The metamorphosis of hydromorphone

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INTRODUCTION

Hydromorphone hydrochloride, one of the oldest of the extant opioid analgesics, has been in clinical use for more than 70 years. Its use by the oral route in chronic pain and hospice/palliative medicine settings has been limited, however, largely owing to its relatively short duration of action. With the recent US Food and Drug Administration (FDA) approval of a once-daily extended-release formulation of the drug (Palladone, Purdue Pharma LP, Stamford, CT), hydromorphone joins morphine, oxycodone, and fentanyl as the only extended-release opioids available on the United States market. Here, we review the history, pharmacokinetics, and other relevant issues concerning this invaluable opioid, and also discuss the role of the new formulation in the management of chronic pain.

HISTORY

Hydromorphone [also Dilaudid (Knoll Laboratories, Mount Olive, NJ), dihydromorphinone, dihydromorphenone, morphinone] was synthesized, patented, and clinically introduced in post–World War I Germany.[1] It was only the second semisynthetic derivative of morphine (Figure 1). The first, diacetylmorphine (heroin), introduced by Bayer Laboratories in 1898, was outlawed by Congress in 1924.[2,3] By the time hydromorphone was introduced in the United States in 1932, it had already been the subject of more than 200 scientific papers in Europe.[4] Championed by Alvarez of the Mayo Clinic, it was purported to be superior to morphine, the only other strong opioid at the time, in most essential respects: less nausea and vomiting, constipation, euphoria, tolerance, respiratory depression, sedation, and most importantly, addiction potential.[4-7] Indeed, it was even briefly lauded as a possible cure for morphine addiction. An early newspaper article[8] described the new drug as follows:

> "AN IMPORTANT NEW DRUG
>
> "Di-hydro-morphinone-hydrochloride. "That's it. The Mayo Clinic at Rochester developed it, the word and the drug, for it means a drug, a pain relieving drug, five times as potent as morphine, as harmless as water and with no habit forming qualities.
>
> "The medical journals say it is particularly useful in the operation of cases where other drugs seem to offer no relief from pain. Unlike morphine, there are no pleasurable sensations to its use, however, and if the doctors reckon correctly its use may go far toward curing addicts of the morphine habit."
>
> *Montgomery (AL) Advertiser*, Dec. 18, 1932

From 1929 to 1939, the National Research Council's Committee on Drug Addiction conducted exhaustive research on the morphine molecule and its analogs, producing more than 150 semisynthetic and more than 300 synthetic compounds, of which more than 30 were tested clinically.[9] None of these drugs—including hydromorphone—proved to be the "holy grail" of opioids: a morphinelike analgesic with few side effects and little or no potential for addiction. As the search for the perfect analgesic continued, hydromorphone research decreased dramatically, and it took its place among a growing number of opioid analgesics.[10]

The social upheaval that characterized the 1960s was accompanied by a surge in drug abuse that would reach ever-higher peaks in the 1980s.[2] In 1971, President Nixon named drug abuse "public enemy number one," and declared a war on drugs. As if rising to meet this challenge, hydromorphone would begin to chart a parallel history as an opioid of choice for illicit use. (Ironically, Elvis Presley, enlisted by Nixon in his drug war, and made a "Federal Agent-at-Large" in the Bureau of Narcotics and Dangerous Drugs, was probably addicted to hydromorphone at the time he served. When he died in 1977, the drug was among an assortment of pharmaceuticals found in his body.[11,12])

