Extradural sufentanil by patient-controlled analgesia or nurse-administered compared with optimal morphine in a high dependency unit: effects on oxygenation and pain relief after abdominal surgery

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Summary
The incidence of apnoeic episodes (> 12 s) was measured in 30 surgical patients allocated randomly to one of three analgesic regimens and all nursed in a high dependency unit. Ten patients received i.m. morphine (mean 52 (range 30-80) mg), administered on request. The remaining 20 patients received extradural sufentanil as an initial bolus dose of 50 μg followed by a bolus of 10 μg, either self-administered using PCA (10 patients: mean 275 (range 130-450) μg) or administered by a nurse on request (10 patients: 144 (70-200) μg). With i.m. morphine apnoeic episodes were maximal 2–3 h after administration while after extradural sufentanil, apnoeas were maximal within a few minutes. (Br. J. Anaesth. 1994; 73: 634-638)

Key words

Extradural morphine results in respiratory depression occurring unpredictably long after its administration [1, 2]. This late onset is attributed to the low fat solubility of morphine. Morphine persists in slowly circulating cerebrospinal fluid (CSF), with cephalad spread producing late respiratory depression [3]. Opioids with high lipid solubility pass rapidly from the CSF into other tissues leaving little remaining available for cephalad spread [4] but with the potential for significant quantities to pass into the systemic circulation.

Sufentanil is a synthetic opioid related chemically to fentanyl, with a very high lipid solubility (over 1000 times that of morphine). It is the most potent of the commonly available opioids and has a very high affinity for the μ opioid receptor [5], while its clearance from the CSF has been shown in clinical studies to be rapid [6]. The analgesic efficacy of sufentanil has been demonstrated in a range of surgical procedures, from peripheral orthopaedic procedures [7] to thoracic surgery [8]. Thus respiratory depression after extradural sufentanil may have different characteristics from that associated with less soluble agents. A study of extradural sufentanil administered to volunteers demonstrated marked depression of respiration; however, normal volunteer subjects had no pre-existing or background pain [9]. The effect on respiration in postoperative patients has not been studied in detail.

We have developed a respiratory monitoring system which provides continuous "breath-by-breath" recording of respiratory performance. Oxygen saturation, expired carbon dioxide concentration (used only to detect flow) and chest wall movements are recorded to analyse respiratory patterns and apnoeic episodes.

In this study we have compared the respiratory effects of two regimens of extradural sufentanil with nurse-administered i.m. morphine for the treatment of postoperative pain. To obtain comparable analgesia using dissimilar techniques, patients were allowed full access to the allocated analgesic regimen. In one group this was achieved using a patient-controlled analgesia (PCA) device to administer the drug through the extradural catheter (group S-P, sufentanil-PCA). In the group without extradural catheters, morphine was administered i.m. on patient request (group M). To ensure prompt treatment, this was done by the nursing staff in a high dependency unit. To test the efficacy of the nursing system and to enable comparisons to be made, a third group was included in which extradural sufentanil was administered by patient request to a nurse (group S-N, sufentanil-nurse) as for the i.m. morphine group.

Patients and methods
Ethics approval was obtained and informed consent from each patient. Patients were included if aged 18-65 yr, weighing 45–100 kg, of ASA grades I–III and undergoing abdominal surgery involving laparotomy. Patients already receiving opioids or antiemetics were excluded. All patients were nursed in a...
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mination and of the times when apnoeic episodes 

were obtained from prescription records. 

administration times for patients in the other groups 

or more. (3) The times at which successful PGA 

ANALYSIS 

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score (100 = worst pain imaginable). 

since the previous evaluation using a visual analogue 

relief every 2 h for 24 h. They scored the worst pain 

desaturation recurred the treatment was repeated. 

patient in whom arterial saturation decreased to less 

than 85%, for lh and then to withdraw it. If 

asked to administer oxygen by MC mask to any 

patients moved to the high dependency unit (HDU) and 

induced with thiopentone 3– 

5 mg kg

1, a non-depolarizing neuromuscular blocking 

agent was given and the trachea intubated. Mechanical ventilation with nitrous oxide and oxygen was supplemented with i.v. fentanyl (up to 

