentrations of M3G (127 nmol per L) and M6G (8 nmol per L) on 30 mg per day of morphine, with complete pain relief. One further patient in this study subsequently appeared to develop paradoxical pain from recurrent squamous cell carcinoma of the cervix with induration of the left vaginal wall associated with neuropathic pain. At the time she gave blood for this study her pain was well controlled and the M3G:M6G was 5.49. The subsequent M3G:M6G was 9.41.

DISCUSSION

This study represents a snapshot of a limited number of pharmacokinetic parameters in a relatively typical group of hospital patients with cancer receiving morphine.

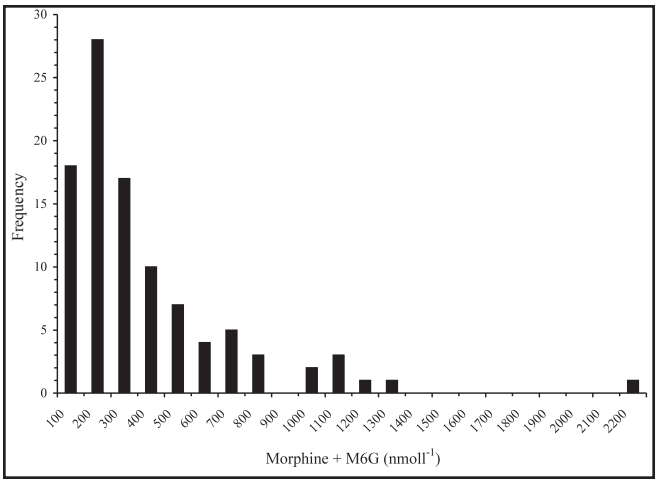

Figure 3. Distribution of plasma concentrations of morphine + M6G.

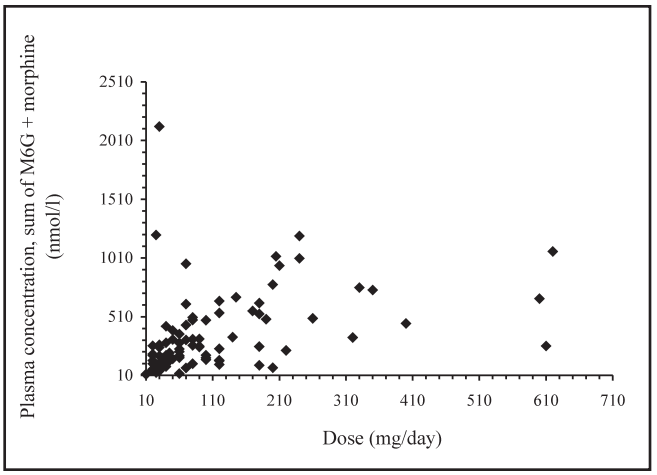

Figure 4. Relationship of dose to [M6G + morphine].

It seems likely that the conclusions from this study could be extrapolated to the wider group of patients on oral morphine. Although M6G is a potent analgesic,[11,15] little is known of the relative contributions of morphine and its metabolites to analgesia and toxicity, and it is obviously impossible to unravel those with a single assay of plasma concentrations. Furthermore, there is no assurance that patients were titrated to optimal or maximally tolerated doses of morphine, and there was no prospective coherent policy for the use of coanalgesics. There are significant limitations inherent in the study design that limit interpretation. Despite this and the inherent danger in performing multiple analyses on a large number of variables, important conclusions can be drawn from this study. M6G appears to contribute significantly to the analgesic potency of oral morphine. For the vast majority of patients, the M3G:M6G ratio is relatively narrow and does not predict for analgesia or toxicity. Even in the upper quartile of the distribution of M3G:M6G, patients were nearly three times as likely to have good as opposed to poor pain relief.

The literature also supports a relatively narrow range of morphine metabolite ratios. In two single-dosing studies of oral morphine in normal volunteers using sufficiently specific methodology to differentiate morphine from M6G, the ratio of M3G:M6G was 5.87:1[3] and 8.08:1.[30] In studies undertaken on patients with reasonably well controlled pain established on oral morphine the plasma M3G:morphine ratios ranges from 4.5:1 to 9.1:1 with a mean of 6.56 (± 1.84).[31-35] Morley et al. were the first to report elevated M3G:M6G ratios in a limited pharmacokinetic analysis of a series of patients with poorly opioid–responsive pain.[36] In 20 patients whose pain had been unsatisfactorily controlled by large doses of opioids, M3G:M6G plasma ratios appeared to be greater than the mean for the normal population, quoted as 5:1. In four of the patients with particularly difficult pain, they found plasma M3G:M6G ratios > 10, with the largest ratio being 35:1. Subsequently, there have been four other studies in patients with poorly controlled pain that have shown ratios similar to those reported in the current study and similar to the values seen in patients in other studies with well-controlled pain. Mean M3G:M6G ratios were 4.44,[37] 5.84,[38] 6.30,[39] and 6.74,[34] an overall mean of 5.83 (± 1.00). These studies also reported cerebrospinal fluid ratios, which ranged from 2.5 to 9.13.

The concepts of paradoxical pain or functional antagonism of morphine metabolites are supported by the differential induction of UDPGT isoenzymes, differences in the K_{max} of isoenzymes that catalyze M3G and M6G production, and the pediatric ratio data. Although UDPGT clearly exists as a number of isoenzymes, such small variation in the ratio of metabolites is very unlikely to owe to polymorphism of the enzyme. There is evidence for heterogeneity of UDPGT with the rat liver glucuronidating relatively more (-)-morphine and the converse being found in human liver[40] in line with the observation that M6G is a far more prevalent metabolite in humans[3,7] than in the rat.[40] Differential induction of UDPGT isoenzymes has been reported for detergents,[41] metal ions,[42] centrally acting drugs,[43] and clofibrate.[35] The differential induction of an isoenzyme may be a reasonable explanation, although there is as yet no direct evidence to support genetic polymorphism or differential induction of isoenzymes influencing the metabolism of morphine. Indeed, the current view is that UDPGT B7 glucuronidates at both positions and the isoforms UGT2B7Y and H do not account for the variability in the plasma or urine concentrations of these glucuronides in human populations.[44,45] One reason for selecting greater than two hours post-morphine administration as the cutoff for blood sampling was the observation that M3G and M6G have slightly different mean t_{max} after the administration of oral morphine to normal volunteers[3] of 1.4 (± 0.5) and 1.25 (± 0.4) hours, respectively, and that there is an increased M3G:M6G ratio during the first 30 minutes after IV morphine

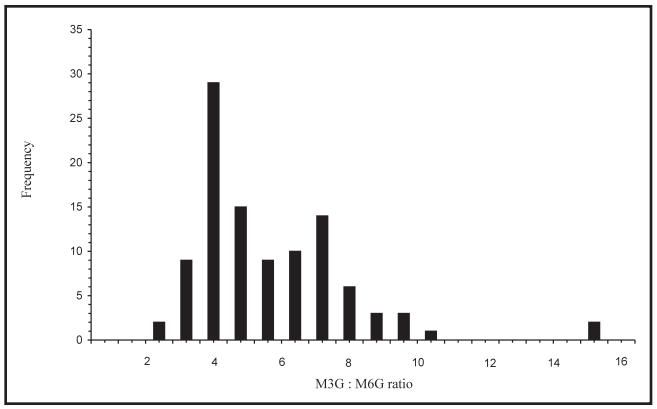

Figure 5. Frequency distribution of M3G:M6G ratio.

and one hour after oral morphine.[3] Therefore, M3G is not only produced in larger amounts, but also more quickly than M6G. This is more likely explained by the relative ease of glucuronidation at the 3 position on the phenanthrene ring, however, in line with in vitro work that reported the mean rate of production of M3G (V_{max}) as 0.94 (mol per min per mg) and that of M6G as 0.13 (mol per min per mg).[31] It is possible that this discrepancy of V_{max} explains Hartley et al.'s observation of altered ratios associated with the premature liver.[46] In this study, no alteration of the M3G:M6G ratio with dose was observed. This is not surprising, as the capacity of human liver glucuronidation of morphine reported in vitro is almost 10,000 times greater than the maximum plasma concentration of morphine in this study, a K_m of approximately 2 mmol per L.[30]

In this study, pain was generally well controlled, with effective pain relief in more than 80 percent of patients. Patients with pain that is difficult to control, most typically neuropathic or incident (i.e., precipitated by locomotor activity) pain, are commonly treated with an increasing number of drugs, and the finding of an association of NSAIDs and antiepileptic medications with excess toxicity is perhaps not surprising. The association of higher concentrations of plasma morphine with tricyclic antidepressants has been described, and may owe to a direct effect on liver metabolism. Indeed, this may be a pharmacokinetic explanation for some of the improvement in morphine–poorly responsive pain, for which they are often used.[43] A more likely explanation, however, is that patients with worse pain had higher morphine concentrations because of higher doses of oral morphine. Although the numbers are small, there appeared to be no data to support an alteration in M3G:morphine or M3G:M6G ratios in patients on tricyclic antidepressants.

It is apparent that the glucuronides can, when present in very large amounts, cause considerable toxicity.[8] A number of population studies have reported a correlation between renal dysfunction and steady-state M6G or morphine concentrations,[33,34,47,48] but none has demonstrated a correlation between specific side effects and higher metabolite concentrations. Tiseo et al. reported a moderate but significant correlation between the M6G:morphine ratio and urea ($r = 0.4$, $p < 0.001$) and creatinine ($r = 0.45$, $p < 0.001$) concentrations, but not with other clinical variables in 109 cancer patients on oral and parentral morphine.[47] Obtundation was more commonly associated with liver dysfunction than with renal impairment, and while seven of nine episodes of respiratory depression or obtundation were associated with M6G concentrations of >4 mmol per L, 13 further patients had similarly high concentrations of M6G but normal biochemistry and minimal toxicity. In a smaller study in which plasma M3G and M6G concentrations were significantly ($p < 0.001$) higher in patients with elevated serum creatinine concentrations, this was concluded to be an aggravating factor in the nausea and vomiting and cognitive function profile of palliative and terminal care patients with significant renal function impairment.[47]

A number of investigators have attempted to correlate plasma concentrations of morphine with measures of analgesia in similar point-prevalence studies. Tiseo et al. found that metabolic dysfunction was a better predictor of myoclonus and cognitive impairment than an increased M6G:morphine ratio.[47] Faura et al. reported that M6G + morphine concentrations in their "optimally controlled" group were more than twice those in the "moderate control" group [751 (± 194) vs. 277 (± 42) nmol per L) and suggested a threshold of 400 nmol per L for optimal analgesia.[2] In a smaller study of 40 patients starting slow-release morphine, the mean trough serum morphine concentration associated with pain relief was 66 nmol per L.[49] In our study, although a similar relationship was found, it was not possible to define a specific threshold.

