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Does intrathecal fentanyl produce acute cross-tolerance to i.v. morphine?

D. W. COOPER, S. L. LINDSAY, D. M. RYALL, M. S. KOKRI, S. S. ELDABE AND G. A. LEAR

Summary

We have examined the hypothesis that intrathecal fentanyl at operation can increase postoperative i.v. morphine requirements. We studied 60 patients undergoing Caesarean section. All received intrathecal 0.5% plain bupivacaine 2 ml combined with either fentanyl 0.5 ml (25 μg) (group F) ($n=30$) or normal saline 0.5 ml (group S) ($n=30$). In addition, 10 ml of an extradural solution (fentanyl 1 ml (50 μg) combined with 0.5% bupivacaine 9 ml) was administered after delivery. Extradural solution was only given before delivery if the intrathecal injection failed to produce a block above T6 or the patient required further analgesia. Postoperative analgesia was provided with i.v. morphine patient-controlled analgesia. At operation, intrathecal fentanyl reduced the need to administer extradural solution before delivery, increased the anaesthetist's satisfaction with analgesia and reduced nausea, but increased pruritus. Up to 6 h after delivery there was no difference in postoperative morphine requirements or pain scores. Between 6 h and 23 h there was a 63% increase in morphine requirements in group F. We consider the most likely explanation for this finding to be that intrathecal fentanyl induced acute spinal opioid tolerance. (*British Journal of Anaesthesia* 1997; **78**: 311–313).

Key words

Anaesthetic techniques, extradural. Anaesthetic techniques, intrathecal. Anaesthesia, obstetric. Anaesthetics local, bupivacaine. Analgesics opioid, fentanyl. Analgesics opioid, morphine. Pain, postoperative. Potency, analgesic. Potency, drug, tolerance.

A prospective audit of postoperative i.v. patient-controlled analgesia (PCA) at our institute produced an unexpected observation. During the first 24 h after regional anaesthesia for Caesarean section, the dose of morphine was 47% greater for patients who had received intrathecal fentanyl at operation compared with those who had not. This led us to hypothesize that intrathecal fentanyl at operation can increase postoperative i.v. morphine requirements. In order to examine this hypothesis we have conducted a controlled study.

Methods and results

This randomized, double-blind study was approved by the local hospital Ethics Committee. After obtaining informed consent we studied 60 ASA I–II patients undergoing morning elective Caesarean section.

Combined intrathecal and extradural analgesia was performed at L3–4 or an adjacent space. Patients received 0.5% plain bupivacaine 2 ml intrathecally combined with either fentanyl 0.5 ml (25 μg) (group F) ($n=30$) or normal saline 0.5 ml (group S) ($n=30$). The intrathecal solution was prepared by an anaesthetist who was not involved with patient management.

The extradural solution (10 ml) was prepared by combining fentanyl 1 ml (50 μg) with 0.5% bupivacaine 9 ml. This was administered between delivery and the end of operation when block regression would allow. Increments were only given before delivery if the intrathecal injection failed to produce a block above T6 or the patient required further analgesia. Additional extradural solution, consisting of 0.5% bupivacaine without fentanyl, could also be administered to achieve adequate block. If additional analgesia was needed after delivery then i.v. alfentanil was given as required. At the end of operation patients received rectal diclofenac 100 mg, unless contra–indicated. I.v. morphine was available via a disposable PCA device. This delivered a maximum bolus of 1 mg with a 5-min chamber refilling time. No more diclofenac was given before completion of the study at 10:00 on the first morning after operation.

At the end of operation the volume and timing of extradural solution given were recorded. The most severe pain experienced during operation was assessed using a visual analogue score for pain (VAS) (100-mm scale: 0 = no pain, 100 mm = worst pain imaginable). The presence or absence of nausea, vomiting, pruritus and drowsiness during operation was assessed by the patient. Pruritus and drowsiness were graded as mild, moderate or severe. Both the anaesthetist and the patient made a verbal rating score (VRS) for satisfaction with analgesia during operation (0 = excellent, 1 = good, 2 = fair, 3 = poor).

