

## *A Double-blind Comparison of the Efficacy of Methadone and Morphine in Postoperative Pain Control*

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This study reports the results of a double-blind, parallel-group comparison of intravenous methadone with morphine for the control of postoperative pain. Twenty patients (ASA Status 1 or 2) undergoing a surgical procedure involving an upper abdominal incision were randomly allocated to the methadone ( $n = 10$ ) or morphine ( $n = 10$ ) treatment groups. The patients were administered a 20-mg intraoperative opioid dose and 5-mg intravenous increments of opioid from precoded syringes in response to pain in the recovery and surgical wards. There was no significant difference between the mean  $\pm$  SD amount of supplementary methadone ( $8 \pm 6.3$  mg) and morphine ( $9 \pm 9$  mg) required in the recovery ward to provide initial pain control. The time from initial pain control to the first supplementary dose in the surgical ward was significantly different ( $P < 0.01$ ) in the methadone group ( $20.7 \pm 20.2$  h) when compared to the morphine group ( $6.2 \pm 3.0$  h). Further, patients required significantly less ( $P < 0.001$ ) methadone ( $11.5 \pm 8.5$  mg) than morphine ( $41 \pm 14.1$  mg) in the surgical ward to provide adequate pain relief throughout the duration of the study (*i.e.*, 60 h). There was a significant difference in visual analogue pain scores between the methadone and morphine groups on postoperative days 1 and 2, suggesting the quality of pain relief was similar for both treatment groups. Blood opioid-concentration monitoring indicated that there was a relationship between blood opioid concentration and pain relief. The minimum effective concentration (MEC) (mean  $\pm$  SD) values of methadone and morphine were  $59.2 \pm 24.1$  ng/ml and  $14.7 \pm 4.8$  ng/ml, respectively. However, there was a significantly larger ( $P < 0.001$ ) intrasubject variability in the coefficient of variation in MEC for morphine ( $39.4 \pm 6.6\%$ ) compared with methadone ( $17.8 \pm 10.4\%$ ). (Key words: Analgesics: methadone; morphine. Pain: postoperative. Pharmacodynamics: methadone; morphine.)

PREVIOUS STUDIES from this Department<sup>1-3</sup> have indicated that prolonged postoperative pain relief can be observed following appropriate methadone doses. The average duration of pain relief was approximately 20 h following a titration procedure that cautiously elevated the blood methadone concentration to a level above the minimum effective concentration (MEC) for each patient.<sup>3</sup>

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Prolonged pain relief was observed because the blood methadone concentration declined slowly as a result of the low methadone clearance.<sup>2</sup> Smaller supplementary intravenous methadone doses administered when pain returned provided a similar duration of pain relief. In addition, a relationship between blood methadone concentration and pain relief was established.<sup>3</sup>

However, these were "open" studies of the efficacy of methadone for control of postoperative pain and could, therefore, be liable to bias. Study designs where the investigators evaluating pharmacodynamic effects are unaware of the drugs that have been administered are considered to yield more meaningful results. Therefore, this article reports the results of a double-blind comparison of methadone and morphine in postoperative pain control in patients having a surgical procedure involving an upper abdominal incision. Morphine was chosen as the comparative opioid because a relationship had been established between blood morphine concentration and postoperative pain relief,<sup>4</sup> and morphine had been used as the standard opioid in similar studies for a considerable time. The previously described<sup>3</sup> titration procedure was used because it ensured that each patient had effective pain control when discharged from the recovery room. No crossover component was incorporated into the present study as any opioid agent is usually administered for only 2-3 days in uncomplicated postoperative recovery and methadone can have a duration of pain relief lasting 48 h.<sup>2</sup>

### Methods

This study was approved by the Clinical Investigation Committee and the Drugs and Therapeutics Advisory Committee of the Flinders Medical Centre, and informed consent was obtained from all patients.

