British Journal of Anaesthesia **91 (3)**: 368–72 (2003)
DOI: 10.1093/bja/aeg197

BJA

Minimum dose of intrathecal diamorphine required to prevent intraoperative supplementation of spinal anaesthesia for Caesarean section

S. Saravanan[1], A. P. C. Robinson[1], A. Qayoum Dar[2], M. O. Columb[3] and G. R. Lyons[1]*

[1]Obstetric Anaesthesia, St James's University Hospital, Leeds, UK.
[2]Sheri Kashmir Institute of Medical Sciences, Srinagar, Kashmir. [3]Anaesthesia and Intensive Care, South Manchester University Hospital, Withington, UK

**Corresponding author: Department of Anaesthesia, St James's University Hospital, Leeds LS9 7TF, UK. E-mail: glyons@blocked.org*

Background. Intraoperative discomfort during spinal anaesthesia for Caesarean section is the commonest cited anaesthetic cause of litigation in obstetric practice. Intrathecal opioids are used to improve intraoperative comfort and postoperative analgesia for these operations. The minimum intrathecal diamorphine dose that prevents intraoperative supplementation requires determination.

Method. After ethics committee approval, 200 ASA I, II women with ⩾37 weeks gestation and planned for elective Caesarean section under combined spinal–epidural anaesthesia were recruited. They were randomized into four groups to receive hyperbaric bupivacaine 0.5% 12.5 mg with diamorphine 0.2, 0.3, 0.4 or 0.5 mg by intrathecal injection. The need for intraoperative i.v. supplementation with alfentanil, time to first requests for postoperative analgesia, incidence of nausea and vomiting and requirement for antiemetic and antipruritic were noted.

Results. Intraoperative supplementation was inversely proportional to the dose of diamorphine used (P=0.004). The ED_{95} value for intrathecal diamorphine to prevent intraoperative supplementation was 0.39 mg. Mean time interval for request for postoperative analgesia was 446 min in the 0.2 mg group, 489 min in the 0.3 mg group, 601 min in the 0.4 mg group and 687 min in the 0.5 mg group (P=0.003 for trend). Incidence of nausea, vomiting and pruritus increased with dose of diamorphine used (P values for trend: nausea, 0.04; vomiting, 0.008; pruritus, 0.004). Requests for antiemetic increased with dose but achieved significance only for requirement for second antiemetic (P=0.03). Request for antipruritic did not achieve significance.

Conclusion. The ED_{95} for the amount of intrathecal diamorphine required to prevent intraoperative supplementation during spinal anaesthesia for Caesarean section is 0.4 mg in clinical terms. Times to first requests for analgesia, incidence of nausea, vomiting and pruritus increase with dose.

Br J Anaesth 2003; **91**: 368–72

Keywords: anaesthetic techniques, intraoperative supplementation; anaesthetic techniques, minimum dose; anaesthetic techniques, subarachnoid; analgesics opioid, diamorphine

Accepted for publication: May 9, 2003

Pain during regional anaesthesia for Caesarean delivery is the most commonly cited anaesthetic cause of litigation in obstetric practice.[1] The use of spinal (epidural and intrathecal) opioids to control postoperative pain has become established practice in recent years and increasingly they are also being used to improve intraoperative comfort. Diamorphine is licensed for use in the UK but not for intrathecal use. Despite this, it is widely used in obstetric practice and its safety and efficacy as a postoperative analgesic have been investigated extensively.[2–5] Diamorphine is a lipophilic opioid which diffuses out of the cerebrospinal fluid soon after administration.[6] As there

is little drug available for rostral spread, diamorphine is unlikely to produce delayed respiratory depression. The lipophilic nature of diamorphine should promote rapid onset of analgesia after spinal administration.[7]

