Patient controlled analgesia used to assess the efficacy and potency of a new opioid

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Patient controlled analgesia (PCA) is widely used for the management of postoperative pain. PCA also permits a comparison to be made among analgesics in the clinical setting because it limits the variability introduced by third parties. Use of PCA to establish efficacy and potency data for an investigational drug, pentamorphone, compared with morphine is reported. Pentamorphone was found to be more efficacious than morphine in the first hour after surgery because significantly more patients were able to achieve a visual analogue scale of less than 30 mm with pentamorphone. Thereafter pentamorphone and morphine were found to be equally efficacious. Initially pentamorphone may be more potent than morphine based on the greater volume of morphine used in the first hour of therapy. However, a potency ratio could not be determined because this result was under conditions of unequal analgesia. The potency ratio determined at 24 h of therapy under equianalgesic conditions (252:1) is similar to previously reported potency data from laboratory studies (200:1). This study supports the use of PCA as a model to investigate and compare new drugs to establish their efficacy and potency.

Key Words: Morphine, Patient controlled analgesia, Pentamorphone, Postoperative
Patient controlled analgesia (PCA) is widely used for the management of postoperative pain and is highly effective in providing adequate pain relief (1,2). With appropriate choice of opioid doses and lockout intervals, patients using PCA can obtain pain relief regardless of the specific pharmacodynamic and pharmacokinetic properties of the opioids chosen (3-5). Thus PCA should be useful as a research tool to compare opioids (6,7). Efficacy can be studied through determination of the degree of pain relief obtained – using a visual analogue scale (VAS) – with each analgesic at various time points. Further, under equianalgesic conditions with PCA, an estimate of relative potency can be made between two opioids through a comparison of the total amount of opioid used.

We present the results of efficacy and potency determination using PCA with a new drug, pentamorphone, versus morphine, after lower abdominal surgery. Pentamorphone (14-beta-n-pentylaminomorphinone) is a morphine derivative with a high lipophilicity and fairly stable cardiovascular effects (8,9). In animal studies pentamorphone had a shorter onset and duration than morphine (10). With these properties, pentamorphone is expected to be a useful drug for PCA.

**PATIENTS AND METHODS**

After institutional review board approval at Duke University Medical Center, written informed consent was obtained from 60 patients scheduled to undergo lower abdominal surgery (exploratory laparotomy, abdominal hysterectomy, oophorectomy, etc). Only American Society of Anesthesiologists physical status I or II patients between 20 and 69 years who were within 20% of their ideal body weight were considered for this study. Patients were excluded if they had received a general anesthetic during the preceding month or were on any opioid medication during the month before surgery.

Patients underwent standardized education on the use of the Abbott Lifecare PCA (Illinois). The pamphlet details that patients should use the PCA expectantly and keep their pain level at a manageable, mild level was emphasized. In addition, education served to allay potential fears or social mores regarding the use of a PCA machine. As a part of the process, patients were instructed on how to complete a linear VAS (on a scale of 1 to 100).

Patients were randomly assigned, in a double-blind fashion, to one of two groups. Twenty patients received morphine and the other 40 received pentamorphone for postoperative analgesia. The potency of pentamorphone has previously been determined in a laboratory setting with human volunteers (9). The data from this study were used to derive the initial dosing for pentamorphone compared with morphine. Estimated equipotent doses of morphine (1 mg/mL) and pentamorphone (5 µg/mL) were prepared for the PCA pump by the pharmacy.

Anesthesia was standardized to include thiopental, 60% to 70% nitrous oxide and isoflurane supplemented with less than 6 µg/kg fentanyl as necessary to maintain adequate anesthesia. Vecuronium was used for neuromuscular blockade and was antagonized with neostigmine and glycopyrrolate at the end of the procedure.

In the postanesthesia care unit (PACU) a loading dose of 0.04 mL/kg of the randomized analgesic was administered via an Abbott Lifecare PCA. This translated into either 40 µg/kg morphine or 0.2 µg/kg pentamorphone. This loading dose of opioid was given when a VAS greater than 50 mm was recorded by the patient, and was repeated up to three times for a VAS greater than 50 mm while in the PACU. If these loading doses provided inadequate analgesia, patients were excluded from the study and conventional analgesia was started. PCA settings were standardized to a maintenance dose of 0.02 mL/kg and a lockout interval of 8 mins. Patients were discharged from the PACU to a routine postoperative floor when awake with a satisfactory level of analgesia. A VAS (completed by the patient), sedation scale and side effects (completed via observation and open questions) were recorded at 10, 20 and 30 mins and at 1, 4, 8, 12, 16, 20 and 24 h.

