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Tramadol premedication in operative extraction of the mandibular third molar: a placebo-controlled crossover study

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ORIGINAL ARTICLE

Tramadol premedication in operative extraction of the mandibular third molar: a placebo-controlled crossover study

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Abstract

Anxiolytic drugs are widely used for premedication in oral surgery. Since anxiety is usually associated with the fear of pain, we tested the effects of the analgesic tramadol in premedication before operative extraction of the mandibular third molar under local anesthesia. In a double-blind crossover study, 20 patients were randomized to receive 100 mg oral tramadol or placebo 1 h before operation. Anxiety, nausea, dryness of the mouth, pain and discomfort were recorded before administration of the drug, immediately before and after operation, and 0.5, 1, and 2 h postoperatively using ungraded 0–100 mm VAS scales. Blood pressure and heart rate were measured at the same times; vigilance was tested using the Maddox Wing Test and sensorimotor performance using the Trieger Dot Test; hemoglobin oxygen saturation (SpO_2) was measured using a pulse oximeter. In addition, SpO_2 and heart rate were recorded continuously in nine patients using a pulse oximeter connected to a computer. The surgeon assessed the quality of operating conditions on the VAS scale. Tramadol delayed and decreased the need of analgesics on the day of operation ($p<0.05$). The operating conditions were better in patients on tramadol premedication than in those on placebo during the first operation ($p<0.05$), but no differences were seen in patient well-being between treatments. The second operation was less stressful than the first. Tramadol is recommended only with special indications for premedication of patients undergoing third molar extraction under local anesthesia.

Key Words: *Dental care, opioid analgesics, oral surgery, tramadol premedication*

Introduction

Operative removal of the lower third molar is a common procedure in oral surgery [1]. Fear and anxiety often occur in these patients preoperatively, and during surgery the patients may experience discomfort [2,3]. Pain is often more intense after third molar extraction than after many other types of oral surgery [1] and can be associated with cardiovascular and respiratory effects harmful to the compromised patient.

In addition to mental preparation, these patients may benefit from premedication. As well as showing the expected drug effects, the patients should be easily arousable, cooperative, and fit for early discharge after the operation. Midazolam is the most widely used premedication in oral surgery. Its main effect is anxiolysis, but it also reduces the need for analgesics [4] and is as an adjunct to pain control. Another approach in premedication, tested in this study before extraction of the third molar, is the use of an analgesic to comfort the patient during an operation under local anesthesia and to reduce postoperative pain through pre-emptive analgesic mechanisms. In addition to their analgesic effects, several narcotic analgesics have been shown to decrease the level of anxiety, too [5,6].

The aim of this study was to test the suitability of tramadol, a weak synthetic opioid, for premedication before oral surgery. The risk of dependence is low, and the drug does not cause any clinically significant cardiovascular or respiratory depression [7,8]. Our hypothesis was that tramadol alleviates discomfort, blunts cardiovascular and respiratory responses, and makes the operation easier for the surgeon and postoperatively less painful for the patient. Extraction of the lower third molars is a reproducible surgical

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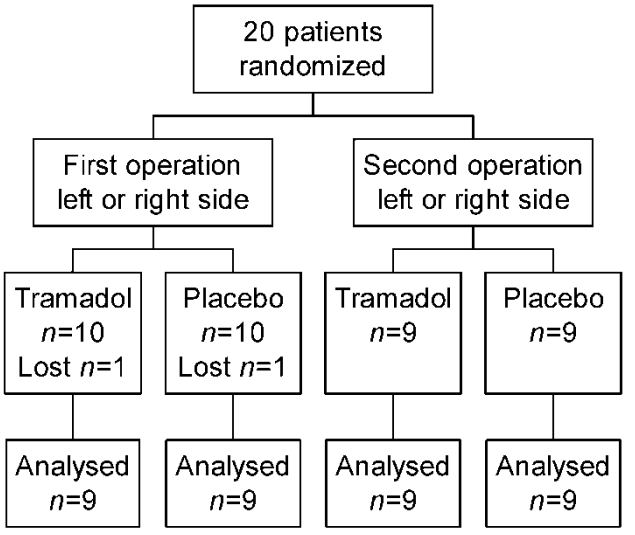

Figure 1. Study diagram of the patients with bilaterally impacted mandibular third molars scheduled for operative extraction on separate occasions. Two patients were deleted from the series after the first operation: one patient with tramadol premedication had an adverse reaction to erythromycin and another patient with placebo premedication never showed up for the second session.

operation and the extraction made on separate occasions allows the patient to act as his/her own control [9].