Hydromorphone tablets, known by abusers as dillies

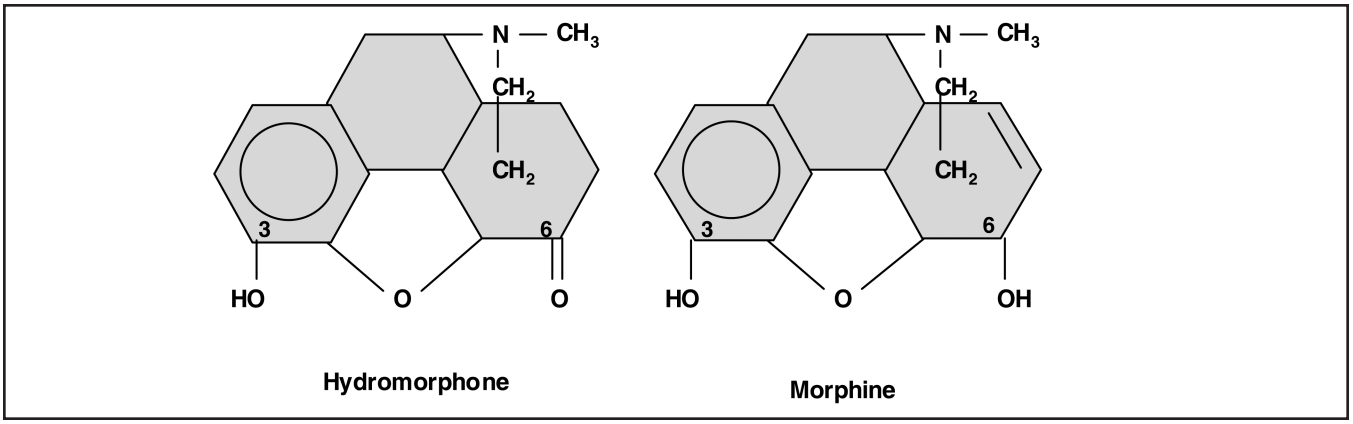

Figure 1. Molecular structures of hydromorphone and morphine.

(also dust, D, little D, juice, smack, footballs, and, tellingly, drugstore heroin), have acquired significant street value, in part because the rush of the injected drug is described as being akin to that of heroin.[13,14] In 1971, approximately 1 percent of patients admitted to drug treatment facilities in Miami-Dade (FL) were hydromorphone abusers. By 1974, the figure had risen to 10 percent. More than 90 percent of these hydromorphone abusers were injecting the oral formulation of the drug, and 83 percent were also abusing heroin.[15] In 1976, more than 50 percent of patients applying to another south Florida drug treatment program were addicted to hydromorphone.[16] Apparently, this changed little by 1984.[17] The drug became a feature of popular culture—the subject of television (Hill Street Blues 1983 episode, "Praise Dilaudid"), cinema (Gus Van Sant's 1989 "Drugstore Cowboy"), and popular music (Velvet Acid Christ's 1999 "Dilaudid (postponed)"). The problem continues to the present, with diversion of hydromorphone reported by Drug Enforcement Agency (DEA) field offices in many large US cities.[18]

The drug sells for a premium on the street, with current prices ranging from $5 to $100 per tablet (2, 4, 8 mg), depending on the geographic region.[18,19] In comparison, the street price for the more available OxyContin (Purdue Pharma LP) generally does not exceed $1 per milligram.[20] According to the DEA, the number of hydromorphone-related emergency room visits increased by approximately 300 percent from 1996 (937) to 2001 (2,667)[18]—about the same as oxycodone, but far fewer than fentanyl.[21] To put these numbers into context, the abuse of the Schedule III hydrocodone [e.g., Lortab (UCB Pharma Inc., Smyrna, GA), Vicodan (Knoll Laboratories)] exceeds that of hydromorphone and each of the other Schedule II opioids, and the abuse of illicit drugs greatly exceeds that of all prescription opioids.[21]

Of note, it has recently been reported that generic hydromorphone—as opposed to brand-name Dilaudid—has little street value.[22] The generic formulation is apparently more difficult to extract from its inert, bulk-adding filler (i.e., is poorly water soluble, even when heated to the boiling point), and therefore more likely to become blocked in the hypodermic needles of intravenous abusers.[13,22]

And yet, hydromorphone is an excellent opioid analgesic and an invaluable part of the pain pharmacopoeia. As a pure μ-receptor agonist, it has no analgesic ceiling. It is one of the most potent oral opioids—roughly five times as potent as morphine—a feature that compensates for a relatively low oral bioavailability. Its oral use is increasing: the number of hydromorphone prescriptions more than doubled from 1998 (470,000) to 2003 (970,000), owing in part to a parallel decline in OxyContin prescriptions.[18] Its intravenous use is increasing as well, as meperidine [Demerol (Sanofi Winthrop, Morrisville, PA)] begins its fade into obsolescence.[23] Successful use by a variety of other routes, including rectal, subcutaneous, intramuscular, epidural,[24] intrathecal,[25] and inhalational,[26] has also been reported. Phase I studies of its intranasal use are underway.[27]

PHARMACOKINETICS

Hydromorphone has relatively poor oral bioavailability due to high hepatic first-pass metabolism,[28] but this is offset by its relative potency (Table 1). Its short elimination half-life (i.v., 2.5 to 3.0 h; p.o., 2.5 to 4.0 h) necessitates frequent administration.[29] It is metabolized in the liver, primarily via glucuronidation, to hydromorphone-3-glucuronide (H3G) in a manner analogous to that of the metabolism of morphine to morphine-3-glucuronide (M3G), with traces of dihydromorphine and dihydroisomorphine.[28] None of the metabolites are believed to have significant analgesic action. H3G, however, is neuroexcitatory—10 times more so than its parent compound and 2.5 times that of M3G—although it has not yet been determined how readily this metabolite crosses the blood-brain barrier.[30,31] Steady-state concentrations of H3G may exceed that of the parent compound by 20- to 50-fold.[31] The metabolites, along with approximately 6 percent