The extraordinarily large dose range for morphine has been interpreted as evidence for the development of tolerance.[33] This study reports a significant correlation between dose and time on morphine ($p = 0.04$). It has generally been concluded that the escalation in dose relates to worsening pain to a greater extent than to the development of tolerance, and there is little evidence for addiction in cancer patients on morphine. There was no correlation between M3G:M6G ratio and duration of treatment ($p = 0.65$) in contrast with the observation that M3G appeared to correlate with the development of tolerance in different infusion regimens in rats.[22] In fact, Smith and Smith's study was constructed such that an effect of different exposures to morphine could not be excluded and appears to be a more likely explanation for the observation.

Morphine remains one of the central treatments for cancer-related pain. An improvement in our understanding of the metabolism of morphine during the last 25 years has revealed the importance of M6G as an active metabolite. There is still very little evidence to implicate

M3G in tolerance or an adverse therapeutic profile in even a very small minority of patients. Our experience in normal volunteers very much suggests that M3G is devoid of significant activity.[50] Although further pharmacokinetic-pharmacodynamic modeling may help our understanding of the analgesic effects of morphine and M6G, the challenge now is to develop M6G analogs to benefit patients rather than simply rely on endogenous M6G production from morphine.

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ORIGINAL ARTICLE

Prescription opioid dependence and treatment with methadone in pregnancy

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ABSTRACT

Prescription opioids are used medically to treat pain, but their diversion and abuse continues to escalate in the United States.[1] Abuse of OxyContin (Purdue Pharma LP, Stamford, CT), a timed-release form of oxycodone, is a major focus of public health and law enforcement agencies.[2] The rise in opioid abuse may lead to an increase in opioid dependence in pregnancy, which was a focus of this study. Our retrospective chart review examined the demographics and patterns of opioid addiction of pregnant women admitted to an inpatient psychiatric unit in an academic medical center in central Kentucky. Charts of 94 women admitted from January 2001 to May 2004 were reviewed. Information obtained included demographics and details of their opioid use, including the specific opioid(s) used, route of administration, and duration of use. Treatment information included length of hospital stay, stabilizing dose of methadone, comorbid drug use, and concomitant Axis I diagnoses. Most women were in their mid-twenties and in the second trimester of pregnancy when they sought treatment. Benzodiazepines were the most common comorbid drugs of abuse and the most frequent medical complication of their drug use was hepatitis C, newly diagnosed in 11 patients. This study demonstrates the need for further research in prescription opioid dependency in pregnancy, methadone maintenance therapy, the safety of detoxification, and neonatal outcomes.

Key words: opioids, oxycodone, methadone maintenance therapy, addiction, pregnancy

INTRODUCTION

Prescription opioids are used to relieve chronic pain associated with cancer, bursitis, dislocation, fractures, neuralgia, arthritis, low back pain, and other injuries.[3] OxyContin, distributed beginning in 1995 by Purdue Pharma, LP (Stamford, CT), is a timed-release form of oxycodone that is manufactured as a long-acting analgesic for moderate to severe pain.[1] Oxycodone and hydrocodone are prescribed in numerous formulations, with combination prescription medications with acetaminophen and aspirin including Lortab (UCB Pharma, Inc., Smyrna, GA), Percocet (Endo Pharmaceuticals, Chadds Ford, PA), and Percodan (Endo Pharmaceuticals) as some of the most widely prescribed and abused forms. The opioid agonist effects of these medications relieve pain, but also have the potential to produce feelings of euphoria, as with heroin. Although these prescription narcotics are typically swallowed, substance abusers may crush the pills and take them orally, snort them, or dilute the crushed pill in water and inject the solution intravenously.[1]

Abuse of opioids has occurred for many years, but it gained more attention in the late 1990s as the abuse of prescription opioid pain relievers steadily increased in the United States.[3] According to the Drug Abuse Warning Network, opioid pain relievers accounted for more than 119,000 emergency department visits in 2002, with oxycodone and hydrocodone named in 40 percent of those visits. Opioid pain relievers were mentioned as frequently as heroin or marijuana in emergency department visits related to drug abuse.[2]

Several eastern states—Maine, West Virginia, Virginia, Kentucky, Pennsylvania, Ohio, and Florida—are disproportionately affected by opioid abuse, with their use now spreading to the western states of Arizona, California, and Alaska.[1] In eastern Kentucky, the diversion and abuse of opioid pain relievers is a major focus of public health concern. Eastern Kentucky counties lead the nation in grams of narcotic pain medications distributed on a per capita basis. According to the Drug Enforcement Agency, in 2003, 19,366 dosage units of diverted pharmaceutical drugs were seized by local Kentucky agencies.[4] In response to this rapid increase, a new Office of Drug Policy was formed in August 2004 that is responsible for coordinating the state's drug-fighting efforts.[5]

Drug abuse in pregnancy is a nationwide problem, with an estimated 221,000 women using illegal drugs during their pregnancy of the more than 4 million women

that give birth each year.[6] Of these births, 9,000 fetuses are exposed to narcotics—heroin or methadone—which is two to three neonates per 1,000 births in the United States.[7] Kentucky state officials, in 2000, mandated pregnant women experiencing opioid withdrawal symptoms be placed on methadone maintenance therapy (MMT). In Kentucky, 334 pregnant women visited a treatment facility for opioid abuse from 1999 to 2003. Statewide, there was a steep rise from 16 women seeking treatment in 1999 to a more than 700 percent increase in 2003 to 115 women. This increase has stimulated the medical community to readdress the issues of appropriate treatment—MMT versus detoxification—and comprehensive outpatient follow-up for these women.

The goal of our study was to develop a current profile of prescription opioid addiction and dependence in pregnancy. The recommended treatment of choice in opioid dependence in pregnancy since the 1970s has been MMT, to prevent fluctuating levels of opioids that cause fetal withdrawal symptoms and consequently decrease the risk for spontaneous abortion of the fetus or premature delivery.[8,9] Few studies have focused on prescription opioid abuse and the multiple drugs that entails, however. The majority of research has focused on heroin addiction in pregnancy leading to dosage recommendations for MMT in this population.

We collected information on the demographics of opioid abusers, effective doses of MMT, and medical and obstetrical complications related to opioid abuse, which also may differ from previous research in heroin-addicted populations. We hypothesized that inpatient treatment for opioid dependence during pregnancy would be increased in eastern Kentucky from the years 2000 to 2004 with the overall increase in prescription opioid abuse and the mandate in Kentucky that prescription opioid–dependent pregnant women be placed on MMT. Other focuses included investigating the average dose of methadone used for MMT, which we thought would differ from heroin-addicted pregnant women. Examining the number of patients with chronic pain syndromes was also important to determine if there would be higher rates in our study group than heroin-addicted pregnant women because prescription opioids are used to relieve pain.

METHODS

The authors performed a retrospective chart review from an inpatient psychiatric unit at the University of Kentucky Chandler Medical Center to determine the demographics and medical treatment of prescription opioid–dependent pregnant women. The hospital is a regional facility that serves the eastern and central portions of Kentucky and averages 1,800 deliveries per year. Information gathered during the paper chart review was performed by one reviewer, therefore relying on a single interpretation of the medical record. Uniform psychiatric history and physical forms were used during the years of this study, thus making the data consistent between medical records because standard questions on the form included details of drug use including types of drugs used, duration of use, and comorbid drug use per patients' reports. Interviewers typically recorded patients' drugs of choice and route of administration as well, which is discussed later in the paper. Although detailed information was gathered from all 94 medical records, chart reviews were limited by their retrospective nature and the information the interviewer gathered. The data collected for this study were considered good, owing to the specific substance abuse data gathered through a structured admission interview.

A computer-generated list of admissions of women with the primary or secondary diagnostic code for drug dependence, antepartum (ICD-9 code 648.33) admitted from January 2001 to May 2004 was compiled, which totaled 130 admissions. Ninety-four of these pregnant women had an Axis I diagnosis of Opioid Dependence and were included in the study. Some patients had multiple admissions during a single pregnancy, but only the first admission with the initiation of MMT was included. During the 41 months of the study, one woman had two pregnancies, but only the first pregnancy was included in the study.

Pregnant women with opioid dependence in this study were admitted to the inpatient psychiatric unit unless they had complications and needed inpatient obstetrical monitoring. When these patients were admitted to the psychiatric unit, an initial evaluation was performed by an obstetrician. Women were started on scheduled doses of methadone and had withdrawal checks, which combined subjective and objective signs and symptoms of opioid withdrawal, performed every four hours. Depending on their withdrawal scores, they may have received supplemental doses of methadone. During their hospital course, patients who complained of pain were also monitored using a pain rating scale of 1 to 10. The women were hospitalized until their methadone dose was consolidated into a once-a-day dosing schedule.

Data gathered from the medical records included demographic information regarding age, race, geographic area, marital status, gestational age of the fetus, and number of previous children. Information specific to the patient's opioid use included her preferred opioid, route of administration, duration of use, and comorbid drug use. Treatment data were obtained including stabilizing dose of methadone, days to stabilization, complications of initiating MMT or detoxification, length of hospital stay, and concomitant Axis I diagnoses. These data were then analyzed using descriptive statistics and computer software (SPSS 12.0, SPSS Inc., Chicago, IL, and GraphPad

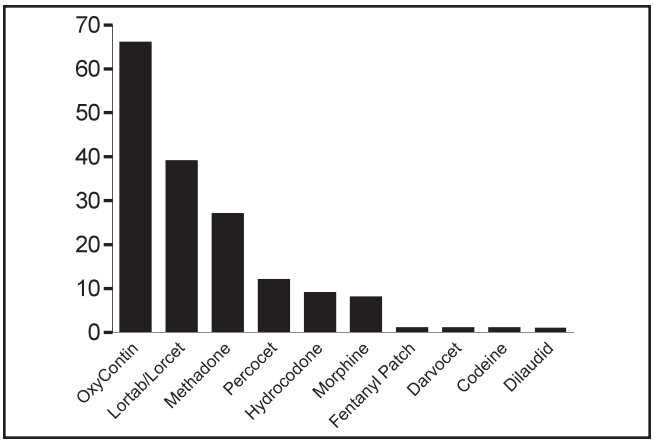

Figure 1. Number of times specific opioids were mentioned in patient interviews as having been used during the pregnancy.

