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PLASMA CONCENTRATIONS OF METHADONE DURING POSTOPERATIVE PATIENT-CONTROLLED EXTRADURAL ANALGESIA†

Y. SHIR, D. EIMERL, F. MAGORA, D. DAMM, J. SCHULTE-MONTING AND J. CHRUBASIK

SUMMARY

Plasma concentrations of methadone were measured by gas chromatography in 16 patients receiving extradural methadone by continuous infusion for relief of postoperative pain. Venous blood samples were taken after a loading dose of extradural methadone 2 mg and during infusion of 0.46 mg h^{-1} plus patient-controlled increments of 0.2–1 mg. Mean (SD) plasma concentration of methadone was 9.8 (2.1) ng ml^{-1} at 15 min; this did not change significantly during the first 2 h, after which it increased gradually to 32.2 (4.6) ng ml^{-1} ($P < 0.001$) at the end of 24 h. The mean quantity of extradural methadone required to produce effective analgesia was 10.3 (1.8) mg during the first 12 h after operation and 6 (1.0) mg for the subsequent 12 h. The mean amount of methadone for effective analgesia on the second day was 7.6 (1.1) mg. No adverse effects were detected during the 2–3 days of methadone therapy. Plasma concentration of methadone increased significantly during patient-controlled infusion of extradural methadone in the first 24 h after operation, suggesting rapid vascular uptake. Systemic activity of the drug contributes to the analgesic effect of extradural methadone.

KEY WORDS

Analgesics, opioid: methadone. Analgesia: patient-controlled. Analgesic techniques: extradural. Methadone.

Many investigators have examined the pharmacokinetics and analgesic effects of extradural injections of opioids [1–4]. Studies on vascular absorption of opioids such as pethidine [5] and fentanyl [6] have demonstrated that a major portion is absorbed initially by direct vascular absorption from the extradural space, followed by uptake from CSF.

Until 1987 [7], there have been no studies of the plasma concentrations of methadone produced by extradural administration in bolus dose or continuous infusion. The extent of systemic uptake is influenced mainly by lipid solubility [8, 9]. Methadone has a much higher lipid partition coefficient than morphine (116 *vs* 1.42) and therefore has more rapid onset of action, with less likelihood of delayed respiratory depression [10]. It has been shown that methadone has a potency similar to that of morphine; it produces effective analgesia following extradural administration, but with fewer side effects [11–13]. Its lack of urinary complications makes it particularly suitable for postoperative analgesia [13]. However, rapid vascular absorption in combination with slow plasma clearance [14, 15] may result in systemic cumulation after repeated extradural injections or continuous extradural infusion.

The present study was designed to assess the safety of continuous extradural infusion of methadone, by measurement of plasma concentrations

Y. SHIR, M.D.; D. EIMERL, M.D.; F. MAGORA, M.D.; Department of Anaesthesiology, Hadassah University Hospital, P.O. Box 12000, 91120 Jerusalem, Israel. D. DAMM, Research Department, Hoechst. J. SCHULTE-MONTING, PH.D., Department of Biometrics and Medical Statistics, University of Freiburg, Federal Republic of Germany. J. CHRUBASIK, M.D., Department of Anaesthesiology, University Hospital, Zurich, Switzerland. Accepted for Publication: February 8, 1990.

Correspondence to F.M.

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TABLE I. *Patient data*

Patient No.	Age (yr)	Sex	Surgical procedure
1	58	F	Hemicolectomy
2	60	F	Mid sternotomy
3	28	M	Colonic surgery
4	26	M	Vagotomy pyloroplasty
5	61	M	Abdomino–perineal resection
6	81	M	Choledochojejunostomy
7	56	F	Abdomino–perineal resection
8	64	M	Abdomino–perineal resection
9	73	M	Aorto–bifemoral bypass
10	75	M	Cholecystectomy
11	58	F	Cholecystectomy
12	66	M	Resection of abdominal aortic aneurysm
13	53	F	Cholecystectomy
14	46	F	Hemicolectomy
15	64	M	Radical cystectomy
16	54	F	Hemicolectomy

of methadone during its use in postoperative patient-controlled analgesia.