### PATIENTS

Twenty patients (ASA status I or II) undergoing a surgical procedure involving an upper abdominal incision (table 1) were included in the study. No patient had any opioid administration for at least 2 weeks prior to the initiation of this study. Patients were not selected in any way other than being the first or second patient on the morning operating list in order to provide for the maxi-

TABLE 1. Duration of Pain Relief, Age, Weight, Type of Operation and Perioperative Opioid Requirements in Methadone and Morphine Study Patients

Patient Number	Type of Operation	Age (yr)	Weight (kg)	Sex	Intraoperative Opioid (mg)	Opioid in Recovery Room (mg)	Duration of Pain Relief (h)
<b>Methadone group</b>							
1	Nissen*	30	82.5	M	20	15	8.0
2	Cholecystectomy	21	70.4	F	20	10	9.5
3	Cholecystectomy	50	80.0	M	20	5	58.0
4	Cholecystectomy	58	80.3	M	20	5	58.0
5	Cholecystectomy and HSV†	47	91.0	F	20	10	9.3
6	Cholecystectomy	36	84.3	M	20	20	5.5
7	Cholecystectomy	20	49.3	F	20	5	12.5
8	Cholecystectomy	33	104.7	M	20	0	22.6
9	HSV	38	75.0	F	20	10	8.2
10	Cholecystectomy	39	64.1	F	20	0	15.6
Mean ± SD		37.2 ± 12.1	78.2 ± 15			8 ± 6.3	20.7 ± 20.2
Range		20-58	49.3-104.7			0-20	5.5-58
<b>Morphine group</b>							
11	Nissen*	57	69.3	F	20	0	7.8
12	Cholecystectomy	24	90.8	F	20	0	11.4
13	HSV†	31	97.4	M	20	20	3.1
14	Gastrectomy	44	50.2	F	20	15	5.5
15	Cholecystectomy	50	103.2	M	20	5	3.8
16	Nissen	32	105.4	M	20	0	5.1
17	Nissen and HSV	50	73.6	M	20	5	8.5
18	Cholecystectomy	39	72.0	M	20	15	8.9
19	Cholecystectomy	47	76.1	M	20	5	6.4
20	Cholecystectomy	20	70.4	F	20	25	1.6
Mean ± SD		39.4 ± 12.3	80.8 ± 17.7			9 ± 9	6.2 ± 3.0
Range		20-57	50.2-105.4			0-25	1.6-11.4
Significance		NS	NS			NS	P < 0.01

NS = Not significant.

\* Represents a Nissen fundoplication.

† Represents a highly selective vagotomy.

imum time of close observation in the recovery ward. The patients were randomly allocated to the methadone (n = 10) or morphine (n = 10) treatment groups.

#### OPIOID SOLUTIONS

The hospital pharmacy at Flinders Medical Centre dispensed precoded syringes (10 ml) for each patient. Each syringe contained 10 ml of a 1 mg/ml solution of either methadone or morphine. The intraoperative and postoperative opioid requirements of each patient were satisfied by administering preset volumes from these syringes (*vide infra*). Each patient was administered only one opioid (*i.e.*, either methadone or morphine) for the duration of the study (60 h).

#### ANESTHETIC TECHNIQUES

Patients were premedicated with oral diazepam, 0.15 mg/kg one h prior to induction of anesthesia. Anesthesia was induced with a sleep dose of thiopentone, and suxamethonium was used to facilitate intubation. Anesthesia

was maintained with nitrous oxide/oxygen, and enflurane (0.5-1%) was used as a supplement as indicated on clinical grounds. Pancuronium was used as the muscle relaxant. Ten minutes after induction of anesthesia, 20 ml of the coded opioid solution (either methadone or morphine) equivalent to 20 mg was administered intravenously. This loading dose has been used in previous studies.<sup>1-3</sup> All surgical procedures lasted for at least 60 min. Neostigmine/atropine were used to reverse neuromuscular blockade at the termination of the surgical procedure. In no patient was it necessary to administer naloxone to initiate spontaneous respiration.

#### ADMINISTRATION OF OPIOIDS FOR POSTOPERATIVE PAIN CONTROL

The previously described titration procedure was used to treat postoperative pain.<sup>3</sup> Briefly, 5 ml of the same opioid solution as used intraoperatively was administered intravenously when the following three criteria were satisfied: 1) the patient complained of pain of sufficient intensity to require supplementary opioid administration,

2) the patient had an unstimulated respiratory rate of greater than 10 breaths/min, and 3) the patient had no other signs of significant CNS depression. The volume of the "top-up" doses was set at 5 ml, as this was shown to be effective in a previous study.<sup>3</sup>

A latency period of at least 30 min was required between successive supplementary 5-ml doses to enable a thorough assessment of the pharmacodynamic effects of the previous dose. The previous three criteria had to be satisfied before any supplementary pain relief could be administered.

