ELSEVIER

Ambulatory Surgery 4 (1996) 25–29

Ambulatory Surgery

The efficacy and safety of postoperative pain management with tramadol for day case surgery

P. Coulthard*, A.T. Snowdon, J.P. Rood

Oral and Maxillofacial Surgery, Department of Dental Medicine and Surgery, University Dental Hospital of Manchester, Higher Cambridge Street, Manchester, M15 6HI UK

Accepted 5 May 1996

Abstract

The efficacy and safety of the centrally acting analgesic, tramadol hydrochloride (Zydol), was investigated in 20 day case patients undergoing removal of impacted third molar teeth under intravenous sedation and local anaesthesia. A single 100-mg dose of tramadol was administered intravenously just prior to induction of sedation with midazolam. Tramadol was well tolerated and provided good postoperative analgesia. There was no evidence of respiratory depression and tramadol did not have any sedative effect. It is suggested that tramadol is a useful addition to the analgesic armamentarium for use in out-patient and day-case oral surgery.

Keywords: Analgesia postoperative; Tramadol; Oral surgery; Day case surgery

1. Introduction

Although many variants of opioids and non-steroidal anti-inflammatory drugs (NSAIDs) have been introduced in pain management, there are still challenging problems in clinical practice [1]. Whilst morphine may remain the gold standard for the treatment of severe acute pain in in-patients, it is not suitable for out-patients and day-case surgery postoperative pain control. Respiratory depression can be a serious complication of opioid use and the problems of tolerance, addiction and abuse are well known [2]. Weak opioids like codeine have proven to be pro-drugs of morphine-like metabolites and to be flawed by problems of those similar to morphine [3]. The NSAIDs remain first-line therapy for dental postoperative pain which is largely inflammatory in origin but have problems of gastric toxicity and bronchospasm [4–7] and have limited use in the control of severe rather than mild or moderate pain [1,8].

Tramadol is described as a centrally acting analgesic that has demonstrated that it is possible to differentiate between effective analgesia and severe opioid-typical side effects, that moderate to severe pain can be relieved without respiratory depression, constipation, euphoria and with a greatly minimised abuse and dependency potential [9]. The analgesic properties of tramadol are not completely explained by action via opioid receptors, as in some pain models its antinociceptive effect is only partially antagonised by naloxone. A second mechanism of action has been described which results in inhibition of the descending monoaminergic systems [10–12]. The dual mode of action is claimed to result in a synergistic potentiation of analgesia by the component effects and weakly expressed side-effects. The presence and relevance of this mode of action in humans is supported by the findings of Dayer et al. [12] and Sunshine [13]. The objective of the study was to assess the efficacy and safety of intravenous (i.v.) tramadol hydrochloride (Zydol) in

* Corresponding author. Oral and Maxillofacial Surgery, Department of Dental Medicine and Surgery, University Dental Hospital of Manchester, Higher Cambridge Street, Manchester, M15 6HI, UK. Tel.: +44 161 2756650; fax: +44 161 2756776.

PII S0966-6532(96)00108-4

patients undergoing surgical removal of an impacted third molar tooth under local anaesthesia and intravenous (i.v.) sedation. The study was double-blind, randomised and placebo-controlled.

2. Methods

Twenty patients who required removal of an impacted lower third molar, with bone removal and tooth division, and who might also have required extraction of an upper ipsilateral third molar were entered into the study. Patients were to be aged 18–45 years, weigh between 50 and 100 kg and be in general good health. The main exclusion criteria were: pregnancy or lactation; history of epilepsy or other clinically-significant co-existing disease; history of alcohol, narcotic or other drug abuse; recent or concomitant use of MAO inhibitors or other medication likely to interfere with the study drug or its assessment and a history of hypersensitivity to opioid drugs. All patients entering the study gave written informed consent prior to its commencement and ethics committee approval of the protocol was obtained.

The study was blinded by means of a saline placebo solution with identical packaging to the tramadol and only the patient's number as an identifier. Whether the medication assigned to a given patient number was active or placebo was determined according to a computer-generated randomisation code. Patients were assigned their study numbers sequentially as they entered the study. The tramadol intravenous solution was supplied as 100 mg/ml in clear ampoules. All treatments were carried out by the same operator and all assessments by a single research nurse.

