PATIENT-CONTROLLED ANALGESIA WITH EXTRADURAL MORPHINE OR PETHIDINE

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With patient-controlled analgesia (PCA), the patient is allowed to self-administer small bolus increments of an analgesic drug by means of a programmable pump device. The method has proved to be effective in relieving postoperative pain [1–6]. A wide variety of analgesic drugs have been used, mostly by the i.v. route, but also i.m. [7].

The extradural administration of opioids has been used clinically since 1979 to relieve both acute and chronic pain [8]. Several adverse effects, including respiratory depression, urinary retention, itching, nausea and vomiting have been reported following extradural morphine [9]. Some of the adverse effects are elicited at supraspinal centres to which the drug is thought to be transported with cerebrospinal fluid (CSF) bulk flow [10,11]. Absorption across the dura from the extradural space and removal from CSF is slower for morphine than for pethidine, probably because of differences in lipophilicity [12]. Theoretically, the risk of eliciting supraspinal adverse effects should be smaller when using a more lipophilic compared with a hydrophilic drug. Extradural morphine has been reported to be longer acting than extradural pethidine, fentanyl and methadone [13], but the relative efficacy and adverse effects of different opioids are largely unknown.

The purpose of this study was to combine the concept of patient-controlled analgesia with that of extradural administration of opioids in order to compare two drugs (morphine and pethidine) with different physicochemical properties and receptor binding characteristics.

SUMMARY

Two groups of patients were allowed to self-administer morphine (n = 17) or pethidine (n = 15) extradurally after abdominal surgery, for a mean period of 16 h. Bolus increments of morphine 1 mg or pethidine 20 mg were administered by programmable pump. Pain relief from extradural patient-controlled analgesia (PCA) was excellent in all but two patients in the morphine group. Pain relief was not qualitatively different between the two groups. No clinical respiratory depression was seen. The average consumption of extradural morphine was 0.52 ± 0.29 mg h⁻¹ (range 0.19–1.04 mg h⁻¹) and of pethidine 18.0 ± 8.1 mg h⁻¹ (5.8–35.4 mg h⁻¹). This yields an equianalgesic dose relationship of 1:35. Morphine consumption was more irregular than pethidine consumption. Morphine and pethidine plasma concentrations measured during PCA were well below the reported minimum analgesic plasma concentrations in most cases. Several patients, particularly in the pethidine group, tended to increase their opioid consumption during PCA. This could be explained by an increasingly smaller fraction of the pethidine bolus being absorbed to the subarachnoid space during frequent repetitive dosing. The large inter-individual variation in consumption makes it impossible to recommend a standard dose of extradural morphine or pethidine for analgesia of predictable duration and with a minimum of adverse effects.

PATIENTS AND METHODS

The study was approved by the ethics committee of the Medical Faculty of Uppsala University.

Thirty-two patients undergoing major abdominal surgery gave their informed consent to
participate in the study. A majority of the patients suffered from inflammatory bowel disease or peptic ulcer. None had signs or symptoms of renal or hepatic dysfunction, psychiatric disease or a history of drug or alcohol abuse. Individual patient data are shown in tables I–III.

After an overnight fast, all patients were premedicated with diazepam 10–15 mg by mouth and atropine sulphate 0.5 mg i.m. Anaesthesia was induced with thiopentone and a single dose of droperidol 5 mg. Orotracheal intubation was performed after pancuronium bromide 0.1 mg kg⁻¹. An extradural catheter was placed at the lower thoracic or lumbar level. The lungs were ventilated mechanically with 30% oxygen in nitrous oxide. Additional increments of pancuronium 1–2 mg were given as required. Intraoperative analgesia was provided with increments of fentanyl in 0.1–0.2 mg doses to suppress signs of surgical stress.

When the surgical procedure was completed, the trachea was extubated and the patient transferred to a recovery room where s/he remained overnight. Routine observations included checks, at least every 60 min, of arterial pressure, heart rate and ventilatory frequency.