#### BLOOD SAMPLING

Blood samples (3 ml) were collected and placed into lithium heparin tubes at the following times after the 20-ml intraoperative dose: 2, 5, 10, 15, 30, 60, 90, 120 min, and hourly for 8 h and then three hourly until 0800 h the next day (postoperative day 1) when hourly samples were collected. Patients were not disturbed for routine blood sampling between 2400 and 0600 h to allow a period of rest free from disturbances associated with the study. Again, three hourly samples were collected overnight and reverted back to hourly on the second postoperative day.

The blood sampling protocol reverted back to the rapid-sampling sequence (*e.g.*, 2, 5, 10 min, etc.) following any supplementary opioid administration.

A blood sample was collected immediately prior to the administration of supplementary pain relief, and this opioid concentration was defined as the minimum effective concentration (MEC) as in our previous studies.<sup>2,3</sup> In all patients, the previously mentioned criteria 2 and 3 were always satisfied and, therefore, supplementary pain relief was administered when the patient requested it. Criteria 2 and 3 were included to prevent supplementary pain relief being administered when it was contraindicated by the patient's general condition.

Resident anesthetic staff administered the opioid solution after normal working hours (1800 to 0800 h). Each resident was fully aware of the aims of the study and was aware of the three criteria, previously described, that must be satisfied prior to the administration of supplementary pain relief.

A blood sample to estimate MEC and a 5-min postadministration sample were collected by the resident staff overnight because of the more limited time they could spend with the patient due to other clinical commitments.

The blood samples were frozen ( $-15^{\circ}\text{C}$ ) until the end of that patient study when the code was broken and the samples were assayed for the appropriate opioid. Blood samples were assayed within 7 days of collection, and there was no loss of either methadone or morphine during storage (unpublished data).

#### ASSAY OF METHADONE AND MORPHINE IN BLOOD SAMPLES

The amount of methadone in blood samples was quantitated by gas chromatography with nitrogen-phosphorous detection.<sup>2</sup> Morphine was quantitated by high-performance liquid chromatography with electrochemical detection as previously described.<sup>5</sup> The standard curves for both assays were linear, and passed through the origin and the lower limit of detection was 1 ng/ml of either methadone or morphine.

#### PAIN SCORES

The postoperative pain was estimated by the linear visual analogue pain scale (VAPS), which is a 10-cm ungraduated line. The left-hand margin (corresponding to a score of zero) represents no pain, while the right-hand margin (corresponding to a score of 10) represents the worst pain imaginable. The VAPSs were administered by one of the principal investigators. The same investigator was assigned to administer all VAPSs for a particular patient.

The VAPSs were measured at hourly intervals from 0800 to 1700 h on the first and second postoperative days and immediately prior to any supplementary pain relief.

#### STATISTICAL ANALYSIS OF DATA

The Statistical Package for the Social Sciences<sup>6</sup> was used for all statistical analysis. The subprograms used included *t*-test (unpaired Students *t*-test) and range of nonparametric tests (NPAR). The statistical analysis (unpaired *t*-test) was performed on log (to the base 10) transformation of the duration of pain relief data, as this transformation satisfied the basic assumption of this test, namely, that the variances of both groups should be equivalent. A level of significance of at least  $P < 0.05$  was required to reject the null hypothesis.

#### Results

Table 1 indicates the range of surgical procedures undergone by the patients in each group. There was no significant difference between the patients in the methadone and morphine treatment groups with respect to age, weight, and sex distribution. It should be emphasized that all opioid doses were administered with the investigators blinded to the contents of the syringes other than that they contained 1 mg/ml of either methadone or morphine.

Table 1 also shows that there was no significant difference between the amount of either methadone ( $8 \pm 6.3$  mg, range 0–20 mg) or morphine ( $9 \pm 9$  mg, range 0–25 mg) administered in the recovery ward to provide ini-

tial pain relief. At this point, the patients were discharged from the recovery room to their surgical ward and the duration of pain relief noted. In the surgical ward, there was a highly significant ( $P < 0.01$ ) difference in the mean ( $\pm$ SD) duration of pain relief between the methadone group ( $20.7 \pm 20.2$  h) and the morphine group ( $6.3 \pm 3.0$  h). The duration of pain relief ranged from 5.5 to 58 h in the methadone treatment group and from 1.6 to 11.4 h in the morphine treatment group. Thus, the range of duration of pain relief indicated by the ratio of maximum/minimum values is approximately the same for both treatment groups.