Analysis of variance for repeated measures was used for comparison between the groups. The Mann Whitney U test was used for comparison of nonparametric data. P<0.05 was considered significant. Results are given as a mean ± SD.

**RESULTS**

The two groups showed no differences in age, height or weight, duration of surgical procedure and total amount of intraoperative fentanyl used (Table 1). Initial VAS scores showed no statistical difference before the first loading dose of pentamorphone (81±18 mm) or morphine (83±18 mm). The VAS following the initial loading dose of pentamorphone (51±31 mm) and morphine (63±32 mm) showed no statistical difference. However, the VAS was significantly lower at 20, 30 and 60 mins in the pentamorphone group compared with the morphine group (P<0.05) (Figure 1). The percentage of patients who received pentamorphone with a VAS less than 30 mm was significantly greater than the percentage of

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<th>TABLE 1 Demographics and total fentanyl used</th>
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![Figure 1](image) Bar graph representing visual analogue pain scale comparing pentamorphone with morphine. *P<0.05
those who received morphine at 10, 20 and 30 mins, and 1 and 4 h (P<0.05) (Figure 2).

The cumulative volume of opioid used in each time period is depicted in Figure 3. During the initial period, patients in the pentamorphone group used less volume versus patients in the morphine group. This difference was statistically significant at 10, 20 and 30 mins (P<0.05). By 4 h, patients in both groups used equal volumes of opioid. After 24 h, the total volume of analgesic used was 62.9±27.9 mL in the morphine group and 50±30.1 mL in the pentamorphone group.

An estimated potency ratio can be derived from the total 24 h volumes of analgesic used. For morphine, 62.9 mL equals 62900 µg of morphine and for pentamorphone 50 mL equals 250 µg of pentamorphone. The ratio of morphine to pentamorphone used is approximately 252:1, which represents an potency ratio as it was derived under equianalgesic conditions.

There was no difference between the groups in the level of sedation or side effects (Table 2). Fifteen per cent of the patients in the morphine group and 20% of the patients of the pentamorphone group (difference was not significant) were excluded in the PACU because adequate analgesia could not be obtained with the three allowed loading doses.

DISCUSSION
PCA has been proposed to be a useful research tool to determine the efficacy of various agents and modes of therapy for pain (6,7). In this investigation we used the modality of intravenous PCA to determine efficacy and potency data about a new opioid, pentamorphone, compared with morphine.

The value of PCA as a research tool is partly due to the limitations of some of the alternate methods used to compare analgesics. For example, minimum effective analgesic concentration (MEAC) is determined by measuring opioid concentration just before the request for additional analgesia. It is an accurate method to determine the potency of various opioids but is cumbersome in the clinical setting. Alternatively, electroencephalograms (EEGs) have been used to compare opioids and determine potency ratios (11). The relative potency for analgesia of an opioid may parallel the relative potency of morphine, compared with morphine. However, no measure of an EEG change has correlated with pain or relief of pain. Another technique to evaluate relative opioid potency is to determine the opioid concentration required to produce a 50% minimum anesthetic concentration (MAC) of an inhalational agent (12). Although this is an objective measurement, it is a measure of anesthesia of which pain is only a component.

This study was designed as a fixed dose analgesic comparison study that used PCA to eliminate the need for a third party to respond to patient request for pain medication. Further, multiple fixed doses over 24 h were observed, allowing comparison of analgesic efficacy and potency at various points after surgery and allowing patients to titrate the analgesic individually to their pain needs. This study design is in contrast to classic single dose analgesic studies, in which a single dose of a test drug is compared with placebo and a positive control drug for several hours after administration (13-15). Although single dose studies allow the comparison of analgesics at a given time, a study using PCA should allow for a more meaningful comparison of analgesic agents over a clinically relevant postoperative time period.