Table 1. Common opioid equivalents		
	Intravenous (mg)	**Oral (mg)**
Hydromorphone	1.2	6
Morphine	10	30
Oxycodone	N/A	20
Methadone*	1 – 3	2 – 6
Meperidine	75	300

* Methadone conversion ratios remain to be further elucidated and conversions should be done with caution. See, for example, Lawlor PG, Turner KS, Hanson J, et al.: Dose ration between morphine and methadone in patients with cancer pain. *Cancer.* 1998; 82(6): 1167-1173.

unchanged hydromorphone, are excreted via the kidney and accumulate in renal insufficiency.[28,32]

CHOOSING HYDROMORPHONE

There are several reasons to consider the use of hydromorphone for the treatment of moderate to severe pain:

1. Converting patients from parenteral to oral opioids (and vice versa) is simplest when the opioid moiety remains the same. Thus, for example, for a patient who has done well on intravenous hydromorphone—with an acceptable balance between analgesia and side effects—and who requires continued therapy with a strong oral opioid, it is clinically simple and pharmacodynamically logical to continue with oral hydromorphone, using a 5:1 oral-to-parenteral conversion ratio.[33]

2. Similarly, in patients with moderate to severe pain requiring a strong opioid analgesic, and with a history of good response to hydromorphone, it is logical and appropriate to initiate therapy with this drug.

3. For patients who have responded well to hydrocodone (Vicodan, Lortab, and others) for moderate pain, they may do well with hydromorphone for severe pain. The hepatic metabolism (via the CYP2D6 enzyme system) of hydrocodone yields hydromorphone as an active, O-demethylated metabolite, with 30 times the μ-receptor binding affinity of the parent compound. It has been suggested that hydromorphone contributes to the analgesic effect of hydrocodone.[34-36]

4. Hydromorphone, thus far, appears to have no significant stigma among the general population and may be more acceptable to patients with a legitimate need for strong opioid therapy, but who balk at the mention of some of the Schedule II agents. This may seem a small matter, but opioids acquire baggage that may discourage their appropriate use by patients in pain. OxyContin is only the most recent and devastating example of this. Others, including methadone, and, indeed, even morphine have their own baggage. For this reason it is inconceivable that heroin, a fine opioid (and widely used in the treatment of cancer pain in the United Kingdom), could ever be accepted as a legitimate analgesic in the United States.

5. Individual variability in opioid response to satisfactory analgesia as well as intolerable side effects are commonly seen and likely owe to a number of factors including genetic polymorphism, differing pain mechanisms, and accumulation of opioids and/or their metabolites.[33,37] Hydromorphone can thus be a valuable option for patients who do poorly on other opioids. For example, a retrospective study of 55 palliative care patients who underwent opioid rotation because of intolerable side effects found that 80 percent of patients rotated from morphine to hydromorphone experienced statistically significant symptom improvement, as measured by visual analog scale (for pain, nausea, and drowsiness), Mini-Mental Status Examination (for cognitive dysfunction), and physician and nursing notes.[38] Another retrospective study of 80 cancer patients who underwent opioid rotation (most from morphine to hydromorphone)

Table 2. Approximate palladone conversion ratios				
Palladone (mg) Oral CR hydromorphone	12 q 24 h	16 q 24 h	24 q 24 h	32 q 24 h
MS Contin (mg) Oral CR morphine	30 q 12 h	45 q 12 h	60 q 12 h	90 q 12 h
Avinza, Kadian (mg) Oral CR morphine	60 q 24 h	90 q 24 h	120 q 24 h	180 q 24 h
OxyContin (mg) Oral CR oxycodone	20 q 12 h	30 q 12 h	40 q 12 h	60 q 12 h
Duragesic (mcg/hr) Transdermal CR fentanyl	25	25 – 50	50	75

because of side effects and/or lack of effective analgesia, found that 73 percent clinically improved, as measured solely by physician and nursing notes.[37]

6. In settings in which urine opioid screening is contemplated, hydromorphone—but not, for example, hydrocodone, oxycodone, or fentanyl—will reliably screen positive in available field test kits.[18]

Likewise, the following are relative contraindications to the use of hydromorphone:

1. Allergy (absolute contraindication) or intolerance to hydromorphone favors use of an alternate opioid analgesic.

2. Renal insufficiency reduces the clearance of the putative neuroexcitatory metabolites H3G and the 6-hydroxy epimers.[32] As noted previously, steady-state plasma levels of H3G may exceed that of the parent drug by 20- to 50-fold.[31] In patients with renal insufficiency this ratio may exceed 100.[31] Hydromorphone, however, has been used successfully in patients with renal insufficiency as well as those on dialysis.[38,39] In this population, caution should be used and patients should be closely monitored.[39]

3. Hepatic insufficiency may decrease metabolism and elimination of hydromorphone.[28] Caution should be exercised in this patient population.