Prism 4, GraphPad Software, Inc., San Diego, CA) to calculate standard deviation and construct histograms to reveal trends of prescription opioid–dependent pregnant women including their demographics, opioid use, rates of admission, and substance abuse and medical treatments.

RESULTS

As hypothesized, admission numbers of prescription opioid–dependent pregnant women to the inpatient psychiatric ward at the University of Kentucky increased from 2001 to 2003; only partial data were collected for 2004. The initial admissions for treatment for pregnant women with opioid dependence increased from 11 admissions in 2001 to 25 admissions in 2002, and 46 admissions in 2003. Thirteen patients were admitted from January to May of 2004. The average age of these 94 prescription opioid–dependent pregnant women was 24.5 years, with a range of 18 to 43 years. Ninety-three (98.9 percent) of the women were Caucasian, with only one African American (1.1 percent). Eighty-two (87.2 percent) women were from a rural area, defined as any city or town outside of Lexington, considered the only urban center in eastern or central Kentucky. Only 12 (12.8 percent) of the patients were from Lexington.

The women's marital status on admission was recorded and did not include prior marriages or pending divorces. Thirty-five (37.2 percent) women were single at the time of their admission. The number of women married or divorced was similar, with 26 (27.7 percent) women married and 22 (23.4 percent) divorced. Nine (9.6 percent) of the patients had legal separations and two (2.1 percent) of them were widowed. The average number of children the women had before the pregnancy on admission was 1.3. For 19 (20.2 percent) women, it was their first pregnancy. The study did not include whether patients had maintained legal custody of their previous children. When examined in the context of marital status, married women averaged 1.38 children, single women one child, and divorced women 1.54 children before their current pregnancy.

Obstetrical information was also gathered including gestational age of the fetus, which was dated by physical examination and ultrasonography from an obstetrician at an outside hospital or clinic or by the inpatient obstetrical team at the University of Kentucky. The average gestational age for these pregnancies was 21.2 weeks. Thirty-one (33 percent) of the 94 women presented for admission in their first trimester, with the earliest presentation at five weeks and five days. Thirty-nine (41.5 percent) women of the patients sought treatment in their second trimester, while 22 (23.4 percent) women were not treated until their third trimester. Two (2.1 percent) women's pregnancies were not dated during admission owing to short hospitalization.

Opioid Dependence was part of an Axis I diagnosis in all 94 women, and they reported use of a wide variety of prescription opioids (Figure 1). Data gathered during the chart review included all of the opioids mentioned by the patients during the admission interview whether or not it was their drug of choice. OxyContin was mentioned by patients most frequently at 66 times, and Lortab or Lorcet followed at 39 mentions. Other frequently mentioned opioids included methadone, Percocet, hydrocodone, and morphine, in that order.

Use of a single prescription narcotic was reported by 47 patients, whereas 47 reported multiple opioids of abuse. OxyContin was reported in 28 of the single-prescription opioid patients and by 40 of the patients reporting multiple opioid use. The average dose of OxyContin was 152.4 mg in women who reported their daily amount, with a standard deviation of 147.8 mg and a mean of 154.1 mg (n = 68). The minimum dose reported by women on admission was 25 mg and the maximum was 1,000 mg, thus the range was 975 mg. On average, the patients had been abusing prescription narcotics for 2.9 years. Their preferred route of administration of OxyContin was snorting, which was seen in 24 (35.3 percent, n = 68) women. However, oral administration—swallowing or chewing—and intravenous use were very similar in reported use, with 23 (33.8 percent) patients swallowing or chewing the pills and 19 (27.9 percent) patients using it intravenously. Two (3 percent) patients reported multiple routes of administration without a recorded preference.

Comorbid abuse of prescription and illicit drugs was common in this study group. Marijuana was the most common illicit drug reported, and benzodiazepines were the most commonly reported prescription drugs abused (Figure 2). Alprazolam (Xanax, Pfizer, Inc., New York, NY) was the most frequently reported benzodiazepine with 42 (44.7 percent) patient mentions. Cocaine was

also mentioned by 30 (31.9 percent) patients on admission. Other comorbid drugs included amphetamines, LSD, and heroin. Tobacco use by patients was also gathered during the study, with 71 (75.5 percent) of the 94 patients reporting regular cigarette smoking during their pregnancy. Seven (7.4 percent) women reported alcohol use during their pregnancy, with one drinking daily, one drinking every other day, and the remaining five reporting binge drinking. Negative blood alcohol levels were reported in 32 women, and no positive levels were recorded.

It is routine for patients being admitted to this inpatient psychiatric unit to have a urine drug screen, which screens for common drugs of abuse and prescription medications. The laboratory at the University of Kentucky uses a combination of immunoassay, thin-layer chromatography, gas chromatography, and mass spectroscopy to detect common prescription medications and drugs of abuse in urine samples. Seventy-eight (83 percent) of the 94 patients had urine drug screens performed and documented. Of the 16 (17 percent) who did not have a recorded urine drug screen, eight of those had one performed at an outside hospital. The drugs of abuse other than opioids most commonly seen on the urine drug screens were benzodiazepines and marijuana (Table 1). Although benzodiazepines were detected in 40 (51.3 percent, n = 78) urine samples, only three women had significant benzodiazepine withdrawal symptoms and required detoxification with clonazepam or diazepam.

Forty-six (48.9 percent) of the women had previous inpatient or outpatient treatment for substance abuse before admission. Five (5.3 percent) of the patients had previously been on MMT, and eight (8.5 percent) who presented for admission had already started on MMT. On average, it took 4.92 days to stabilize patients on methadone and the length of hospitalization was 7.4 days, with a median of 6.86 days. Stabilization was defined as not requiring supplemental doses of methadone during a 24-hour period, which were given for specific subjective and objective withdrawal scores. It did not require a lack of drug craving. The average discharge dose of methadone was 42.5 mg once daily to negate withdrawal symptoms. Only one patient was discharged on a twice-a-day dosing schedule.

All patients included in the study had a diagnosis of Opioid Dependence made by the clinical judgment of the inpatient psychiatrists and supported by *Diagnostic and Statistical Manual-IV* criteria. While the patients were hospitalized, they were evaluated for comorbid Axis I diagnoses. Polysubstance Abuse or Dependence was in the diagnosis of 22 women. The most frequently diagnosed mood disorder was depression—Major Depressive Disorder or Depressive Disorder, Not Otherwise Specified. Anxiety disorders requiring medication also occurred, with three patients diagnosed with Anxiety Disorder, Not Otherwise Specified and another three patients with Panic Disorder (Table 2).

Table 1. Number of times specific drugs were detected on urine drug screen

Drug	Times detected
Benzodiazepines	40
Marijuana	12
Cocaine	5
Amphetamines	4
Carisoprodol (Soma)	3
Barbiturates	3

Several patients did report using prescription opioids for chronic pain syndromes. Three women had a diagnosis of lower back pain, one owing to severe scoliosis, another to degenerative discs, and one resulting from a motor vehicle collision. The only African-American woman in the study had severe pain owing to sickle cell disease. One woman had been on narcotics for three months for kidney stones, and another had persistent pain from a talus fracture sustained in a motor vehicle collision. Thus, six (6.4 percent) women of the 94 included in the study had a formal chronic pain diagnosis.

Several other medical conditions were diagnosed and treated while the patients were hospitalized. Hepatitis C was newly diagnosed in 11 (11.7 percent) patients, with nine of those confirmed by ribonucleic acid polymerase-chain reaction before discharge from the psychiatric unit. Other diagnoses included left lower lobe pneumonia, multiple abscesses on one patient's upper extremity, and nephrolithiasis. The most serious complication during hospitalization of these 94 women occurred when one patient was given supplemental doses of methadone for subjective withdrawal symptoms only and the woman became apneic and cyanotic. The patient was intubated and placed on a naltrexone (Narcan, Endo Pharmaceuticals) intravenous drip for four hours and then readmitted to the psychiatric ward.

Obstetrical issues included three reports of decreased fetal movements, four nonreactive nonstress tests, fetal heart decelerations in two patients both over 33 weeks of gestational age, premature contractions in two patients, and marginal placental abruption in a patient abusing cocaine and opioids. Multiple congenital anomalies were found in a fetus during admission on ultrasonography in one patient. No miscarriages occurred while the patients were hospitalized, including those placed on MMT, and in the three women who underwent

Table 2. Number of opioid-dependent pregnant women receiving a comorbid Axis I diagnosis	
Comorbid Axis I diagnosis	**Number of patients**
Polysubstance abuse/dependence	22
Benzodiazepine dependence	8
Depressive disorder, NOS	6
Anxiety disorder, NOS	3
Panic disorder	2
Cannabis dependence	2
Substance induced mood disorder	1
Alcohol dependence	1
Bipolar affective disorder, NOS	1
Malingering	1
NOS, not otherwise specified.	

opioid detoxification in their second trimester.

Thirteen (13.8 percent) patients required a second admission during their pregnancy. These admissions were not included in the data set. Reasons for readmission included continued polysubstance abuse or patients' noncompliance with outpatient treatment requiring redosing of methadone in an inpatient setting.

DISCUSSION

The average prescription opioid–dependent pregnant woman admitted to the inpatient psychiatric unit in our study was a 24-year-old Caucasian woman from a rural town in eastern Kentucky in her second trimester using OxyContin. Demographically, our study is reflective of recent national trends with regard to age, race, and geographic location according to the 2003 National Survey on Drug Use and Health. Young adults aged 18 to 25 years are more likely to abuse prescription narcotics than adolescents or adults older than 26 years.[10] Although our data are consistent with national trends, the average age of our patients may not be entirely representative of opioid abuse in pregnancy in this region, as the psychiatric unit at the University of Kentucky admits only those patients 18 years old or above. Thus, the data may be skewed to an older average age, as teenage pregnancies complicated by opioid abuse are not included.

The predominance of women living in rural settings using prescription opioids is likely correlated with the prevalence of opioid diversion in rural areas. The Appalachian area (i.e., Kentucky, Tennessee, and West Virginia) is designated as a high drug trafficking area by the DEA for prescription narcotics.[11] The scarcity of people, fewer law enforcement officers, and the lower socioeconomic status of rural areas allow opioid diversion to flourish. Opioid diversion provides a significant financial resource for this population, with OxyContin being sold for $1.00 per milligram and few opportunities for gainful employment in such remote areas.

