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Comparison of tramadol and morphine via subcutaneous PCA following major orthopaedic surgery

Purpose: To compare subcutaneous PCA tramadol with subcutaneous PCA morphine for postoperative pain relief after major orthopaedic surgery and for the incidence of side-effects.

Methods: In a double-blind randomised controlled study 40 patients (20 in each group) self-administered either tramadol or morphine for 72 hr after surgery via sc PCA. The following variables were recorded at various time intervals: (I) pain score by means of a visual analogue scale, (ii) drug consumption and total PCA demands, (iii) vital signs (blood pressure and heart rate), (iv) oxygen saturation and respiratory rate, and (v) side-effects (sedation, nausea/vomiting, pruritus, urinary retention and constipation).

Results: Both drugs provided effective analgesia. The mean consumption in the first 24 hr was 792 ± 90 mg tramadol and 42 ± 4 mg morphine. Thereafter, consumption of both drugs declined markedly. Moderate haemodynamic changes were observed in both the tramadol and morphine groups (with a maximum 20% decrease in mean blood pressure and a maximum 17% increase in heart rate) during the 72 hr period. Both tramadol and morphine were associated with a clinically and statistically significant ($P < 0.001$) decrease in oxygen saturation, but without changes in respiratory rates. Desaturation was less marked with tramadol. Tramadol appeared to cause more nausea and vomiting than morphine. Sedation was mild and only seen during the first few hours after surgery in both groups.

Conclusion: Tramadol is an effective analgesic agent for the relief of acute postoperative pain when administered by PCA via the subcutaneous route. Under these conditions tramadol behaves much like morphine with a similar side-effect profile.

Objectif: Comparer le tramadol et la morphine administrés par ACP par voie sous-cutanée pour le soulagement des douleurs postopératoires en chirurgie orthopédique majeure et leurs effets secondaires.

Méthodes: Dans cette étude randomisée, contrôlée et en double aveugle, 40 patients (20 dans chaque groupe) se sont administrés du tramadol ou de la morphine par ACP par voie sous-cutanée pendant les 72 premières heures postopératoires. Les paramètres suivants ont été mesurés à intervalles réguliers: (i) le score de douleur par échelle visuelle analogue, (ii) les doses d'analgésiques utilisées par les patients et le nombre total de demandes d'ACP, (iii) les signes vitaux (tension artérielle, fréquence cardiaque), (iv) la saturation d'oxygène et la fréquence respiratoire, (v) les effets secondaires (sédation, nausées et vomissements, prurit, rétention urinaire et constipation).

Résultats: Le tramadol et la morphine ont montré tous les deux une analgésie efficace. La dose moyenne utilisée dans les premières 24 heures postopératoires était 792 ± 90 mg de tramadol et 42 ± 4 mg de morphine. Par la suite les doses utilisées ont rapidement décliné pour les deux médicaments. Des modifications hémodynamiques modérées ont été observées dans les deux groupes (réduction de 20% de la tension arterielle et augmentation de 17% de la fréquence cardiaque). Le tramadol et la morphine ont tous les deux entrainé une diminution de la saturation d'oxygène ($P < 0,001$) mais sans changement de la fréquence respiratoire. La désaturation était moins importante avec le tramadol. Le tramadol a semblé causer plus de nausées et vomissements que la morphine. Le degré de sédation a été modéré dans les deux groupes et n'a duré que quelques heures après la chirurgie.

Conclusion: Le tramadol est un analgésique efficace quand il est administré par ACP par voie sous-cutanée. Dans ces conditions le tramadol est semblable à la morphine avec des effets secondaires comparables.

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TRAMADOL (Tramal®) is a centrally acting analgesic agent with weak affinity for opioid receptors and with modulatory effects on central monoaminergic pathways. The antinociceptive effect of tramadol appears to result from both opioid and non-opioid receeptor mechanisms.[1,2] Inhibition of noradrenaline reuptake and stimulation of serotonin release may play an important role in its analgesic profile.[3,4] Several clinical studies have confirmed the analgesic efficacy of tramadol in patients with acute and chronic pain.[5–10] Its dual mode of action may provide some advantages over pure opioid analgesics; the side-effects, especially, appear less troublesome.[2,5,10]

Patient controlled analgesia (PCA) with opioids is now an established and effective method for postoperative pain relief. It can be used via the *iv* or *sc* routes with good results.[11–13] Side-effects of PCA opioids, such as nausea and vomiting, sedation, and pruritus, however, can be problematic in some patients.