#### METHADONE TREATMENT GROUP

Figure 1 shows the blood methadone concentration (ng/ml) as a function of time (h) for the duration of the study. The patient (number 8) was a 33-yr-old man undergoing a cholecystectomy. It is apparent that the 20-mg intraoperative dose required no supplementation in the recovery ward and provided pain relief until 22.6 h postoperatively (table 1). The MEC for methadone was 30 ng/ml at this time. The initial 5-mg supplementary methadone dose provided an additional duration of pain relief of 8 h and a second MEC estimate of 37 ng/ml. A second 5-mg supplementary dose resulted in pain relief for the duration of the study (29.4 h), providing a total

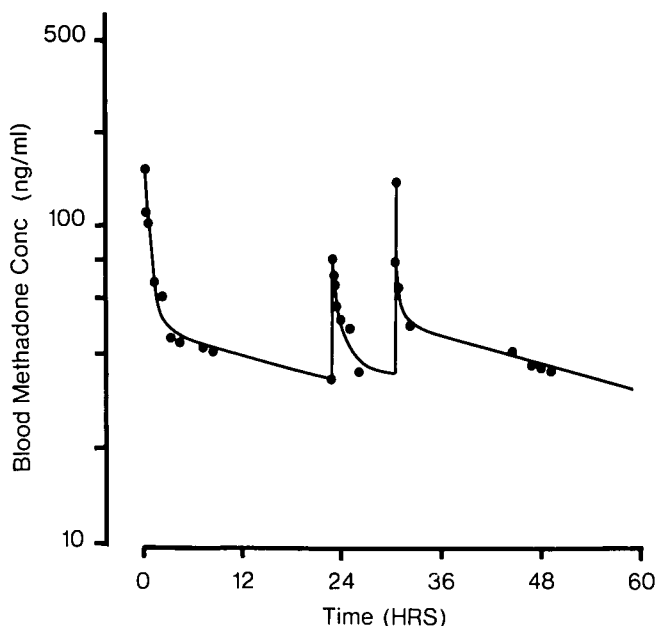


FIG. 1. Blood methadone concentration (ng/ml) as a function of time (h) following the administration of various methadone doses to a patient who underwent a cholecystectomy. The initial intravenous 20-mg dose resulted in pain relief lasting 22.6 h. The patient (number 8) was administered two supplementary 5-mg methadone doses in the surgical ward, resulting in a total methadone dose of 30 mg for the duration of the study (60 h). The mean minimum effective concentration (MEC) value for this patient was 34 ng/ml.

TABLE 2. Amount of Either Methadone or Morphine Administered in the Surgical Ward

Patient Number	Number of Doses in Ward	Dose in Ward (mg)	Total Dose* (mg)
<b>Methadone treatment group</b>			
1	5	25	60
2	2	10	40
3	0	0	25
4	0	0	25
5	2	10	40
6	2	10	50
7	3	15	40
8	2	10	30
9	2	10	40
10	5	25	45
Mean $\pm$ SD	2.3 $\pm$ 1.7	11.5 $\pm$ 8.5	39.5 $\pm$ 10.9
Range	0-5	0-25	25-60
<b>Morphine treatment group</b>			
11	8	40	60
12	4	30	50
13	13	65	105
14	9	45	80
15	10	50	75
16	6	30	50
17	5	25	50
28	5	25	60
19	8	40	65
20	10	60	105
Mean $\pm$ SD	7.8 $\pm$ 2.8	41 $\pm$ 14.1	70 $\pm$ 21.1
Range	4-13	25-65	50-105
Significance	$P < 0.003$	$P < 0.001$	$P < 0.001$

\* Represents the 20-mg intraoperative dose together with the dose administered in the recovery room and surgical wards.

methadone dose of 30 mg (table 2) and a mean MEC value of 34 ng/ml (table 3).

#### MORPHINE TREATMENT GROUP

Figure 2 shows the blood morphine concentration (ng/ml) as a function of time following various morphine doses in a 57-yr-old woman undergoing a Nissen fundoplication for gastric reflux (patient number 11). The 20-mg intraoperative loading dose was sufficient to provide pain relief while the patient was in the recovery ward, and a supplementary 5-mg morphine dose was administered in the surgical ward (7.8 h, table 1). The MEC value associated with this supplementary dose was 9.4 ng/ml. However, supplementary morphine doses were required at regular intervals for the remaining 52 h, providing a total morphine dose of 60 mg (table 2). The mean MEC value was 9.3 ng/ml in this patient (table 3).