4. Morphine-induced neuroexcitation is thought to owe to M3G accumulation. Because of the structural similarity between and M3G and H3G, strong consideration should be given to opioid rotation (i.e., substitution) to a structurally dissimilar opioid.[30]

5. A history of drug addiction is an important consideration. Hydromorphone has been shown to be more "likeable" than morphine (at equianalgesic doses) to addicts and normal volunteers.[40,41] This may be related to hydromorphone's greater lipid solubility, which leads to more rapid passage across the blood-brain barrier.[42]

STUDIES OF CONTROLLED–RELEASE HYDROMORPHONE

There are several reasons to consider using a controlled-release opioid formulation for stable, moderate to severe pain. The major drawback of hydromorphone has been its short elimination half-life, necessitating frequent administration. Minimizing the dosage frequency is more convenient for patients and facilitates uninterrupted sleep. It also increases treatment compliance, which in turn improves consistency of analgesia and quality of life.[43] For patients with a history of substance abuse, controlled-release products may decrease the positive reinforcement associated with the frequent, as-needed use of immediate-release opioids.[42]

Until this year, only three non-parenteral opioids were available in the United States in controlled-release forms: morphine [MS Contin (Purdue Pharma LP), Kadian (Astra Zeneca Pharmaceuticals LP, Wilmington, DE), Avinza (Ligand Pharmaceuticals, San Diego, CA), and generic], oxycodone (OxyContin and generic), and transdermal fentanyl (Duragesic, Janssen Pharmaceutical Products LP, Titusville, NJ). Hydromorphone is now the fourth. Controlled release hydromorphone formulations, however, are not new—they have been available as twice-daily formulations in Canada and Europe since the 1990s.

Table 3. Listing of retail prices for medications				
Palladone #30	12 q 24 h $237.29	16 q 24 h $278.09	24 q 24 h $385.59	32 q 24 h $487.49
MS Contin #60	30 q 12 h $130.79	45 q 12 h	60 q 12 h $248.69	100 q 12 h $368.899
Morphine (generic) #60	30 q 12 h $69.69	45 q 12 h	60 q 12 h $183.49	100 q 12 h $270.09
Avinza #30	60 q 24 h $207.59	90 q 24 h $312.69	120 q 24 h $343.59	180 q 24 h
Kadian #30	60 q 24 h $198.99	100 q 24 h $276.99	120 q 24 h	180 q 24 h
OxyContin #60	20 q 12 $192.29	30 q 12	40 q 12 $341.39	60 q 12
Duragesic #10	25 q 72 h $192.69	25 – 50 q 72 h	50 q 72 h $343.39	75 q 72 h $486.39
*Walgreens Pharmacies, Jacksonville, FL, 1/24/05.				

REPORTS OF IMMEDIATE- AND CONTROLLED-RELEASE HYDROMORPHONE

The first report on the Canadian product appeared in 1994. In this multicenter study, 48 patients with stable, severe cancer pain were enrolled in a randomized, double-blind, double-dummy crossover evaluation comparing controlled-release with immediate-release hydromorphone. The results showed no significant differences between the two formulations in daily opioid dose, rescue medication use, pain intensity, side effects, or patient drug preference.[46] Of note, three of the investigators on the study were employed by the drug manufacturer, Purdue Frederick.

A report of another Canadian controlled-release hydromorphone, this one a Knoll Pharmaceuticals product (Eduardo Bruera, MD, *personal communication*, 11/10/04), appeared in 1996. In this multicenter study, 95 adult patients with stable, severe cancer pain were enrolled in a randomized, double-blind, double-dummy crossover study of controlled-release and immediate-release hydromorphone. The controlled-release drug was found to be as safe and effective as the immediate-release drug, with no differences in total daily opioid dose, rescue medication use, pain scores, side effects, or patient drug preference. Patient acceptance was high, with 95 percent of patients choosing to continue the controlled-release drug in the open follow-up phase of the study.[47]