OxyContin was the most frequently mentioned prescription opioid used in this study, and women were almost evenly distributed in their preferred route of administration. OxyContin is a form of oxycodone that can be used via snorting, ingesting, or injecting, which allows changes in administration to produce a long-lasting euphoria with increasing tolerance. Although eastern Kentucky is considered a low-injecting area, the use of OxyContin intravenously is becoming more widespread since it first became available in 1995. Intravenous use is likely on the rise because fewer milligrams of OxyContin are needed to produce its euphoric effects when it is injected and thus is less expensive.

Maternal use of opioids is not the only concern for potential effects to the fetus, but also the high comorbidity seen with smoking and alcohol in opioid-dependent pregnant women. Seventy-five percent of the women in the study were smokers. Studies have reported that 70 to 90 percent of substance abusers also are moderate to heavy smokers.[8] Although high rates of tobacco use are seen in substance users, the fact that the study was conducted in Kentucky is also a mitigating factor. Kentucky is a state with a large production of tobacco and high usage rates. In studies reporting high smoking rates, there is also a high prevalence of comorbid alcohol abuse in substance abusers.[8] The rates of alcohol use were low in this group, however, with only seven women reporting any alcohol use and two of those with daily or every-other-day patterns. Patients often underreport alcohol use, but none of the blood alcohol levels obtained in 32 of the women had any detectable ethanol in this study. Alcohol serum concentrations have a short half-life, however, thus decreasing the number of patients abusing alcohol detected through this test. Smoking and alcohol present medical concerns for the fetus that can overlap with findings in neonates exposed to opioids. Whereas alcohol can cause a constellation of birth defects defined within fetal alcohol syndrome, alcohol and nicotine can cause intrauterine growth retardation or small for gestational age neonates and confuse causation of these findings with maternal opioid use.

Only 16 women in the study reported no comorbid drug use, but all of these 16 women were smokers. Two women reported no comorbid drug use and no smoking or alcohol use. Marijuana and benzodiazepines were the drugs most frequently abused other than opioids per patient report and urine drug screens performed. Previous studies have shown that 40 percent of patients entering MMT use cocaine as well as heroin.[12] Although

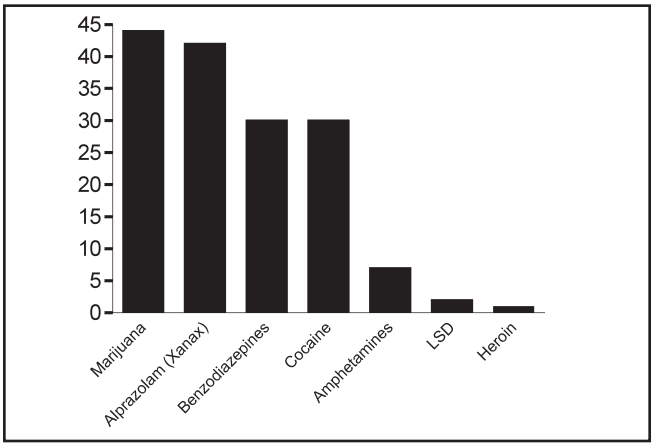

Figure 2. Frequency of comorbid drugs used with opioids in the 94 women in the study.

30 women reported using cocaine, it was only detected in five of the 86 urine drug screens performed. This may owe to the short half-life of cocaine, which is typically seen for only 72 hours in the urine after use. Only 22 (23.4 percent) of the women in this study were given a comorbid diagnosis of Polysubstance Abuse or Dependence; however, there were multiple illicit drugs reported on admission (Figure 1). Again, a difference in half-lives and discrepancies in urine drug screens—cross reactivity with other medications, lack of sensitivity in detecting semi-synthetic opioids, and windows of detection time—may have skewed the data and demonstrated an under reporting and under diagnosis of Polysubstance Abuse.[13]

Medical complications of drug abuse are another concern for maternal and fetal and neonatal outcomes. There were 11 patients with a new diagnosis of hepatitis C while admitted to the inpatient psychiatric ward during the period of this study. Another study had a wider range of 67 to 84 percent of MMT patients infected with hepatitis C virus.[12] With increasing intravenous drug use in prescription opioid users, human immunodeficiency syndrome, hepatitis B, and hepatitis C, as well as other infectious risks, such as endocarditis or sepsis, will continue to escalate and should be rigorously screened for in pregnant women, as they may lead to further obstetrical or fetal complications. Hepatitis C in intravenous drug users has been shown in studies to be as prevalent as 90 percent.[14]

The average dose of methadone on discharge from the unit in these women was 42.5 mg. This is a lower dose than is typical for heroin-dependent pregnant women. An equivalent methadone dose for the women in our study would be 75 to 100 mg, with the average dose of OxyContin reported as 152.4 mg. One study shows most heroin-addicted users require 60 to 120 mg per day of methadone to achieve optimal effects.[12] Another study reports heroin-addicted women who received an average methadone dose less than 80 mg had a trend toward a higher incidence of illicit drug abuse before pregnancy, highest neonatal abstinence score, need for neonatal treatment for withdrawal, and duration of withdrawal compared to women who were on 80 mg or more.[8,15] This study concluded that maternal methadone doses do not correlate with neonatal withdrawal, and, thus, maternal benefits of effective methadone dosing are not offset by neonatal harm. The goal of the inpatient stabilization period of the women in this study was to minimize withdrawal symptoms, not to prevent recidivism. A maintenance dose of methadone during hospitalization was based on signs and symptoms of withdrawal—tachycardia, hypertension, elevated temperature, vomiting, diarrhea, piloerection, myalgias, and headache. Once withdrawal checks were no longer significant, that dose was consolidated to a once-a-day dose. Drug craving was not considered in the dose of methadone while hospitalized, which could partially account for the low dose of methadone. Also, patients may have over reported their prescription opioid use—the range was 975 mg, with a standard deviation of 147.8 mg—in an effort to obtain methadone and prevent continued withdrawal.

Only three (3.2 percent) of the 94 patients in this study underwent detoxification from opioids with a methadone taper. All of them occurred in the second trimester, which historically is the most widely accepted time, owing to decreased risk of miscarriage in the first trimester and fetal withdrawal and premature delivery in the third trimester.[8] Only 39 women presented for treatment in their second trimester, however. This low rate of detoxification is reflective of the continued concern about harm to the fetus combined with concern that women will continue to abuse opioids on release from an inpatient facility if they undergo detoxification. Although there were no miscarriages, one woman was admitted to the obstetrical service in preterm labor. She had a history of preterm delivery and was stabilized and transferred to the psychiatric ward for further treatment. Another pregnancy was complicated by multiple congenital fetal anomalies seen on ultrasonography; however, further investigation revealed normal chromosomes in the fetus. The biologic cause of the anomalies was not determined before discharge, but the literature does not support opioid abuse as the cause.

There were 47 comorbid Axis I disorders diagnosed in the 94 women in the study. According to studies, more than 40 percent of patients with addictive disorders also have mental disorders.[12] Often, patients may be attempting to self-medicate with illicit drugs when they do not have the financial means to seek appropriate medical treatment. The majority of the diagnoses in this group of women were related to other substances of abuse, not affective or psychotic disorders. This further reiterates the commonality of polysubstance use in opioid dependency.

Chronic pain and evaluation of pain are issues pertinent to the patients in this study. Only six of the 94 women were diagnosed with a chronic pain syndrome on Axis III. This

may owe to inadequate records or insufficient evaluation of pain in these patients, but pain relief does not appear to be the only reason for abuse of these drugs. Reviewing the preferred methods of use reveals almost equal numbers snorting and injecting opioids as taking them orally. These more potent methods provide a heightened sense of euphoria, which may indicate a need to self-medicate a mood disorder. Only seven women in this study were diagnosed with a primary affective disorder, which is statistically less than the general population. The inpatient physicians may not have diagnosed a mood disorder secondary to the patients' concomitant opioid abuse and short hospitalizations, however. Thus, there are several reasons that may contribute to opioid abuse, but further research needs to be conducted to determine the percentage of women attempting to treat pain syndromes.

CONCLUSION

MMT in pregnancy continues to be a controversial issue for medical professionals who treat the mother and fetus. With the increasing number of prescription opioid–dependent pregnant women seen in our study, however, it will continue to be a clinically relevant medical issue. Our study shows a lower dose of methadone than expected to stabilize women using supratherapeutic doses of prescription opioids. It must be recognized that the goal of methadone in the inpatient setting was to relieve withdrawal symptoms to prevent fetal withdrawal and decrease the risk for fetal demise. Further research needs to be conducted on appropriate doses of methadone for women who are prescription opioid users in an outpatient setting, because the majority of the research involves heroin-addicted women. The question remains whether or not lower doses of methadone in prescription opioid–dependent pregnant women will prevent further abuse during pregnancy. Medical detoxification is another option that is not adequately addressed in this study, but merits further research. Addiction does not resolve with detoxification; thus, supports must be in place for pregnant women to help avoid recidivism.

With only six of the 94 women included in the study receiving a chronic pain diagnosis, it is clear that pain must be evaluated more diligently. Often, women in the study began using narcotics for a short-term pain issue that acted as a gateway to abuse of the drug. Thus, the medical community must be aware of the addictive power of opioids when prescribing them to relieve short-term pain and discuss this with patients, including family histories of addictive disorders. Physicians must also be careful to not be insensitive to the needs of patients with chronic pain and must work to provide comprehensive services to help alleviate pain and allow people to be productive.

Long-term outcomes must continue to be studied in neonates with prescription opioid and methadone exposure to evaluate neurobehavioral outcomes. Comprehensive programs that target the mother-infant dyad through educational and emotional support from peers and professionals can ameliorate these consequences.[8] Our study reiterates the need for further studies in maternal and fetal outcomes of pregnancies affected by prescription opioids as the number of pregnant women addicted to these medications seeking treatment increases in eastern Kentucky. More research will lead to evidence-based treatment with the goal to decrease prescription opioid abuse in pregnancy and provide appropriate comprehensive services to improve long-term outcomes.

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ORIGINAL ARTICLE

Use of a comprehensive survey as a first step in addressing clinical competence of physicians-in-training in the management of pain

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ABSTRACT

Deficiencies in practice, knowledge, and competence among physicians are important contributing factors to the unsatisfactory level of analgesic care in hospitalized patients. By way of a comprehensive survey, we characterized these deficiencies within an internal medicine residency program as an initial step in designing remedial educational strategies. To do so, an anonymous 43-item survey was administered to residents in an internal medicine program. A total of 61 residents (69 percent) responded.