A summary of the amount of either methadone or morphine administered to patients in the surgical ward is given in table 2. There was a significant difference ( $P < 0.001$ ) between the amount of methadone ( $11.5 \pm 8.5$  mg) and morphine ( $41 \pm 14.1$  mg) administered in the

TABLE 3. Minimum Effective Concentrations in Methadone and Morphine Treatment Groups

Patient Number	MEC*	CV MEC†
Methadone treatment group		
1	74	4
2	81	7
3	34	ND‡
4	69	ND
5	87	26
6	89	19
7	53	13
8	34	15
9	49	22
10	22	36
Mean ± SD	59.2 ± 24.1	17.8 ± 10.4
Range	22-89	4-36
Morphine treatment group		
11	9.3	48
12	13	38
13	23	40
14	21	36
15	13.4	36
16	10	31
17	19	32
18	13.4	41
19	10	52
20	14.5	40
Mean ± SD	14.7 ± 4.8	39.4 ± 6.6
Range	9.3-23	31-52
Significance	$P < 0.001$	$P < 0.001$

\* Represents minimum effective concentration (ng/ml).

† Represents the coefficient of variation (i.e.,  $\frac{SD \times 100}{mean}$ ) for the MEC estimate for each patient.

‡ Represents not determined, as there was only one estimate of MEC.

surgical ward (table 2). This difference was reflected in the number of doses ( $P < 0.005$ ) administered in the ward, with a median number of two for methadone and eight for morphine. This significant difference between the methadone and morphine groups was also apparent when considering the total opioid dose, which is the sum of the intraoperative dose and the opioid administered in the recovery and surgical wards (table 2).

There was no significant difference between the mean VAPS measured for the patients in the methadone group ( $1.14 \pm 1.1$  cm) when compared with the patients in the morphine group ( $2.03 \pm 1.3$  cm) on postoperative day 1. Similarly, there was no significant difference between the mean VAPS for the patients in the methadone ( $1.06 \pm 1.4$  cm) or morphine ( $2.03 \pm 1.5$  cm) groups on postoperative day 2. Further, there were no significant differences in VAPS between day 1 or day 2 for either the methadone or morphine group.

There was a relationship between blood opioid concentration and pain relief that permitted estimates of MEC for patients in both the methadone (for example, fig. 1) and morphine (for example, fig. 2) treatment groups. The mean ( $\pm$ SD) MEC for methadone was  $59.2 \pm 24.1$  ng/

ml, which was significantly greater ( $P < 0.001$ ) than the MEC for morphine ( $14.7 \pm 4.8$  ng/ml). However, the coefficient of variation in MEC (i.e., CV MEC, table 3) for methadone ( $17.8 \pm 10.4\%$ ) was significantly less ( $P < 0.001$ ) than the corresponding value for morphine ( $39.4 \pm 6.6\%$ ).

The incidence of vomiting and pulmonary infections was noted in the patients of both treatment groups. No patient was diagnosed as having a pulmonary infection throughout the study period. There was no significant difference in the incidence of vomiting in the patient of the morphine group (seven patients) when compared with the patients of the methadone group (six patients).

### Discussion

There were highly significant differences in the duration of pain relief and the amount of opioid administered in the surgical ward between the methadone and morphine treatment groups. The duration of pain relief in the methadone treatment group was significantly longer than the duration of pain relief following morphine administration. It should be noted that the investigators were unaware as to which opioid group the patient had been allocated when performing the assessment of whether supplementary pain relief was indicated. The duration of pain relief reported in this "blinded" study is not significantly different from that reported in our previous studies<sup>2,3</sup> involving an open evaluation of efficacy of metha-