The amount of morphine self-administered was

DAVID W. COOPER, MB, BS, FRCA, SUSAN L. LINDSAY, MB, BS, FRCA, DAVID M RYALL, MB, CHB, FRCA, MANMOHAN S. KOKRI, MB, BS, FRCS, FRCA, SAMEH S. ELDABE, MB, CHB, FRCA, GARY A. LEAR, MB, CHB, FRCA, Department of Anaesthetics, South Cleveland Hospital, Middlesbrough, Cleveland TS4 3BW.
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Table 1 Postoperative morphine requirements, pain scores and overall side effects (median (interquartile range) or percentage). ⋆$P<0.05$ (Mann-Whitney); †$P<0.05$ (Kruskal-Wallis)

	Morphine (mg h^{-1})				
	0–3 h	3–6 h	6–23 h		
Group F	0.7 (0.0–2.0)	2.7 (1.3–4.0)	3.1 (1.9–4.8)⋆		
Group S	1.0 (0.2–2.0)	2.7 (2.0–4.0)	1.9 (1.5–2.3)		
	Pain scores (mm)				
	REC	3 h	6 h	10 h	23 h
At rest					
Group F	0 (0–2)	5 (0–15)	26 (10–34)	23 (7–34)	30 (11–50)
Group S	0 (0–8)	3 (0–20)	12 (1–25)	23 (8–38)	24 (5–30)
On coughing					
Group F	1 (0–10)	10 (1–27)	33 (11–58)	32 (14–56)	33 (21–59)
Group S	0 (0–11)	16 (1–43)	27 (21–44)	34 (25–52)	32 (21–57)
	Side effects (%)				
	Nausea	Vomiting	Pruritus	Drowsiness	
Groups F/S					
During operation	27/57 †	7/20	60/7†	43/20 $P=0.06$	
In recovery (REC)	7/3	0/0	63/13†	40/20 $P=0.09$	
REC–3 h	10/7	3/4	63/41†	47/26	
3–6 h	17/14	7/0	30/34	62/59	
6–10 h	34/41	14/21	38/43	79/56	
10–23 h	35/27	14/12	69/65	83/59	

recorded at 3, 6 and 10 h after delivery and at 10:00 on the first morning after operation. VAS at rest and on coughing was recorded in recovery at 15 min after operation (REC), at 3, 6 and 10 h after delivery and at 10:00. Assessments of side effects were made in recovery and for the periods REC–3 h, 3–6 h, 6–10 h and 10 h–10:00. A VRS for satisfaction with postoperative analgesia was recorded at the end of the study.

A computer package (SPSS) was used for statistical analysis. Results were compared using Mann–Whitney and Kruskal–Wallis tests, with $P<0.05$ taken as significant.

Two groups of 30 patients were studied. They were matched for age, height, weight, previous Caesarean section, duration of operation, tubal surgery and duration of study. Group F received a similar total dose of extradural solution (median 10 (interquartile range (IQR) 10–10) ml) as group S (10 (IQR 10–10) ml). However, before delivery, less extradural solution was given in group F; 17% of group F received extradural supplementation (5 (IQR 3–11) ml) compared with 40% of group S (9 (IQR 5–10) ml) ($P<0.05$, Mann–Whitney). I.v. alfentanil was given to 7% of patients in group F compared with 23% in group S ($P=0.07$, Kruskal–Wallis). Median pain scores for the most severe pain experienced during operation were 0 (IQR 0–13) mm for group F and 6 (IQR 0–18) mm for group S ($P=0.07$, Mann–Whitney). The anaesthetist's satisfaction with operative analgesia was greater for group F (93% excellent, 3% good, 3% fair, 0% poor) than for group S (72% excellent, 17% good, 10% fair, 0% poor) ($P<0.05$, Kruskal–Wallis), but there was no difference in patient satisfaction with analgesia. Intrathecal fentanyl reduced nausea during operation but increased pruritus: 60% of group F were itchy (44% mild, 44% moderate and 11% severe) compared with 7% of group S (100% mild) (table 1).