200 µg) and enflurane. In groups S-P and S-N, an 

extradural catheter was inserted at a level corre-

sponding to the highest dermatome involved in 

skin incision. Early postoperative analgesia was 

provided in the recovery ward by a bolus dose of 

extradural 0.25% bupivacaine 5–10 ml in groups S-

P and S-N, and i.v. morphine as required in group 

M. When they were awake and stable, patients were 

moved to the high dependency unit (HDU) and 

respiratory monitoring was commenced. In groups S-P and S-N an initial dose of sufentanil 50 µg was 

administered when pain returned. Subsequent doses of 10 µg were given either by a Cardiff Palliator with 

a lockout time of 10 min (group S-P) or by the 

nursing staff (group S-N). Group M received i.m. 

morphine 10–15 mg on request, the dose being 

decided by the nursing staff, as is the usual practice 

for this regimen in the HDU. 

Arterial oxygen saturation was monitored con-

tinuously by pulse oximetry (Novametrix 500) with 

the low saturation alarm set at 85%. Movement of 

gas with respiration was recorded by measurement 

of carbon dioxide in gas from a nasal cannula (Datex 

Normocap). This concentration varied reliably be-

between 0 and 4.5% with respiration, even during 

mouth breathing and speech. Chest wall movements 

were detected by differential manometry of pressure 

capsules in the suprasternal notch and lower chest 

wall; the output signal was related to the amplitude 

of chest wall excursion. This was used only to 

indicate chest movement. A continuous paper chart 

recording of these variables was made from arrival in 

the HDU until the end of the study. Nurses were 

asked to administer oxygen by MC mask to any 

patient in whom arterial saturation decreased to less 

than 85%, for 1 h and then to withdraw it. If 

desaturation recurred the treatment was repeated. 

Patients were asked to assess the quality of pain 

relief every 2 h for 24 h. They scored the worst pain 

since the previous evaluation using a visual analogue 

score (100 = worst pain imaginable). 

ANALYSIS 

The 24-h multichannel chart recording was analysed 
to provide the following information. (1) The 

number, times and duration of episodes in which 

arterial saturation decreased to less than 85%. (2) 

The number, times and duration of apnoeas of 12 s 
or more. (3) The times at which successful PCA 
demands were made by patients in group S-P. Drug 
administration times for patients in the other groups 
were obtained from prescription records. 

The record of the exact times of drug adminis-

tration and of the times when apnoeic episodes 
ocurred permitted analysis of the temporal re-

lationship between each administration and the 

subsequent respiratory events. The null hypothesis 
that the observed apnoeas were temporally unrelated 
to administration of analgesic drugs was tested by 
the creation of a computer model (method developed 
by, and Apple Macintosh software available from, 
J.M.S.). For each patient, the times at which posterior cutaneous analgesia was administered were noted. 
The times at which apnoeas occurred were also 

recorded. Data for central and obstructive events 

were considered separately. For each apnoeic event, 
the time elapsed since the most recent administration 
of opioid was calculated (Td-a). All such times from 
each treatment group were pooled and frequency 
distribution histograms of Td-a constructed for each 
type of apnoea in each treatment group. This 
procedure was then repeated 100 times for each 
apnoeic event, replacing the time of the apnoea with 
computer generated random numbers and the results 
averaged into dose to random event times (Td-r). 
The frequency distribution of Td-r was again 
calculated for each treatment group. This 
distribution was therefore that which would be expected 
if the apnoeic events were temporally unrelated to 
administration of opioids. It was then possible to 
compare the distribution of Td-a with that of Td-r 
and draw statistical inferences on differences using 
binomial distribution. Subtraction of the distribu-
tion of Td-r from that of Td-a then produces a 
graph of the amount by which the observed incidence 
of apnoeas exceeds the expected incidence plotted 
against the time elapsed since the most recent dose of 

drug. 