The purpose of this study was to assess the efficacy of tramadol compared with morphine using *sc* PCA in patients with acute post-operative pain for (a) the degree of analgesia, (b) the incidence of opioid side-effects, and (c) the safety in terms of the cardiovascular and respiratory systems.

Methods and patients

The study was approved by the Human Ethics Committee of the University of the Witwatersrand. The patients, after giving their informed consent to enter the trial, were instructed in the use of the PCA device. Forty patients, ASA class I and II, scheduled for elective major orthopaedic surgery were enroled in the study. Exclusion criteria included: (1) age outside 18–70 yr, (2) morbid obesity, (3) hypotension or uncontrolled hypertension, (4) bradycardia, arrhythmias, heart block and other conduction disturbances, (5) significant lung pathology, (6) renal and liver dysfunction, (7) substance abuse disorders, (8) known sensitivity to morphine or tramadol, and (9) inability to operate the PCA device. The patients were randomised to receive either tramadol or morphine postoperatively (20 patients in each group).

A standardised general anaesthetic technique (thiopentone, vecuronium, halothane or isoflurane with a 50% mixture of O_2/N_2O) was used for all patients. Intra-operative analgesia consisted of 0.3 $\mu g \cdot kg^{-1}$ sufentanil with incremental doses of 0.1 $\mu g \cdot kg^{-1}$.

At the end of sugery, the PCA device (CADD PCA, Pharmacia-Deltic) was connected to the patient via a *sc* catheter sited over the deltoid muscle. A bolus of either 40 mg tramadol or 2 mg morphine was administered with the PCA immediately on arrival in the recovery room. Thereafter, the patients were left to activate the PCA pump.

The following parameters were recorded at regular intervals:

1 Pain score was assessed by means of a modified visual analogue scale (VAS) ranging from 1 to 5 (1 = No pain, illustrated with a smiling face to 5 = worst pain imaginable, illustrated with a crying face). This modification of the standard 100 mm VAS pain score which has been previously validated for children,[14] was better understood by our patients who are often illiterate. Pain scores were recorded at 0, 2, 4, 6, 12, 36, 48, 60 and 72 hr postoperatively.

2 Drug consumption was recorded at 0, 15, 30, 45, 60 and 90 min and then at 2, 3, 4, 6, 12, 24, 36, 48, 60, and 72 hr postoperatively. The total number of PCA demands, that is met and unmet demands (falling within the lock-out interval of the PCA), was also noted at the same time intervals.

3 Vital signs were monitored at 0, 1, 2, 3, 4, 6, 12, 24, 36, 48, 60 and 72 hr. These included measurements of mean arterial blood pressure (MAP) and heart rate (HR) with a non-invasive device (Dynamap R).

4 Haemoglobin oxygen saturation, while breathing room air, was measured with a pulse oximeter (Ohmeda Oxicap R). Respiratory rate was counted over one minute. These variables were measured at 0, 30, 45, 60 and 90 min and then at 2, 3, 4, 6, 12, 24, 36, 48, 60, and 72 hr post-operatively. When oxygen saturation decreased below 90%, the patient was given oxygen 40% to breathe by mask. Subsequent saturation levels were measured, after temporary discontinuation of oxygen therapy, until a stable reading was obtained breathing room air.

5 The patients were asked for potential side-effects of the drugs including postoperative nausea and vomiting (PONV), pruritus, urinary retention, constipation at 1, 2, 3, 4, 6, 12, 24, 36, 48, 60 and 72 hr. Side-effects were graded as moderate or severe. Sedation levels were also noted at the same time intervals and graded as: 0 = No sedation, 1 = sedated but awake, 2 = asleep but waking up easily, 3 = drowsy (needs shaking), 4 = responds only to pain, 5 = comatose.

The criteria for active intervention to alleviate side-effects were persisting or recurring severe complaints. Temporary catheterisation of the bladder and pharmacological treatment of PONV and pruritus with prochlorperazine or promethazine were carried out, when indicated.

