Comparison of intrathecal fentanyl and diamorphine in addition to bupivacaine for Caesarean section under spinal anaesthesia

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Background. Co-administration of small doses of opioids and bupivacaine for spinal anaesthesia reduces intraoperative discomfort and may reduce postoperative analgesic requirements in patients undergoing Caesarean section. Fentanyl and diamorphine are the two most frequently used agents in UK obstetric anaesthetic practice.

Methods. Seventy-five healthy parturients scheduled for elective Caesarean section under spinal anaesthesia using hyperbaric 0.5% bupivacaine, were randomly allocated to additionally receive intrathecal fentanyl 20 μg, diamorphine 300 μg or 0.9% saline. Patients also received i.v. cyclizine and rectal diclofenac.

Results. Less supplementary intraoperative analgesia was required by patients in either opioid group (4%) compared with the control (32%) (P<0.05). Twenty four hours after spinal injection, total mean (SD) postoperative morphine requirement was significantly lower if diamorphine was administered (31 (21) mg), in comparison with the other two groups (control 68 (26) mg; fentanyl 62 (26) mg) (P<0.05). Reduced visual analogue pain scores were evident 12 h following diamorphine, but observed only for 1 h after fentanyl when compared with the control (P<0.05). Mild pruritis was more common for 2 h after either spinal opioid (P<0.05), but no inter-group differences were observed for the remainder of the first 24 h. Patients displayed deeper levels of sedation both acutely and 12 h after administration of intrathecal fentanyl (P<0.05).

Conclusions. Both intrathecal opioids reduce intraoperative discomfort, but only diamorphine reduced postoperative analgesic requirement beyond the immediate postoperative period.

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Small doses of opioids administered directly into the cerebrospinal fluid (CSF) have been found to be very effective in controlling symptoms of pain in many clinical situations.¹ This technique has also been used in an attempt to minimize discomfort during and after Caesarean section.²⁻⁴ However, beneficial analgesia has to be balanced against known adverse effects, including respiratory depression, emetogenesis and pruritis. With many opioids currently available, agent and dosage selection are known to influence this risk–benefit balance.⁵ Recent work has indicated that intrathecal fentanyl is used by over 40% of UK obstetric anaesthetists; more than twice as frequently as diamorphine.⁶ Both have been investigated in attempts to quantify their most effective doses when used for spinal anaesthesia for elective Caesarean section.⁷ ⁸ However, there appears to be little information on whether one is more suitable than the other in this situation.

The principal objective of our investigation was to compare the postoperative analgesic properties of fentanyl and diamorphine (in conjunction with bupivacaine), when administered at apparently optimum dosage. In the course of the study, we also examined the intraoperative and potential adverse effects of these intrathecal opioids.

Methods

Prior to commencing the investigation, approval was obtained from both the regional ethical and the hospital...
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research committees. Patients were selected from a cohort scheduled for elective Caesarean section, classified as either ASA I or II, and having no specific contra-indications to receiving non-steroidal anti-inflammatory drugs. Written informed consent was obtained from each, after discussing the study objectives, patient-controlled analgesia (PCA) system and rectal diclofenac administration. Participants were randomly allocated to one of control, fentanyl or diamorphine groups using a sealed envelope technique. Patients were premedicated orally with ranitidine 150 mg the night before and 2 h prior to surgery, in addition to receiving 30 ml of 0.3 M sodium citrate immediately before being escorted to theatre.

With the patient in the sitting position, i.v. access was established using a 16-gauge cannula, and a baseline non-invasive arterial pressure measurement taken. A fluid preload of 2 litres of warmed compound sodium lactate solution was then infused intravenously over approximately 10 min, using a pressurized infusion device. After infiltrating the skin and inter-spinous ligament over the L3/4 interspace with 1% lidocaine 2 ml, the subarachnoid space was entered using a 24-gauge pencil-point spinal needle. Once free flow of CSF had been recognized, the intrathecal (i.t.) anaesthetic solution was injected over 20 s, aspirating CSF at the end of the injection to confirm needle position. All patients received 2.75 ml of hyperbaric 0.5% bupivacaine, in addition to 1 ml of unknown adjuvant, constituting a total volume of 3.75 ml. Patients allocated to the control group had 1 ml of 0.9% saline added to their bupivacaine. Similarly, patients in the fentanyl group had 1 ml of fentanyl 20 μg ml⁻¹, and those in the diamorphine group had 1 ml of diamorphine 300 μg ml⁻¹, added to the bupivacaine.