The null hypothesis that the incidence of apnoeas 
with respect to the time since the last dose of opioid 
was not different between groups was tested using 
chi-square for trends [10]. 

Statistically significant differences in visual ana-
logue scores (mean for each patient) and respiratory 
variables (totals for each patient) between groups 
were tested using the Kruskal–Wallis one-way 
ANOVA (for non-parametric independent samples). 
Visual analogue pain scores were also compared 
using the Mann–Whitney U test and from this 
confidence intervals for the difference between 
groups were derived. 

To calculate the power of the study, parametric 
ANOVA was performed using 2 and 27 degrees of 
freedom and the ø non-centrality variable produced 
was calculated [11]. This gave an estimate of power 
using parametric techniques. The power of the 
Kruskal–Wallis test was found by multiplying this 
by 3/n [12]. 

Results 

PATIENT DATA 

Six patients were excluded because of inadvertent 
violation of the study design during administration 
of the anaesthetic (four patients) or failure of local 
anaesthetic to produce a demonstrable extradural 
block in the recovery ward (two patients). The 
treatment allocations of these patients was returned 
to the randomization pool so that at the end of the 
study there were 10 patients in each group. 

Extradural sufentanil vs i.m. morphine 

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Age, weight, sex and operation type distributions of the patients in each of the three groups were similar (table 1). The surgical procedures were biliary, vascular, gynaecological or gastrointestinal.

**DRUG DOSAGE**

Patients in group M received a mean total dose of morphine 52 mg (range 30-80 mg) in the 24-h period. Some of this was given i.v. in the recovery ward (mean 7 (0-12) mg). Patients in group S-P received a mean total dose of sufentanil 275 μg (130-450 μg), whereas patients in group S-N received only 144 μg (70-200 μg). This difference was statistically significantly ($P < 0.02$) (Mann-Whitney).

**APNOEIC EPISODES**

None of the differences in apnoeic episodes between groups was statistically significant. There was no correlation between the total dose of drug administered and total duration of either central or obstructive apnoeas in any of the groups studied. The total number of apnoeas and their durations were similar in each group (table 2). The $\phi$ non-centrality variable produced using parametric ANOVA with 2 and 27 degrees of freedom corresponded to a minimum value for the power of the study of 0.67. Multiplying by $3/\pi$ gives a power of 0.64. From this the probability of a type II error (inappropriately accepting that there is no real difference) is 36%.

**TEMPORAL RELATIONSHIP BETWEEN DOSES AND APNOEIC EVENTS**

The incidence of apnoeas was greater after administration of morphine and sufentanil than would be expected by chance (see method). The time course of the excess of apnoeic events is expressed graphically for each of the treatment groups in figure 1. Time zero in each case is the time at which the drug was given.

In the morphine group the incidence of apnoeas increased steadily to a maximum at about 2 h after administration of a dose of i.m. morphine. The difference between the observed incidence and that expected by chance was highly statistically significant at 90 and 120 min ($P < 0.001$, binomial distribution test for single proportion).

In the sufentanil group the peak incidence of apnoeas occurred within a few minutes of administration of a bolus of sufentanil into the extradural space. By 30 min the incidence had decreased markedly and by 1 h was close to that expected by chance. The initial difference between observed and expected incidences was highly significant ($P < 0.005$, binomial distribution test for single proportion).

The difference in the pattern of apnoeas with respect to time between the morphine and each of the sufentanil groups was found to be significant (group M vs group S-P, group M vs S-N, both $P < 0.001$, chi-square test for trends; group S-P vs group S-N, ns).

