Regional Anesthesia and Pain

Continuous epidural infusion of racemic methadone results in effective postoperative analgesia and low plasma concentrations

[La perfusion péridurale continue de méthadone racémique produit une analgésie postopératoire efficace et de faibles concentrations plasmatiques]

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Purpose: To compare two protocols of epidural administration of racemic methadone for postoperative analgesia (continuous infusion and intermittent bolus), focussing on plasma concentration, analgesic efficacy and side effects.

Methods: Ninety patients undergoing abdominal or lower-limb surgery were randomly assigned to two groups in a prospective double-blind design. The continuous infusion patients ($n=60$) received initial doses of 3 to 6 mg followed by 6 to 12 mg by continuous infusion over 24 hr. The bolus administration patients ($n=30$) received repeated boluses of 3 to 6 mg of racemic methadone every eight hours. Pain intensity was assessed on a visual analog scale. Amount of supplementary analgesia was recorded, as was the incidence of side effects. Plasma methadone concentrations were determined by high performance liquid chromatography. Treatment was continued for 72 hr.

Results: Pain relief was good and comparable in both groups throughout the three days of treatment. No accumulation of plasma racemic methadone was observed in either group, although the concentrations were significantly higher in the bolus group. Miosis was significantly more frequent in the bolus group.

Conclusion: Plasma methadone concentrations were significantly lower with continuous infusion. Plasma methadone accumulation, which is considered the main disadvantage for its purported influence on the incidence of side effects, did not occur at the doses used over the three days of treatment that we report.

Objectif : Comparer deux protocoles d'administration épidurale de méthadone racémique (perfusion continue et bolus intermittent), pour

analgésie postopératoire: concentration plasmatique, efficacité analgésique et effets secondaires.

Méthode : Quarante-vingt-dix patients qui furent soumis à une intervention chirurgicale abdominale ou des membres inférieurs ont participé à cette étude prospective. Ils ont été divisés en deux groupes de manière randomisée et en double-aveugle. Le groupe de patients avec perfusion continue ($n=60$) a reçu une dose initiale de 3 à 6 mg suivie de 6 à 12 mg en perfusion continue toutes les 24 h. Le groupe des patients avec bolus a reçu des bolus répétés toutes les huit heures de 3 à 6 mg de méthadone racémique.

L'intensité de la douleur a été mesurée avec une échelle visuelle analogique. On a enregistré les besoins supplémentaires d'analgésie, ainsi que l'incidence des effets secondaires. La concentration de méthadone plasmatique a été déterminée par chromatographie liquide d'haute résolution. Le traitement a été poursuivi pendant 72 h.

Résultats : Le soulagement de la douleur a été bon et comparable entre les deux groupes pendant les trois jours du traitement. On n'a pas observé d'accumulation plasmatique de méthadone racémique dans aucun groupe; néanmoins les concentrations ont été significativement plus élevées dans le groupe bolus. La présence de myosis a été significativement plus fréquente dans le groupe bolus.

Conclusion : La perfusion continue est une technique sûre; elle est indiquée parce que la concentration plasmatique de méthadone a été significativement plus basse qu'avec les bolus. L'accumulation plasmatique de méthadone, qui est considérée comme le principal inconvénient de son influence sur l'incidence des effets secondaires n'est pas observée avec les doses utilisées pendant les trois jours de ce traitement dans aucun des deux groupes.

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THE clinical use of spinal opioids, including methadone, has been considered safe for about 25 years at doses recommended, provided no additives are present in the solution.^{1,2} Epidural delivery of lipophilic opioids has aroused interest in recent years because such compounds provide the same analgesic efficacy as hydrophilic morphine but have stronger metameric fixation in the spinal cord and, consequently, a lower risk of respiratory depression caused by the ascending migration of drugs.³ Nevertheless, lipophilia increases the vascular absorption of epidural opioids, and recent studies have demonstrated that highly lipophilic fentanyl is equally effective by epidural and *iv* routes and that resulting plasma concentrations are similar,⁴⁻⁶ suggesting that analgesia provided by lipophilic opiates given epidurally may be due to systemic effects. Methadone, an opioid as potent as morphine,⁷ but less lipophilic than fentanyl, has been used in our hospital since 1990 for postoperative epidural analgesia and chronic pain with satisfactory results at doses lower than those required by the *iv*, *im* or subcutaneous routes.⁷⁻¹⁰ Unlike fentanyl, however, methadone has a low plasma clearance and this property, together with its still relatively high liposolubility, can be associated with progressive increases in plasma concentrations with accumulation over the course of treatment.¹⁰⁻¹²