The intrathecal adjuvant solutions were prepared prior to performing the spinal injection by a separate anaesthetist who had no further involvement with each patient. All were prepared under strict aseptic technique, using 0.9% saline where reconstitution and dilution were required. Once prepared, all were deposited into a sterile transparent bag, which was then sealed and labelled with the trial number. The solution was presented in a 2 ml syringe, 1 ml of which was added to the 2.75 ml of bupivacaine. Thus, the anaesthetist who managed each case was unaware of which solution had been administered.

On completion of the spinal injection, the patient was placed in the supine position, with 15° lateral tilt (right hip uppermost). Arterial pressure was measured by an automatic non-invasive monitor at intervals of 1 min, until it became stable. Arterial pressure was monitored at 5-min intervals thereafter until the completion of surgery. If systolic arterial pressure decreased by 30 mm Hg from baseline (or to an absolute value of 90 mm Hg), or if the patient complained of symptoms indicative of incipient hypotension (e.g. nausea), i.v. ephedrine was administered in increments of 6 mg as required.

The level of anaesthesia was deemed adequate for surgery when loss of cold sensation to ethyl chloride spray was evident from dermatomes L2 to T5. If the patient experienced discomfort during surgery, i.v. alfentanil was administered in 250 μg increments as required for relief. After delivery of the neonate and clamping of the umbilical cord, i.v. syntocinon 10 i.u. was given. An attending paediatrician assessed the neonatal Apgar scores at 1 and 5 min after delivery. According to our usual practice, all patients received i.v. cyclizine 50 mg and diclofenac 100 mg per rectum after the completion of surgery. A urinary catheter was left in situ according to our unit policy, to be removed 24 h later.

Immediately following the procedure, patients were transferred to a dedicated recovery ward, and remained there for 1 h. At this point a Graseby 9300 PCA (Watford, Herts, UK) system was attached to a valved Y-connector in the intravenous fluid infusion line, close to the cannula. The PCA was set to deliver a 1 mg bolus of morphine upon demand, with a lock-out time of 3 min and no background infusion. Patients then returned to a six-bedded maternity ward, where they were under constant supervision by a midwife. Anti-emetic (intramuscular (i.m.) cyclizine 50 mg) and anti-pruritic (i.m. chlorpheniramine 10 mg) therapy were also prescribed, to be given every 8 h as required. No other analgesic medication was prescribed for the first 24 h following the spinal injection. After this time, the PCA device could be substituted for analgesics in the form of acetaminophen 1 g and codeine phosphate 8 mg orally 6 hourly, and diclofenac 100 mg per rectum 16 hourly, as required.

Formal assessment of the patients was conducted at 1, 2, 6, 12, and 24 h after the spinal injection. Pain was recorded on a 0–100 mm visual analogue scale (VAS) using a ruler device donated by Napp Pharmaceuticals Ltd. (Cambridge, Cambridgeshire, UK). Nausea and pruritus were assessed on a modified four point ordinal scale.9 Level of sedation was assessed using another four point ordinal scale. Both scoring systems are outlined in Table 1.

Data analysis

After discontinuation of the PCA system, the Graseby 9300 device was interrogated by a link to a desktop computer using Hyperterminal® (Hilgraeve Inc., Monroe, Michigan, USA) supported by Microsoft™ Windows ’98, in order to obtain the hourly morphine consumption data. Based upon previous work,3 a sample size of 25 patients per group was estimated to detect an inter-group difference of morphine 20 mg requirement 24 h after intrathecal injection (α=0.05, β=0.8). Statistical tests were performed using SPSS™ v9.0 and Graphpad Instat™ v3.05 for Microsoft™ Windows ’98, and results are reported as absolute values, mean (SD or 95% confidence intervals), or median (inter-quartile range) or (range) where appropriate. At selected times after surgery, the morphine consumption and VAS pain scores of the three groups were compared using analysis of variance (with Bonferroni post-hoc analysis). Intraoperative ephedrine and...
alfentanil requirements, neonatal Apgar scores, and postoperative patient nausea, pruritis and sedation scores were analysed by a Kruskal-Wallis test (with Dunn’s post-hoc test). Categorical data were examined using \( \chi^2 \) analysis. A \( P \) value of less than 0.05 was considered statistically significant.