The patient was placed in the supine position and the tramadol or placebo administered by slow (100 mg over 2 min) bolus injection via an indwelling cannula in the dorsum of the hand. This was immediately followed by induction of sedation with the 2 mg/ml preparation of intravenous midazolam (Hypnovel). The latter was titrated slowly, via the same cannula, to the desired sedation end point, but not exceeding 10 mg. Local anaesthesia was induced with prilocaine 4% solution without vasoconstrictor and therefore shorter acting. The time at which the study medication was administered, the dose of midazolam administered and the times at which surgery started and ended were recorded. At tooth division the intraoperative pain was assessed by the patient according to the verbal rating scale (VRS): none, mild, moderate or severe.

Immediately after the completion of surgery, the first postoperative pain assessment was made as a baseline measure. The pain assessments were made by means of a 100-mm visual analogue scale (VAS) and a verbal rating scale (VRS). The VAS was marked at one end 'I have no pain' and at the other, 'The worst pain imaginable'. The VRS was presented as none, mild, moderate and severe. Further assessments were made every 15 min until 2 h after baseline and then at 2 h 30 min and finally at 3 h after baseline. Postoperative analgesia, if required, was ibuprofen, 200 mg tablets, the dosage being 400 mg. The time at which any patient requested and took the escape analgesia was recorded.

Shortly before the patient was discharged from hospital, the patient and the investigator made global assessments of the study therapy. Global assessments of the efficacy and tolerability of the medication, and the quality of the sedation, were made by means of the VRS: poor, satisfactory or excellent.

Safety was evaluated by continuous recording by automatic sphygmomanometer and pulse oximeter of blood pressure, pulse rate and arterial oxygen saturation. Any clinically significant deviations in any of these parameters was recorded as an adverse event. Patients were asked for symptomatic complaints using indirect questioning at each assessment. A phrase such as 'Is anything other than the surgery pain bothering you?' was used. All symptoms were recorded as adverse events, whether or not deemed to be causally associated with the study medication. The time of discharge was recorded and the reason for any delay in discharging the patient was noted. At follow-up, 15 days after surgery, the patient was questioned about any adverse events which may have occurred since the end of the study. At this time the patient also made a final global assessment of the study therapy.

3. Results

All 20 patients who were recruited into the study were included in both the efficacy and safety analyses. Ten patients were randomised to receive tramadol and 10 to receive placebo. Statistical analysis was performed using SPSS (production release for Windows). All significance tests were two-tailed and carried out at the 5% level. All summaries of data were by treatment group.

Demographic details are shown in Table 1. Mean midazolam doses were 7.7 mg and 6.8 mg in the tramadol and placebo groups, respectively. Taking

Table 1
Demographic details of study patients

	Tramadol	Placebo	Overall
Number of patients	10	10	20
Male	4 (40%)	4 (40%)	8 (40%)
Female	6 (60%)	6 (60%)	12 (60%)
Mean age (years)	24	27	25.5
Mean weight (kg)	72.4	66.1	69.3

Table 2
The areas under the visual analogue (VAS) curves assessing 3 hof postoperative pain

	Tramadol	Placebo
Number of patients	10	10
Using analysis as if rescue medication was not taken[a]		
Median	0.9	7.9
Range	0.0–27.0	0.3–33.2
Using substitution for missing data and for data recorded after first use of escape analgesia[a]		
Median	2.1	13.4
Range	0.0–36.4	0.2–61.2

[a]Treatment comparison, byWilcoxon Rank Sum Test, <IT>P</IT> = 0.005

body weight into account, the mean dose of midazolam was 0.11 mg/kg for both groups. All patients received 4.4 ml of prilocaine for the removal of the lower third molar and 2.2 ml for the extraction of the upper if this was carried out. The mean duration of surgery was 14.4 min in the tramadol group and 12.5 min in the placebo group. The overall duration ranged from 9 to 22 min.

3.1. Efficacy

3.1.1. Intraoperative pain severity

Six patients in the tramadol group reported no intraoperative pain. Of the four who did report pain, all patients reported it as mild. These figures were the same for the placebo group.