When the patient requested pain relief a programmable PCA-pump (Prominjet, Pharmacia, Sweden) was connected to the extradural catheter. The PCA pump was programmed to deliver incremental doses of 1 mg of preservative-free morphine hydrochloride 1 mg ml⁻¹ (17 patients), or 20 mg of pethidine hydrochloride 25 mg ml⁻¹ (15 patients), with a minimum time interval of 30 min between doses. Patient-controlled administration commenced in the afternoon after surgery and continued until the following morning. No other analgesics were administered during the period of PCA. However, those who experienced insufficient pain relief from extradural PCA were offered i.v. PCA.

The hourly consumption of morphine or pethidine during PCA was recorded, as were the patients’ average time intervals between doses. Pain was assessed by means of a visual analogue scale (VAS) consisting of a horizontal 100-mm line marked “No pain” at its left end and “Worst imaginable pain” at its right end. The patients were not shown their previous ratings. Pain was assessed before the start of PCA, twice during the period 1–4 h after the start, and when PCA was discontinued.

Pain relief was calculated as percent reduction of pain:

\[
\frac{\text{VAS before PCA} - \text{VAS during PCA}}{\text{VAS before PCA}} \times 100
\]

On the 3rd or 4th day after operation, the patient was asked to give an overall assessment of the pain relief from extradural PCA on a four-point scale ranging from “insufficient” to “very good” analgesia. Reports of adverse effects listed in table IV were obtained by direct questioning.

Venous blood samples for drug assay were collected during the PCA period at times not less than 15 min after a dose. The plasma was separated and frozen at −20 °C until analysed. Morphine and pethidine were assayed with gas-liquid chromatography using electron-capture detection [14, 15]. The limit of detection of the method was 1 ng ml⁻¹ for morphine and 5 ng ml⁻¹ for pethidine.

Student’s t test for independent means or the chi-square test were used for comparison of the groups; \( P < 0.05 \) was considered to represent statistical significance.

Dose administration patterns were analysed individually with respect to regularity/irregularity. The coefficient of variation of the time intervals between consecutive doses was calculated for each individual using the equation:

\[
\text{Coefficient of variation (\%)} = \left( \frac{\text{SD (dose interval)}}{\text{Mean (dose interval)}} \right) \times 100
\]

RESULTS

Clinical course

The clinical course of all patients was uncomplicated. There were no significant differences between the morphine and pethidine groups with regard to age, sex, weight, body surface area, duration of operation, consumption of fentanyl during operation, intraoperative blood loss or between these factors and postoperative requests for analgesia (table I).

There were no significant changes in, or differences between the groups with regard to breathing frequencies. No frequencies less than 12 b.p.m. were recorded during PCA.

Disorders of micturition could not be detected since most of the patients had urinary catheters.
Self-administration of morphine

PCA lasted for a mean period of 16.7 ± 2.6 h in the morphine group (table II). Two of the 17 patients (Nos 16 and 17) experienced insufficient pain relief despite having administered three and four doses of morphine, respectively. They were offered i.v. PCA with morphine, and obtained satisfactory relief.

The remaining 15 patients were satisfied with the pain relief from extradural morphine, and consumed 0.52 ± 0.29 mg h⁻¹ (range 0.19–1.04 mg h⁻¹).

Pain assessment on the 100-mm VAS scale before PCA averaged 52.8 ± 13.8 mm. Pain relief at the end of the PCA period was 71.1 ± 27.7 % reduction of pain. Maximum pain relief recorded was 73.1 ± 27.1 %.

Morphine consumption tended to follow an irregular pattern. The mean time interval between doses was 166 ± 107 min. The mean coefficient of variation of the time intervals was 60.9 ± 26.2 %. The time intervals did not change in any uniform pattern during the PCA period.
### Table II. Data from the PCA period in the morphine group

Opioid consumption during PCA, duration of the PCA period, mean (± SD) time between doses, plasma concentrations of opioid, pain assessment on a visual analogue scale (VAS) before PCA, maximal pain relief recorded and pain relief at the end of the PCA period as % reduction of initial pain.