However, little has been established firmly concerning plasma racemic methadone concentrations, although high concentration gradients resulting from intermittent boluses of methadone could, theoretically, favour intravascular absorption. Continuous epidural infusion of methadone should be effective at total doses lower than those of intermittent injections, therefore leading to lower plasma racemic methadone concentrations. If such is the case, methadone by continuous infusion could provide good postoperative analgesia, lower plasma concentrations and fewer side effects. To test this hypothesis we compared two protocols for the epidural administration of racemic methadone for postoperative analgesia (continuous infusion and intermittent bolus), focussing on plasma concentrations, analgesic efficacy and side effects in a randomized, prospective double-blind study.

Methods

Ninety patients over the age of 18 yr, ASA I–III physical status and scheduled for abdominal or lower limb surgery, were enrolled after approval by the Ethics and Research Committee of our hospital. No patients with liver disease with abnormal coagulation tests contraindicating epidural catheterization were enrolled. Likewise, patients who had difficulty reporting pain

on a visual analog scale (VAS), were excluded, as were those receiving concomitant drugs that bind proteins that could replace opioids. On the day before surgery, informed consent to participation in the study was obtained from each patient after the planned postoperative analgesia technique had been explained along with the means for evaluating pain on a VAS from 0 to 10. Each patient was also told of the possibility of receiving supplementary analgesia if required.

Patients were randomly assigned to one of two groups using a randomizing function available within Microsoft Excel. The continuous infusion group (MCI) patients ($n=60$) received epidural racemic methadone by continuous infusion and the bolus group (MB) patients ($n=30$) received epidural racemic methadone in intermittent boluses. All eligible surgical patients who could benefit from epidural analgesia with opioids were enrolled consecutively until 90 patients had entered the study. The same anesthesiologist was responsible for gathering the preoperative and postoperative data, which were analyzed by personnel blinded as to which analgesic regimen had been assigned to each patient. Every eight hours a bolus of saline solution or methadone 0.1% solution was injected into the pump whether connected to the patient or not. Variables were recorded and analyzed by a statistician unaware of the analgesic regimen.

Methadone regimens

The initial methadone bolus dose for both groups was calculated according to the usual practice in our hospitals and reported elsewhere.^{8,13,14} Doses ranged from 3 to 6 mg, and were calculated by adding the following three items: age (>60 yr=1 mg, 60 yr=2 mg); weight (<60 kg=1 mg, 60 kg=2 mg); and site of operation (upper abdominal=2 mg, lower abdominal and lower limbs=1 mg).

The initial dose was given before closure of the surgical wound began. From then on MB patients received the same dose every eight hours and the MCI patients received a continuous infusion amounting to twice the initial dose over 24 hr. In this way, both groups received the same total amount of methadone on the first day; after that, however, MCI patients received two thirds of the dose given to MB patients.

Methadone was prepared in 0.1% solutions, with no additive. In the MCI group, an infusion pump (Kabi Pharmacia Deltec CADD-PCATM, model 5800, St Paul, MN, USA) with a simple infusion system that did not allow additional boluses was used for MCI.

Anesthesia and epidural analgesia techniques

The anesthetic technique was left to the attending anes-

thesiologist's choice, to be chosen among balanced general anesthesia, epidural anesthesia with local anesthetics, or combined epidural-general anesthesia. For patients receiving general anesthesia the epidural catheter was inserted in the operating room before induction. Epidural puncture was performed at D8–D10 for surgery above the umbilicus, at D11–L1 for surgery below the umbilicus and at L2–L5 for lower limb surgery. The catheter was inserted 3 cm in a cephalad direction. A test dose of 3-mL of 0.5% bupivacaine with epinephrine 1:200,000 was administered and heart rate was monitored to rule out intravascular injection. When combined anesthesia (epidural + general) was used, an epidural catheter was placed before induction of general anesthesia, and intraoperative analgesia with epidural bupivacaine 0.5% was used. The last dose of *iv* fentanyl for general anesthesia and the last dose of local anesthetic for epidural or combined anesthesia were given at least 30 min before start of wound closure.