All the PCA pumps were prepared by a nurse not involved in the trial and programmed to deliver 0.4 ml bolus on demand with a lockout interval of five minutes. The concentrations and demand doses delivered were respectively 50 mg·ml^{-1} and 20 mg for tramadol, and 2.5 mg·ml^{-1} and 1 mg for morphine. The display on the PCA screen, was set so as to be identical for all the pumps and to allow for "blinding" of the patient and of the investigators.

The analysis of variance (ANOVA) was used to test for differences in mean blood pressure, heart rate, and haemoglobin oxygen saturation between the tramadol and morphine groups. Differences were further assessed with the unpaired, two-tailed, Student's t test. Differences within groups were also tested with ANOVA for repeated measurements. Pain score differences between patients receiving tramadol and morphine were analysed with the Mann-Whitney test. The Chi-square test was used to assess differences between tramadol and morphine in the incidence of side-effects. A P value < 0.05 was considered statistically significant. A power analysis indicated that 36 patients, or less, would be required to show differences that might be considered clinically significant between the two groups, using $\alpha = 0.05$ and $\beta = 0.1$, for VAS scores (to detect a difference of 1 with an assumed σ of 0.8), drug consumption at 24 hr (to detect a difference of 0.5 mg·hr^{-1} morphine or "equipotent" 5 mg·hr^{-1} tramadol with an assumed σ of 0.5 and 5 respectively) and haemoglobin oxygen saturation (to estimate a difference of 4% with an assumed σ of 5%).

Results

There were no differences between the two groups of patients in terms of age, weight, or type of surgery. However, the random allocation of patients to each group resulted in more men receiving tramadol and more women receiving morphine (Table I). This was in spite of a similar number of men (19) and women (21) enrolled in the trial.

Both tramadol and morphine provided effective analgesia, as judged by the VAS pain scores, and improved the pain from severe to mild/moderate within 12 hr. The onset of analgesia appeared faster with tramadol leading to lower, although not statistically significant, pain scores in the first few hours postoperatively. Pain scores, thereafter, were marginally lower for tramadol (Table II).

The cumulative consumption of tramadol and morphine over 72 hr is shown in Table III. Graphically the consumption curves are very similar and are virtually superimposable when a 20:1 conversion factor is applied (Figure 1a), suggesting a potency ratio of 20:1

TABLE I Patient characteristics

Characteristics		*Tramadol*	*Morphine*
n		20	20
Age (yr)		49 ± 3	49 ±3
Weight (kg)		68 ± 3	71 ± 3
Sex	Male	13	6
	Female	7	14
Surgery	Hip	8	7
	Femur	7	4
	Knee	3	5
	Tibia	2	4

Values represent the number of patients in each group except for "age" and "weight" which are expressed as means ± SEM.

TABLE II Pain scores

Time (hr)	*Tramadol*	*Morphine*
0	4.8 ± 0.1	4.6 ± 0.2
2	3.7 ± 0.2	4.1 ± 0.2
4	3.0 ± 0.2	3.6 ± 0.2
6	2.8 ± 0.2	3.2 ± 0.2
12	2.5 ± 0.2	2.8 ± 0.2
24	2.2 ± 0.2	2.5 ± 0.2
36	2.1 ± 0.1	2.2 ± 0.2
48	1.8 ± 0.1	1.9 ± 0.2
60	1.7 ± 0.1	1.8 ± 0.1
72	1.5 ± 0.1	1.4 ± 0.1

Pain scores were obtained with a modified visual analogue scale ranging from 1 = no pain to 5 = worst pain imaginable. Values are the means ± SEM of 20 observations at the stated times for each group. Differences between tramadol and morphine pain scores at the given times were analysed with the Mann-Whitney test. None were statistically significant.