The results indicated that patient-controlled analgesia (PCA), a standardized pain scale, and an opioid equivalence table were underused. Competence in opioid conversion was suboptimal, but completion of an oncology rotation and familiarity with the opioid equivalence table predicted greater competence in this area ($p = 0.007$ and $p = 0.001$, respectively).

Self-perceptions of adequacy of training and pain-management competence were predictors of knowledge ($p = 0.026$ and $p = 0.038$, respectively). Attitudes regarding opioid analgesia were generally satisfactory (i.e., low "opiophobia" score), although the risk of addiction was still overestimated.

The characterization of deficiencies in pain management in a residency program is an essential step in the design and implementation of educational interventions. Administration of a comprehensive survey is a simple and effective method of gathering this data and has the additional benefit of promoting awareness of pain management issues. Our experience served to establish, among other findings, the didactic value of experience on an oncology floor; this result substantiates the value of practical experience in the gaining of clinical competence in pain management. Interventions that capitalize on the findings of the survey and the interest in pain management generated by its administration are currently ongoing at our institution.

Key words: education, opioid analgesia, pain management, survey

INTRODUCTION

Pain management has for many years been recognized as an area of clinical care in need of improvement.[1] Despite the availability of an effective armamentarium of analgesic drugs and techniques, an unacceptably high percentage of patients in the inpatient[2-7] and ambulatory settings[4,7-9] report unrelieved pain. Explaining and dealing with this inconsistency is a vexing issue that over the last few years has generated much discussion.[10-12] Numerous "barriers" to effective pain management have been identified, with the burden of responsibility being shared by a wide spectrum of involved parties including healthcare professionals,[13-16] patients,[2,17] medical educators,[18-20] and government regulatory agencies.[21]

The last decade has seen a number of initiatives aimed at improving pain management, with several guidelines published that stipulate appropriate standards of pain care in hospitals.[22-24] Most recently, the Joint Commission for the Accreditation of Hospital Organizations (JCAHO) has made available a comprehensive set of standards governing pain management to which all accredited facilities will be expected to adhere.[25]

The limitations and shortcomings of previous attempts to improve analgesic care that focused solely on physician education and the changing of attitudes regarding opioid analgesia have been recognized.[10] Accordingly, the focus of more recent initiatives has been to bring about changes on an institutional level, with the implementation of quality improvement programs. Issues such as patient empowerment and the implementation of nursing protocols that are more efficient at identifying and assessing pain have been prominent in recent guidelines.[26-28]

Nevertheless, the role of physicians in the process should not be overlooked or underestimated. Good evidence exists that pain management skills, knowledge, and perceptions are deficient in a broad range of physician populations,[15,29-32] and our perception was that the

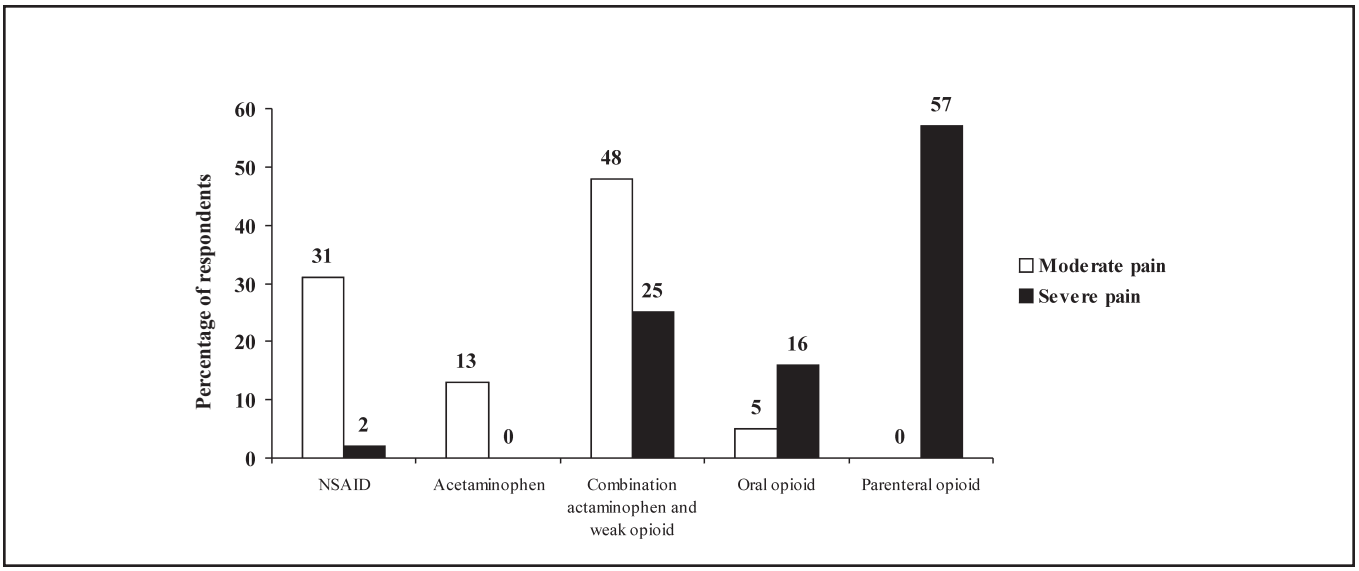

Figure 1. Choice of analgesic agents for moderate and severe pain.

internal medicine resident house staff at our institution was no exception.

After discussion with interested attending physicians, pharmacists, nurses, and residents, a survey was designed to study and quantify various aspects of resident pain management that were perceived to be poor. Our focus was to glean information that would be of use in the design and implementation of future remedial interventions. We sought to identify any correlation between measured performance variables and various resident subgroups, information that would be useful in evaluating the strengths and weaknesses in the pain education component of our residency program at baseline. In addition, we wished to qualitatively evaluate residents' subjective perceptions regarding their training and competence in analgesia.

MATERIALS AND METHODS

Sample selection

A 43-item questionnaire (Appendix 1) was made available to all internal medicine residents at Albert Einstein Medical Center, a teaching hospital in urban Philadelphia. Participation was voluntary, and completed surveys were submitted anonymously.

Survey design

Following discussion with clinicians, pharmacists, quality improvement officers, and residents at the institution, various aspects of pain management practice, competence, and perception were identified that warranted study. Published guidelines pertinent to institutional standards of analgesic care, specifically those of the American Pain Society and of JCAHO,[22,25] were made use of during this initial planning process and influenced the focus of the survey. The medical literature was searched for similar studies, and specifically for previously validated tools that would be useful in studying the identified areas of interest.

Variables

The questionnaire contained sections on the following:

- Pain management practices: Documentation of pain, use of a pain scale, compliance with the World Health Organization (WHO) "analgesic ladder" guidelines, use of patient-controlled analgesia (PCA), and use of an opioid equivalence table were surveyed.

- Reluctance to prescribe opioids: Items were selected from a previously published study measuring "opiophobia" in practicing physicians.[29] Respondents indicated their level of agreement with six statements concerning the appropriateness of narcotic analgesia in various settings. A 7-point Likert scale was used.

- Knowledge about pain and its treatment: Residents' knowledge was assessed using 14 true-or-false questions. Of these questions, 13 had been used in a previous study.[29]

- Opioid conversion skills: A simple clinical scenario was presented and respondents were asked to indicate correct dosage and duration for various opioid substitutions. This section was

Table 1. Demographics and performance in knowledge and opioid conversion

			Number (percent)	Knowledge score (percent)[a]	p value	Opioid conversion score[b]	p value[c]
All residents			61 (100)	66.4		2.30	
Year of training		PGY1	31 (50.8)	65.7	0.357	2.29	0.920
		PGY2	15 (24.6)	65.7		2.20	
		PGY3/4	15 (24.6)	68.6		2.40	
Gender		Male	38 (62.3)	69.7	0.040	2.34	0.638
		Female	23 (37.7)	60.9		2.22	
Place of training		American graduate	20 (32.8)	65.7	0.824	2.15	0.567
		International graduate	41 (67.2)	66.7		2.37	
Self-perception regarding adequacy of training		Adequate	26 (42.6)	72.3	0.026	2.46	0.344
		Inadequate	31 (51.9)	62.4		2.19	
Self-perception regarding competence		Competent	26 (42.7)	70.9	0.038	2.54	0.209
		Incompetent	26 (42.7)	61.3		2.15	
Completion of oncology rotation	All residents	Yes	33 (54.1)	69.0	0.174	2.67	0.007
		No	28 (45.9)	63.3		1.86	
	PGY1	Yes	8 (25.8)	72.3	0.050	3.25	0.008
		No	23 (74.2)	63.4		1.96	
	PGY2	Yes	13 (86.7)	67.0	0.484	2.46	0.044
		No	2 (13.3)	57.1		2.20	
	PGY3/4	Yes	12 (80.0)	69.0	0.843	2.50	0.503
		No	3 (20.0)	66.7		2.40	
Familiarity with opioid equivalence table		Yes	45 (73.8)	67.3	0.475	2.58	0.001
		No	16 (26.2)	63.8		1.50	
Personal experience of pain		Yes	10 (16.3)	70.0	0.453	2.30	0.960
		No	51 (83.7)	65.7		2.29	

PGY, post-graduate year; [a] Percentage of 14 true or false questions answered correctly; [b] Mean score of four multiple-choice questions answered correctly; [c] Mann-Whitney test was used to calculate significant differences.

Table 2. Self-reported practices regarding documentation and discharge planning				
	Never	**Occasionally (< 50 percent)**	**Frequently (> 50 percent)**	**Always**
Do you ask about and document a patient's pain on your initial history and physical?	1 (1.6)	17 (27.9)	26 (42.6)	17 (27.9)
Do you ask about and document a patient's pain in your progress notes?	1 (1.6)	9 (14.8)	40 (65.6)	11 (18.0)
When documenting pain, do you use a pain scale (e.g., 1 to 10)?	3 (4.9)	20 (32.8)	29 (47.5)	9 (14.8)
When discharging a patient, do you assess, address, and document their outpatient chronic pain requirements?	4 (6.6)	34 (55.7)	19 (31.1)	4 (6.6)
Percentages appear in parentheses.				

designed to assess basic principles of opioid conversion and dosage, and the scenarios and opioid agents used were appropriate to our institution.

- Self-perception regarding analgesic training and competence: Residents indicated whether they considered themselves competent and adequately trained in pain management, and specified situations in which they believed they had received their most beneficial training.

Data analysis

Knowledge scores for various subgroups were compared using t-tests or analysis of variance. Differences in scores for opioid conversion skills were measured using the Mann-Whitney test. The above analyses were computed using SPSS version 10.0 (SPSS Inc., Chicago, IL).