A Canadian product, Palladone XL (Purdue Pharma LP), which is reported to be identical to the American product (Sharon Weinstein, MD, *personal communication*, 10/27/04), was the subject of a recent abstract that reported the results of two well-controlled, multicenter clinical trials involving more than 300 (mostly cancer pain) patients. Both trials demonstrated stable and satisfactory analgesia over the entire 24-hour dosing period, as measured by numeric rating scale and number of rescue doses.[48]

COMPARISONS WITH OTHER CONTROLLED-RELEASE OPIOIDS

A 1997 Canadian study compared extended-release hydromorphone with extended-release oxycodone.[49] Forty-four patients with stable, chronic cancer pain were enrolled in this randomized, double-blind, double-dummy crossover evaluation. There were no significant differences in pain scores, as measured by visual analog and 5-point categorical scales (with mean daily doses of 124 ± 22 mg oxycodone, and 30 ± 6 mg per day hydromorphone); rescue medication use; or patient drug preference. Drowsiness, also measured by visual analog scale, was more common with oxycodone than with hydromorphone (28 vs. 19 patients), but the side effect profile was otherwise similar.

PALLADONE

Palladone (probably from the Latin, *pallium*, or "cloak") was approved by the FDA on September 24, 2004,[50] and started shipping to wholesale drug distributors on January 6, 2005.[51] A Schedule II opioid, it is available in four strengths: 12-, 16-, 24-, and 32-mg, once-daily, controlled-release capsules. The capsules contain hydromorphone in an ammonio methacrylate copolymer core.[29] The nominal 12-mg dosage is approximately equal to 60 mg of oral morphine (e.g., MS Contin, 30 mg p.o. q 12 h) and, as such, is appropriate for use only in

opioid-tolerant individuals with constant, moderate to severe pain, and with an anticipated extended period of use (Table 2).

Palladone is not intended for use in opioid-naïve individuals or those in whom planned duration of strong opioid therapy is less than weeks. Neither the capsules nor the contained hydromorphone pellets should be chewed or crushed, but in patients who cannot swallow the capsule, the opioid pellets contained therein can be sprinkled on soft foods such as applesauce or pudding. The pellets can also be mixed with water and administered via gastrostomy tube with no change in the absorption profile. Food has a negligible effect on absorption,[29] but alcohol can compromise the integrity of the controlled-release mechanism and should therefore be avoided during use.[52] Thus, in patients with alcohol use disorders, Palladone should probably be avoided.

The drug displays a biphasic absorption profile, with an initial early peak and a later, more sustained peak, with C_{max} occurring at a mean of 8.4 hours, and therapeutic plasma levels maintained over 24 hours. Compared to immediate-release hydromorphone, Palladone displayed nearly 40 percent less fluctuation in plasma levels (Purdue Pharma LP, 6/99).

Palladone is the most expensive of the extended-release opioids, although not dramatically more costly than the once-daily morphine formulations. The cost differential also tends to diminish at higher dosages (Table 3).

Palladone is subject to the same restrictions as all Schedule II opioids. In addition, in an effort to avoid a repeat of the OxyContin debacle, the manufacturer, in conjunction with the FDA, has instituted further safeguards in an effort to minimize inappropriate prescribing, diversion, and illicit use, without limiting access to patients with legitimate need for this opioid. These safeguards include the following:

- a carefully phased rollout of the drug over the initial 18 months;
- educational efforts directed toward physicians, patients, and caregivers;
- clear and appropriate drug labeling, including a "black box" safety alert warning of the dangers of abuse, addiction, and respiratory depression;
- an FDA-approved patient medication guide, to be distributed with each prescription;
- appropriate training for sales agents; and
- a multifaceted program for monitoring and surveillance of the drug.[50]

Although these measures may serve to minimize nonmedical use of this drug, some misuse of Palladone is inevitable due to the inherent abuse liability of opioids, their widespread availability for legitimate medical purposes, the criminal demand for such substances, and the imperfect nature of control systems.[21]

SUMMARY

Hydromorphone, one of the oldest and most potent of opioids, is an effective alternative to morphine. With a variety of routes of administration, it has an efficacy similar to that of morphine. The FDA has recently approved the first commercially available extended-release formulation, a once-daily hydromorphone for the management of moderate to severe pain in opioid tolerant individuals with an anticipated extended period of use. The formulation exhibits less peak-to-trough fluctuation in plasma concentration, while providing analgesia statistically indistinguishable from its immediate-release counterpart. The manufacturer and the FDA have articulated a plan to minimize unskillful prescribing and abuse/diversion through education, supply-chain integrity, and surveillance. It is anticipated that Palladone will be a valuable addition to the limited armamentarium of extended-release opioids.

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