Treatment lasted three days. Patients were monitored in the postanesthesia recovery room for the first 12 to 24 hr after surgery. Urinary catheters were removed after the patient had been transferred to the ward.

Pain assessment

Pain intensity was evaluated by patients on the VAS postoperatively at rest two, 12, 24, 48 and 72 hr after closure of the wound and with movement at 24, 48 and 72 hr. The need for supplementary analgesia was also recorded. Supplementary analgesia consisted of 2 g *iv* of metamizol (nonsteroidal anti-inflammatory agent), or alternatively, 30 mg *iv* of ketorolac every six hours if the patient was allergic to metamizol. The same anesthesiologist recorded postoperative pain scores for all the patients.

Variables monitored

Plasma racemic methadone concentrations were determined with high performance liquid chromatography (HPLC) from venous blood samples drawn 24, 48 and 72 hr after surgery just before administration of the next drug dose.¹⁵

The following data were recorded for analysis: age; sex; weight; height; ASA physical status; associated diseases; type, duration, and site of operation; number of metameres affected by surgery; anesthetic technique used; doses of fentanyl and of local anesthetic during surgery; and the interval between the last doses of these drugs and the end of surgery.

Side effects

Whenever pain was assessed, the presence or absence of the following side effects was also recorded: urinary

retention, nausea or vomiting, itching and miosis. Therefore, side effects were recorded at two, 12, 24, 48 and 72 hr after surgery. Each patient was asked specifically about side effects as was nursing staff. We also monitored signs of sedation or respiratory depression and searched for mention of side effects in the patients' charts. Arterial blood gases were analyzed before surgery and two, 12 and 24 hr after surgery. During the first 24 hr, continuous monitoring of SpO₂ by pulse oximetry and respiratory rate was accomplished by means of Hewlett Packard monitors (models 54S or 56S, Saronno, Italy). Desaturation events during that period were classified as mild (SpO₂ <93% but ≥90%) or severe (SpO₂ <90%). Bradypnea was defined as a respiratory rate ≤10 breaths·min⁻¹, hypoventilation as a PaCO₂ >45 mmHg or a 10% increase in preoperative PaCO₂ in hypercapnic patients, and hypoxemia as PaO₂ <70 mmHg or a 10% drop in baseline value in hypoxemic patients. Supplementary oxygen was administered for postoperative hypoxemia. Sedation was assessed as grade 1: awake-nervous; grade 2: awake-calm; grade 3: sleepy; grade 4: asleep-arousable; grade 5: fast asleep; or grade 6: not arousable (Ramsay scale).¹⁶ Other side effects that might be related to opioid administration, such as dysphoria, hallucinations, dizziness, hiccups or abdominal distension, were also recorded.

Statistical analysis

A chi-square test was applied to qualitative variables. Quantitative variables were first studied by using the nonparametric Kolmogorov-Smirnov test to verify if they followed a normal Gaussian-type distribution. Results showed that the aforementioned distribution was not followed. We therefore used a Wilcoxon signed rank test to compare paired data, and a Mann-Whitney U test to compare non-paired data. The number of patients to be enrolled was calculated using the EPISTAT program. The first aim was to assess whether tolerability was better in the MCI group. Previously a pilot study had been conducted, and a sensitivity of 30%, a statistical power of 90% (β error 0.10), a first species risk of 5% (α error 0.05), constant f=10.50 was estimated. The number of patients calculated to be necessary was 24 in the control group and 48 in the study group. As continuous infusion of methadone is considered controversial and because of great inter-individual pharmacokinetic variability, we decided to enroll a larger number of patients, recruiting 30 and 60 patients, respectively, for the control and study groups. Every comparison was made using two tailed analysis. *P* values were significant if they were less than 5% (*P* < 0.05). The SPSS statistical pack version 4.0 was used.