RESULTS

Of 88 eligible residents who received the survey, a total of 61 residents submitted completed questionnaires (69 percent). Relevant demographics are reported in Table 1.

Pain management practices

As shown in Table 2, documentation of pain is not consistent, and the standardized pain scale appears to be underused. Residents report not consistently addressing issues of pain management when discharging patients.

Residents' choices of analgesic agents for various severities of pain are shown in Figure 1. PCA was reported to be used often by 25 percent of residents. The remainder reported using PCA rarely (64 percent) or having no experience with the technique (12 percent) (Figure 2).

The opioid equivalence table was described by 50 percent of residents as being used routinely (> 50 percent of

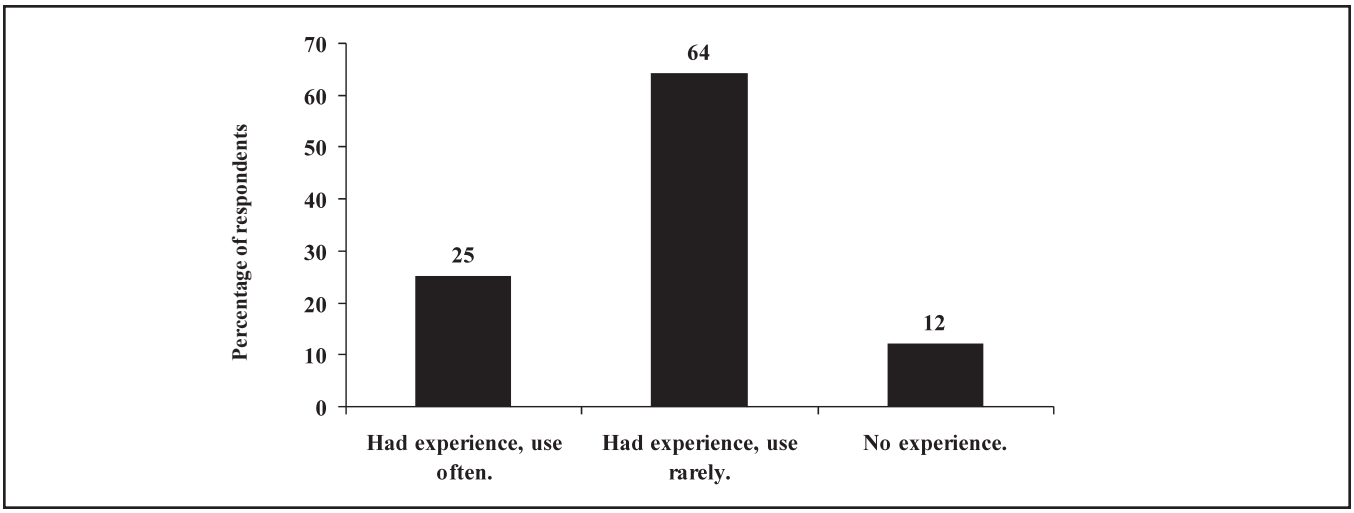

Figure 2. Reported experience with patient-controlled analgesia.

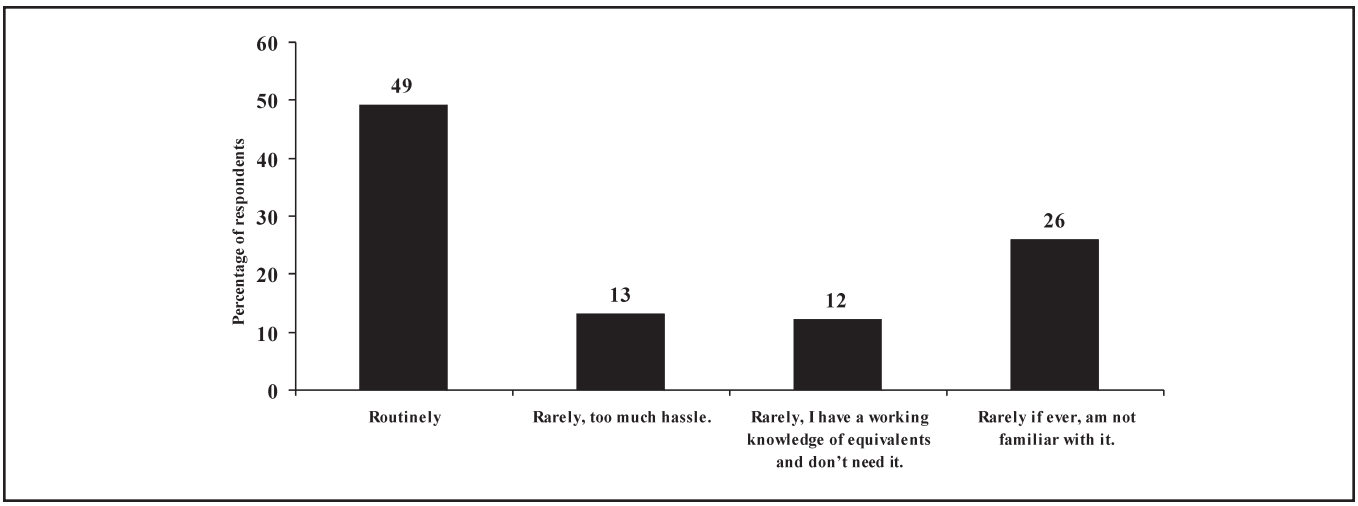

Figure 3. Reported use of opioid equivalence table.

the time), whereas the remainder described using it rarely, because it is "too much hassle" (13 percent), because they "don't need it" (12 percent), or because they are not familiar with it (26 percent). (Figure 3).

Knowledge scores

The mean score for this section (percentage of 14 true-or-false questions answered correctly) was 66.4 percent (standard deviation, 16.5 percent).

Self-perception of adequacy of training and pain management competence were predictors of knowledge (mean scores 72.4 percent vs. 62.4 percent, $p = 0.026$; and 70.9 percent vs. 61.3 percent, $p = 0.038$, respectively). The majority of residents (62 percent) incorrectly believed that psychological dependence on narcotics very frequently results from legitimate prescriptions. The mistaken belief that increased requests for analgesia indicate tolerance, rather than increased underlying pain, was held by 85 percent of residents, and 53 percent of residents did not agree (incorrectly) with the statement that almost all cancer patients should receive opioids for relief of pain.

Opioid conversion skills

Four multiple-choice questions were administered, each testing one of the following basic aspects of opioid analgesia: knowledge of the relative potency of parenteral to oral morphine, the ability to convert a fixed immediate-release morphine regimen to long-acting morphine, knowledge that oral hydromorphone is considerably more potent than oral morphine, and familiarity with the usual dosing frequency of immediate-release morphine. Only 12 residents answered all questions correctly (20 percent) (Table 3).

Approximately one-half of the residents (51 percent) were unable to convert an intravenous morphine infusion regimen to an equivalent regimen of immediate-release oral morphine, and a majority of residents (59 percent) were unable to make the same conversion to an equivalent regimen of long-acting oral morphine (MS Contin, Purdue Pharma, LP, Stamford, CT) (Table 4).

Opioid conversion skills were significantly better in residents who had completed a dedicated oncology floor month (mean scores, 2.7 vs. 1.86; $p = 0.007$). Residents who reported use of the opioid equivalence table rarely because they were unfamiliar with it performed significantly worse in the opioid conversion skills section when compared to other residents (mean score, 2.58 vs. 1.50; $p = 0.001$). There was no significant difference in opioid conversion skills across program years.

Reluctance to prescribe opioids

Agreement with six statements included in the survey was indicative of a reluctance to use opioid analgesia for various reasons, notably, concern about addiction and the notion that narcotics should be reserved for severe, cancer-related pain. For each of the statements, Likert scale scores were summed and averaged, such that a score of 1 indicated the least "opioid reluctance" and 7 the most. The statements that generated the highest scores on the "opioid reluctance" scale were those that reflected concern about the risk of addiction. For simplicity, the percentage of respondents agreeing or disagreeing with each statement (1 to 3 signifying agreement, 5 to 7 disagreement, 4 excluded) was also evaluated and is reported in Table 5. Almost one-half (44 percent) of the residents believed that when narcotics are used to control chronic pain, addiction is a common outcome, and 21 percent believed that more than 5 percent of patients who receive narcotics for pain subsequently become addicts. Comparison of "opioid reluctance" scores for

Table 3. Overall performance in opioid conversion questions	
Opioid conversion skill scores (number of questions answered correctly)	**Number of residents (percent)**
0	2 (3.3)
1	14 (23.0)
2	21 (34.4)
3	12 (19.7)
4	12 (19.7)

various subgroups, notably, gender, year of program, completion of oncology floor rotation, and personal experience of pain, did not reveal any significant differences.

Subjective perception regarding competence and training

A minority of residents (43 percent) indicated that they considered themselves competent in pain management, and 51 percent did not believe they had received adequate training in pain management (Table 6). The majority of residents (75 percent) believed they had received their best training in pain management during residency. The remainder indicated their best training was received in medical school. Within the former group, 57 percent specified the oncology rotation as their most valuable learning experience. Only four residents (7 percent) reported that they had received their best training in analgesia from formal academic conferences.

DISCUSSION

The administration of this comprehensive survey provided insight into existing practical and attitudinal deficiencies in pain management within our residency program. In the area of pain management practice, documentation of pain is unsatisfactory. This result corroborated the findings of a chart review performed at our institution in which consistent daily assessment and documentation of pain was observed in less than 40 percent of the charts.[33] Compliance with the WHO "analgesic ladder" principles is generally satisfactory, although a tendency to prescribe less-potent agents than is appropriate is noted.

Residents who reported not using an opioid conversion table because they were unfamiliar with this tool predictably performed poorly in the opioid conversion skills section (mean score, 37.5 percent) as compared to other residents (mean score, 64.4 percent). This group represents an obvious target for educational intervention.

The mean score for the 14-question knowledge section was 66.4 percent. There was no significant difference in mean scores when program years were compared, suggesting that the knowledge elements tested by the survey are not addressed by our residency program. Knowledge deficits that emerged included overestimation of the prevalence of addiction and tolerance to opioid analgesia and underestimation of the extent that opioids are indicated in cancer patients. There was strong correlation between residents' knowledge scores and their self-perception of their competence in pain management and the adequacy of their training.

Reluctance to prescribe opioids, or "opiophobia" as it has been called in the literature,[34] is prevalent in healthcare providers and is a significant factor in the undertreatment of pain. We note that a large proportion of residents overestimate the risk of addiction resulting from opioid analgesia. Despite the availability for several years of good evidence to the contrary,[35] misconception regarding the risk of patient addiction remains prevalent and represents a target for education.