TABLE III Cumulative dose of drug consumed and drug requested

Time	*Tramadol(mg)*		*Morphine(mg)*	
	CON	REQ	CON	REQ
0	40	40	2	2
15 min	68 ± 5	104 ± 19	4 ± 0.2	6 ± 0.8
30 min	91 ± 7	188 ± 43	5 ± 0.3	12 ± 2.1
45 min	114 ± 42	265 ± 66	6 ± 0.4	21 ± 4.0
60 min	133 ± 11	355 ± 84	8 ± 0.6	38 ± 11
90 min	200 ± 19	646 ± 174	10 ± 0.9	69 ± 25
2 hr	230 ± 22	868 ± 265	12 ± 1.2	83 ± 31
3 hr	312 ± 30	1342 ± 522	14 ± 1.5	93 ± 31
4 hr	369 ± 36	1462 ± 534	17 ± 1.8	100 ± 32
6 hr	458 ± 50	1600 ± 598	20 ± 1.9	108 ± 32
12 hr	564 ± 67	1868 ± 583	27 ± 2.9	128 ± 36
24 hr	792 ± 90	2199 ± 603	42 ± 4.3	156 ± 37
36 hr	1064 ± 119	2586 ± 673	55 ± 5.5	182 ± 38
48 hr	1294 ± 153	2804 ± 744	67 ± 6.7	213 ± 44
60 hr	1514 ± 179	3151 ± 753	79 ± 8.5	232 ± 45
72 hr	1696 ± 207	3852 ± 880	90 ± 10.1	254 ± 46

Values are expressed as mean ± SEM and represent the cumulative doses of either tramadol or morphine consumed (CON) or requested (REQ) measured by the PCA device at the stated postoperative times.

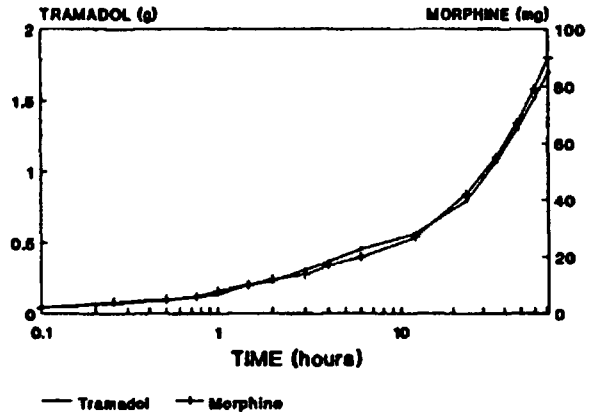

FIGURE 1a Mean cumulative doses of tramadol and morphine consumed (met demands) with subcutaneous PCA during the 72 hr postoperative period.

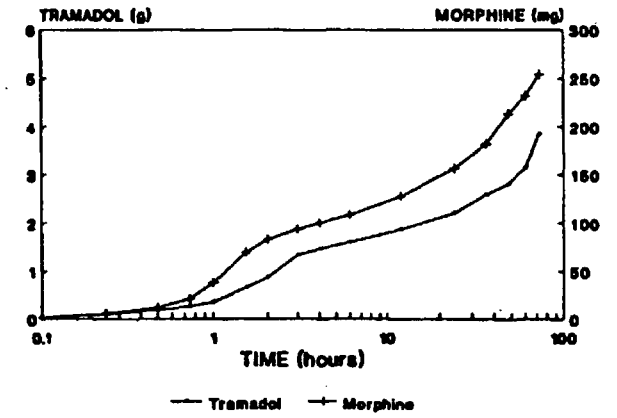

FIGURE 1b Mean cumulative doses of tramadol and morphine requested (total of met and unmet demands) with subcutaneous PCA during the 72 hr postoperative period.

for morphine to tramadol. The total dose requested, being the total of the met and unmet demands of the PCA device, was markedly more than the dose consumed for both drugs (Table III), and the difference was relatively larger for morphine than for tramadol (Figure 1b). However, the hourly consumption of tramadol or morphine was always well below the maximum allowable by the PCA (240 mg·hr^{-1} for tramadol and 12 mg·hr^{-1} for morphine). There was a marked decrease in hourly consumption as time progressed for both tramadol and morphine (Table IV). In a potency ratio of 20:1, the hourly consumption of tramadol and morphine was similar (Figure 2a). During the first three hours, for both tramadol and morphine, there was a pronounced discrepancy between the number of met demands of the PCA and the total number of demands (Figures 2b, 2c). Thereafter, the difference was much less marked for both drugs as most of the demands were met.

Mean arterial blood pressure (MAP) and heart rate (HR) were not different between the two groups during the study period. However, within each group, there was a decrease in MAP from 24 hr onwards ($P < 0.05$), with maximum 17% and 20% changes from baseline respectively for tramadol and morphine. This relative hypotension was associated with increases in HR in both groups, with maximum increases of 17% and 15% respectively for tramadol and morphine (Table V).

