ORIGINAL ARTICLE

No potentiation of fentanyl by use of transdermal buprenorphine in patients undergoing fast-track anesthesia for open-heart surgery

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ABSTRACT

Simultaneous use of opioids with a different pharmacological profile during anesthesia may lead to unexpected prolongation of effects. In addition, long-term use of transdermal buprenorphine may result in a reduced sensitivity to opioid anesthesia.

In a prospective study, possible overlap of opioid effects and vigilance was determined in a group of patients (n = 22) using a buprenorphine patch for at least two months for treatment of chronic pain, and undergoing fentanyl-based fast-track enflurane anesthesia for open-heart surgery. The patients using buprenorphine were compared with a control group (n = 21) undergoing similar open-heart procedures with no opioid other than fentanyl on board. Aside from time to extubation, total dose of fentanyl, postoperative blood gases, and vigilance assessment score were used to determine possible overlap of opioid effects and/or development of opioid tolerance in the buprenorphine group compared to the control group. Both groups had similar operation and anesthesia times and comparable doses of fentanyl (0.69 mg ± 0.23 vs. 0.67 mg ± 0.16 SD). There was no significant difference in postoperative arterial blood gases (PaO_2 136 ± 48 torr vs. 128 ± 35 torr SD; PCO_2 43.3 ± 3.3 torr vs. 41.9 ± 1.2 torr SD), time until extubation (27 ± 22 min vs. 33 ± 24 min), and postanesthetic vigilance and recovery score (6.8 ± 1.0 vs. 7.5 ± 0.8, arbitrary units) between the two groups.

Because of adaptive mechanisms and the development of tolerance in patients using buprenorphine, respiratory depression or sedation does not project into the postoperative period. The significant ($p < 0.05$) lower incidence of nausea and emesis in patients with transdermal buprenorphine owes to the development of tolerance to these opioid-related side effects.

Key words: transdermal buprenorphine, fentanyl, opioid anesthesia, prolongation, potentiation, side effects, open-heart surgery

INTRODUCTION

An increasing number of patients receive an opioid for the relief of chronic benign pain.[1,2] Little is known regarding patients who have used opioids over a long period of time because of chronic pain who subsequently undergo an operation using an opioid-based technique. It is the general belief that a mixture of opioids with different modes of action results in an unpredictable interaction, causing additive, or even synergistic, effects[3] with potential cardiovascular depression, prolonged awakening, and longer intubation times.

Also, in such patients, the rational choice of the anesthetic agent is crucial because tolerance may have developed,[4] and an opioid-based anesthesia technique may require higher than normal doses to achieve sufficient antinociceptive effect.[5,6]

With the recent introduction of transdermal buprenorphine (Transtec, Napp Pharmaceuticals, Cambridge, UK; Grünenthal, Aachen, Germany) for the treatment of chronic pain, an increasing number of patients scheduled for operation are receiving this potent opioid.[7-9] Our prospective open-label study was therefore undertaken to assess the response of these patients when they received an additional opioid for anesthesia.

Patients undergoing open-heart surgery were selected because in these cases anesthesia is rarely administered without the addition of an opioid. In such cases, it is important to establish whether patients receiving buprenorphine are resistant to the antinociceptive action of fentanyl, as demonstrated by patients receiving morphine.[10] Also, because fentanyl is a necessary adjunct to the anesthetic regimen, evaluation of potential interaction is of particular interest, especially because buprenorphine has been shown to act as a partial agonist at the μ-opioid receptor, capable of reversing the action of a pure μ-ligand such as fentanyl.[11] On the other hand, it has also been demonstrated in pain therapy with buprenorphine that higher than normal doses of the pure agonist morphine

Table 1. Demographic data of two groups of patients undergoing open-heart surgery with and without transdermal buprenorphine medication

Group	Gender (M/F)	Age (years)	Height (cm)	Weight (kg)	Operation time (min)	Anesthesia time (min)	Total fentanyl (mg)
Buprenorphine plus fentanyl (n = 22)	17/5	62 ± 13	175 ± 8.9	80 ± 18	224 ± 46	285 ± 44	0.69 ± 0.23
Fentanyl alone (n = 21)	17/4	65 ± 12	172 ± 8.0	79 ± 11	225 ± 58	309 ± 71	0.67 ± 0.16

are not required when it is administered concurrently.[12] Therefore, the following questions remain: Is there an increased need for fentanyl during an opioid-based anesthetic technique in patients using buprenorphine? Does the anesthesiologist have to anticipate a possible prolonged respiratory depression after a fentanyl-based enflurane anesthetic technique when patients have been using buprenorphine chronically? And, lastly, do patients with two opioids on board demonstrate a prolongation of awakening that results in the need for a longer intubation time, conflicting with the contemporary, fast-track motif?