The ability of intrathecal diamorphine to improve perioperative comfort has been demonstrated, but to date the emphasis has been on identifying an optimal dose for postoperative analgesia after Caesarean delivery. Intraoperative supplements were required in 30–50% of women given hyperbaric bupivacaine 0.5% 2.0–2.6 ml for spinal anaesthesia at Caesarean section,[2 8] but if diamorphine 0.125–0.25 mg was given in addition the incidence fell to 10%.[2] In a retrospective audit of 400 cases of elective Caesarean delivery in our unit using a combination of heavy bupivacaine 12.5 mg with diamorphine 0.2 mg, 17% of women required intraoperative i.v. alfentanil supplementation. In a pilot study of 40 patients, increasing the dose of intrathecal diamorphine to a maximum of 0.5 mg abolished the need for i.v. supplementation but at the expense of increasing nausea, vomiting and pruritus.[3] Within the diamorphine dose range of 0.2–0.5 mg, there may be a dose that would reduce the need for intraoperative supplementation to a clinically acceptable level. The aim of this study was to identify the lowest dose of intrathecal diamorphine for use during spinal anaesthesia for Caesarean section that reduced intraoperative analgesic supplementation below 5%.

Method

This was a randomized, prospective, double-blind study. After ethics committee approval, women who had completed 36 weeks of pregnancy and were scheduled for elective Caesarean section under regional anaesthesia were recruited. Written informed consent was obtained at a preoperative visit the day before. Women >180 cm or <150 cm in height, >110 kg or <50 kg in weight or having an allergy to diclofenac were excluded.

Women were randomized according to a computer-generated code into four groups to receive intrathecal diamorphine 0.2, 0.3, 0.4 or 0.5 mg in combination with hyperbaric bupivacaine 12.5 mg. The anaesthetic management of the women was standardized. Premedication consisted of lansoprazole 30 mg given orally 90 min before operation and 30 ml of 0.3 M solution of sodium citrate in the anaesthetic room. Standard monitoring included continuous electrocardiogram, pulse oximetry and non-invasive blood pressure monitoring. A fluid preload of colloid 500 ml was administered via a 16 gauge i.v. cannula over 10–15 min during preparation for regional anaesthesia. A two-space combined spinal epidural technique was used. An epidural catheter was sited in the second lumbar interspace in the sitting position. An i.v. test dose of lidocaine 1 mg kg^{-1} was administered before the catheter was fixed in place. Spinal anaesthesia was performed via the third lumbar interspace using a 27 gauge pencil point needle.

Diamorphine was prepared under aseptic precautions in a fixed volume (0.5 ml) of normal saline by an anaesthetist who was not subsequently involved in the study. This was added to the of hyperbaric bupivacaine 0.5% 2.5 ml w/v so that each woman received an intrathecal injection of 3.0 ml. After this, the women were helped to lie supine with a left lateral tilt. Another 500 ml of colloid containing ephedrine 30 mg was connected to the i.v. cannula and titrated against the mean arterial blood pressure. Hypotension was recorded when the mean arterial blood pressure fell to <80% of the baseline recording. Anaesthesia was considered adequate when a sensory level to light touch was obtained at the fifth thoracic dermatome (T5) or above. Women failing to reach this level of anaesthesia were withdrawn from the study and further local anaesthetic was administered via the epidural cannula according to our standard practice.

Women were encouraged to report discomfort at any time during the procedure. If it happened, supplementary analgesia was offered. If felt needed and accepted by the patient, aliquots of alfentanil 0.25 mg were administered i.v. as required. At delivery of the baby a slow bolus of oxytocin 10 U was administered i.v. and an umbilical blood sample was collected for gas analysis. On completion of surgery, all women received diclofenac 100 mg per rectum. The duration of the procedure was taken as the time from spinal injection to the last abdominal suture.