3.1.2. Postoperative VAS pain scores

The primary efficacy variable is the area under the curve (AUC) of the postoperative pain assessments measured using a VAS. AUCs are summarised by presenting the median and range for each treatment in Table 2. The study protocol stated that pain assessments need not be continued after a patient had taken postoperative analgesia. However, patients who did take postoperative analgesia carried on with the assessments of pain until 3 h after the baseline assessment. In order to accommodate these additional data, the AUCs were calculated in two different ways. In the first method assessments made after a patient had taken postoperative analgesia were analysed as if the analgesia had not been taken. In the second method, assessments made after a patient had taken postoperative analgesia were assumed to be missing, and all missing assessments were substituted using the last observation carried forward (LOCF) method. Using the first method, the median standardised AUC was 0.9 in the tramadol group compared with 7.9 in the placebo group. The smaller values indicate less overall pain. The difference between treatment groups tested using the Wilcox Rank Sum test achieved statistical significance ($P = 0.005$). Using substitution for missing data and data recorded after the first use of postoperative analgesia, the median standardised AUCs were 2.1 and 13.4 in the tramadol and placebo groups, respectively. Again the treatment difference was statistically significant ($P = 0.005$).

3.1.3. Postoperative VRS scores

Of patients in the tramadol group, 50% reported no pain and 50% reported mild or moderate pain. No patient reported severe pain. In the placebo group 10% of patients reported no pain and 80% reported mild or moderate pain. Of all patients, 10% reported severe pain. The treatment difference was statistically significant ($P = 0.005$).

3.1.4. Time to first postoperative analgesia

The number of patients who had taken escape analgesia by each postoperative pain assessment is illustrated in Fig. 1. Of the patients in the tramadol group, 20% had taken postoperative analgesia up to 1 h 45 min from baseline, compared with 50% in the placebo group. All patients took ibuprofen only. The mean time to escape analgesia was 119 min for the tramadol group and 89 min for the placebo group.

3.1.5. Time to hospital discharge

The mean time to hospital discharge was 204.2 min and 205.9 min for the tramadol and placebo groups, respectively.

3.1.6. Global assessment of intraoperative analgesia

In both treatment groups the investigators assessment was 'satisfactory' or 'excellent' for almost all patients, and 90% of the patients' assessments at discharge and follow-up were rated 'satisfactory' or 'excellent'. There was no statistically significant difference between groups.

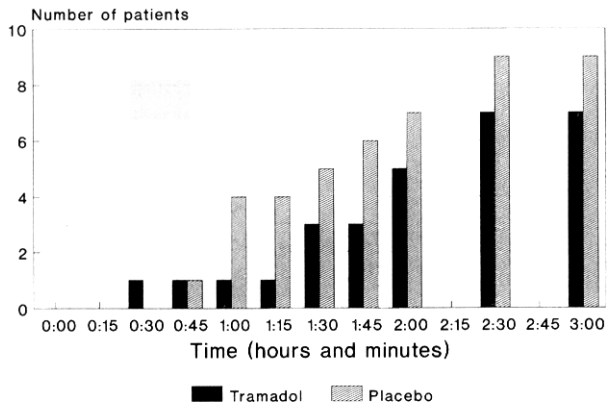

Fig. 1. Number of patients who had taken escape analgesiaby each postoperative pain assessment.

3.1.7. Global assessment of intraoperative sedation

The assessment by the investigator at discharge, and assessments by the patient at both discharge and follow-up were 'excellent' for almost all patients, and showed no statistically significant difference between treatment groups.

3.1.8. Global assessment of postoperative analgesia

At hospital discharge the investigator rated postoperative analgesia as excellent in 90% of the tramadol group compared with 40% of the placebo group. The treatment difference was statistically significant. At hospital discharge 70% of patients in the tramadol group rated postoperative analgesia as excellent compared with 50% in the placebo group. At follow-up 90% of tramadol patients and 40% of placebo patients gave a rating of excellent.

3.2. Safety: adverse events

There were no clinically significant changes in pulse rate, blood pressure or arterial oxygen saturation in any patient during the study. At follow up, one patient receiving tramadol reported postoperative nausea.