METHODS

After Institutional Review Board approval, 22 patients scheduled to undergo coronary artery bypass grafting (CABG, n = 17), mitral valve replacement (n = 3), or closure of an atrial septal defect (n = 2), and who had been using transdermal buprenorphine for at least two months for chronic back pain [35 µg per h (n = 19) or 70 µg per h (n = 3); Table 1] were incorporated in a prospective and open-label study. Patients received the following premedication: 0.15 mg per kg diazepam plus 2.8 mg per kg phenobarbital given orally the night before operation. On the morning of operation, a further oral dose of 0.15 mg per kg diazepam was followed by a combination of 0.7 mg per kg pethidine and 0.35 mg per kg promethazine given subcutaneously 60 minutes before surgery.

In the induction area, in addition to electrocardiogram pregelled electrodes (lead II), a frontotemporal three-lead Bispectral Index (BIS) electrode was attached to measure the depth of anesthesia. The left radial artery was cannulated to measure blood pressure, and a catheter introduced via the jugular vein to measure the central venous pressure. Also, a rectal temperature probe was placed for continuous temperature monitoring during controlled hypothermia. Once instrumentation was complete, control values for blood pressure, heart rate, and arterial blood gases were recorded, and anesthesia induced with a loading dose (4.5 µg per kg, i.v.) of fentanyl. This was followed by the neuromuscular-blocking agent pancuronium bromide (0.12 mg per kg, i.v.). If the hypnotic effect was insufficient (BIS > 40) and the patient still responded to verbal commands, an additional dose of thiopental was given (1.5 mg per kg, i.v.). After laryngoscopy and intubation, anesthesia was maintained with enflurane (1.0 to 2.5 vol percent in oxygen) to obtain steady hypnotic effects using a BIS value between 30 and 40. An additional dose of fentanyl (1.5 µg per kg) was administered to guarantee stress-free anesthesia before sternal split, when the BIS value rose above 50 and/or the cardiovascular response increased by 20 percent above preinduction levels. During cardiac bypass, anesthesia was maintained by direct administration of the volatile agent (1 vol percent) into the oxygenator. Whenever possible, no opioid was administered after bypass. Fast-track anesthesia was achieved by tapering down the volatile agent toward the end of surgery. Patients with stable cardiovascular parameters were extubated within 60 minutes of the end of operation. Exclusion criteria for patients not undergoing fast-track anesthesia were as follows: an unstable cardiovascular system with need for catecholamines and/or arrhythmia, pathologic preoperative pulmonary function test with high $PaCO_2$ and/or low PaO_2 values, and postoperative bleeding through chest tubing.

For comparison purposes, a similar group of patients (n = 21) undergoing elective open-heart surgery (CABG, n = 13; tricuspid valve replacement, n = 1; closure of an atrioseptal defect, n = 2, atrioventricular defect, n = 5), underwent the same anesthetic procedure, with no opioid other than fentanyl on board.

In addition to intraoperative antibiotics, all patients received the nonsteroidal anti-inflammatory drug metamizol (2 g i.v.) plus acetaminophen (1 g i.v.) before extubation for postoperative pain relief.

Before anesthesia and 60 minutes after extubation, the following variables were measured:

- Heart rate and blood pressure via an indwelling arterial catheter.
- BIS value from an Aspect (Newton, MA) electroencephalogram monitor using a frontotemporal electrode montage.

- Arterial blood gases (PaO_2, $PaCO_2$) from repetitively drawn arterial blood samples.

Postoperatively, the state of the patient was assessed using a modified postanesthetic vigilance and recovery score, as originally devised by Aldrete and Kroulik[13] (Table 2). An independent observer unaware of the anesthetic regimen evaluated parameters such as muscle activity, respiration, circulation, state of consciousness, and temperature 60 minutes after extubation. The time at which patients required a postoperative analgesic was also recorded, using the visual analog scale (VAS; from 0 to 10). When a score above 5 was noted for the last three assessments, piritramide (3 mg i.v.) was administered until the VAS score dropped below 3. Last, but not least, the incidence of nausea and/or emesis was recorded in all patients by the independent observer who, while taking pain scores, also questioned patients on these side effects. If any patient complained of nausea, the HT3-antagonist granisetron (2 mg) was administered intravenously.