**Table 1** Patients characteristics (mean (range) or number) in the PCA sufentanil (group S-P), nurse-administered sufentanil (group S-N) and i.m. morphine (group M) groups

<table>
<thead>
<tr>
<th>Group</th>
<th>n</th>
<th>Sex (M/F)</th>
<th>Age (yr)</th>
<th>Weight (kg)</th>
<th>Abdominal incision upper/lower</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group S-P</td>
<td>10</td>
<td>7/3</td>
<td>50 (26-63)</td>
<td>69 (51-87)</td>
<td>6/4</td>
</tr>
<tr>
<td>Group S-N</td>
<td>10</td>
<td>5/5</td>
<td>51 (28-65)</td>
<td>74 (54-90)</td>
<td>6/4</td>
</tr>
<tr>
<td>Group M</td>
<td>10</td>
<td>6/4</td>
<td>47 (26-64)</td>
<td>66 (45-86)</td>
<td>5/5</td>
</tr>
</tbody>
</table>

**Table 2** Number and total duration of central and obstructive apnoeic episodes during the first 24 h after operation (mean (range)) in the three groups of patients

<table>
<thead>
<tr>
<th>Group</th>
<th>Number</th>
<th>Total duration(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>S-N</td>
<td>29.0 (0-63)</td>
<td>433 (12-1605)</td>
</tr>
<tr>
<td>S-P</td>
<td>25.3 (0-58)</td>
<td>328 (12-768)</td>
</tr>
<tr>
<td>M</td>
<td>26.0 (0-65)</td>
<td>334 (12-816)</td>
</tr>
</tbody>
</table>

**Figure 1** Mean incidence of apnoeas each 30-min interval after each dose of opioid in the morphine (●), PCA sufentanil (○) and nurse-administered sufentanil (●) groups.

**Figure 2** Mean postoperative pain scores, measured by visual analogue scale (VAS, 0-100) in the morphine (●), PCA sufentanil (○) and nurse-administered sufentanil (●) groups. Typical SEM values at 2-24 h were 7.97 for PCA-sufentanil, 7.2 for nurse-administered sufentanil and 7.33 for i.m. morphine.

**VISUAL ANALOGUE SCORES**

Mean pain scores over the 24-h period are shown in figure 2. The calculated power of the conclusion that there was no difference in pain scores was 0.73. From
this the probability of a type II error (inappropriately accepting that there is no real difference) is 27%. The difference between the groups was also tested using the Mann–Whitney test, and confidence intervals generated from this are shown in table 3.

A correlation between total dose of drug administered over 24 h and mean pain score over 24 h was demonstrable in group S-P (Spearman rank correlation coefficient = 0.69, \( P < 0.05 \)). In the morphine group and the other sufentanil group, total drug dose and pain scores were unrelated.

### ARTERIAL SATURATION

In each group, five of 10 patients required supplementary inspired oxygen for episodes (mainly obstructive) in which arterial saturation decreased to less than 85% on more than one occasion. In addition, one patient in group S-N had a self-terminating episode of desaturation immediately after the initial bolus dose of sufentanil 50 μg. He subsequently required no oxygen therapy. In designing the study, it was felt to be unethical to allow hypoxaemia to persist untreated and oxygen was administered as required. The durations of the hypoxaemic episodes were thereby shortened by an unknown amount. No attempt is therefore made to present measured durations of hypoxaemia.

### Discussion

We have found that in patients who received extradural sufentanil for postoperative pain relief, major interference with respiration was common. Compared with that associated with i.m. morphine, it was similar in magnitude but showed a different time course, with the highest incidence of apnoeas occurring much earlier after administration of sufentanil.

Individual 24-h morphine requirements ranged from 30 to 80 mg. These are similar to total doses reported in studies in which PCA i.v. morphine was used and are also within maximum doses prescribed by i.m. regimens (10–15 mg, 4 hourly as required) [13]. In ward practice, compared with HDU, it is usual for patients to receive much less than the maximum permitted dose, and therefore poorer pain relief.

The requirement for extradural sufentanil by continuous infusion has been reported as a 24-h cumulative total dose of 180–300 μg [14] and the duration of a 50-μg bolus was reported as mean 108 min (range up to 240 min) [15]; these data predict a mean 24-h requirement of 200 μg with a range from 90 μg (the upper limit was not stated). Therefore, our study agreed closely with previously published work on dose requirements.