TABLE I Demographic characteristics, ASA physical status, associated diseases and type of surgery for the continuous infusion methadone group (MCI) and the intermittent methadone bolus group (MB)

	Group MCI n=60	Group MB n=30
Age (yr)	60.7 (14.3)	57.3 (15.4)
Height (cm)	159.2 (8.6)	161.3 (9.9)
Weight (kg)	71.3 (16.6)	67.6 (11.3)
Male	23 (38.3%)	14 (46.7%)
ASA I	-	1 (3.3%)
ASA II	18 (30.0%)	10 (33.3%)
ASA III	42 (69.2%)	19 (63.3%)
Obesity	4 (6.7%)	1 (3.3%)
Liver disease	0	2 (6.7%)
Chronic obstructive pulmonary disease	9 (15.0%)	4 (13.3%)
Upper abdominal surgery:	37 (61.7%)	20 (66.6%)
- Cholecystectomy ± biliary duct exploration		
- Total and partial gastrectomy		
- Nephrectomy (subcostal)		
- Upper umbilical eventration		
Lower abdominal surgery:	19 (31.6%)	7 (23.3%)
- Right hemicolectomy		
- Sigmoidectomy		
- Anterior resection of the rectum		
- Hysterectomy ± double		
- Annexectomy ± omentectomy		
Limb surgery:	4 (6.7%)	3 (10.0%)
- Total hip replacement		

Values are means (standard deviation) or number of patients (%). Differences between the groups were not statistically significant.

Results

The two groups were comparable as to demographic features, ASA physical status, associated diseases and site of surgery (Table I). The most frequently used anesthetic technique in both groups was combined general and epidural anesthesia, with a maximum fentanyl dose of 0.15 mg given during anesthetic induction. There were no statistically significant differences between the two groups in distribution of anesthetic technique or components, duration of surgery or number of metameres affected (which was in relation with the type of surgical incision; see Table II).

Pain assessment

Pain intensity evaluated both at rest and with movement is shown in Table III. All mean VAS scores were below 3 for both groups throughout the study period either at rest or with movement and were not different between groups. In both groups, the highest mean VAS scores appeared two hours after surgery. From then on, pain diminished gradually and signifi-

TABLE II Anesthesia for the continuous infusion methadone group (MCI) and the intermittent methadone bolus group (MB)

	Group MCI n=60	Group MB n=30
Combined anesthesia (general + epidural) (patients)	49 (81.7%)	25 (83.3%)
General (patients)	6 (10.0%)	3 (10.0%)
Epidural (patients)	5 (8.3%)	2 (6.7%)
Total dose of <i>iv</i> fentanyl (mg)	0.13 (0.05)	0.15 (0.06)
Interval from last fentanyl dose to the end of operation (min)	146.6 (74.3)	150.2 (65.6)
Number of metameres affected by incision	4.33 (1.16)	4.47 (1.28)
Volume of local anesthetic (mL) (bupivacaine 0.5 %)	15.55 (5.6)	14.31 (5.2)
Duration of surgery (min)	179.2 (61.2)	178.7 (62.8)

Values are means (standard deviation) or numbers of patients (%). No significant differences between groups.

cantly at each recording ($P < 0.001$). Mean VAS scores with movement in both groups were significantly higher than those at rest 24, 48 and 72 hr ($P < 0.0001$) after surgery.

Requirements for supplementary analgesia were not different between groups. Analgesia was achieved with metamizol 2 g *iv* in all cases, even though two analgesics had been made available. The mean requirements were 0.72 times per patient in the MCI group, and 0.73 times per patient in the MB group. In both groups, need was greater at two hours (22.5% of all patients) and at 12 hr (26.7%) after surgery. Requests for supplementation later fell to 8.3% of all patients at 24 hr and to 4% at 72 hr.

Side effects

Table IV summarizes the incidence of side effects in both groups, which was not different in most cases. The incidence of miosis, however, was significantly higher in the MB group ($P = 0.0114$). Vomiting and/or nausea affected identical proportions (46.7%) in both groups and, along with hypoxemia and hypoventilation, were the most frequent side effects. Bouts of mild oxygen desaturation occurred in more than half the patients in each group and severe desaturation events were seen in 26.7% of MCI group patients and in 13.3% of MB group patients, although the difference was not statistically significant.

Plasma racemic methadone concentrations

Table V gathers the plasma methadone data for both groups. The mean plasma racemic methadone con-

TABLE III VAS scores for pain assessment at rest and with movement for the continuous infusion methadone group (MCI) and the intermittent methadone bolus group (MB)

Time	Group MCI n=60	Group MB n=30
Preoperative	0.65 (1.62)	0.85 (1.87)
After two hours	1.82 (2.33)	2.90 (3.48)
After 12 hr	1.36 (1.93)	1.17 (1.64)
	At rest / with movement	At rest / with movement
After 24 hr	0.68 (0.86) / 2.40 (1.82)	0.80 (1.51) / 2.22 (2.32)
After 48 hr	0.36 (0.72) / 1.97 (1.67)	0.72 (1.50) / 1.73 (1.73)
After 72 hr	0.30 (0.78) / 1.66 (1.86)	0.40 (0.98) / 1.37 (1.36)

Values are means (standard deviation). No significant differences between groups. VAS=visual analogue scale.