All women were observed in the postanaesthetic care room on the delivery suite for a period of 2–3 h and on a general postnatal ward thereafter, with monitoring of vital signs as for any other routine operation. Epidural catheters were removed in the postanaesthetic care room before the women were taken to the postnatal ward. Women were followed up by a blinded observer 1, 2, 4, 8 and 24 h after operation to monitor requests for analgesia and record the prevalence of nausea, vomiting and pruritus. Times to first analgesia and requests for antiemetic and antipruritic medication were recorded. We used a standard on-request regime for postoperative medication.

A combination of oral paracetamol 1 g with codeine phosphate 60 mg, 4-hourly to a maximum of four times in 24 h and diclofenac 50 mg 8-hourly to a maximum of 150 mg in 24 h, was given for analgesia. Women requesting analgesia in the recovery room received bupivacaine 0.25% 10 ml w/v via their epidural catheter. Intramuscular prochlorperazine 12.5 mg 8-hourly was the first-choice antiemetic and ondansetron 4 mg i.v. was used as rescue if prochlorperazine failed to control nausea and vomiting. Subcutaneous nalbuphine 10 mg 8-hourly to a possible maximum of 30 mg was given as an antipruritic.

The following observations were recorded: need for i.v. intraoperative supplementation (incidence and amount of alfentanil used); hypotension; umbilical blood gas analysis; duration of procedure; postoperative requests for analgesia, time to request for first analgesia; prevalence of nausea,

Table 1 Patient characteristics. Results are mean (SD), or median (range)

	Diamorphine dose (mg)			
	0.2 (*n*=50)	**0.3 (*n*=50)**	**0.4 (*n*=50)**	**0.5 (*n*=50)**
Women achieving anaesthesia to T5 (*n*)	42	47	48	49
Age (yr)	29.6 (5.0)	29.2 (4.7)	29.8 (6.6)	29.4 (5.4)
Height (cm)	161 (7)	160 (7)	161 (7)	160 (7)
Weight (kg)	76 (14)	77 (13)	77 (16)	81 (15)
Gestation (weeks)	38 (36–42)	38 (36–41)	38 (36–42)	38 (37–41)
Nulliparas/multiparas (*n*)	9/41	13/37	11/39	10/40

Table 2 Operative and analgesic details of women achieving anaesthesia to the T5 dermatome. Results are mean (SD) or median (range). *Expanded Fisher's exact test; †analysis of variance. NS=not significant

	Diamorphine dose (mg)				***P***
	0.2 (*n*=42)	**0.3 (*n*=47)**	**0.4 (*n*=48)**	**0.5 (*n*=49)**	
Women requesting intraoperative alfentanil (*n*)	8	6	3	0	0.0046*
Hypotension (*n*)	22	26	23	30	NS
Duration of operation (min)	56 (15)	58 (14)	61 (10)	59 (15)	NS
Umbilical artery pH	7.27 (7.12–7.37)	7.27 (7.05–7.39)	7.28 (7.06–7.38)	7.27 (7.03–7.45)	NS
Women with no analgesic request in 1st 24 h (*n*)	2	1	5	5	NS
Time to first analgesia (min)	446 (407)	489 (377)	601 (405)	668 (396)	0.03†

vomiting and pruritus; and requests for antiemetic and antipruritic (time to first and number of times required).

Statistical analysis

Patient characteristics were compared using analysis of variance, the Mann–Whitney test and χ^2 analysis where appropriate. Primary outcome data were subjected to both intention-to-treat and treatment analyses. The association of dose with efficacy was tested using the Fisher-Freeman–Halton exact test. The Armitage test for trend was used to assess dose-dependency. Probit regression was used to estimate the effective dose in 95% of subjects (ED_{95}), with 95% confidence intervals (CI). Further analysis of analgesic details and side-effects included the χ^2 test for linear trend. Two-sided $P<0.05$ was defined for significance. Software used was Excel XP (Microsoft) and SPSS version 10.0 (SPSS, Chicago, IL, USA).

The primary outcome variable was defined as the need for intraoperative supplementation, and the sample size of 50 for each group was determined using pilot study data. A four-group study design required at least 190 subjects to detect an effect size of 0.24 as significant at $P<0.05$ with power >0.8.