Patients and methods

Twenty ASA class I patients (16 F, 4 M; mean age 25.8 ± 8.1 (SD) years; weight 62.7 ± 8.8 kg, height 168.2 ± 5.9 cm) were randomized in a double-blind crossover study (Figure 1). The patients had bilaterally impacted mandibular third molars scheduled for operative extraction. They were otherwise healthy and not on any drugs except for a few women on oral contraceptives. The patients with known hypersensitivity to any component of the drugs involved were excluded. The following preoperative data were recorded clinically and using an orthopantomograph: 1. Status of the oral mucosa in the operative area: healthy/infected, 2. stage of tooth impaction: complete bony impaction/partial bony impaction/mucosal impaction, and 3. position of the impacted tooth: horizontal/mesio-angular/disto-angular/vertical.

After written informed consent had been obtained, the patients were randomized using the envelope method. There were 20 envelopes, 1 for each patient. Inside the envelope were 2 closed envelopes with 100 mg tramadol (Tramal ; Orion, Espoo, Finland) or placebo tablets, marked "operation 1" or "operation 2" and patient number. The tramadol and placebo tablets obtained from Orion looked similar. Nobody knew the drug that the patients received during premedication. The code list was in a sealed envelope in the Department and was not opened until the study had been completed.

One hour before the operation the patients received the premedication 100 mg oral tramadol or placebo. The other medication was used during the second operation in the crossover fashion as described above. The patients were operated on under local anesthesia using mandibular nerve blockade and buccal infiltration (Xylocain® dental adrenalin 20 mg/ml + 12.5 μg/ml; Dentsply Pharmaceutical, York, Pa., USA) by the same surgeon (R.-P.H.) with over 30 years' experience. Some patients in both groups needed additional doses of the local anesthetic during the operation. A standardized surgical procedure was used during the operation, one tooth being operated on at a time. The side to be operated was not randomized. A mouth rinse of 0.2% chlorhexidine (Corsodyl®; ICI-Pharma, Finland) solution for 1 min was used before surgery. Duration of the operation was measured from incision of the mucosa to completion of the last suture. One hour before operation, the patients were given 1 million IU of oral phenoxymethylpenicillin potassium (V-Pen Mega®; Orion, Espoo, Finland), and administration was continued postoperatively 3 times a day for 6 days. Erythromycin 500 mg (Ermysin®; Orion) was given to patients allergic to penicillin. The time between the two operations was 46.5 (9–175; median, range) days.

The degree of anxiety, nausea, dryness of mouth, pain and discomfort was recorded before administration of the premedication, immediately before and after the operation, and 0.5, 1, and 2 h postoperatively using the VAS [horizontal ungraded visual analog scale 0 (not at all) –100 (worst imaginable) mm] [10]. The surgeon assessed the operating conditions with VAS at the end of surgery.

Vigilance was assessed using the Maddox Wing Test [11], sensorimotor performance using the Trieger Dot Test [12]; heart rate, systolic and diastolic blood pressures, and hemoglobin oxygen saturation (SpO2) were recorded at the same times. In the Maddox Wing Test, the degree of exophoria was measured in prism diopters indicating impairment of extraocular muscular balance [11]. In the Trieger Dot Test, the number of dots connected with a line in 10 s was calculated. In addition, heart rate and hemoglobin oxygen saturation were recorded in nine patients continuously using a pulse oximeter (Satlite; Datex-Ohmeda, Helsinki, Finland) connected to a computer. Six SpO_2 and heart rate signals were stored per minute in these patients during the whole operation. After operation, the patients were given 15 capsules of ketoprofen 50 mg (Ketorin®; Orion) against postoperative pain and three tablets of a combination preparation containing paracetamol 500 mg and codeine phosphate 30 mg (Panacod®; Sanofi-Synthelabo, Finland) as a rescue analgesic to be taken as needed. The patients recorded the use of analgesics and other medication for 4 days postoperatively.

The Joint Ethics Committee of the Turku University Medical Faculty and the Turku University Central Hospital approved the study.

Table I. Position of the lower third molars operated on

	Tramadol premedication ($n=18$)	Placebo premedication ($n=18$)
Horizontal	3	2
Mesioangular	7	7
Distoangular	2	3
Vertical	6	6

No statistically significant differences between the patients with tramadol or placebo premedication.