STATISTICAL ANALYSIS

Before starting the prospective open-label study, a priori power analysis was performed. This was necessary to calculate the number of patients needed to demonstrate a possible statistical significance between the buprenorphine and a control group. Based on a previous study of patients after open-heart surgery, it was necessary to detect a difference of maximal power values by 50 percent, an effect level of 1.0, with an error of 5 percent. To demonstrate significance with a power of 80 percent, at least 20 patients were necessary.

The multiple analysis of variance (ANOVA) nonparametric test was used to calculate statistically significant differences within one group at different time points. Because patients did not fulfill Gaussian distribution, the Mann-Whitney two-tailed test was used when computing a significant difference between groups. Statistical significance was defined as a p-value of < 0.05.

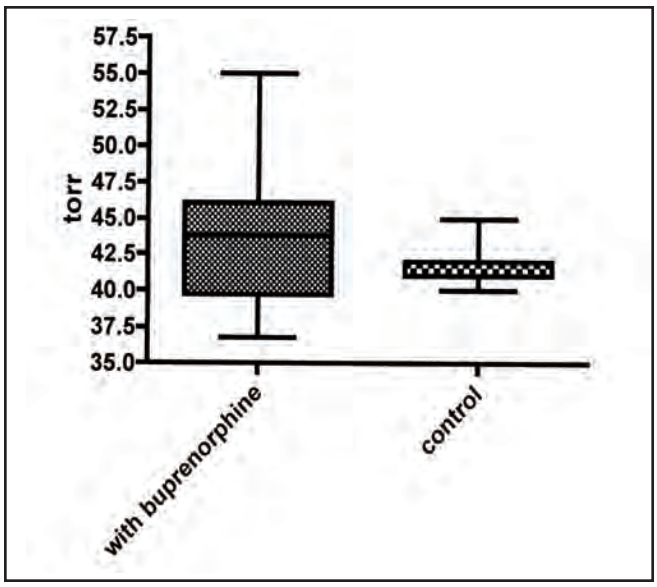

Figure 1. Box plots of arterial $PaCO_2$ values in two groups of patients after open-heart surgery with and without a buprenorphine patch (mean ± SD).

RESULTS

There was no significant difference in demographic data of patients using a buprenorphine patch for at least two months for chronic back pain and those patients without transdermal buprenorphine undergoing open-heart surgery (Table 1). In addition, there was no significant

Table 2. Modified Aldrete score

	0	1	2
Conscious state	Nonresponsive	Responds to stimuli	Fully awake
Activity	No movement of extremities	Moves two extremities voluntarily or on command	Moves four extremities voluntarily or on command
Respiration	Apneic	Dyspnea, shallow or limited breathing	Able to breathe deeply and cough freely
Circulation	Systolic BP > 20 percent of preanesthetic level	Systolic BP ± 11 to 20 percent of preanesthetic level	Systolic BP within 10 percent of preanesthetic level
Temperature	< 35.0°C or > 37.5°C	35.0°C to 36.5°C	36.5°C to 37.5°C

BP, blood pressure.

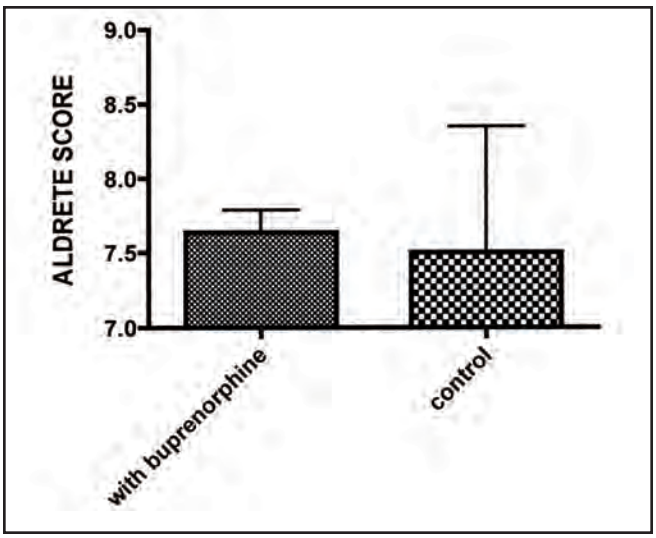

Figure 2. Postoperative vigilance assessment score in two groups of patients with and without buprenorphine after open-heart surgery in fentanyl-based enflurane anesthesia (mean ± SD).

difference between the two groups in regard to total time of operation, total time of anesthesia, and the total dose of fentanyl being administered for anesthesia (Table 1).