Oxygen saturation (SpO_2) declined from baseline values in both the morphine and the tramadol groups ($P < 0.001$). The degree of desaturation, however, was less severe and the onset occurred later with tramadol (Table VI). The oxygen desaturation was not associated with changes in respiratory rates which were similar in both groups at all times studied (Table VI).

TABLE IV Hourly drug consumption

Time (hr)	*Tramadol (mg·hr^{-1})*	*Morphine (mg·hr^{-1})*
1	133 ± 11	8 ± 0.6
2	93 ± 15	3.9 ± 0.7
3	77 ± 11	2.6 ± 0.6
4	60 ± 10	2.4 ± 0.4
6	44 ± 10	1.5 ± 0.3
12	14 ± 3	1.1 ± 0.2
24	22 ± 4	1.2 ± 0.1
36	22 ± 4	1.1 ± 0.1
48	19 ± 4	1.0 ± 0.1
60	18 ± 3	1.0 ± 0.2
72	15 ± 3	0.9 ± 0.1

Values are expressed as mean ±SEM and represent the hourly consumption of either tramadol or morphine at the stated postoperative times.

TABLE V Mean arterial blood pressure (MAP) and heart rate (HR)

	Tramadol		*Morphine*	
Time (hr)	*MAP (mmHg)*	*HR (min^{-1})*	*MAP (mmHg)*	*HR (min^{-1})*
0	112 ± 6	84 ± 3	116 ± 7	96 ± 6
1	100 ± 4	83 ± 3	102 ± 5	87 ± 4
2	101 ± 4	86 ± 3	103 ± 4	91 ± 4
3	104 ± 4	89 ± 3	103 ± 5	96 ± 4
4	105 ± 3	91 ± 3	104 ± 4	99 ± 4
6	103 ± 4	95 ± 3	94 ± 3*	104 ± 3
12	98 ± 3	98 ± 3*	99 ± 3	105 ± 3
24	93 ± 3*	95 ± 4	98 ± 4	103 ± 3
36	94 ± 2*	99 ± 3*	93 ± 3*	110 ± 3*
48	93 ± 3*	96 ± 3	94 ± 3*	107 ± 3
60	93 ± 3*	99 ± 4*	89 ± 3*	102 ± 3
72	97 ± 3*	91 ± 2	92 ± 3*	96 ± 3

Values represent the means ±SEM of 20 observations.
*$P < 0.05$ compared with the baseline value (0 hr) for each group. No statistically significant differences exist between groups.

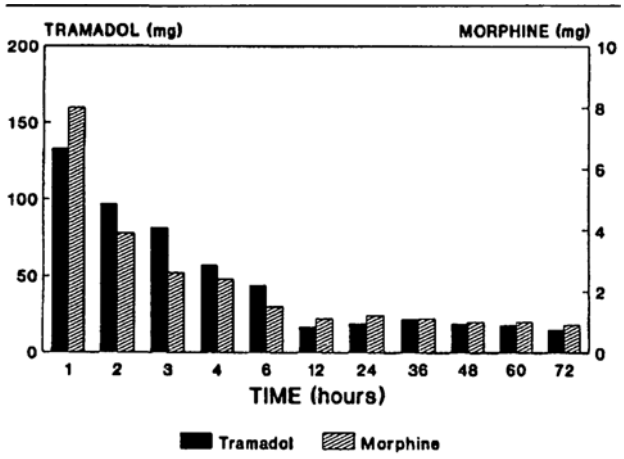

FIGURE 2a Mean hourly consumption of tramadol and morphine by subcutaneous PCA at the stated postoperative time intervals.

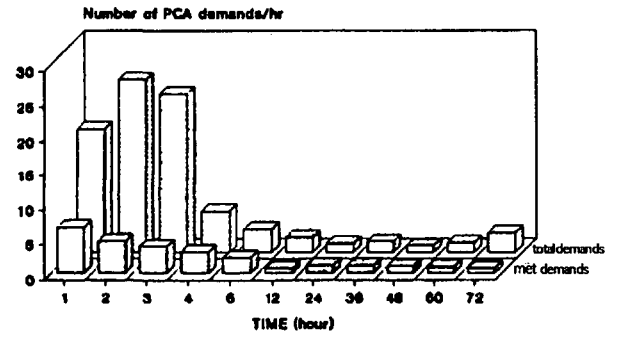

FIGURE 2b Mean hourly number of PCA demands for tramadol.