Table II. Operating conditions when tramadol or placebo was administered as premedication during the first or second operation. VAS scores on a 0 (poor) –100 mm (good) scale estimated by the oral surgeon. Means ± SD

	Tramadol premedication ($n=18$)	Placebo premedication ($n=18$)	p
First operation			
VAS	85.8 ± 19.0	55.7 ± 23.6	<0.05
Second operation	n.s.	<0.05	
VAS	72.8 ± 19.4	79.0 ± 15.2	n.s.

Statistics

Values are presented as means ± SD for normally distributed variables and median (lower–upper quartiles) for non-normally distributed variables. Data from the 2×2 crossover trial were analysed using the two-sample *t*-test and the Mann-Whitney U-test [13]. First, carryover effects were tested at a 0.10 significance level. If the carryover effects were not significant, period and treatment effects were assessed using a 0.05 significance level. Analyses were done separately for each time-point. The SAS System for Windows (release 8.02; SAS Institute Inc., Cary, N.C., USA) was used in statistical computations.

The primary endpoint of this study was patient comfort during the operation characterized by VAS. Twelve (anxiety), 16 (pain), and 18 (somnolence) patients were required, respectively, to detect a 100% difference in VAS score values between the treatments with a statistical power of 90% and an α risk error of <0.05. It was assumed that only a marked difference in test values has clinical implications.

Results

Two of the patients were excluded after their first operation, because one patient with tramadol premedication had an adverse reaction to erythromycin; the other patient, with placebo during the first operation, never showed up for the second session.

The clinical preoperative status of the lower third molar to be removed was similar in both groups (Table I). In no patient did the molar perforate the oral mucosa. The mucosa above the third molar was infected in two patients in the tramadol group (in one patient receiving tramadol during the first operation and in another receiving it during the second operation), but not in any of the placebo group patients.

The order in the administration of tramadol or placebo, i.e. whether during the first or the second operation, had an effect (= carryover effect) on (1) the quality of operating conditions ($p<0.05$), (2) the need for postoperative analgesics ($p<0.10$), (3) anxiety before operation ($p<0.10$), (4) nausea before operation ($p<0.10$), and (5) dryness of the mouth 1 h after operation ($p<0.10$). The effects of tramadol and placebo could not, therefore, be compared with these values for the study population as a whole.

Whether it was the first or the second operation for third molar removal also had an effect on the results (= periodic effect). Lower values were seen during the second operation than during the first irrespective of the drug in (1) systolic blood pressure before operation ($p<0.05$), (2) anxiety at the end of surgery ($p<0.05$) and 30 min thereafter ($p<0.05$), (3) dryness of the mouth before premedication ($p<0.05$) and 30 min after the operation ($p<0.10$), and (4) discomfort before premedication ($p<0.05$). Higher values were seen during the second operation in (1) hemoglobin oxygen saturation before operation ($p<0.05$) and (2) Trieger Dot Test values before premedication ($p<0.05$) and before operation ($p<0.05$).

The total amount of local anesthetic used during tramadol premedication [4.5 (3.6–5.4) ml (median, lower-upper quartile) of Xylocain® dental adrenalin 20 mg/ml + 12.5 μg/ml] was lower than during placebo [5.4 (5.2–5.7) ml] ($p<0.05$). By contrast, the duration of dental extraction [11.9 ± 4.6 min (mean ± SD) after tramadol premedication versus 12.9 ± 5.4 min after placebo] and time to discharge after operation [141.0 (131–154) min (median, lower-upper quartile) versus 137.0 (130–142) min, respectively] showed no differences between the premedications.

The quality of the operating conditions was better during the first operation in the patients who had received tramadol compared with placebo ($p<0.05$, Table II). By contrast, no such effect was seen when the effects of tramadol and placebo were compared during the second operation. The operating conditions, however, were better in patients who received placebo during the second operation than in those who received it during the first operation ($p<0.05$). No such effect was seen with tramadol.