In the postoperative period there was no difference in arterial blood gases 60 minutes post extubation. With pure oxygen inhalation, arterial PaO_2 was characterized by a mean of 136 torr (± 48 SD) in the group with and by a mean of 124 torr (± 16 SD) without buprenorphine. With regard to arterial $PaCO_2$, there was a mean of 43.3 torr (± 3.3 SD) in patients with buprenorphine and a mean of 41.9 torr (± 1.2 SD) in the group without, reflecting no significant difference between the two sets of patients (Figure 1). Also, none of the patients in both groups had to be reintubated because of a late respiratory depressive effect.

Such lack in prolongation of opioid effects with an overlap into the postoperative period is also reflected in the postoperative vigilance assessment score. Data were taken 60 minutes after extubation when patients were supervised in the intermediate-care unit with no arousal stimuli around them, which may have accounted for any change in the state of vigilance. Aldrete score was 7.6 (arbitrary units) in the group with buprenorphine, compared to a mean of 7.5 (arbitrary units) in patients having received only fentanyl (Figure 2). These data demonstrate no significant difference between the two groups of patients.

Similar to the state of vigilance, postoperative cardiovascular parameters were similar in both groups, 60 minutes after extubation. Mean systolic blood pressure was 133 mmHg (± 11 SD) in patients receiving buprenorphine, and 124 mmHg (± 11 SD) in patients that were not. Such lack in difference was also mirrored in the diastolic pressure, which was 69 mmHg (± 9 SD) in patients with and 68 mmHg (± 8 SD) in patients without buprenorphine.

Statistical analysis of heart rate changes in the postoperative period had to be omitted because nine patients in the group with and 13 patients in the group without buprenorphine were paced with an external pacemaker using a fixed frequency of 90 beats per minute.

The majority of patients (85 percent) required additional analgesia for postoperative pain relief as early as 20 to 30 minutes after extubation. Although there was no significant difference between the two groups in regard to the time of first demand, there was a tendency of patients with buprenorphine for a later demand (22.5 ± 10 minutes SD vs. 15.8 ± 12.7 minutes SD).

Even though total intraoperative requirement for fentanyl was not appreciably higher in patients not receiving transdermal buprenorphine, none of the 22 patients receiving the buprenorphine complained of nausea or experienced bouts of emesis postoperatively. This is significant ($p < 0.05$), because 24 percent of all patients not receiving buprenorphine demonstrated nausea, emesis, or both.

DISCUSSION

These are, to our knowledge, the first results obtained in patients receiving transdermal buprenorphine for chronic pain who underwent open-heart surgery while using fentanyl during anesthesia. Such data are important, as they reflect a possible interaction of two opioid analgesics with different characteristics. One is the potent opioid fentanyl, 200 to 300 times more potent than morphine, and a pure μ-agonist.[14] The other opioid, buprenorphine, is a partial μ-agonist with a potency 40 times that of morphine, which unlike fentanyl is an antagonist at the opioid κ-receptor,[15] characterized by a long duration of action.[16] More importantly, we addressed the question of whether the coadministration of fentanyl on buprenorphine results in an additive effect, with sequelae that involve the cardiovascular, respiratory, and central nervous systems, as reported by others.[17]

Few researchers have used buprenorphine during CABG surgery.[18-20] Contrary to these studies, however, buprenorphine was administered by the transdermal route in our patients. Although a decline in the plasma level of buprenorphine can be anticipated with the start of cardiopulmonary bypass, resulting in an increase in the elimination half-life ($t_{1/2}\beta$), there was no prolongation of respiratory depressive and sedative effects. Such increase in $t_{1/2}\beta$, although not measured, can be derived from data seen with other opioids (fentanyl, alfentanil, and sufentanil),[21,22] an effect owing to hemodilution and hypothermia, and which should have resulted in a prolongation of $t_{1/2}\beta$ of buprenorphine. However, because receptor occupation and not plasma level is the relevant