PATIENTS AND METHODS

We studied 16 patients (seven women) aged 26–75 yr, undergoing major elective abdominal or thoracic surgery (table I). All patients gave informed consent to the study, which was approved by the local Ethics Committee. All patients received general anaesthesia; premedication and anaesthetic technique were not standardized, but included supplementation with low doses of fentanyl 1–2 mg kg^{-1} i.v. After induction of anaesthesia, a catheter was inserted 2.5 cm into the extradural space via an upper lumbar interspace for administration of methadone.

On completion of surgery, a loading dose of 0.1 % racemic methadone hydrochloride 2 mg in 10 % glucose was injected through the extradural catheter, which was connected to a 5-ml plastic syringe containing methadone. The syringe was driven by an automatic, portable, battery-operated infusion pump (Graseby, Medical M 26, England). The rate of infusion was set to deliver methadone 0.46 mg h^{-1} for the first 24 h after surgery, after which it was reduced to 0.35 mg h^{-1}. For the first 2 h, repeated doses of methadone to a total of 6 mg were administered by the investigator if the patient reported severe pain. Thereafter, the patients and the nursing staff were instructed not to allow the pain to increase above a level of 3 (see below), and to add further boluses of 0.2–1.0 ml solution if pain relief was inadequate. The syringe was refilled by the nurse according to the regimen, which permitted additions of methadone up to 5 mg every 6 h. Escape analgesia was provided by systemic opioids.

The amount of methadone required for good analgesia was calculated separately for the first two 12-h epochs and the second day after operation. The patients were observed in the recovery room during the study period and ventilation was monitored at frequent intervals; blood-gas tensions were measured 1 h after surgery and at least twice daily thereafter.

Analgesic efficacy was assessed by a subjective five-point pain score (0 = no pain; 1, 2 = mild pain; 3 = discomforting pain; 4 = distressing pain; 5 = unbearable pain, intervals 0.5). During the first 3 h of administration of methadone, the pain score was assessed every 30 min by one of the investigators, who collected blood samples and administered additional analgesia if necessary. For the remainder of the observation period, the average of frequent score assessments (every 1 h for the first 12 h, every 4 h for the remainder of the study period) was calculated for the first and second days after surgery. These two scores were used for statistical evaluation.

Central venous blood samples were collected in heparinized tubes before and at 15, 30, 45, 60 min and 2, 3, 4, 6, 8, 12 and 24 h after the first dose of extradural methadone. The blood was centrifuged and the plasma samples were frozen and transported to Frankfurt (W. Germany) for analysis. Plasma concentrations of methadone were measured by gas chromatography using a Hewlett–Packard 5730 apparatus with a nitrogen phosphorus detector and a Spectra Physics model SP 4270 integrator [16]. This assay is sensitive to concentrations of less than 1 ng ml^{-1} in plasma samples as small as 1 ml. The extraction procedure for methadone as modified by one of the authors (J.S.-M.) utilizes acid–base partitioning steps which allow a large number of samples to be processed rapidly. The coefficient of variation was 3.5–22 % over a concentration range of methadone 1–50 ng ml^{-1}. The technique was linear up to 200 ng ml^{-1} [7].

Linear least square regression was used for statistical analysis of plasma concentrations of methadone. Mean analgesic requirements for methadone and patients' pain scores were

TABLE II. *Individual methadone consumption and pain scores during the first 2 days after surgery*

Patient No.	Methadone consumption (mg)		Pain score		Remarks
	1st day	2nd day	1st day	2nd day	
1	18	6	0	0	
2	17	9	2	0	
3	15	8	1	1	Post-op. intubation: 4 h
4	19	8	3	0	Papaveretum 10 mg i.m.
5	16	7	2	2	Post-op. intubation: 10 h
6	16	5	0	0	
7	19	8	3	1	Papaveretum 10 mg i.m.
8	17	8	2	0	Post-op. intubation: 5 h
9	15	9	1	0	Post-op. intubation: 12 h
10	15	7	2	1	Urinary retention
11	13	7	0	0	
12	13	7	1	2	Post-op intubation: 6 h
13	17	7	2	2	
14	18	8	1	1	
15	17	9	1	0	
16	16	7	0	0	
Mean (SD)	16.3 (1.8)	7.6 (1.1)	1.3 (1)	0.6 (0.8)	
P	< 0.05		< 0.05		