No differences were found in the degree of anxiety, nausea, dryness of the mouth, pain or discomfort between the treatments (Table III). No vomiting occurred in any of the patients. The Maddox wing and Trieger tests showed no differences between the premedications, either (Table IV). Systolic blood pressure, heart rate, and pulse oximetry readings were

Table III. VAS scores in patients with tramadol or placebo premedication on a 0–100 mm scale. Median (lower-upper quartile)

	Before premedication ($n=18$)	Before operation	End of operation	After operation 30 min	1 h	2 h
Anxiety						
Tramadol	31.5 (7.0–66.0)	21.0 (6.0–68.0)*	0 (0–14.0)†	0 (0–6.0)†	0 (0–0)	0 (0–0)
Placebo	33.5 (14.0–56.0)	27.5 (12.0–42.0)	0 (0–4.0)	0 (0–0)	0 (0–0)	0 (0–0)
Nausea						
Tramadol	0 (0–0)	0 (0–6.0)*	0 (0–4.0)	0 (0–5.0)	0 (0–8.0)	0 (0–5.0)
Placebo	0 (0–0)	0 (0–0)	0 (0–0)	0 (0–6.0)	0 (0–0)	0 (0–0)
Dryness of the mouth						
Tramadol	0 (0–21.0)†	6.0 (0–25.0)†	0 (0–29.0)	3.5 (0–12.0)†	1.5 (0–9.0)*	0 (0–7.0)
Placebo	6.0 (0–19.0)	4.5 (0–12.0)	0 (0–19.0)	0 (0–14.0)	0 (0–12.0)	0 (0–6.0)
Pain						
Tramadol	0 (0–0)	0 (0–0)	0 (0–0)	0 (0–4.0)	0 (0–16.0)	4.5 (0–22.0)
Placebo	0 (0–0)	0 (0–0)	0 (0–16.0)	0 (0–11.0)	0 (0–12.0)	13.5 (1.0–36.0)
Discomfort						
Tramadol	4.5 (0–20.0)†	9.0 (0–22.0)	17.0 (0–39.0)	8.0 (0–34.0)	9.0 (0–32.0)	12.0 (0–29.0)
Placebo	4.0 (0–16.0)	4.0 (0–18.0)	13.5 (0–42.0)	13.0 (0–26.0)	15.0 (0–32.0)	12.0 (0–38.0)

* Carryover effect, i.e. the order of drugs administered has an effect on the values.
† Periodic effect (VAS test values lower during the second operation than during the first).
No statistically significant differences between the groups.

also similar, but diastolic blood pressure at 30 min after operation was a mean 3.2 mmHg lower after placebo than after tramadol premedication ($p<0.05$, Table V).

Hemoglobin oxygen saturation and heart rate were fully recorded during both operations in nine patients. Mean SpO_2 during the recording was slightly higher after tramadol than after placebo ($p<0.05$, Table VI). By contrast, the mean of the lowest reading in each patient showed no difference between the treatments. In two of the continuously recorded nine patients, SpO_2 was temporarily below 90% after placebo and in one patient after tramadol. Mean heart rate and the means of the lowest and the highest heart rate recordings were also similar between premedications (Table VI).

On the day of surgery, the time after the operation when the patients took their first dose of analgesic was during tramadol premedication 162.5 min (140–201; median, lower-upper quartile) and during placebo 84 min (23.5–139). This difference in time between patients with tramadol or placebo premedication showed a carryover effect. The difference was statistically significant during the first operation ($p<0.05$). On the day of surgery after the first operation, patients with tramadol premedication took ketoprofen orally 75 (50–100) mg (median, lower-upper quartile) and patients with placebo 150 (100–150) mg ($p<0.05$), but during the second operation no such difference was seen on the following 2 days, either. On the day of operation, two patients with tramadol premedication took ibuprofen or paracetamol-codeine tablets in addition to ketoprofen and one patient with placebo premedication, but the difference between the premedications remained statistically significant. One patient had an erythematous adverse reaction to

Table IV. Maddox Wing Test (in diopters; median and lower-upper quartile) and Trieger Dot Test results (dots/10 s; mean ± SD) in patients with tramadol or placebo premedication

	Before premedication ($n=18$)	Before operation	End of operation	After operation 30 min	1 h	2 h
Maddox Wing Test, diopters						
Tramadol	0.6 (0.1–1.1)	1.0 (0.1–1.1)	1.1 (0.1–2.0)	0.6 (0.1–2.0)	1.1 (0.1–2.0)	1.1 (0.5–2.0)
Placebo	1.1 (0.1–2.0)	1.1 (0.1–2.0)	1.1 (0.1–2.0)	1.1 (0.1–2.0)	1.1 (0.5–2.0)	1.1 (0.5–2.0)
Trieger Dot Test, dots/10 s						
Tramadol	28.9 ± 7.3†	31.4 ± 7.8†	31.2 ± 8.0	30.4 ± 8.2	31.2 ± 6.6	32.4 ± 7.2
Placebo	27.4 ± 6.4	30.0 ± 8.7	28.1 ± 5.5	30.5 ± 5.2	33.0 ± 6.4	31.7 ± 7.3

No statistically significant differences between premedications.
† Periodic effect (Trieger Dot Test values higher during the second operation than during the first).