Results

Full data collection was achieved for all of the 75 patients that participated in the investigation. There were no differences with regard to patient age, body mass index, or duration of gestation between the three groups. In addition, there was no significant inter-group difference in terms of patients having undergone a previous Caesarean section (Table 2).

Intraoperative analgesic supplementation was required in significantly more of the patients belonging to the control group (8/25; 32%) compared with either of the opioid groups (both 1/25; 4%) (Table 3). However, there were no differences in total amounts of ephedrine required to maintain normotension during the procedure (median values: control, 12 mg; fentanyl, 12 mg; diamorphine, 9 mg). Similarly, the neonatal Apgar scores after 1 and 5 min were no different between groups (median values at 5 min: control, 10; fentanyl, 10; diamorphine, 10), although when assessed after 1 min, four neonates from the fentanyl group and one from diamorphine group had a score of less than 7.

Morphine consumption from the PCA device was examined on a cumulative and hourly basis (Table 4). When 24 h had elapsed after intrathecal injection, patients who received i.t. diamorphine had used significantly less morphine than those in the control and fentanyl groups (mean values: control, 68 mg; fentanyl, 62 mg; diamorphine, 31 mg). Cumulative morphine consumption of patients who received fentanyl was significantly lower than those in the control group until 4 h, but thereafter no significant difference was observed.

Hourly morphine consumption is represented by the 2-h moving average and is illustrated in Figure 1. Patients in the fentanyl group used less analgesia than those in the control group until 4 h, but thereafter no significant difference was observed.

Table 1 Ordinal scales used to assess severity of nausea, pruritis and level of sedation

<table>
<thead>
<tr>
<th>Score</th>
<th>Nausea and pruritis assessment</th>
<th>Sedation assessment</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>no symptoms</td>
<td>awake and alert</td>
</tr>
<tr>
<td>1</td>
<td>mild symptoms, but not requesting treatment</td>
<td>drowsy, but responds to verbal stimulus</td>
</tr>
<tr>
<td>2</td>
<td>moderate symptoms, requesting treatment</td>
<td>drowsy, but responds to physical stimulus</td>
</tr>
<tr>
<td>3</td>
<td>symptoms persisting despite treatment</td>
<td>unresponsive</td>
</tr>
</tbody>
</table>

Table 2 Patient characteristics expressed as mean (SD) and proportions

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Control</th>
<th>Fentanyl</th>
<th>Diamorphine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td>31.5 (4.6)</td>
<td>32.6 (5.0)</td>
<td>30.3 (5.4)</td>
</tr>
<tr>
<td>Body mass index (kg m(^{-2}))</td>
<td>27.4 (3.3)</td>
<td>27.9 (3.6)</td>
<td>27.5 (2.9)</td>
</tr>
<tr>
<td>Gestation (weeks)</td>
<td>38.1 (0.6)</td>
<td>38.0 (0.7)</td>
<td>37.9 (0.9)</td>
</tr>
<tr>
<td>Previous Caesarean section (yes)</td>
<td>68%</td>
<td>52%</td>
<td>76%</td>
</tr>
</tbody>
</table>

Table 3 Intraoperative pain, ephedrine requirements, duration of surgery and neonatal Apgar scores, classified according to intrathecal group. Results are expressed as absolute numbers (%), median [inter-quartile range] or [range]. 

<table>
<thead>
<tr>
<th>Observation</th>
<th>Control</th>
<th>Fentanyl</th>
<th>Diamorphine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Spinal injection to end of surgery time (min)</td>
<td>49 (30-56)</td>
<td>47 (30-50)</td>
<td>42 (25-54)</td>
</tr>
<tr>
<td>Apgar @ 1 min (score)</td>
<td>8 (8-9)</td>
<td>9 (6-10)</td>
<td>9 (6-10)</td>
</tr>
<tr>
<td>Apgar @ 5 min (score)</td>
<td>10 (9-10)</td>
<td>10 (9-10)</td>
<td>10 (9-10)</td>
</tr>
</tbody>
</table>

Table 4 Summary of postoperative morphine requirements, classified according to intrathecal adjuvant. Results are expressed as mean (standard deviation). 