Practical competence in the use of opioids was found to be poor, with a prevalence of ignorance about even the rudiments of opioid prescription being unacceptably high. This finding is in keeping with that of previous studies evaluating competence in the practical use of opioid analgesia, wherein medical students and residents

Table 4. Opioid conversion skill according to key competencies	
Opioid conversion competence	**Number of residents (percent)**
Knowledge of the relative potency of parenteral to oral morphine	30 (49.2)
Ability to convert a fixed immediate-release morphine regimen to long-acting morphine	25 (41.0)
Knowledge that oral hydromorphone is considerably more potent that oral morphine	34 (55.7)
Familiarity with the usual dosing frequency of immediate-release morphine	51 (83.6)

Table 5. Attitudes regarding use of opioids			
Statements indicating reluctance to prescribe opioids	**Agree (percent)**	**Disagree (percent)**	**"Opiophobia" mean score (1 to 7)**
Using narcotics to relieve the pain of benign conditions is ill advised.	30	64	1.59
Narcotics should be restricted to the treatment of severe intractable pain.	12	80	1.51
Persons who fit the "profile" of a likely drug abuser should never be treated with narcotics.	8	66	2.02
Any patient who is given narcotics for pain relief is at significant risk for addiction.	16	82	1.41
When narcotics are used to control chronic pain, addiction is a common outcome.	44	51	2.59
More than 5 percent of patients who receive narcotics for pain subsequently become addicts.	21	59	2.16

have performed dismally.[36-38] Neglect in attention to precision in dosage, duration of action, and drug equivalence is unfortunately commonplace in the prescription of narcotic analgesics.

We found no significant difference in opioid conversion skills between residents in different program years. Residents in their third year of the program, despite having two more years of clinical experience, performed no better in this section than the interns.

It was not surprising that residents who had completed a rotation on the oncology floor were significantly more competent that those who had not. During this month, residents have significant exposure to the management of patients with pain and gain considerable experience in the use of opioids. Furthermore, oncology faculty address the issues of pain control more consistently, and with more attention to detail. There is close supervision of the analgesic care of patients, and attention is given to the training of residents in this regard, which does not seem to happen as consistently on the general medicine floors.

These findings are not at odds with residents' own perceptions. The belief of 26 of the residents (43 percent) that their best training in analgesia occurred during the oncology rotation was borne out by performances in the "opioid conversion skills" section of the survey.

Subsequent to the survey, several interventions have been undertaken at our institution. These include a new emphasis on the teaching of opioid skills to residents on the floor in the context of real patient care; the issuing of laminated "pain management cards" with an opioid conversion table to all residents and instruction in its use; dedicated lunchtime conferences during which case scenarios illustrating appropriate attitudes in opioid analgesia and opioid prescribing skills are presented and discussed; and e-mailing of a series of challenging pain management cases to all residents, with prizes awarded for the best answers submitted in response. Lastly, results of the survey were presented at medicine grand rounds, during which its findings were received with keen interest by residents and attending physicians alike.

Consequent to these steps, pain management has become a "talking point" and a focus of academic activity.

Table 6. Settings (within residency) in which residents believed they had received their most beneficial training in pain management	
	Number of residents (percent)
Oncology rotation	26 (42.6)
ICU rotation	6 (9.8)
Geriatrics rotation	1 (1.6)
Firm conferences	2 (3.3)
Other conferences	2 (3.3)
Electives	2 (3.3)
Handbook	1 (1.6)
GMF	6 (9.8)
Not applicable (best training received during medical school)	15 (24.6)
ICU, intensive care unit; GMF, general medicine floor.	

This interest and enthusiasm is unprecedented at our institution and will hopefully translate into better care for our patients. Information regarding clinical outcomes of our efforts to date is at this time not available. Nevertheless, despite the absence of this data, we believe that our favorable experience is of interest and has value to anyone involved in a residency program who wishes to take steps to improve house staff competence in the management of pain.

It is well recognized that education and changing of physician attitudes will go only a fraction of the way toward the ultimate goal of bringing about outcome-based improvement in analgesic practice. Furthermore, the effects of educational interventions have too often been shown to be short lived,[39] and changing physician behavior is notoriously difficult.[40,41] Nevertheless, the physician-dependent elements in the broad picture of analgesic care should not be neglected. Evaluation of existing problem areas in the context of a residency program is an appropriate and important first step in planning remedial action.

Further study that evaluates the effect of interventions implemented consequent to the survey (currently ongoing at our institution) is warranted.

NOTE

This work has been previously presented at the Pennsylvania Coalition of Internal Medicine, ACP-ASIM, Annual Meeting, 2002 (Poster presentation) and the 36th Annual Meeting of the American Association for Cancer Education, 2002 (Poster presentation). The abstract was published, but not presented, in the Proceedings of the American Society of Clinical Oncology, 2003.

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APPENDIX 1 – QUESTIONNAIRE

❑ PGY 1 ❑ PGY 2 ❑ PGY 3 ❑ PGY 4
❑ Categorical ❑ Transitional ❑ Preliminary
❑ Male ❑ Female
❑ American graduate ❑ International graduate

Have you completed a rotation in inpatient oncology yet (Tower 8)?
❑ Yes ❑ No ❑ Not applicable

Where have you received your most beneficial and useful training in pain management?
❑ Medical school. ❑ Residency. ❑ Other (specify:)_____

If residency, specify where.
❑ In-patient oncology rotation ❑ ICU rotation
❑ Geriatrics rotation ❑ Firm conferences
❑ Other conferences ❑ Electives (specify:) _____
❑ Other (specify:)_____

Have you, or a close family member, ever experienced an acute pain syndrome as a hospital inpatient?
❑ Yes ❑ No

Do you ask about, and document, patient's pain on your initial H and P?
❑ Never ❑ Occasionally (< 50%) ❑ Frequently (> 50%) ❑ Always

Do you ask about, and document, patient's pain in your progress notes?
❑ Never ❑ Occasionally (< 50%) ❑ Frequently (> 50%) ❑ Always

When documenting pain, do you use a pain scale (e.g. 1-10)?
❑ Never ❑ Occasionally (< 50%) ❑ Frequently (> 50%) ❑ Always

When discharging a patient, do you assess, address and document their outpatient chronic pain requirements?
❑ Never ❑ Occasionally (< 50%) ❑ Frequently (> 50%) ❑ Always

The following would be my first choice in prescribing for an inpatient with moderate pain (4-6/10);

- ❑ NSAID alone ❑ Acetaminophen alone
- ❑ Acetaminophen/opioid combination (e.g. Tylenol #2)
- ❑ Oral opiate. ❑ Parenteral opiate
- ❑ Other (specify:)_____

The following would be my first choice in prescribing for an inpatient with severe pain (7-10/10);

- ❑ NSAID alone ❑ Acetaminophen alone
- ❑ Acetaminophen/opioid combination (e.g. Tylenol #2)
- ❑ Oral opiate. ❑ Parenteral opiate
- ❑ Other (specify:)_____

With regard to patient controlled analgesia (PCA);

- ❑ I have had experience with it, am 'comfortable' prescribing it, and use it often.
- ❑ I have had some experience with it, but am not 'comfortable' prescribing it, and use it rarely, if ever.
- ❑ I have had no experience with it.

When prescribing or changing opiate analgesia regimens, I use an opiate equivalence table;

- ❑ Routinely.
- ❑ Rarely, too much hassle.
- ❑ Rarely, I have a working knowledge of equivalents and don't need it.
- ❑ Rarely if ever, am not familiar with it.

For each of the following statements indicate your opinion by placing a number (1-7) in the box adjacent to it.

1 Strongly agree 2 Generally agree 3 Agree somewhat 4 Neither agree nor disagree
5 Disagree somewhat 6 Generally disagree 7 Strongly disagree

- ❑ I believe I have received adequate training in pain management.
- ❑ I consider myself competent in pain management.
- ❑ Narcotics should be restricted to the treatment of severe intractable pain.
- ❑ Persons who fit the 'profile' of a likely drug abuser should never be treated with narcotics.
- ❑ Using narcotics to relieve the pain of benign conditions is ill-advised.
- ❑ Any patient who is given narcotics for pain relief is at significant risk for addiction.
- ❑ When narcotics are used to control chronic pain, addiction is a common outcome.
- ❑ More than 5 percent of patients who receive narcotics for pain subsequently become addicts.
- ❑ Almost all pain can be relieved with treatment.
- ❑ The majority of patients having chronic pain are undermedicated.
- ❑ Psychological dependence on narcotics very frequently results from legitimate prescriptions.
- ❑ Suicide with an overdose of narcotics prescribed for pain occurs very frequently.
- ❑ The best judge of pain intensity is the patient.
- ❑ The healthcare provider is the best judge of pain intensity.
- ❑ Pain in a cancer patient is most likely due to treatment.
- ❑ The tumor itself is most likely the cause of pain in the cancer patient.
- ❑ Pre-existing conditions not related to the cancer cause the most pain for cancer patients.
- ❑ Increasing requests for analgesics indicate unrelieved pain.
- ❑ Increasing requests for analgesics indicate tolerance to the analgesic.
- ❑ Almost all cancer patients suffer pain.
- ❑ Almost all cancer patients should receive opiates to relieve pain.
- ❑ Patients on opiate analgesia will almost always require laxatives to prevent opiate-induced constipation.

A patient receiving a morphine IV infusion @ 2.5 mg/hr is to be changed to oral analgesia with equivalent analgesic dosage.
For each of the following drugs, what would be the most appropriate dosage regimen;
Please attempt all questions.

NB. DO NOT USE ANY REFERENCES.

Oral morphine:

- ❑ 10 mgs q4h.
- ❑ 15 mgs q4h.
- ❑ 30 mgs q4h.
- ❑ 45 mgs q4h.

MSContin (extended release morphine):

- ❑ 20 mgs q8h.
- ❑ 15 mgs q12h
- ❑ 30 mgs q12h.
- ❑ 90 mgs q12h.

Dilaudid (hydromorphone, oral):

- ❑ 2 mgs q4h.
- ❑ 8 mgs q4h.
- ❑ 30 mgs q4h.
- ❑ 45 mgs q12h.

Usual dosing frequency for morphine (immediate release) is:

- ❑ Hourly.
- ❑ q3-4h.
- ❑ q6-8h.
- ❑ q12h.