Table V. Hemodynamic data and hemoglobin oxygen saturation in patients with tramadol or placebo premedication (mean ± SD)

	Before premedication ($n=18$)	Before operation	End of operation	After operation 30 min	1 h	2 h
Systolic blood pressure, mmHg						
Tramadol	124.2 ± 9.1	121.4 ± 8.1†	122.6 ± 14.9	117.6 ± 12.1	113.6 ± 9.8	120.0 ± 10.0
Placebo	125.1 ± 7.8	124.5 ± 11.3	130.0 ± 12.8	117.9 ± 12.3	118.6 ± 7.1	123.1 ± 11.1
Diastolic blood pressure, mmHg						
Tramadol	81.5 ± 9.8	77.9 ± 9.4	77.6 ± 7.9	78.4 ± 7.0‡	76.9 ± 6.9	78.7 ± 8.3
Placebo	83.3 ± 8.8	80.5 ± 9.1	85.1 ± 13.6	75.2 ± 5.9	77.0 ± 8.5	82.5 ± 11.3
Heart rate, beats/min						
Tramadol	82.9 ± 14.0	75.1 ± 11.9	74.1 ± 13.4	73.8 ± 13.8	69.7 ± 9.6	68.1 ± 13.6
Placebo	81.8 ± 15.0	74.9 ± 12.3	79.1 ± 12.6	71.8 ± 9.1	70.4 ± 8.7	67.1 ± 9.5
Hemoglobin oxygen saturation (SpO_2), %						
Tramadol		98.1 ± 0.9†	97.5 ± 1.1			
Placebo		97.8 ± 0.9	97.5 ± 1.1			

† Periodic effect (SpO_2 values higher during the second operation than during the first).
‡ $p < 0.05$, difference between tramadol and placebo premedication at 30 min after operation.

erythromycin during the first operation and was therefore excluded from the series. No other complications occurred in any of the patients

Discussion

Notably, in this kind of 2 × 2 crossover study, the study design should be considered in the statistical analysis instead of simply comparing the test results between groups. Our statistical analyses showed that in some respects the order in which the test drugs were administered had an effect on the results (carryover effect). Our study also involved the well-known phenomenon that a patient may feel their first operation more stressful than the following operation (periodic effect).

Besides the above general findings, a main finding of our study was that the operating conditions were better during the first operation when the patients had received tramadol as premedication than when they had received placebo. This phenomenon was not seen during the second operation since, due to the periodic effect, the operating conditions had improved in the placebo group to the level of the tramadol group. Such an improvement was not found in the tramadol group between the first and second operations. Despite the improved operating conditions, however, the operation times were similar during both treatments. Another finding of practical significance was that during their first operation patients in the tramadol group later needed analgesics, and the need was less after tramadol premedication than after placebo.

By contrast, no differences were seen between the treatments in VAS anxiety, nausea, and dryness of the mouth, pain or discomfort scores. We used the visual analog scale (VAS) and not for example Corah's Dental Anxiety Scale (DAS) [14,15]. The VAS scale measures various aspects of subjective feelings and is better suited to follow-up studies than DAS. In this study, it was assumed that only a marked difference in test values is of clinical significance, but the patient VAS scores in this study were close to each other after tramadol and placebo premedication. Neither was there any difference between the groups in the Maddox Wing Test or Trieger Dot Test results, systolic blood pressure, heart rate, or pulse oximeter readings. The temporary difference of 3.2 mmHg in diastolic blood pressure between the treatments is not clinically important. Of minor clinical importance is the finding that hemoglobin oxygen saturation was 0.3% higher

Table VI. Hemoglobin oxygen saturation (SpO_2) and heart rate measured by continuous monitoring during operation (mean ± SD)

	Tramadol premedication ($n=9$)	Placebo premedication ($n=9$)	p
Hemoglobin oxygen saturation (SpO_2), %			
SpO_2, mean	97.8 ± 0.8	97.5 ± 0.6	< 0.05
Lowest reading in each patient, mean	94.8 ± 3.3	93.0 ± 4.7	
Heart rate, beats/min			
Heart rate, mean	88.8 ± 20.1	91.2 ± 14.8	
Lowest reading in each patient, mean	71.6 ± 22.6	71.7 ± 16.7	
Highest reading in each patient, mean	109.3 ± 18.1	110.6 ± 12.8	

p = Difference between patients with tramadol or placebo premedication.

after tramadol than after placebo on continuous monitoring.