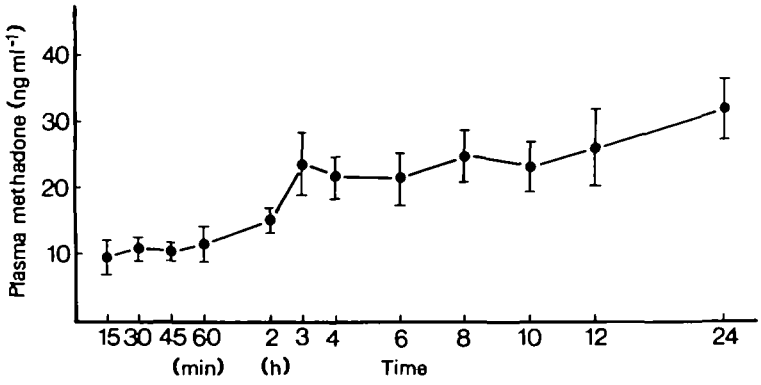

FIG. 1. Mean plasma concentration of methadone during the first 24 h after operation, with continuous patient-controlled extradural infusion of methadone.

analysed by paired Student's *t* test. $P < 0.05$ was considered significant.

RESULTS

The mean amount of methadone consumed during the first day was 16.3 (SD 1.8) mg (range 13–19 mg) (table II). During the first 12 h, mean consumption of methadone was 10.3 (1.8) mg, whereas during the next 12 h of treatment a mean of only 6 (1.0) mg provided analgesia ($P < 0.05$). As the rate of injection was set at 5 mg/11 h, the doses used indicate substantial need for supplementary methadone during the first postoperative period, with little or no supplement during the second 12 h. Onset of analgesia was rapid: 5–10 min after bolus injection, either self-administered or given by the nurse. On the second day, significantly smaller quantities of extradural methadone were needed, with a mean value of 7.6 (1.1) mg (range 5–9 mg) ($P < 0.05$). During these two days, the pain scores were 1.3 (1) and 0.6 (0.8), respectively ($P < 0.05$). Two patients who reached the prescribed limits of extradural methadone in the first hours following surgery, had a pain score of 3, 15 min after supplementation with methadone, and received papaveretum 10 mg i.m.

In five patients, artificial ventilation was continued for 4–12 h after surgery. Otherwise,

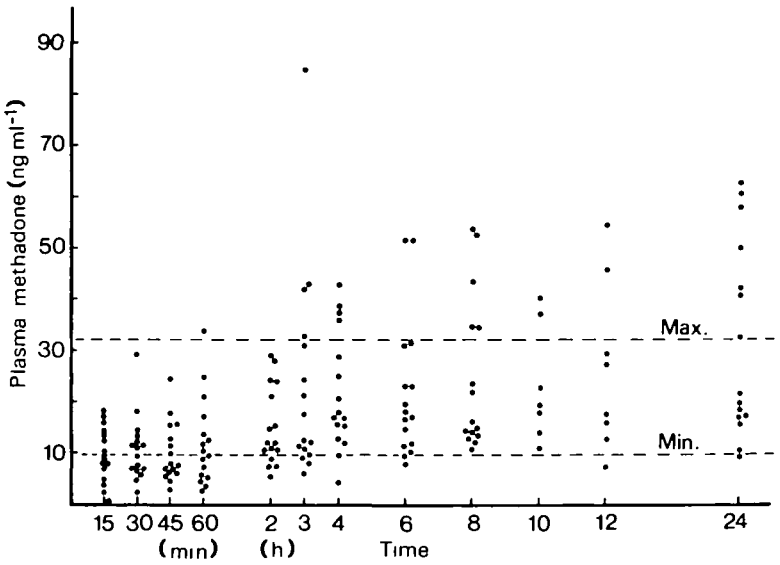

FIG. 2. Individual plasma concentrations of methadone during the first 24 h after operation, with continuous patient-controlled extradural infusion of methadone. Min. = Mean minimum plasma concentration of methadone in the 16 patients studied, after 15 min; Max. = mean maximum plasma concentration of methadone in the 16 patients studied, after 24 h.

there were no respiratory complications or marked deviation from normal values in blood-gas tensions.