Results

The personal and obstetric characteristics of the 200 women recruited to the study were similar between the four groups (Table 1). Fourteen women failed to reach the required T5 level of anaesthesia at the start of surgery, leaving 186 for analysis. The number of women achieving anaesthesia to T5 increased in proportion to diamorphine dose, but the numbers in each group did not reach statistical significance (expanded Fisher's exact test, $P=0.056$). The operative and analgesic details of women achieving anaesthesia to the T5 dermatome are given in Table 2. There were no significant differences between the groups with respect to the incidence of hypotension, duration of operation or fetal outcome, as measured by umbilical artery pH. However there was a significant reduction in requests for intraoperative supplementation. In particular, no requests were made by women who had received diamorphine 0.5 mg. The ED_{95} (95% CI) of intrathecal diamorphine to provide intraoperative comfort in combination with hyperbaric bupivacaine 12.5 mg was 0.39 mg (95% CI 0.325–0.551 mg).

Intention-to-treat analysis of the effect of diamorphine on supplement requirements ($n=200$) gave a highly significant inverse association (χ^2 test, $P=0.0001$) between the dose of intrathecal diamorphine and the number requiring supplementation, and this relationship was dose dependent (χ^2 for linear trend, $P<0.0001$). There was a 6% (95% CI 3–10%) decrease in the requirement for intraoperative supplementation for each 0.1 mg increment in diamorphine dose.

The number of study women with no analgesic request in the first 24 h was not significantly different between groups, but the time to requesting first analgesia was. It varied from

Table 3 Postoperative side-effects in women receiving intrathecal diamorphine. *Data were missing for four women failing to achieve T5 anaesthesia; †χ^2 test for linear trend

	Diamorphine dose (mg)				*P* value for trend†
	0.2 (*n*=46)*	0.3 (*n*=50)	0.4 (*n*=50)	0.5 (*n*=50)	
Nausea (*n*)	19	24	28	30	0.04
Vomiting (*n*)	13	22	26	27	0.008
Antiemetic requested (*n*)	7	12	12	17	0.04
Second antiemetic required (*n*)	0	0	1	4	0.009
Pruritus (*n*)	34	38	40	48	0.004
Antipruritic requested (*n*)	7	11	5	10	NS

446 min in the diamorphine 0.2 mg group to 668 min in the 0.5 mg group (Table 2). This again was dose-dependent (*P*=0.03).

The postoperative side-effects in women receiving intrathecal diamorphine are summarized in Table 3. Nausea, vomiting, antiemetic requests and pruritus all increased in a dose-dependent manner with increasing diamorphine. *P* values for these outcomes were 0.04 for nausea, 0.008 for vomiting and 0.04 for antiemetic requests (χ^2 test for linear trend).

Discussion

This study demonstrates an inverse dose-dependent effect of diamorphine on the need for intraoperative supplementation that was statistically significant. In absolute terms, the dose of intrathecal diamorphine that reduced the intraoperative supplementation rate to <5% was 0.5 mg, but this does not necessarily reflect the ED_{95} value. None of the patients in this group required supplementation. If regression analysis is used to derive the ED_{95}, the value obtained is 0.39 mg, which is equivalent to diamorphine 0.4 mg in clinical terms. The aim of our study was to determine the lowest dose of intrathecal diamorphine that achieved an intraoperative supplementation rate of <5%, and our interpretation of the results brings us to select the derived dose of 0.4 mg. The incidence of nausea, vomiting and pruritus also increased with the dose. In choosing the lower of the two successful doses, we hoped to achieve a better balance of efficacy with side-effects.

At the conclusion of this study we adopted 0.4 mg for routine spinal anaesthesia for Caesarean section. After this, a retrospective analysis of 100 consecutive spinal anaesthetics showed that i.v. supplementation was required in 2%. This reinforced our decision to choose 0.4 mg.