Nausea and dizziness are the most common adverse effects of tramadol [16,17]. In a study by Collins et al. of the effects of tramadol on dentoalveolar surgical pain, 39% of patients on high doses of tramadol (100 mg four times a day orally), or 12% on moderate doses (50 mg four times a day), but only 6% on low doses (50 mg twice a day) withdrew from the study owing to nausea, vomiting, dizziness, or drowsiness [18]. In another study in patients undergoing third molar extraction under general anesthesia, the incidence of nausea and vomiting was high in the patients on intravenous tramadol and ondansetron during operation [19]. In fact, the incidence of nausea and vomiting is lower after oral than after parenteral administration [17]. Accordingly, in our study, oral tramadol had no effect on nausea VAS scores compared with placebo. Further, when we calculated the number of patients showing a nausea VAS score over zero at any time, no difference was found between the effects of tramadol and placebo. Moreover, after tramadol premedication, only 3 of the 18 patients reported a nausea VAS score above 40 at any time compared to 2 patients after placebo. No patient in our series complained of the other common adverse effect, dizziness. An explanation for the absence of these adverse effects in our study could be the single moderate oral dose. The cardiovascular effects seen in our patients were slight during operation in both groups, and the hemoglobin oxygen saturation remained at a safe level.

The degree of anxiety in our patients was rather high before premedication. It decreased slightly after premedication but did not disappear until the end of operation. From this aspect, a benzodiazepine would have been a more suitable premedication than tramadol, since tramadol, unlike many other opioids [5,6], had no effect on the level of anxiety in our study. The slightly lower need of the local anesthetic after tramadol premedication is of minor clinical importance.

The patients with both premedications were maintained pain-free. As postoperative analgesic, ketoprofen was found sufficient for pain relief. Tramadol has been used as an effective postoperative analgesic after dentoalveolar operations, too [18]. The effect of preoperatively administered tramadol persisted postoperatively in our study on the day of operation as a delayed and lower need for analgesics during the first operation compared with placebo. We did not investigate whether this was a sign of the preemptive treatment principle [20], but another study of the removal of impacted third molars under local anesthesia found no such effect [21].

Tramadol is a racemic mixture of (+) tramadol and (–) tramadol [22] with two synergistic mechanisms of action. Its main metabolite is a μ-agonist, but tramadol also inhibits the uptake of noradrenaline and 5-hydroxytyptamine (5-HT) in the central nervous system, and facilitates 5-HT release [22]. These effects are attributed to the separate enantiomers of tramadol. Tramadol is metabolized by hepatic cytochrome P450 to 11 demethylated metabolites, of which the (+)-enantiomer of O-desmethyltramadol (M1) possesses analgesic properties [23,24]. By contrast, the monoaminergic component of tramadol analgesia is probably mediated by (+)- and (–)-tramadol [23]. The O-demethylation to M1 is dependent on the enzyme spartane oxygenase CYP2D6, an isoenzyme of the cytochrome P450 system. Seven to 10% of Caucasians are deficient in this enzyme [25] and are poor metabolizers of tramadol with reduced analgesia [23,26]. The analgesic effect in these poor metabolizers is primarily due to the effect of monoaminergic pathways. We saw differences in the postoperative consumption of analgesics, but no conclusions could be drawn as to whether these were due to differences in the extent of tramadol metabolism, since no analyses were made in this respect.

In conclusion, tramadol given during lower third molar extraction improved the quality of operating conditions during the first operation, and delayed and decreased the need for postoperative analgesics. It had no effect on anxiety or other aspects of patient comfort. Tramadol cannot be recommended for routine premedication in third molar extraction but it may be indicated when pain is a problem or when non-steroidal anti-inflammatory analgesics are inadequate or contraindicated.

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