Two patients in group F and one patient in group S did not receive diclofenac. Patients were studied for a mean of 23 h after delivery (table 1). Up to 6 h after delivery there was no difference in morphine requirements. Between 6 and 23 h after delivery morphine requirements were 63% greater for group F. There was no difference in postoperative pain scores, patient satisfaction with analgesia, nausea, vomiting or drowsiness. The increased pruritus with intrathecal fentanyl persisted into the early postoperative period.

Comment

These results support the hypothesis that intrathecal fentanyl at operation can increase postoperative i.v. morphine requirements.

How could this be explained? If there was greater pre-emptive analgesia with intrathecal fentanyl it would have been expected to produce the opposite effect to that encountered. The most likely explanation is that intrathecal fentanyl produced acute opioid tolerance. Acute tolerance at the spinal level could increase systemic morphine requirements in two ways; first, by reducing the effect of morphine acting directly on spinal receptors; second, indirectly, by reducing the effect of endogenous spinal opioids. This could also reduce the effectiveness of supraspinal morphine acting via the descending pain control pathways.

Tolerance is a well recognized phenomenon that is dependent on dose of opioid and duration of

exposure. With i.v. fentanyl acute tolerance can develop in dogs within 3 h.[1] Spinal opioids can also produce tolerance but it has not been considered to be a problem with short-term postoperative extradural or intrathecal use.[2]

High lipophilicity limits rostral spread after intrathecal administration. This can allow high concentrations of opioid at the spinal level without producing clinically significant respiratory depression or sedation. We believe that high spinal receptor occupancy with the potent opioid fentanyl produced acute tolerance after a single intrathecal dose. Nociceptive stimulation has been reported to inhibit the development of tolerance.[3] Local anaesthetic block and rectal diclofenac may therefore have contributed to the development of acute tolerance by reducing nociception. The use of extradural fentanyl may also have contributed to its development by increasing the total spinal dose.

Intrathecal fentanyl was beneficial at operation, reducing extradural anaesthetic requirements and increasing the anaesthetist's satisfaction with operative analgesia. Nausea was also reduced, probably because of more effective visceral afferent inhibition, but pruritus increased. After operation we found no benefits from intrathecal fentanyl. The lack of a difference in postoperative analgesia within the first 6 h was probably because both groups received extradural analgesia and rectal diclofenac.

We consider that this study provides evidence for a single dose of intrathecal fentanyl producing acute spinal opioid tolerance. This phenomenon clearly warrants further investigation. Our findings, in conjunction with a previous study which found no advantage from using more than 6.25 μg of intrathecal fentanyl,[4] have led us to reduce the total dose of spinal fentanyl given to Caesarean section patients.

References

1. Askitopoulou H, Whitwam JG, Al-Khudhairi D, Chakrabarti M, Bower S, Hull CJ. Acute tolerance to fentanyl during anesthesia in dogs. *Anesthesiology* 1985; **63**: 255–261.
2. Gebhart GF. Some mechanistic insights into opioid tolerance. *Anesthesiology* 1990; **73**: 1065–1066.
3. Colpaert FC, Niemegeers CJE, Janssen PAJ. Nociceptive stimulation prevents development of tolerance to narcotic analgesia. *European Journal of Pharmacology* 1978; **49**: 335–336.
4. Hunt CO, Naulty JS, Bader AM, Hauch MA, Vartikar JV, Datta S, Hertwig LM, Ostheimer GW. Perioperative analgesia with subarachnoid fentanyl–bupivacaine for Cesarean delivery. *Anesthesiology* 1989; **71**: 535–540.