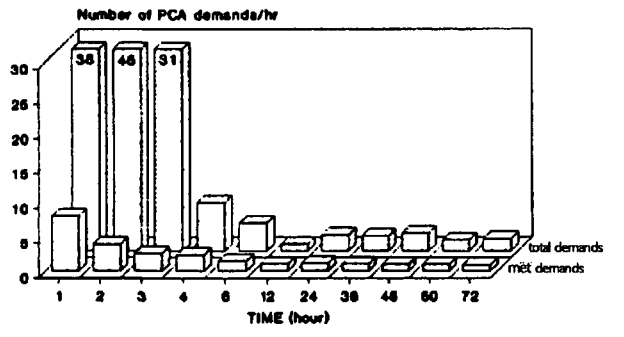

FIGURE 2c Mean hourly number of PCA demands for morphine.

TABLE VI Oxygen saturation (SpO_2-min^{-1}) and respiratory rate (RR)

	Tramadol		*Morphine*	
Time	*SpO2(%)*	*RR (min^{-1})*	*SpO2(%)*	*RR (min^{-1})*
0	97 ± 0.2	19 ± 0.9	97 ± 0.6	21 ± 1.1
30 min	93 ± 1.2	18 ± 0.8	93 ± 2.5	20 ± 1.0
60 min	94 ± 0.7	18 ± 0.9	89 ± 2.1*	20 ± 1.2
90 min	94 ± 0.9	19 ± 0.9	90 ± 2.1	19 ± 1.2
2 hr	93 ± 1.0	19 ± 0.9	89 ± 2.0†	18 ± 1.0
3 hr	92 ± 0.8	20 ± 1.0	89 ± 1.2*‡	19 ± 1.1
4 hr	91 ± 1.2‡	21 ± 1.0	88 ± 1.0‡	20 ± 1.2
6 hr	89 ± 0.7‡	22 ± 1.1	86 ± 1.5‡	21 ± 1.4
12 hr	87 ± 1.1‡	21 ± 1.2	87 ± 1.1‡	20 ± 1.3
24 hr	87 ± 1.6‡	21 ± 1.2	84 ± 1.8‡	20 ± 1.2
36 hr	86 ± 1.3‡	22 ± 1.2	84 ± 1.4‡	21 ± 1.2
48 hr	87 ± 1.6‡	20 ± 1.0	87 ± 1.7‡	19 ± 0.9
60 hr	87 ± 1.6‡	20 ± 1.1	86 ± 1.1‡	19 ± 1.1
72 hr	89 ± 1.4‡	19 ± 1.0	90 ± 0.9‡	19 ± 0.8

Values represent the means ±SEM.
*$P < 0.05$ for comparison between morphine and tramadol.
†$P < 0.05$, ‡$P < 0.001$ for comparison with the baseline value (0 hr) for each group.

TABLE VII Incidence of side-effects with tramadol and morphine

VIIa *Number of patients complaining of side-effects*

Values represent the number of patients in each group who complained of at least 1 episode of the mentioned side-effect. (PONV: Postoperative nausea and vomiting).

Side-effect	*Tramadol*	*Morphine*
PONV	13	8
Pruritus	5	7
Urinary retention	8	15
Constipation	4	2

VIIb *Number of complaints of side-effects*

Values represent the total number of complaints during the 72 hours post-operative period. Patients were asked for the presence of side-effects at the time intervals indicated in "Methods."

	Tramadol		*Morphine*	
Side-effect	*Moderate*	*Severe*	*Moderate*	*Severe*
PONV	32	11	27	8
Pruritus	8	0	20	0
Urinary retention	13	7	24	21
Constipation	4	0	4	5

The frequency and severity of side-effects were noted for each patient during the trial. In the tramadol group, 65% of patients complained of at least one episode of postoperative nausea and vomiting (PONV) compared with 40% in the morphine group (Table VIIa). Overall, there were 43 complaints of PONV with tramadol. Most were of moderate severity and there was a range from one to seven complaints per patient during the 72 hr postoperative period. With morphine, 35 complaints were recorded, ranging from one to six per patient (Table VIIb). There was no discernable relationship between the onset of PONV and either the

time after first administration of the drugs, or the amount of drug consumed. Three patients receiving tramadol and two receiving morphine were treated with prochlorperazine im to alleviate PONV.