TABLE IV Side effects, ventilatory and arterial blood gas variables for the continuous infusion methadone group (MCI) and the intermittent methadone bolus group (MB)

Side effects	Group MCI n=60	Group MB n=30
Sedation	4 (6.7%)	2 (6.7%)
Myosis	2 (3.3%)*	5 (16.7%)*
Pruritus	2 (3.3%)	4 (13.3%)
Nausea and/or vomiting	28 (46.7%)	14 (46.7%)
Urinary retention	4 (6.6%)	4 (13.3%)
Dysphoria	4 (6.7%)	0
Hallucinations	0	0
Headache	0	0
Abdominal distension	1 (1.7%)	0
Dizziness	2 (3.3%)	1 (3.3%)
Hypoxemia	34 (56.7%)	13 (43.3%)
Hypoventilation	12 (20.0%)	11 (36.7%)
Bradypnea	3 (5.0%)	3 (10.0%)
Mild O ₂ desaturation	37 (61.7%)	17 (56.7%)
Severe O ₂ desaturation	16 (26.7%)	4 (13.3%)

Values are numbers of patients (%). Statistically significant difference * $P < 0.05$.

centration in the MB group was significantly higher than in the MCI group ($P=0.002$) at 24, 48 and 72 hr. In both groups, mean plasma racemic methadone concentrations decreased with time ($P=0.002$) and the rate of decrease was similar in both groups.

Discussion

Both methadone dosing regimens in our study provided similar and satisfactory postoperative analgesia. The VAS values reported by patients with both regimens throughout the three days of treatment were under 3 even during movement, providing evidence of analgesic efficacy, which was further confirmed by the scarce need for supplementary analgesia. Moreover, continuous

TABLE V Plasma concentrations of methadone over the course of three days for the continuous infusion methadone group (MCI) and the intermittent methadone bolus group (MB)

Time	Group MCI n=60	Group MB n=30
	ng·mL ⁻¹	ng·mL ⁻¹
After 24 hr	77.69 (106.94)	111.88 (99.47)*
After 48 hr	50.29 (29.39)	70.80 (30.64)*
After 72 hr	49.05 (24.35)	77.76 (29.80)*

Values are means (standard deviation). Statistically significant difference (* $P < 0.01$).

infusion allowed effective analgesia to be achieved with lower total methadone doses in this study. Plasma methadone concentrations were significantly lower with continuous infusion. Plasma methadone accumulation, which is considered the main disadvantage of this drug, did not occur at the doses used over the three days of treatment that we report.

A key aspect of this study was the design and calculation of the dosing regimen for each group. Epidural doses of opioids are usually based on empirical calculations and on clinical experience. Thus, the intermittent injection regimen was designed according to our usual experience of ten years duration in our respective hospitals.^{9,10} Methadone dosages, in our practice, are based on patient weight, age and expected pain intensity, with an interval between doses of eight hours. Thus, our results are reported and compared as total doses rather than mg·kg⁻¹. The continuous infusion regimen was designed to decrease the methadone dose after the first day, based on the findings of Shir *et al.*,¹⁴ who reported that methadone requirements in patient-controlled analgesia with continuous infusion and boluses on demand decreased by one third after the second day of treatment.

Plasma racemic methadone concentrations in this study showed great inter-individual variability, as already described by others,^{14,17} and a lack of accumulation of methadone (since plasma concentrations in both groups were higher the first day of treatment than on the following two days). Intermittent bolus administration produced higher plasma concentrations at all times, even on the first day of the study, when both groups received similar doses. This finding seems to indicate different vascular absorption patterns for intermittent injections and continuous infusion of epidural methadone, perhaps related to vascular absorption with sudden increases in drug concentration after a bolus injection. Consistent with our interpretation are pharmacokinetic studies of methadone which demonstrate

great inter-individual variability in blood clearance.¹⁵ Methadone's half-life is linked to route of administration and ranges from six to eight hours when given by *im* injection. Given orally, methadone has a half-life of 12 to 18 hr for a single dose and 13 to 47 hr for repeated doses. The effective plasma concentration for analgesia is more than 100 ng·mL⁻¹ when methadone is administered intravenously. We believe, therefore, that the analgesic effect of methadone in our study was not related to plasma methadone, since the concentrations were lower than 100 ng·mL⁻¹.⁷