PUMP TAMPERING POSSIBLE BY PATIENTS IN OPIOID ADMINISTRATION

According to the Institute for Safe Medication Practices (ISMP), a case recently occurred in which a hospitalized patient with chronic pain was able to increase the rate of his hydromorphone infusion. This particular patient was receiving hydromorphone via a CADD-Prizm VIP pump (Smiths Medical, London, United Kingdom) at home. The admitting physician prescribed the same dose of hydromorphone as the patient had been receiving at home and allowed the patient to use his own pump while in the hospital.

The hospital-based pain service team followed the care of the patient at home but was not notified of his admission until the following morning, when a resident called to question why the patient's hydromorphone infusion was running at a different rate than prescribed. The pain service physician was unable to see the patient until later in the day, and the resident did not investigate further. Once the visit was made, when the physician looked at the pump's patient history log, it was discovered that the patient had somehow manipulated the infusion rate and given himself frequent unprescribed boluses. The patient's home CADD pump was replaced with a hospital CADD pump (different model) and secured with a tackle box and padlock to ensure no further tampering.

How did the patient gain the knowledge to manipulate the pump and obtain and use the lock level code to alter the pump settings, and then the clinician code to administer bolus doses? At the request of the Food and Drug Administration and others to provide readily accessible information, the pump's user manual is available on the manufacturer's Web site. This provides patients with knowledge about how to program the pump. The codes, however, appear only in the hard copy of the user manual. It is likely that the patient obtained the lock level and clinician codes from the pump he used at home by observing practitioners during pump programming. A much less remote possibility is that the codes, which are the same for this pump throughout the United States when shipped from the manufacturer, have been communicated via the Internet or email.

The ISMP has the following recommendations to prevent such a situation from occurring in the future:

- Shielding and scrolling: When programming a pump, always block patient (and visitor) views and use the scroll up or down keys, if available.

- Checks and balances: Require home-care and hospital nurses to track cumulative doses over time (four-hour increments for inpatients) while referencing the pump's patient history log for comparison to the prescribed dose.

- Investigate: Consider the possibility of patient tampering (or an error) if the amount administered does not match the prescribed dose, or if the patient's sedation level, respiratory status, or behavior appears different than expected.

- Staff education: When educating staff and other caregivers to use pumps, stress ways to minimize the risk of patients and visitors learning the programming codes.

- Check security features: All pumps used for opioid infusions (and new pumps considered for purchase) should be checked to ensure that the locking mechanism for the compartment that holds the medication is functional and reliable.

- Use hospital pumps: To enhance security, use hospital-approved pumps only to administer opioids to hospitalized patients. Do not allow patients to use their pumps from home.

- Monitor opioid use: Pharmacies that supply opioids to home-care patients and hospital pharmacists who dispense opioids should monitor the amounts dispensed to ensure that they match the prescribed doses. Any discrepancies should be investigated immediately.

- Screen patients: Carefully screen patients with chronic pain to ensure that they are appropriate candidates for opioid infusions. Inform patients that opioid use will be monitored.

- Change pump codes: Some pumps offer biomedical staff the capability of changing the lock level and clinician codes. Consider changing the codes temporarily for patients at risk for tampering.

- Use a pain service: If you offer a pain service, notify the team immediately on admission of a patient with chronic pain, especially if the patient has been receiving opioids in the home setting.

This appeared as an Institute for Safe Medication Practices Medication Safety Alert on April 7, 2005.

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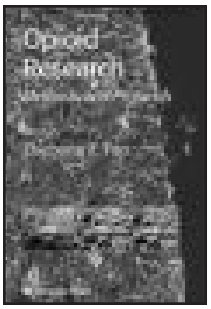


***Opioid Research: Methods and Protocols*. Edited by Zhizhong Z. Pan, PhD. Published by Humana Press, Totowa, NJ, 2003; 308 pp.**

Our understanding of opioid dynamics comes as a result of the molecular characterization of opioid receptors and signaling pathways. Molecular techniques include polymerase chain reactions (PCR), molecular cloning, reverse transcriptase replication (RT-PCR) of mRNA for gene expression, and modification and amplification of cDNA for splice variance of native opioid receptor genes. Techniques to study opioid receptor dynamics and secondary messenger interactions include the use of radiolabeled ATP for cyclic AMP–dependent kinases and fluorescent tagging of kinase substrates combined with chromatography for other important kinases. In situ hybridization by RT-PCA allows for in vitro analysis of functional receptor expression that are both native or derived from recombinant chimeric opioid genes. Animal models have been instrumental to our understanding of opioid responses, spinal analgesia, neuropathic pain, and opioid reinforcement (psychologic dependents). Laboratory research using these techniques is key to advancing our understanding of opioid agonist intrinsic efficacy (receptor activation relative to receptor binding), analgesic tolerance and non–cross tolerance important to opioid rotation, equianalgesia, and the unique agonist pharmacology that governs individual responses. Opioid-resistant pain, spinal opioids, neuropathic pain, and addiction are important topics in the area of cancer pain as well as noncancer pain management.

The text by Dr. Zhizhong Pan and colleagues is a laboratory manual that provides details on the techniques used for opioid receptor and agonist research and agonist-receptor dynamics. The contributors are among the most important researchers in the area of opioid receptor and agonist research. The book is divided into three parts: 1) molecular characterization of opioid receptors, 2) mapping and detection of endogenous opioids, and 3) model systems for opioid function. There is a small section, like an appendix, titled "Clinical Application." All chapters include an introduction to the clinical importance of the technique to be described, followed by a detailed "recipe" for the laboratory procedure, and, at the end, "notes" on the personal experience and preferences with regard to research technique and the pitfalls to various approaches. The text is well written and well edited. I felt that the book was full of details that at times were "over my head," but did fill in gaps to my understanding particular to the basic science of opioid pharmacology.

The two chapters at the end are "appendices" that include a brief and basic chapter on acute, chronic, and cancer pain, and a chapter on addiction and its management. The chapter on acute, chronic, and cancer pain, although well written, seems disconnected from the rest of the text and too basic for the level of the text. The chapter on addiction and its management, I surmise, ties into Chapters 18 and 19 and provides a clinical correlate to the animal research on place conditioning, drug reward, drug aversion, and opioid self-administration.

I believe the text could be expanded, particularly the last two chapters, to include chapters on the following:

1. The clinical relevance of opioid intrinsic efficacy (corresponding to Chapters 2, 4, 5, and 7), which would include a discussion on the controversial RAVE theory (receptor activation vs. endocytosis), partial agonists, and full agonists;

2. Analgesic tolerance (corresponding to Chapters 3, 5, 6, and 16);

3. Non–cross tolerance between opioids, equianalgesia, and opioid rotation (corresponding to Chapters 1, 2, 7, 9, and 13);

4. Opioid pharmacodynamics and individual responses to opioids (corresponding to Chapters 12, 13, and 14);

5. Spinal opioids in clinical practice (corresponding to Chapter 15); and

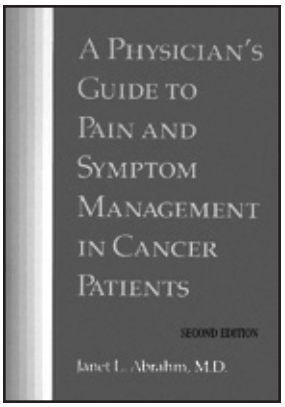
6. Management of neuropathic pain (corresponding to Chapter 17).

Connecting the text to corresponding clinically relevant subjects would make it more attractive to clinicians and stimulate a dialogue necessary for translational research.

The text is an important addition to basic science researchers. However, clinicians are likely to find little practical information. The book gave me a great appreciation for the work of these basic scientists who have contributed to our understanding of opioid responses. Hopefully, in time, what is learned in the laboratory will advance opioid practices beyond present day "trial and error" empiricism.

Reviewed by Mellar P. Davis, MD, FCCP, Director of Research, Harry R. Horvitz Center for Palliative Medicine, The Cleveland Clinic Foundation, Cleveland, Ohio.

BOOK REVIEW



***A Physician's Guide to Pain and Symptom Management in Cancer Patients*. Janet L. Abrahm, MD. Published by Johns Hopkins Press, Baltimore, 2000; 398 pp.**

This "how to do it" text authored by noted palliative specialist Dr. Janet Abrahm is a nicely organized, thoughtful, thorough book that should be on the shelf of all who care for cancer patients.

The book is logically organized, with Part I addressing unique concerns of cancer patients and their families, including the delivery of bad news, through treatment, and on into the end stages of life. In each of these chapters pragmatism is the rule, with patient vignettes used to emphasize certain important points. Bold boxes called "Practice Points," containing practical, bulleted issues, are nicely intermingled with the text. An excellent example is found on page 19, titled "Discussing advance care planning." These boxes highlight and emphasize particular aspects of the chapter.

Part II of the book deals with specific pain and symptom management issues. Again, this section is logically organized, with assessment coming first. Next, pharmacologic and nonpharmacologic pain management strategies are explored. The next chapter explores managing other distressing symptoms. Finally, the chapter titled "The Last Days ... and The Bereaved" addresses practical management of the dying patient and care of the family during this period.

Pharmacologic management of pain and other bothersome symptoms is handled with superb precision and excellent background research, in addition to the practical "how to do it" knowledge. One notable deficit in the pharmacologic section is the lack of in-depth information on methadone dosing and conversion to methadone. This is likely due to the recent (post-publication) upswing in the use of methadone for analgesia in cancer pain, and I am certain future editions will address this thoroughly.

Dr. Abrahm coverage of the anesthetic/surgical techniques, including neuraxial infusions, nerve blocks, and neural ablation, is very thorough and well researched. She provides a nice overview of the role of these therapies in refractory pain syndromes, with an in-depth description of each technique with the indications and evidence for these modalities. I have not previously encountered such a logical, easy to understand, precise, and accurate description of the techniques that I often use in my own practice.

It is rare to find a readable, useful juxtaposition of well-referenced scholarly background research and pragmatic "how to do it" knowledge. This book nicely combines these two often-exclusive domains. The "how to do it" portions will be most useful for the palliative medicine, oncology trainee, hospice or supportive care nurse, and others in this field. The more experienced clinicians in the field will appreciate the depth of research, extensive references, and the very helpful detailed explanation of how the author handles various problematic issues. The title suggests that this book is expressly for physicians, and I would suggest modifying the title in future editions, as many advanced practitioners, nurses, and family members would benefit from this well-written text.

Reviewed by Allen W. Burton, MD, Associate Professor of Anesthesiology and Pain Medicine, University of Texas M. D. Anderson Cancer Center, Houston, Texas.