factor in mediating an opioid effect, any possible increase in $t_{1/2}\beta$ is irrelevant. This assumption is underlined by receptor binding and displacement studies,[23,24] in which buprenorphine has an eight- to 11-fold higher affinity than the short-acting fentanyl.[25,26] Furthermore, buprenorphine demonstrates a much slower dissociation rate from the receptor site than fentanyl,[15] so it may be concluded that, despite any probable decline in plasma levels, receptor occupation remained high in the group of patients receiving buprenorphine. Thus, receptor occupancy in the present patient population can be assumed to be similar during pre- and intraoperative periods, especially because buprenorphine patches had been used previously over a long term. With a steady binding of buprenorphine at receptor sites, any additional injection of fentanyl would be likely to interact with the pre-existing opioid. Contrary to widely held belief, however, the injection of fentanyl did not result in an additive effect followed by a prolongation and possible potentiation of opioid action. This is demonstrated in postoperative arterial blood gases and vigilance assessment scores, which reflect a possible prolongation of opioid action after patients have been extubated. Because all patients inhaled pure oxygen via a facemask at a flow rate of 3 to 6 L per min, high values are typical. Therefore, arterial $PaCO_2$ can be considered a more sensitive marker for prolonged opioid action on respiration. Because arterial $PaCO_2$ and the Aldrete score were not different among the two groups, one may presume that receptor occupation by buprenorphine was not high enough to enhance the opioid effects of fentanyl. This presumption can be excluded because patients' transdermal patches were not removed and they induced sufficient analgesia in chronic pain patients, lasting for at least three days preoperatively.

Such lack of additive effects, when compared to a control group without buprenorphine, may be explained by the following reasons. First, fentanyl is metabolized in large amounts during the course of anesthesia, and hemodilution takes place during cardiopulmonary bypass; consequently, clinically relevant plasma concentrations may no longer exist postoperatively, so no effects of the opioid combination can be detected. Although fentanyl plasma concentrations may have declined with the start of cardiopulmonary bypass, it is receptor occupation and not plasma level that is the relevant predictor in mediating an opioid effect.[27] Most importantly, however, long-term prior use of buprenorphine (minimum period, two months) means that these patients cannot be regarded as opioid naïve. Adaptive mechanisms, especially those regarding respiration and sedation, have led to a compensatory mechanism and the development of adaptation such that a lower level of respiratory depression, a lower incidence of nausea and emesis, and, similar to patients without buprenorphine, no increase in the sedative effect and depression in vigilance score can be expected. This adaptation process is a typical trait in chronic pain patients taking opioids for a protracted period, resulting in the respiratory center being less sensitive to opioids and having a tolerance to their sedative and emetogenic effects.[1,28] This is in line with our results, in which the presence of buprenorphine before the administration of fentanyl did not prolong respiratory depression or time until extubation when compared to a control group. On the contrary, development of selective adaptation led to an observable reduction in nausea and emesis.

The previous use of buprenorphine did not induce an antagonistic effect[11,29] in the present patient population, because both groups needed similar amounts of fentanyl during surgery. One reason for this lack of antagonism is the receptor reserve, a characteristic feature of buprenorphine,[16] which allows an additional opioid to interact with so-called free, unoccupied receptors and initiate an analgesic effect. Such receptor reserve owes to the high affinity of buprenorphine to the receptor site, resulting in a smaller fractional occupancy than fentanyl, with lesser dosages and lesser receptor binding to elicit an analgesic effect.[30,31] Moreover, the antagonistic effect of buprenorphine only becomes apparent when the partial agonist is administered after a pure opioid ligand such as fentanyl, thus reversing the depressed respiratory drive and increased vigilance.[11,29] Because of the high affinity for the opioid μ-receptor,[32] buprenorphine is able to reverse the respiratory depressant effect of fentanyl. As buprenorphine was not given after fentanyl in these open-heart surgery patients, no antagonistic effect could be observed in the present patient population. In addition, there was no evidence of tolerance to the antinociceptive effect of fentanyl, which would have been indicated by a need for higher doses than the group not being on buprenorphine. Contrary to the present patient population, Leon-Casaola and coworkers observed dosages three times higher of an opioid for postoperative analgesia in opioid-dependent patients.[33] This difference very likely owes to the diverse antinociceptive mode of action of buprenorphine, which contrary to fentanyl is mediated via μ-opioid receptor subtypes[26,34,35] and the interaction with a different subset of intracellular G-proteins,[36] resulting in less development of tolerance to the analgesic effect.

In summary, this prospective study clearly demonstrates that patients who use transdermal buprenorphine over a long period, and who require opioid-based anesthesia, experience neither an additive nor an antagonistic effect. The reason is that such patients cannot be regarded as opioid naïve and they have already adapted to an opioid agent. When a pure μ-receptor ligand such as fentanyl is subsequently given as a bolus, because of partial tolerance and higher levels for respiratory and cardiovascular depression and sedation, there is no consequential overlap of effects into the postoperative period.

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