<table>
<thead>
<tr>
<th>No.</th>
<th>PCA consump. (mg h⁻¹)</th>
<th>PCA duration (h)</th>
<th>Time between doses (min)</th>
<th>Plasma concn (ng ml⁻¹)</th>
<th>VAS before PCA (mm)</th>
<th>Reduction of pain</th>
<th>Maximal</th>
<th>At end of PCA</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0.42</td>
<td>16.6</td>
<td>142 ± 115</td>
<td>3 1 0</td>
<td></td>
<td>50</td>
<td>30</td>
<td>22</td>
</tr>
<tr>
<td>2</td>
<td>0.19</td>
<td>21.6</td>
<td>324 ± 216</td>
<td>3 2 0</td>
<td></td>
<td>40</td>
<td>73</td>
<td>73</td>
</tr>
<tr>
<td>3</td>
<td>0.22</td>
<td>18.1</td>
<td>275 ± 142</td>
<td>2 0 1</td>
<td></td>
<td>33</td>
<td>88</td>
<td>88</td>
</tr>
<tr>
<td>4</td>
<td>0.59</td>
<td>17.0</td>
<td>105 ± 75</td>
<td>2 0 0</td>
<td></td>
<td>31</td>
<td>61</td>
<td>61</td>
</tr>
<tr>
<td>5</td>
<td>0.75</td>
<td>15.9</td>
<td>79 ± 37</td>
<td>0 2 0</td>
<td></td>
<td>41</td>
<td>39</td>
<td>39</td>
</tr>
<tr>
<td>6</td>
<td>0.15</td>
<td>19.6</td>
<td>392 ± 72</td>
<td>4 0 0</td>
<td></td>
<td>50</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>7</td>
<td>0.80</td>
<td>12.5</td>
<td>75 ± 28</td>
<td>0 3 1</td>
<td></td>
<td>54</td>
<td>11</td>
<td>11</td>
</tr>
<tr>
<td>8</td>
<td>0.64</td>
<td>17.2</td>
<td>94 ± 47</td>
<td>0 3 0</td>
<td></td>
<td>68</td>
<td>99</td>
<td>99</td>
</tr>
<tr>
<td>9</td>
<td>0.83</td>
<td>16.8</td>
<td>72 ± 45</td>
<td>0 2 0</td>
<td></td>
<td>44</td>
<td>89</td>
<td>66</td>
</tr>
<tr>
<td>10</td>
<td>0.22</td>
<td>18.3</td>
<td>275 ± 287</td>
<td>2 2 0</td>
<td></td>
<td>66</td>
<td>95</td>
<td>95</td>
</tr>
<tr>
<td>11</td>
<td>0.29</td>
<td>17.3</td>
<td>207 ± 136</td>
<td>1 2 0</td>
<td></td>
<td>52</td>
<td>67</td>
<td>67</td>
</tr>
<tr>
<td>12</td>
<td>0.90</td>
<td>17.8</td>
<td>57 ± 53</td>
<td>0 0 4</td>
<td></td>
<td>73</td>
<td>82</td>
<td>82</td>
</tr>
<tr>
<td>13</td>
<td>1.04</td>
<td>16.3</td>
<td>58 ± 47</td>
<td>1 2 2</td>
<td></td>
<td>66</td>
<td>97</td>
<td>97</td>
</tr>
<tr>
<td>14</td>
<td>0.33</td>
<td>15.3</td>
<td>184 ± 27</td>
<td>1 1 2</td>
<td></td>
<td>73</td>
<td>86</td>
<td>86</td>
</tr>
<tr>
<td>15</td>
<td>0.38</td>
<td>10.6</td>
<td>159 ± 166</td>
<td>2 0 0</td>
<td></td>
<td>51</td>
<td>80</td>
<td>80</td>
</tr>
</tbody>
</table>

Plasma morphine concentrations were low. Fifty-one blood samples were analysed for morphine and 21 of these were below the limit of detection (< 1 ng ml⁻¹), 20 were between 1 and 10 ng ml⁻¹ and 10 were between 10.1 and 20 ng ml⁻¹ (fig. 1).

In the postoperative questionnaires which were completed by those 15 patients who used only extradural PCA, 14 patients rated the pain relief as “very efficient” while one (No. 1) rated the analgesia as “slight”. Three patients each experienced itching, nausea, vomiting and drowsiness.

![Fig. 1. Plasma morphine concentrations during extradural PCA with morphine. The shaded area is the reported mean ± SEM measured plasma morphine concentrations during i.v. PCA with morphine [3].](https://academic.oup.com/bja/article-abstract/60/4/358/246537)
No adverse effects were reported by four patients (table IV).