4. Discussion

The two treatment groups were very similar. Approximately 60% of all patients were female, with no co-existing diseases. Surgery details for the two treatment groups were also similar. All patients received an identical dose of prilocaine and the mean dose of midazolam in the two treatment groups was similar (tramadol 7.7 mg, placebo 6.8 mg). The duration of surgery was slightly longer in the tramadol group compared to the placebo group (mean 14.4 min compared to 12.5 min). There was no statistically significant difference in the patients' intraoperative pain.

4.1. Efficacy

There were clear treatment differences between the groups regarding postoperative pain assessed by the VASs or VRSs. The VAS assessments yielded median AUC values of 2.1 in the tramadol group compared to 13.4 in the placebo group, and this difference was statistically significant. The VRS assessment of postoperative pain also favoured tramadol. Fewer tramadol patients than placebo patients reported any pain (50% compared to 90%). Again this treatment difference was statistically significant ($P = 0.005$).

The global assessments of post-operative analgesia also favoured tramadol, but the difference in time to escape analgesia between the tramadol and placebo groups was not statistically significant.

4.2. Safety

There were no adverse events during the 3-h period of the study in either the tramadol or the placebo group and there was no evidence of respiratory depression in the tramadol group as measured by arterial oxygen saturation. The doses of midazolam administered were similar in both groups indicating that tramadol did not have any sedative effect. One patient indicated a period of nausea without vomiting, lasting several hours, later in the day of the study.

5. Conclusions

Administration of a single, preoperative, 100-mg dose of i.v. tramadol significantly reduces the postoperative pain experienced by patients undergoing removal of impacted third molar teeth under local anaesthesia and intravenous sedation, as assessed by visual analogue and verbal rating scales. Intravenous tramadol was very well tolerated by the study population and was found to be safe to use in combination with midazolam i.v. sedation for day-case patients.

It is suggested that tramadol is a useful addition to the analgesic armamentarium [14].

Acknowledgements

The funding from Gruenenthal Gmbh, Stolberg, Germany, that made this study possible is gratefully acknowledged.

References

[1] Gobbetti JP. Controlling dental pain. *J Am Dent Assoc* 1992; **123** (6): 47–52.
[2] Zenz M, Willweber-Strumpf A. Opiophobia and cancer pain in Europe. *Lancet* 1993; **341**: 1075–1076.
[3] Cowan A. Mechanism of opioid activity. *Curr Opin Anaesthesiol* 1992; **5**: 529–534.
[4] Rainsford KD. Mechanisms of gastrointestinal damage by NSAIDs. *Agents Actions Suppl* 1993; **44**: 59–64.
[5] Blower PR. Non-steroidal anti-inflammatory drugs. *Br J Rheumatol* 1993; **32** (4): 35–38.
[6] McCarthy DM. Nonsteroidal anti-inflammatory drugs — the clinical dilemmas. *Scand J Gastroenterol Suppl*; 1992; **192**: 9–16.
[7] Lee TH. Mechanism of bronchospasm in aspirin — sensitive asthma [editorial]. *Am Rev Respir Dis*; 1993; **148** (6,1): 1442–1443.
[8] Hargreaves KM, Troullos ES, Dioune RA. Pharmacologic rationale for the treatment of acute pain. *Dent Clin North Am* 1987; **31** (4): 675–694.
[9] Dioune RA. New approaches to preventing and treating postoperative pain. *J Am Dent Assoc* 1992; **123** (6): 26–34.
[10] Raffa RB, Friderichs E, Reimann W, Shank RP, Codd EE, Vaught JL. Opioid and non-opioid components independently

contribute to the mechanism of action of tramadol, an atypical opioid analgesic. *J Pharmacol Exp Ther* 1992; **260**: 275–285.

[11] Kayser V, Besson JM, Guilbaud G. Evidence for a noradrenergic component in the anti-nociceptive effect of the analgesic agent tramadol in an animal model of clinical pain, the arthritic rat. *Eur J Pharmacol* 1992; **224**: 83–88.

[12] Dayer P, Collart L, Desmeules J. The pharmacology of tramadol. *Drugs* 1994; **47** (1): 3–7.

[13] Sunshine A. New clinical experience with tramadol. *Drugs* 1994; **47** (1): 8–18.

[14] Tramadol (Zydol) Data Sheet. Searle Pharmaceuticals, PO Box 53, Lane End Road, High Wycombe, Buckinghamshire, HP12 4HL.