<table>
<thead>
<tr>
<th>Time (h)</th>
<th>Control (mg)</th>
<th>Fentanyl (mg)</th>
<th>Diamorphine (mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td>8.3 (9.3)</td>
<td>3.1 (3.7)</td>
<td>2.9 (2.8)</td>
</tr>
<tr>
<td>6</td>
<td>28.5 (12.7)</td>
<td>24.0 (12.6)</td>
<td>12.5 (10.4)</td>
</tr>
<tr>
<td>12</td>
<td>42.4 (18.3)</td>
<td>38.2 (18.5)</td>
<td>17.7 (12.4)</td>
</tr>
<tr>
<td>24</td>
<td>68.4 (26.6)</td>
<td>61.6 (25.5)</td>
<td>31.3 (21.2)</td>
</tr>
</tbody>
</table>

There were no recorded episodes of respiratory depression (respiratory rate of less than 10 bpm) in any of the patients. In addition, there were no significant differences between patient groups in terms of respiratory rate throughout the 24-h observational period. Other adverse effects (sedation, pruritis, and nausea) were graded according to an ordinal scoring system (Table 1). Sedation appeared to be
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Control
• Fentanyl
• Diamorphine

Fig 1 Hourly morphine consumption in the 24 h following intrathecal injection subclassified by patient group. \( P<0.05 \) vs fentanyl; \( P<0.05 \) vs diamorphine.

Fig 2 Visual analogue pain scores (0–100 mm) in the 24 h following intrathecal injection, subclassified according patient group (central bar, median; box area, inter-quartile range; whiskers, range). \( P<0.05 \) vs fentanyl; \( P<0.05 \) vs diamorphine.

Discussion

This study demonstrated that patients undergoing Caesarean section under spinal anaesthesia experienced less discomfort during the procedure when either fentanyl or diamorphine were added to the intrathecal injectate. However, only the addition of diamorphine significantly reduced the need for further analgesia after surgery.

Patients undergoing Caesarean section under spinal anaesthesia may benefit from the co-administration of local anaesthetic and opioid agents, because of improved intraoperative comfort, apparent prolongation of spinal analgesic action, and reductions in postoperative requirements for additional analgesia. However, these advantages need to be balanced against problems such as pruritis, nausea, sedation and respiratory depression. Fentanyl and diamorphine are the two most frequently used spinal opioids by obstetric anaesthetists in the UK, for several reasons. Both are readily available commercially in a preservative free formulation. Both have sufficient lipid solubility to enable rapid penetration of neuronal tissue, hindering cephalad migration induced by CSF currents, the probable cause of side-effects. Diamorphine undergoes metabolism within spinal cord tissue generating active compounds (6-acetyl morphine and morphine). These metabolites are less lipid soluble than the parent drug, and limit their back-diffusion into the CSF. Both fentanyl and diamorphine have been investigated for use in Caesarean section by dose-finding studies.

Fentanyl has been investigated on a dose per kilogram body weight basis in a study where the average patient weight was 80 kg, which approximated to examining effects following doses of 20, 40 and 60 \( \mu \)g. Intraoperative respiratory depression and increased sedation was observed in those that received 40 \( \mu \)g or more. A further study considered a larger number of possible doses, and showed that even a dose of 6.25 \( \mu \)g was sufficient to prolong spinal analgesic action. Patients who received doses of 12.5 and 25 \( \mu \)g displayed a trend toward lower postoperative analgesic requirements, but did not reach statistical significance. However, patients who received doses of 25 \( \mu \)g (or more) experienced troublesome pruritis. Other workers studied the effects following doses of 15 \( \mu \)g and 25 \( \mu \)g, the latter identifying late-onset increases in postoperative analgesic requirements. These studies seem to indicate that in order to maximize postoperative analgesia, whilst minimizing respiratory depression and pruritis, a dose of 20 \( \mu \)g would appear to be optimal.