Three previous dose-finding studies have examined various doses of intrathecal diamorphine in spinal anaesthesia for Caesarean section, but from the point of view of postoperative pain. Skilton and colleagues[4] studied three diamorphine doses: 0.1, 0.2 and 0.3 mg. Similarly, Kelly and colleagues[2] studied the three diamorphine doses of 0.125, 0.25 and 0.375 mg. Stacey and colleagues[9] compared diamorphine 0.5 and 1 mg.[9] All reported improved postoperative analgesia as the dose increased, without evidence of a ceiling effect for analgesia. However, Stacey and colleagues found that a ceiling effect for the incidence of nausea, vomiting and pruritus was reached between 0.5 and 1 mg.

The message from the above studies is that further improvements in post-Caesarean section analgesia might be available from diamorphine doses in excess of 1 mg. The limiting step in the escalation of dose would seem to be the onset of respiratory depression, and none of these studies provide us with convincing information on this. Consequently, despite the wealth of data, we are given no rationale for the selection of the dose which might provide the best balance of efficacy with side-effects.

Our basis for selecting a dose of intrathecal diamorphine was to determine the ED_{95} for the elimination of intraoperative supplementation. Kelly and colleagues reported no i.v. supplementation in their 0.375 mg group, but their sample size was not designed for this outcome. However, their results are compatible with ours. If diamorphine 0.4 mg is selected as the intrathecal dose, we might expect the intraoperative supplementation rate to be <5%, the mean time to first request for analgesia to be 10 h, the incidence of nausea and vomiting to be 56%, and that of pruritus of any degree to be 80%.

A dose of 0.5 mg might yield a small improvement in terms of intraoperative supplementation and will extend the time to first analgesic request by 10%, and the incidence of nausea, vomiting and pruritus will similarly increase in a dose-dependent manner. Nausea and vomiting are particularly distressing side-effects and could represent the limiting step in the use of intrathecal diamorphine. Our incidence of 56% was disappointing, and this requires further attention. As a first step, we have dispensed with prochlorperazine and adopted cyclizine as our first-line antiemetic.[10]

The choice of the two-space combined spinal–epidural anaesthetic technique is in view of the evidence of a 4% incidence of failure of the spinal component for the double space technique compared with 16% for the needle-through-needle technique.[11]

The physicochemical properties of analgesics which confer advantages in intrathecal administration are high lipid solubility and low pKa. The lipid partition coefficient for diamorphine is 280 as opposed to 813 for fentanyl,[7] two commonly used agents for intrathecal use in the UK.[2] Fentanyl has a latency of 6–9 min for onset of analgesia.[7] Although diamorphine has a lower lipid partition coefficient than fentanyl, the shape of the lipid solubility curve when plotted against onset time means that the difference between onset times of the two drugs is very small.[7] Fentanyl has a pKa of 8.4 compared with 7.6 for diamorphine, and this lower pKa of diamorphine allows a higher proportion of active, non-ionized base of 34% compared with fentanyl's 8% at physiological pH.[7] This accounts for the similar latent period of onset of analgesia for the two drugs despite the higher lipid solubility of fentanyl.[7] Consequently, intrathecal diamorphine is effective quickly enough to be of value in Caesarean section. The advantage over fentanyl is the longer duration of action, as shown by Cowan and colleagues.[12] They found lower visual analogue scores at 12 h with diamorphine, and postoperative analgesic requirements were less with diamorphine than with fentanyl. Morphine has latency of 30–60 min for onset of analgesia, in keeping with the lower lipid solubility of 1.4,[7] but it has a longer duration of action of 19–20 h.[13] For this reason, a combination of fentanyl and morphine is sometimes used to achieve both a shorter onset period and a longer duration of action. Diamorphine combines the advantageous effects of these two drugs by virtue of its physical properties.[12 14]

One possible weakness of the study design is the subjective nature of the interaction between the patient and anaesthetist, which determined whether an i.v. supplement was given. Humanitarian considerations made this unavoidable. Any subjective influences would have spread equally across the groups, and the relatively large size of the groups should have suppressed this problem. The idea of patient-controlled analgesia to counter the above weakness is well taken, and this would have removed subjective influences. In defence of our design, we wish to point out that our aim was to reduce i.v. supplementation to $\leqslant 5\%$. To be certain that we achieved our aim it was necessary to remain with anaesthetist-administered supplements.