Using PCA, we compared time to onset of pain relief, amount of pain relief obtained and total volumes of analgesic used, starting with fixed doses calculated from the laboratory-determined potency ratio of 200:1 (9). Adjustment for the standardized size of the loading doses and the PCA bolus doses should have been made by patients, who were freely allowed to administer opioids every 8 mins.

Pentamorphone demonstrated a faster onset of analgesia and a greater degree of analgesia compared with morphine in the first 60 mins of therapy as determined by lower VAS scores (Figures...
Thus, pentamorphine was more efficacious than morphine in the first hour of therapy; thereafter similar VAS scores were obtained, indicating that pentamorphine and morphine were equally efficacious in subsequent hours of therapy.

A greater volume of morphine, compared with pentamorphine, was also used in the first hour of therapy. This result implies that the potency of pentamorphine is greater than 200:1 in the first 60 mins. However, it is difficult to assign a potency ratio because the first hour of therapy did not result in equally efficacious analgesia. Such a decrease in the relative potency of morphine may have been due to a slower opioid receptor equilibration rate for morphine, lack of significant accumulation of morphine-6-glucuronide (a metabolite of morphine with analgesic effects) or the low lipid solubility of morphine compared with pentamorphine. After the first hour of therapy, the total volumes of opioid used were similar with equal analgesia. This result confirms that the laboratory-determined potency ratio of 200:1 (as the potency ratio at 24 hr of therapy) was 252:1. It is important to recognize these probable differences in potency between the early and late phase of dosing with the PCA when establishing clinical dosing regimens, especially the determination of loading doses. However, a meaningful potency ratio should be that established at analgesia equilibrium — after the first hour of therapy for these two drugs.

Patients excluded from the study were treatment failures who did not achieve adequate analgesia after three loading doses within the limits of the study design. They may have achieved adequate analgesia with larger or repeated loading doses. There was a similar percentage of treatment failures in the pentamorphine and morphine groups. Our study also used uneven groups of patients to investigate thoroughly the effects of the new drug, pentamorphine (the effects of morphine are well established). Although the total number of study patients is small, the differences observed were statistically significant.

Results of this study conflict with those of Wong and co-workers (16), who found pentamorphine to be inadequate for the management of postoperative pain. A one-time dose of pentamorphine (0.08, 0.16 or 0.24 µg/kg or placebo) was given and the total amount of morphine used in the first hour only was determined. Wong et al found a trend of decreased pain scores with 0.24 µg/kg pentamorphine, but no significant differences between groups with respect to the amount of morphine needed. In contrast, the present study employed PCA using a large loading dose of pentamorphine (0.2 µg/kg) which could be repeated for up to three doses as necessary. Further, the study continued for the first 24 h after surgery during which the patients titrated themselves to comfort. Thus, inter- and intrapatient differences regarding opioid requirements were overcome, and our study more completely examined the postoperative use of pentamorphine.

There are limitations to the use of PCA to determine relative potency between drugs. Some patients adjust their analgesic use to decrease their pain to an expected level rather than to complete analgesia (17). Other patients are fearful of addiction or side effects such as nausea or somnolence. Still others do not want to assume responsibility for their own analgesia (18). Psychological factors, such as a high level of independence, are associated with less analgesic use whereas aggressiveness may be associated with greater analgesic use (5). However, it has been demonstrated that analgesic use via PCA correlates well with visual analogue pain scales and the McGill pain questionnaire; thus, PCA remains valid for the evaluation of analgesic requirements in the postoperative setting (5).

CONCLUSIONS

We utilized PCA to determine the relative efficacy and potency of a new opioid, pentamorphine, compared with morphine in the postoperative setting. Pentamorphine provided superior analgesia in the first hour of therapy but thereafter pentamorphine and morphine were determined to be equally efficacious. Further, we determined that the original estimation of a 200:1 potency ratio is correct for pentamorphine versus morphine when used clinically in an equianalgesic setting. Pentamorphine may also be more potent than morphine in the first hour of therapy, although equiaxialgesic conditions were not present. From this study we conclude that PCA can be used effectively in the postoperative care setting to determine relevant potency ratios and efficacy data for the comparison of analgesics. We examined PCA used in the intravenous mode, but the technique could also be used in other modes such as epidural administration.

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REFERENCES