Intrathecal administration of diamorphine has also been the subject of dosage analysis. An earlier investigation...
administered doses in 125 μg increments, and found significantly lower postoperative analgesic consumption in patients given 250 or 375 μg, but that the latter group experienced excessive degrees of vomiting and pruritus. A similar study\(^8\) reported lowest analgesic requirements in patients receiving 300 μg, and since this dose did not appear to provoke excessive degrees of pruritus, it was chosen as the optimum dose of diamorphine.

A systematic review of intraoperative analgesia\(^{10}\) identified that approximately 24% of patients that receive only hyperbaric bupivacaine experience unacceptable levels of discomfort during spinal anaesthesia for Caesarean section. The addition of most opioids to the spinal injectate attenuate this effect.\(^{8,16}\) Our investigation found that only 4% (one patient) in either opioid group needed additional analgesia intraoperatively, in contrast to 32% of patients in the control cohort. The number of patients needed to treat with either spinal opioid in order to prevent one patient feeling excessive discomfort is 3.6, indicating a high degree of clinical effectiveness.

When attempting to quantify postoperative analgesic requirements, observation of consumption from a PCA system remains the method least likely to be affected by bias.\(^{18}\) Cumulative morphine consumption, beyond the immediate postoperative period, was significantly lower only in those patients who received diamorphine, when compared with those in either the control or fentanyl groups. Previous studies recognized that diamorphine does possess analgesic sparing qualities,\(^{4,8}\) whilst the findings of others reflect uncertainty over fentanyl’s capacity for similar effects.\(^{3,7,16,17}\) This investigation finds that intrathecal fentanyl does not appear to reduce cumulative analgesic requirements past the point of 4 h.

Analysing the hourly morphine consumption provided additional insight into this finding. Patients in the fentanyl group appear to begin loading themselves with morphine 3 h after spinal injection, only 1 h later than those in the control group. The existence of this extra ‘golden hour’ of analgesia had been noted by previous workers.\(^1,9\) Beyond this 3-h point, the patients in the fentanyl and control groups have no discernible differences in their analgesic requirements. On this evidence, i.t. fentanyl appears to have no long acting analgesic properties. Patients who received diamorphine seem to have a biphasic nature to their analgesic consumption, with one noticeable peak after 5 h, and a second after 20 h, when the requirements of the three groups converge. This represents a significantly lower hourly morphine requirement compared to both the control and the fentanyl groups, and appears to last for up to 19 h following intrathecal administration.

Using a PCA system allows patients to self medicate until they find an individually acceptable level of comfort. Hence, one might not expect to observe any differences in terms of pain experiences. However, the patients’ pain scores also reflect the above pattern of analgesic efficacy, with those who received either opioid in significantly less discomfort when interviewed 1 h after the spinal injection. When interviewed after 2 h, those in the fentanyl group had similar levels of discomfort to those in the control, whilst those in the diamorphine group still complain of less pain. There appears to be no difference between the three groups when questioned after 6 and 24 h, a finding which has been also reported in earlier work.\(^8\) However, the observation after 12 h indicates that the diamorphine group were in significantly less discomfort when interviewed 1 h after the spinal injection. When interviewed after 2 h, those in the fentanyl group had similar levels of discomfort to those in the control, whilst those in the diamorphine group still complain of less pain. There appears to be no difference between the three groups when questioned after 6 and 24 h, a finding which has been also reported in earlier work.\(^8\)

Although opioids confer improved intraoperative (and in the case of diamorphine, postoperative) analgesia profiles,
Concern remains that these may be tempered by an increased incidence of adverse effects.

Respiratory depression is associated with the use of intrathecal narcotics, and analysis of arterial carbon dioxide tension has demonstrated its presence despite a normal respiratory frequency. However, the observation of a lucid patient, breathing at an acceptable rate, currently remains the most clinically applicable method of safeguarding patients from this complication. Previous work has demonstrated that patients undergoing Caesarean section exhibit a degree of resistance to the respiratory depressant effects of intrathecal opioid. This study found that the use of either spinal opioid was not associated with a decreased respiratory rate, in agreement with previous studies.