Plasma concentrations of methadone

Mean plasma concentrations of methadone during continuous infusion with on-demand supplementation in the first 24 h after operation are shown in figure 1. Fifteen minutes after the loading dose of extradural methadone 2 mg and subsequent continuous infusion, the plasma concentration of methadone was 9.8 (2.3) ng ml^{-1}. The value after 60 min was not significantly different (11.9 (2.1) ng ml^{-1}). After the first 1 h, plasma concentration of methadone increased gradually, to mean values of 14.9 (2.8) ng ml^{-1} at 2 h, 21.9 (2.8) ng ml^{-1} at 3 h and 32.2 (4.6) ng ml^{-1} 24 h after operation. Regression analysis showed a significant increase in plasma concentrations of methadone with time, with peak values at the 2 h ($P < 0.05$), 3 h ($P < 0.05$) and 24 h ($P < 0.001$) of extradural infusion of methadone.

Methadone concentrations varied considerably between individuals (fig. 2), although the general trend towards increased concentrations was similar in all patients. On several occasions, high values were recorded in some patients, which corresponded with additional boluses. Although most patients were sleepy during the first few hours after operation, all, including those receiving artificial ventilation, were fully conscious and co-operative. No respiratory depression, haemodynamic instability or neurological changes were observed in any patient. None exhibited signs of atelectasis on the chest x-ray taken the morning following the operation. One of the seven patients without a urinary catheter required temporary catherization of the bladder.

DISCUSSION

This study has shown that postoperative pain associated with major abdominal and thoracic surgery was controlled effectively by continuous lumbar extradural administration of methadone. Intermittent extradural administration of bolus doses of methadone has been reported to produce good analgesia after surgery [11, 13, 17] and extracorporeal shock wave lithotripsy [18]. Extradural methadone 8–12 mg day^{-1} has been reported to give good analgesia for several weeks without toxic effects in patients with chronic pain [19].

The prescribed dose limit of extradural infusion of methadone plus on-demand boluses of up to

5 mg every 6 h was based on other studies and our own previous experience [7, 12, 13, 18, 19]. The mean consumption of methadone in 24 h of our patients was less than the total amount given in bolus injections during the same period after thoracic surgery [17], but greater than the single doses recommended after lower abdominal surgery [13].

Lipophilic opioids are taken up more readily from the extradural space and, therefore, are less likely to cause late respiratory depression than lipophobic drugs. Payne and Inturrisi [10] could not detect methadone in the cisternal CSF of sheep up to 6 h after injection of methadone 2 mg into the lumbar subarachnoid space. In contrast, subarachnoid injection of the same dose of morphine resulted in a concentration of morphine 148 ng ml^{-1} in the cisterna magna, after only 2–3 h. The authors concluded that methadone, as opposed to the hydrophilic morphine, was taken up almost completely into the cord. This concept is supported by previous studies of extradural methadone and the present investigation, in which no central side effects were observed. Continuous infusion of methadone supplemented by patient-controlled boluses prevented onset of severe pain; however, its high lipophilicity leads to rapid vascular absorption. In addition, methadone possesses a long plasma terminal half-life—more than 24 h [20, 21], and this may lead to cumulation during prolonged continuous infusion. The present study has confirmed that methadone passed rapidly into the circulation, as demonstrated by the plasma concentration at 15 min. The relatively constant plasma concentration observed during the first 1 h of continuous infusion may be a reflection of its rapid phase of distribution—6.1 (5.7) min [20]. The significant increase in the subsequent 3 h may have been related either to the kinetics of extradural methadone, or to the increments necessary to treat immediate severe postoperative pain. The slow increase towards the peak concentration of 32.2 ng ml^{-1} at 24 h reflects the long terminal half-life. However, the mean 24 h value was below the minimal analgesic blood concentration (57.9 ng ml^{-1}) reported by Gourlay, Willis and Wilson after i.v. administration [22]. Although high plasma concentrations of methadone were observed occasionally, none reached a toxic value, and there was no clinical evidence of toxicity during the 3 days of treatment.

The good quality of analgesia in the early postoperative period, when blood concentrations were low, is consistent with a spinal site of action of the drug. Because of this increasing blood concentration of methadone, observed during the 24 h of investigation, it would be advisable to reduce the rate of infusion until further studies are performed.

It is concluded that the amounts of methadone infused continuously after upper abdominal and thoracic surgery resulted in satisfactory pain relief; no sign of toxic effects was observed during the study, and the range of plasma concentrations of methadone during the first 24 h remained in the non-toxic range.

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