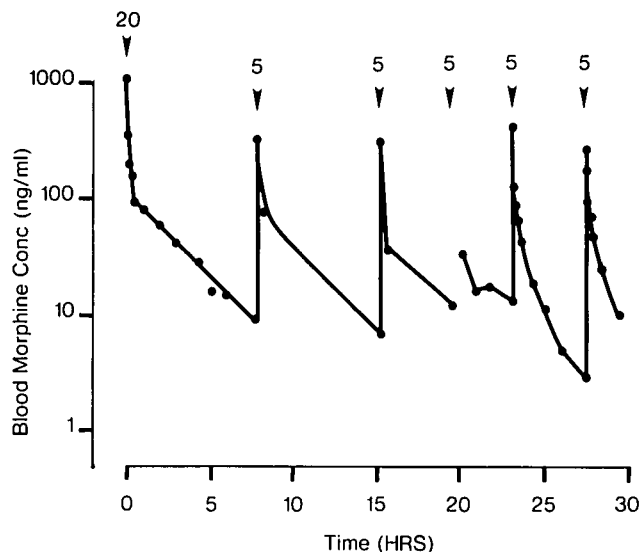


FIG. 2. Blood morphine concentration (ng/ml) as a function of time (h), following the administration of various morphine doses to a patient undergoing a Nissen fundoplication. The numbers above the arrows represent the magnitude of the intravenous morphine dose. The initial 20-mg dose provided pain relief lasting 7.8 h. Thereafter, numerous supplementary morphine doses were required to provide adequate pain relief for the duration of the study (60 h). The total morphine dose was 60 mg and the mean minimum effective concentration (MEC) for morphine was 9.3 ng/ml.

done in the treatment of postoperative pain. In other studies, Spears *et al.*<sup>7</sup> have found a similar duration of pain relief with methadone in a double-blind comparison of methadone and morphine for postoperative pain control following coronary artery bypass surgery.

Further evidence in support of a prolonged duration of pain relief of methadone is provided in table 2: significantly less ( $P < 0.001$ ) methadone ( $11.5 \pm 8.5$  mg) compared with morphine ( $41 \pm 14.1$  mg) was administered in the surgical ward. This significant difference was also apparent when considering the total opioid required for pain relief.

The intravenous titration procedure used in the present study ensured that all patients had adequate pain relief when discharged from the recovery room, irrespective of the opioid treatment group to which they were assigned. Some patients (two in the methadone group and three in the morphine group, table 1) required no additional opioid administration in the recovery ward to supplement the 20-mg intraoperative dose. Examples of such patients are shown in figures 1 and 2, where the duration of pain relief was 22.6 h and 7.8 h from the 20-mg intraoperative dose of methadone and morphine, respectively. However, the majority of patients required supplementary opioid in the recovery ward. The mean amount of methadone supplementation ( $8 \pm 6.3$  mg, range 0–20 mg, table 1) in the recovery ward was not significantly different from the amount of morphine supplementation ( $9 \pm 9$  mg, range 0–25 mg, table 1).

The quality of pain relief assessed from the VAPS measurements was not significantly different between the methadone or morphine treatment groups. Although the majority of patients had a mean VAPS measurement between 1 and 2 cm, all patients reported they had no pain when actually questioned. The method of administering morphine in the present study is similar to that obtained with "demand" infusions, except that a medical staff member, rather than a microprocessor-controlled infusion pump, administers the small intravenous morphine bolus doses in response to pain. Therefore, the quality of pain relief in the methadone treatment group equates to that obtained with a "demand" morphine infusion.

The results presented in figure 1 provide further experimental evidence to support a relationship between blood methadone concentration and pain relief and, therefore, support the concept of a MEC for methadone. The mean MEC values and intrasubject variability (CV MEC, table 3) for the methadone treatment group are similar to previously published values.<sup>3</sup> Similarly, the data in figure 2 support a similar relationship between blood morphine concentration and pain relief. The resultant MEC values of  $14.7 \pm 4.8$  ng/ml are in good agreement with the value of  $16 \pm 9$  ng/ml reported by Dahlstrom *et al.*<sup>4</sup> for postoperative pain control using "demand" analgesia with morphine as the opioid agent.

However, the intrasubject variability in MEC (*i.e.*, CV MEC, table 3) is significantly less for methadone (mean  $\pm$  SD of  $17.8 \pm 10.4$ , range 4–36) when compared with morphine ( $39 \pm 6.6$ , range 31–52). These results suggest that the intrasubject variability in MEC may be less for lipid-soluble opioids such as methadone when compared with hydrophilic opioids such as morphine. This may occur because the equilibration between blood and the opioid receptors is more rapid for lipid-soluble opioids than for hydrophilic opioids. Therefore, blood opioid concentrations for lipophilic opioids are more likely to show greater proportionality to brain concentrations than occurs with hydrophilic opioids.

In summary, the results of this double-blind study comparing intravenous methadone and morphine support the previously documented long duration of postoperative pain relief (mean value of 20.7 h) with methadone. Further, significantly less methadone than morphine was required to provide pain relief for the duration of the study (60 h). The quality of pain relief as assessed by a visual analogue scale was not significantly different between the two treatment groups. The results provide experimental evidence to support a relationship between blood opioid concentration and pain relief for both methadone and morphine.

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