Acute onset sedation has been previously described in association with i.t. fentanyl, and a non-significant trend toward late onset sedation has also been observed. An increased propensity to develop sedation was observed in those patients who received fentanyl, this being statistically significant when observed after 1 and 12 h. Interestingly, it is after 12 h have elapsed that these patients' use of the PCA device declined slightly (Fig. 2), and may be because they are becoming somnolent. In contrast, patients belonging to the control or diamorphine groups did not appear to develop excessive sedation. This is in keeping with a previous study, with similar findings following 250 μg of i.t. diamorphine.

Itching can be a distressing side effect, which is associated with systemic opioid administration, particularly when given neuraxially. Incidence can be as high as 80%, but symptoms are generally mild in nature. The use of non-steroidal anti-inflammatory drugs in the analgesic strategy has been noted to reduce pruritis in a general surgical setting. However, incidence of itching after spinal opioids in patients following Caesarean section remains high despite this intervention. We found itching was present in significantly more patients 2 h after administration of either spinal opioid (approximately 55%), but in only one of these patients was it severe enough to require anti-pruritic therapy. From 6 h onwards the prevalence was no different when given neuraxially. The use of cyclizine as a prophylactic anti-emetic in all our patients, which has anti-histaminic (H₁) properties.

Spinal opioid use can exacerbate postoperative nausea and vomiting, particularly when used at higher dose regimens. This side effect can also be agent specific, with morphine more likely to induce it than diamorphine. Reported incidences vary from 25% following 12.5 μg i.t. fentanyl, to 70% following 300 μg i.t. diamorphine. This investigation identified no significant differences between any of the groups. The incidence was relatively low, ranging from less than 10% in the 2 h immediately postoperatively, to approximately 20% after 12 h. Prophylactic anti-emetic therapy may have helped to limit nausea, especially in the first 5 h after surgery, a strategy not employed in other studies.

This study found that low doses of either spinal opioid had no adverse impact on neonatal condition, when determined by Apgar scoring, which is in concordance with other investigations.

In conclusion, we found that the inclusion of fentanyl or diamorphine in the subarachnoid injectate enhances intraoperative comfort during Caesarean section, with no undesirable effects on haemodynamic stability or neonatal condition. However, i.t. fentanyl appears to provide only 1 h of additional analgesia over hyperbaric bupivacaine alone, has no long acting analgesic sparing effect, but can predispose to greater depth of sedation. When administered in conjunction with i.v. cyclizine and rectal diclofenac, i.t. diamorphine results in significantly lower analgesic requirements for up to 19 h after surgery, whilst appearing not to cause excessive problems of sedation, itching or nausea. Presently, only 20% of obstetric anaesthetists in the UK add diamorphine to intrathecal bupivacaine, the majority preferring fentanyl or no opioid. In the light of our findings, we suggest that this practice should be reviewed.

References

1 Cousins MJ, Mather LE. Intrathecal and epidural administration of opioids. Anesthesiology 1984; 61: 276–310
3 Shende D, Cooper GM, Bowden MI. The influence of intrathecal fentanyl on the characteristics of subarachnoid block for caesarean section. Anesthesia 1998; 53: 702–10
4 Kelly MC, Carabine UA, Mirakhur RK. Intrathecal diamorphine for analgesia after caesarean section. Anaesthesia 1998; 53: 231–7
13 Florez J, McCarty LE, Borison HL. A comparative study in the cat
of the respiratory effects of morphine injected intravenously and into the cerebrospinal fluid. *J Pharmacol Exp Ther* 1968; **163**:448–55


17 Cooper DW, Lindsay SL, Ryall DM, Kokri MS, Eldabe SS, Lear GA. Does intrathecal fentanyl produce acute cross-tolerance to i.v. morphine. *Br J Anaesth* 1997; **78**:311–3

18 Husaini SW, Russell IF. Intrathecal diamorphine compared with morphine for postoperative analgesia after Caesarean section under spinal anaesthesia. *Br J Anaesth* 1998; **81**:135–9


22 Hallworth SP, Fernando R, Bell R, MG Parry, Lim GH. Comparison of intrathecal and epidural diamorphine for elective Caesarean section using a combined spinal-epidural technique. *Br J Anaesth* 1999; **82**:228–32