In the literature reviewed, we found no studies specifically comparing methadone administration by intermittent injection and continuous infusion. Nor did we find studies of plasma methadone concentrations in a patient population as large as ours. As far as we know, only two articles^{14,17} report plasma concentrations for epidural methadone. Wang *et al.*¹⁷ measured concentrations after giving methadone by epidural continuous infusion at the same dose throughout three days of treatment. In 12 patients they found values of 20 (18) ng·mL⁻¹ on the first day of treatment, a concentration that was much lower than any we observed, and of 70 (47) ng·mL⁻¹ on the third day, a concentration similar to that reported herein. We attribute the difference between the first-day findings of Wang *et al.*¹⁷ and ours mainly to sample size. Another difference between our study and earlier ones is the method of measurement of methadone concentration but this methodological difference does not account for the discrepancy in first-day plasma concentrations and does not affect comparison of results.

The higher mean plasma racemic methadone concentrations observed with intermittent injections were generally not associated with statistically significant differences in the incidence of side effects. Nausea or vomiting is a typical side effect of opiates by any route but is also associated with surgery and anesthesia in general, with great variability in reported incidences; the rates of 20% with fentanyl and 14% with sufentanil^{18,19} are very similar to those we found with the continuous infusion of methadone. Hypoventilation (36.7% in the MB group *vs* 20% in the MCI group) and bradypnea (10% in the MB group *vs* 5% in the MCI group) were similar in our study in both groups. The reported incidence of bradypnea with epidural fentanyl is 15%,¹⁹ and the incidence of hypoventilation with epidural fentanyl is 10 to 25%.^{8,19} Reported rates are greater than those we found with the continuous infusion of methadone. Arterial oxygen desaturation was assessed in the first 24 postoperative hours while oxygen was supplied. Nevertheless, we observed a

high incidence of oxygen desaturation with both regimens a finding that merits discussion. Hypoxemia has been shown to be a common event after general anesthesia and to be reduced if epidural analgesia is employed during surgery²⁰ or postoperatively.²¹ Over 56% of the patients in both our groups had episodes of mild oxygen desaturation, with severe desaturation episodes occurring in 26.7% of MCI group patients and in 13.3% of MB group patients. We found only one study²² in the literature reporting a similar incidence of oxygen desaturation. We believe the explanation for the incidence of hypoxemia reported is that we applied more exhaustive respiratory monitoring than is usual beyond the early postoperative period, rather than our use of methadone per se. In more than 80% of our patients, we used combined general-epidural anesthesia, administering only 0.15 mg of fentanyl given at the time of intubation. The interval between the last dose of intraoperative fentanyl and the first dose of methadone was ≥ 30 min, sufficient to ensure that the earlier opiate had been metabolized. Finally, although respiratory depression is the most feared complication of spinal opiates, only minor side effects are usually associated with this technique,²³ as was the case in our study in both groups.

The enrollment of patients undergoing different types of surgery is a potential limitation of our study. Similarity of procedures, we believe, means that nociceptive stimuli were balanced in the two groups (Table I). The association of type of surgery and anesthesia in both groups was also similar. In both groups combined anesthesia was the usual technique employed in abdominal and gynecological surgery (81% in the MCI group and 83.3% of the MB group). Epidural anesthesia was the only technique employed in orthopedic surgery. This means that the relation between anesthetic technique and type of surgery was unlikely to be misleading.

We conclude that both epidural methadone protocols used in this study (continuous infusion and repeated bolus) provide good postoperative analgesia with similar respiratory side effects. Yet, it would seem appropriate to prefer infusion as doses can be reduced after the first day of treatment and plasma concentrations are significantly lower with a continuous infusion. Plasma methadone accumulation did not occur in this study. The percentage of side effects was similar in both groups although the plasma concentrations were very different. Further studies to demonstrate if the CNS opioid concentration, correlates with the incidence of side effects appear warranted, having shown that it is not correlated with the opioid plasma concentrations.

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