**Self-administration of pethidine**

PCA lasted for a mean period of 16.4 ± 1.9 h in the pethidine group (table III). All 15 patients achieved subjectively satisfactory analgesia from extradural PCA. Consumption varied between 5.8 and 35.4 mg h⁻¹ (mean dose of 18.0 ± 8.1 mg h⁻¹).

Before PCA, pain assessment was 53.3 ± 16.9 mm on the VAS scale. At the end of extradural PCA, the pain relief was assessed as 74.0 ± 26.0 % reduction of pain, and maximum pain relief recorded was 84.5 ± 17.7 %.

Pethidine consumption tended to be more regular than morphine consumption. The mean
PCA WITH EXTRADURAL OPIOIDS

TABLE IV. Number of patients reporting subjective adverse effects from extradural PCA in the postoperative questionnaire

<table>
<thead>
<tr>
<th>Effect</th>
<th>Morphine group (n = 15)</th>
<th>Pethidine group (n = 15)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nausea</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>Vomiting</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>Drowsiness</td>
<td>3</td>
<td>6</td>
</tr>
<tr>
<td>Accommodation problems</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Dryness of mouth</td>
<td>5</td>
<td>7</td>
</tr>
<tr>
<td>Sense of happiness</td>
<td>0</td>
<td>4</td>
</tr>
<tr>
<td>Unpleasant dreams</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Pleasant dreams</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Itching</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>Leg numbness</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>No adverse effects</td>
<td>4</td>
<td>4</td>
</tr>
</tbody>
</table>

The time interval between self-administered doses was 84 ± 47 min, and the mean coefficient of variation of the time intervals between doses was 39.3 ± 17.5% which was significantly smaller compared with the morphine group. Several of the patients tended to increase their pethidine consumption during the PCA period.

Mean plasma concentrations of pethidine in 15 patients varied between 71 and 567 ng ml⁻¹, and averaged 309 ± 174 ng ml⁻¹ (fig. 2).

All patients rated the pain relief from extradural PCA with pethidine as “very efficient” in the postoperative questionnaire. Four patients did not report any adverse effects. One patient experienced nausea, one vomiting and one vivid dreams. Four patients experienced a sense of happiness and six reported being drowsy. One patient reported leg numbness (patient No. 25, who consumed 35.4 mg h⁻¹). No patient reported itching (table IV).

DISCUSSION

Analgesic effect, dose requirements and adverse effects

Using extradural PCA, all patients but two were able to achieve adequate analgesia in the immediate postoperative period. There was no significant difference in drug induced pain relief between morphine and pethidine. No clinical respiratory depression occurred, in spite of the relatively large doses consumed by some patients.

The adverse effects elicited were minor, and did not affect the popularity of the method. The incidence of adverse effects was similar in the morphine and pethidine groups.

One of the pethidine patients reported numbness of the legs, which was noted during the PCA period and disappeared rapidly. The numbness might have been caused by the weak local anaesthetic action of pethidine [16].

In earlier studies [2,3] i.v. PCA was used after major abdominal surgery when patients consumed morphine 2.6 ± 1.2 mg h⁻¹ and pethidine 26 ± 10 mg h⁻¹, respectively. Thus the extradural morphine consumption in the present study was only 20% of the i.v. consumption, whereas the extradural pethidine consumption was 70% of the i.v. consumption (table V). The differences between i.v. and extradural consumptions for both drugs are statistically significant (P < 0.001 for morphine and P < 0.02 for pethidine).

Analgesia from both morphine and pethidine has been shown to be longer acting when the drugs are administered extradurally compared with systemic administration [17–19]. Morphine is longer acting than pethidine when administered extradurally in doses of 6 mg and 60 mg, respectively [13]. The equianalgesic dose relationship

<table>
<thead>
<tr>
<th>Route of administration</th>
<th>I.v.</th>
<th>Extralural</th>
</tr>
</thead>
<tbody>
<tr>
<td>Morphine consumption (mg h⁻¹)</td>
<td>2.6 ± 1.0</td>
<td>0.52 ± 0.29</td>
</tr>
<tr>
<td>Relative consumption (extradural morphine = 1)</td>
<td>5</td>
<td>1</td>
</tr>
<tr>
<td>Pethidine consumption (mg h⁻¹)</td>
<td>26 ± 10</td>
<td>18.0 ± 8.1</td>
</tr>
<tr>
<td>Relative consumption (extradural morphine = 1)</td>
<td>50</td>
<td>35</td>
</tr>
</tbody>
</table>
between systemic morphine and pethidine is known to be 1:10 [20]. The present study has revealed a relationship of 1:35 after extradural administration. This reflects the closeness of the site of administration to the opioid receptors in the spinal cord, and differences in CSF kinetics and in opioid receptor affinities [21].