We conclude that the ED_{95} of intrathecal diamorphine for intraoperative analgesia in spinal anaesthesia for Caesarean section is 0.4 mg. Nausea, vomiting and time to postoperative analgesia increase with the dose. Further attention to reduce the incidence of nausea and vomiting is required and the issue of the contribution of intrathecal opioid to final block height is currently being addressed.

References

1 Bogod D. Medico-legal implications. In: Reynolds F, eds. *Regional Anaesthesia in Obstetrics—A Millennium Update*. London: Springer Verlag, 2000; 375–7

2 Kelly MC, Carabine UA, Mirakhur RK. Intrathecal diamorphine for analgesia after caesarean section—a dose finding study and assessment of side-effects. *Anaesthesia* 1998; **53**: 231–7

3 Morris J, Lyons G, Dresner M, Wilson R. Intrathecal diamorphine in combination with bupivacaine for anaesthesia for elective caesarean section—a dose finding study. *Int J Obstet Anaesth* 1997; **6**: 201–2

4 Skilton RWH, Kinsella SM, Smith A, Thomas TA. Dose response study of subarachnoid diamorphine for analgesia after elective caesarean section. *Int J Obstet Anaesth* 1999; **8**: 231–5

5 Dahl JB, Jeppesen IS, Jorgensen H, Wetterslev J, Moiniche S. Intraoperative and Postoperative analgesic efficacy and adverse effects of intrathecal opioids in patients undergoing caesarean sections under spinal anaesthesia: a qualitative and quantitative systemic review of randomised clinical trials. Review article. *Anesthesiology* 1999; **91**: 1919–27

6 Moore A, Bullingham R, McQuay H, Allen M, Baldwin D, Cole A. Spinal fluid kinetics of morphine and heroin. *Clin Pharmacol Ther* 1984; **35**: 40–5

7 Holdcroft A, Thomas TA. Regional anaesthetic techniques. In: *Principles and Practice of Obstetric Anaesthesia and Analgesia*. Oxford: Blackwell Science, 2000; 243

8 Alahuhta S, Kangas-Saarela T, Hollmen AI, Edstrom HH. Visceral pain during caesarean section under spinal and epidural anaesthesia with bupivacaine. *Acta Anaesthesiol Scand* 1990; **34**: 95–8

9 Stacey RGW, Jones R, Kar G, Poon A. High dose intrathecal diamorphine for analgesia after caesarean section. *Anaesthesia* 2001; **56**: 54–60

10 Dill-Russel P, Stacey RGW. Intrathecal opioids and emesis. *Int J Obstet Anaesth* 2001; **10**: 254–5

11 Lyons G, MacDonald R, Mikl B. Combined epidural/spinal anesthesia for caesarean section. Through the needle or in separate spaces? *Anaesthesia* 1992; **47**: 199–201

12 Cowan C M, Kendall J B, Barclay PM, Wilkes R G. Comparison of intrathecal fentanyl and diamorphine in addition to bupivacaine for caesarean section under spinal anaesthesia. *Br J Anaesth* 2002; **89**: 452–8

13 Milner AR, Bogod DG, Harwood RJ. Intrathecal administration of morphine for elective caesarean section. *Anaesthesia* 1996; **51**: 871–3

14 Roulson C, Chan A, Albin M, Carli F. Intrathecal morphine or diamorphine for caesarean section? Preliminary findings. *Int J Obstet Anaesth* 1994; **3**: 173