Pruritus was experienced by 35% of patients given morphine compared with 25% given tramadol. However, the total number of complaints during the trial was, more than double with morphine than with tramadol (Table VIIb). Urinary retention was worse in the morphine group, although no statistical significance could be demonstrated. Twice as many patients complained of this problem and found it to be severe (Table VIIa). Temporary urinary catheterisation was necessary in six patients in the morphine group compared with three in the tramadol group. Once again, no definite peak incidence of urinary retention related to either time or dose of drug used could be identified. Constipation was not often reported as a problem in either group (Table VIIa).

Sedation scores were similar for the tramadol and morphine groups, ranging initially from 1 (no sedation) to 2 (sedated but awake). Very little sedation was seen after 12 hr postoperatively with tramadol and after 36 hr with morphine. Only one patient was drowsy (needed shaking) on one occasion. This occurred at 60 hr after a cumulative dose of 55 mg morphine.

Discussion

This is the first study which has directly compared tramadol with morphine as primary analgesics in a double blind manner by making use of PCA, thus allowing the patients to titrate, without interference, their analgesic needs and to balance them against side-effects. Since large interindividual variations exist in opioid requirements for pain relief, their consumption by PCA may not be a rigorous analgesic outcome measure, yet these variations should apply with the same magnitude to both groups. Our study shows that tramadol administered by the *sc* route with PCA provides effective analgesia for acute postoperative pain and compares well with morphine under the same conditions. The *sc* route was chosen for PCA, based on experience from our Acute Pain Relief service with PCA morphine given to approximately 4,000 patients. We found that the *sc* route is more convenient than the *iv* route of administration and equally effective, with similar doses of morphine consumption and similar pain scores.[11]

Several clinical studies have established the ability of tramadol to relieve pain after a variety of surgical procedures,[6,10,15] and some have compared it favourably with morphine.[16–18] Others report using *iv* PCA tramadol with good results[18–22] but no one has made a double blind comparison of both drugs used exclusively by PCA.

A salient observation of our study was the unexpectedly large amount of tramadol consumed by the patients. In the first 24 hr postoperatively the average consumption of tramadol was 800 mg, while that of morphine was 40 mg. This use of morphine is in keeping with the range of daily PCA morphine consumption noted at our Acute Pain Relief service.[11] The demand for tramadol, however, is higher than found in most other studies using *iv* PCA tramadol. The reported values vary between 250 mg and 650 mg in the first 24 hr after a variety of general surgical or gynaecological procedures.[6] Two studies have shown greater consumption of tramadol (comparable with our results) but both used a continuous background infusion in addition to the PCA boluses.[23,24] The high tramadol usage demonstrated in our study, as compared with others, may be explained by a number of factors. Firstly, the type of the surgery performed must influence the degree of postoperative pain and the amount of analgesia required to relieve it. Only one of the previous reports included patients recovering from major orthopaedic surgery, but they were combined with other patients who had undergone gynaecological surgery.[20] The average tramadol consumption was 258 mg over 21 hr but represented the needs of possibly two dissimilar groups of patients. In fixed dose regimens, analgesia with tramadol is achieved less readily after bone surgery than after abdominal procedures.[25–27] Thus, major orthopaedic procedures necessitate potent analgesia which must be obtained with higher than usual doses of tramadol.

Secondly, the loading dose of analgesic given to our patients in the immediate postoperative period (40 mg tramadol or 2 mg morphine) was probably too small. Inadequate initial control of the pain, as reflected by the early high VAS scores, would account for the high consumption and total dose requested soon after surgery. However, it is clear from our study, that once analgesia with tramadol becomes effective, the average hourly consumption, together with the pain score, decreases rapidly. A similar pattern is seen with morphine consumption.

Thirdly, the increased tramadol requirement may result from its administration via the *sc* route as opposed to the *iv* route. Subcutaneous tramadol may be less immediately bioavailable and this may affect its apparent potency relative to morphine.