The doses of extradural morphine necessary to produce analgesia after abdominal surgery have been reported to be 2–10 mg, with a duration ranging from 4 to 24 h [13,22–24]. The average consumption of morphine during PCA in the present study corresponded to a dose of 12 mg during a 24-h period. The morphine consumption varied five-fold, as did the pethidine consumption. The average consumption of pethidine during PCA corresponded to a dose of 430 mg during a 24-h period. The doses of pethidine consumed during extradural PCA were in accordance with the reported doses of 50–100 mg required to achieve analgesia after abdominal surgery with a reported duration of analgesia ranging from 2 to 10 h [13,25,26]. Although a part of this variability may be accounted for by the pharmacokinetic properties of the drugs, it emphasizes further the differences between individuals in pain perception [27]. The large inter-individual variation makes it impossible to recommend a standard dose of extradural morphine or pethidine for analgesia of predictable duration and with a minimum of adverse effects. Patient-controlled analgesia via the extradural route thus provides an alternative way to give an individualized pain therapy.

Consumption patterns

The consumption patterns during PCA differed in the morphine and pethidine groups. The accumulated doses of two typical patients from the morphine and two from the pethidine group during the PCA period (fig. 3) illustrate that patients self-administering morphine demanded doses at more irregular intervals, as is shown also by the more variable time intervals between doses.

This difference probably reflects differences in CSF kinetics between the two drugs. Morphine is absorbed slowly across the dura, and maximum CSF concentrations are found 60–90 min after extradural injection, whereas pethidine passes the dura more rapidly with maximum CSF concentrations appearing 15–30 min after injection [12]. Because of its lipophilicity, pethidine reaches the receptor sites in the spinal cord more quickly than morphine. This is confirmed by the shorter onset of action of extradural pethidine compared with extradural morphine [22,26]. The slow onset of action of extradural morphine is therefore a disadvantage when the drug is administered by means of PCA.

It is possible that the incremental bolus size of the drugs may influence the total amount consumed during PCA. This is suggested by a pilot
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study in which seven patients were allowed to self-administer 10-mg doses of pethidine extradurally and consumed only $9.7 \pm 5.2 \text{ mg h}^{-1}$ following abdominal surgery [28]. These patients were significantly older ($P < 0.05$) than the patients in the present study, which may account in part for the lower consumption.

CSF and plasma concentrations

The tendency among some of the patients in the pethidine group to increase their consumption during extradural PCA, in addition to the high opioid consumption of some of the patients, may also indicate real differences in single dose and multiple dose kinetics. Only a small fraction, approximately 4%, of an extradural single bolus dose is absorbed to the subarachnoid space [12]. The main fraction of the bolus dose is absorbed rapidly. Because of the large differences in the volumes of distribution [3, 29–31], the concentrations in CSF exceed those in plasma many times. The concentration gradients that result favour the systemic absorption of a second extradural dose. According to this hypothesis, as CSF concentrations gradually increase during repetitive doses, a successively smaller fraction of each dose would be absorbed to the subarachnoid space.

The plasma concentrations were low in the morphine group, and nearly all the measured values were below the reported minimum analgesic concentration of $16 \pm 6 \text{ ng ml}^{-1}$ [3] and 20–40 ng ml$^{-1}$ [32]. It therefore seems safe to conclude that systemic morphine does not contribute to the analgesia.

Minimum effective plasma concentrations of pethidine after i.v. administration have been reported to be 400–500 ng ml$^{-1}$ [2, 33], and this is higher than the mean pethidine plasma concentration achieved during extradural PCA. There was a trend towards increasing plasma concentrations during the PCA period, and systemic pethidine concentrations have probably contributed to the pain relief during the later part of the PCA period.

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REFERENCES