The difference in dose between the two sufentanil groups is difficult to explain. The surgical procedures while not identical, were similar, and even among patients who underwent the same procedure, the trend was preserved. A difference in dosage could occur if nursing staff had been excessively conservative but this was clearly not the case as patients in group S-N reported similar pain scores as those in group S-P. It is likely therefore that patients whose drug was administered by nurses, and who also received much sympathetic reassurance and encouragement at the time the drug was given, especially in the HDU, had less pain and need for drug. This phenomenon was pointed out by Beecher [16] in his earliest observations.

The rapidity and brevity of the respiratory effects of extradural sufentanil compared with those of i.m. morphine are in keeping with its physicochemical characteristics. While sufentanil is cleared rapidly from cerebrospinal fluid [6], minimizing its potential for producing late respiratory depression, it is equally rapidly taken up into blood from the extradural space, making it more likely to produce early respiratory depression. A mean concentration of 1.47 ng ml\(^{-1}\) (SD 2.78 ng ml\(^{-1}\)) was measured in venous blood 2 min after injection of sufentanil 50 μg into the lumbar extradural space in volunteers [9] (assuming a blood volume of 5000 ml) which suggests that on average, more than 10% of the administered dose passes promptly into the bloodstream. Our analysis of the interval between drug administration and apnoeic events confirms that most episodes of interference with respiration occurred within minutes of administration of a bolus of extradural sufentanil.

The clinical significance of disturbances in respiration and hypoxaemia is uncertain although hypoxaemia with saturation less than 85% is usually regarded as severe. No patient experienced prolonged respiratory arrest likely to produce permanent damage or death and no patient required naloxone. However, it was necessary to administer oxygen to several patients in every group to avert unacceptable hypoxaemia.

The incidence of apnoeas after i.m. morphine increased steadily and was maximal at 2 h, probably reflecting the profile of the concentration of the poorly lipid soluble morphine inside the blood–brain barrier.

From this detailed study of a small number of patients in which major but self-terminating apnoeas were demonstrated, no inference can be made on the incidence of major life-threatening respiratory events. To establish with 99% confidence that the incidence of fatal respiratory arrest was less than 0.1%, it would be necessary to study 5000 patients. However, it seems wise to conclude that postoperative oxygen would be a reasonable routine precaution.

### Table 3: Visual analogue pain scores (0–100) (mean (range), No. of individual scores > 50 (where appropriate)) in the three groups of patients. 95% Confidence limits for difference in pain scores (2–24 h): S-P vs S-N = −7.74, +20.23; S-N vs M = −13.4, +11.95; S-P vs M = −10.43, +19.44; (S-P and S-N) vs M = −12.02, +10.47

<table>
<thead>
<tr>
<th>Time (h)</th>
<th>Group S-P</th>
<th>Group S-N</th>
<th>Group M</th>
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<tbody>
<tr>
<td>0</td>
<td>36 (6–84)</td>
<td>23 (0–41)</td>
<td>52 (25–90)</td>
</tr>
<tr>
<td>2–8 h</td>
<td>20 (4–37)</td>
<td>12 (0–90)</td>
<td>28 (4–67)</td>
</tr>
<tr>
<td>9–16 h</td>
<td>28 (0–93)</td>
<td>4 (26–85)</td>
<td>4 (16–40)</td>
</tr>
<tr>
<td>17–24 h</td>
<td>33 (8–90)</td>
<td>21 (0–65)</td>
<td>27 (0–78)</td>
</tr>
<tr>
<td>2–24 h</td>
<td>38 (0–93)</td>
<td>20 (0–85)</td>
<td>23 (0–78)</td>
</tr>
</tbody>
</table>
The methods used for collection of the visual analogue scores were not blind. The power of the study was not sufficient to enable us to state that there was no difference in quality of pain relief between the groups. The 95% confidence intervals of the differences in pain scores were all less than 21% and most were less than 15%.

PCA sufentanil, although requiring a higher dose than nurse-administered extradural sufentanil for a similar degree of pain relief, was not associated with a greater incidence of severe hypoxaemia or apnoea.

References