In this study, a remarkable concordance between tramadol and morphine consumption is observed when a factor of 20 is introduced. This strongly suggests a potency for tramadol of one twentieth that of morphine. Higher potency ratios (from 1/6 to 1/10) have been proposed before with *iv* PCA tramadol;[20,21] but an equipotency ratio of 1/20, derived from minimum

effective analgesic concentrations during PCA, has also been reported.[6] A study looking at the efficacy of *iv* tramadol *vs* morphine for the relief of postoperative pain, found that, for moderate pain, both drugs were equally effective in a 1:10 ratio. However, for more severe pain, tramadol, in the same ratio, was less effective than morphine.[16] Similarly, the rate of analgesic failure and the need for rescue medication is higher with tramadol than with morphine when administered in a 10:1 ratio after major surgery.[25]

As suggested above, the *sc* route of administration for tramadol, as opposed to the *iv* route, may alter its apparent potency via changes in the rates of absorption and metabolism. This is not the case for morphine which remains as effective whether given *iv* or *sc* by PCA.[11,13] The major active metabolite of tramadol, O-desmethyl tramadol, is said to have a higher affinity for opioid receptors than its parent compound,[2,9] and its concentration at any time may be affected by the way tramadol is administered.

The total amount of tramadol or morphine requested by our patients was markedly larger than that consumed in the first three to four hours after surgery. In the early postoperative period, patients are in pain (as shown by their high VAS scores), are still drowsy and trigger the PCA pump in an erratic fashion. Hence, the importance of providing early adequate pain control with generous individualised loading doses of analgesic. The possibility, in our study, of initial inadequate pain control from insufficient analgesic loading is recognised but it is unlikely to influence greatly the inter-drug comparison. Later on in the postoperative period, the difference between the number of met and unmet demands decreased considerably. By then the demands were less frequent and patients became accustomed to using the PCA device, titrating their needs with greater expertise.

Despite randomisation, the distribution of the patients to the two drug groups was uneven, with more men receiving tramadol and more women receiving morphine. The pain threshold and susceptibility to specific side-effects may differ between the sexes.[18] Differences found in the incidence of unwanted side-effects between the two drug groups were not statistically significant. Tramadol appeared to cause substantially more postoperative nausea and vomiting than morphine in our study. The emetogenic effect of tramadol is well described and recognised as one of its more troublesome side-effects.[2,5,10,16] Tramadol scored slightly better than morphine for other unwanted opioid effects, especially as regards urinary retention.

In both the tramadol and morphine groups, moderate and comparable decreases in blood pressure and small increases in heart rate were observed from 12 hr onward, postoperatively. This suggests that both drugs can be used safely under these conditions.

In this study, tramadol was found to be associated with statistically and clinically significant oxygen desaturation, although to a lesser degree than with morphine. Tramadol has been shown to cause little respiratory depression, much less than morphine, when measured by the respiratory rate, minute volume, and $P_{ET}CO_2$ under general anaesthesia,[21] or by using pulse oximetry in awake postoperative patients.[16,28] These studies, however, used "equianalgesic" doses of tramadol and morphine on the basis of an approximate 1:10 potency ratio and relatively small doses of both drugs (50–100 mg tramadol and 5–10 mg morphine). When larger doses of tramadol were used in anaesthetised patients (that is 2 $mg \cdot kg^{-1}$ *vs* 0.143 $mg \cdot kg^{-1}$ morphine corresponding to approximately a 1:20 potency ratio), a decrease in respiratory rate was observed. This, however, was not quite as marked as with morphine.[2,5,6,10,21] It is of interest to note that the relatively large doses of tramadol and morphine which caused substantial decreases in the oxygen saturation in our awake patients, had little, if any, effect on their respiratory rates.

In conclusion, tramadol is an effective analgesic agent when administered *sc* via PCA. Large doses, however, are necessary to achieve adequate postoperative pain relief. Our study challenges some of the claimed clinical differences between tramadol and morphine. It demonstrates that the effectiveness of tramadol is similar to morphine but at a much lower potency than previously suggested. At the large doses required, tramadol has a similar side-effect and safety profile as morphine. Furthermore, analgesia with tramadol costs approximately thirteen times more than morphine, in the relative amounts used by our patients.

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