Tramadol and Acetaminophen Tablets for Dental Pain

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The purpose of this work was to compare the efficacy and time to analgesia of a new tramadol/acetaminophen combination tablet to those of tramadol or acetaminophen (APAP) alone. A meta-analysis was performed of 3 separate single-dose, double-blind, parallel-group trials in patients with moderate or severe pain following extraction of 2 or more third molars. Patients in each study were evenly randomized to a single dose of tramadol/APAP (75 mg/650 mg), tramadol 75 mg, APAP 650 mg, ibuprofen 400 mg, or placebo. Active control with ibuprofen was used to determine model sensitivity. Pain relief (scale, 0–4) and pain intensity (scale, 0–3) were reported at 30 minutes after the dose and then hourly for 8 hours. Total pain relief over 8 hours (TOTPAR8) and the sum of pain intensity differences (SPID8) were calculated from the hourly scores. Time to onset of pain relief was determined by the double-stopwatch technique, and patients were advised to wait at least 2 hours before taking supplemental analgesia. Patients assessed overall efficacy (scale, 1–5) upon completion. In all, 1197 patients (age range, 16–46 years) were evaluable for efficacy; treatment groups in each study were similar at baseline. Pain relief was superior to placebo ($P \leq .0001$) for all treatments. Pain relief provided by tramadol/APAP was superior to that of tramadol or APAP alone, as shown by mean TOTPAR8 (12.1 vs 6.7 and 8.6, respectively, $P \leq .0001$) and SPID8 (4.7 vs 0.9 and 2.7, respectively, $P \leq .0001$). Estimated onset of pain relief was 17 minutes (95% CI, 15–20 minutes) for tramadol/APAP compared with 51 minutes (95% CI, 40–70 minutes) for tramadol, 18 minutes (95% CI, 16–21 minutes) for APAP, and 34 minutes (95% CI, 28–44 minutes) for ibuprofen. Median time to supplemental analgesia and mean overall assessment of efficacy were greater ($P < .05$) for the tramadol/APAP group (302 minutes and 3.0, respectively) than for the tramadol (122 minutes and 2.0) or APAP (183 minutes and 2.7) monotherapy groups. A new combination analgesic, tramadol/APAP, is superior to tramadol or APAP alone with respect to pain relief and duration of action. It is also superior to tramadol alone with respect to time to onset.

Key Words: Tramadol; Analgesia; Acute pain; Acetaminophen; Ibuprofen.

The objective of these studies was to determine the therapeutic profile (efficacy, tolerability, and onset and duration of action) of a combination tramadol/acetaminophen (APAP) tablet for the treatment of acute pain. The dental pain model is frequently used to determine the safety and effectiveness of new analgesics for acute pain. This model evaluates pain relief and pain intensity following the extraction of third molars. However, given the role of inflammation in postoperative dental pain, nonsteroidal antiinflammatory drugs (NSAIDs) usually achieve the greatest pain relief in this model (NSAID > aspirin > opioid/APAP > APAP > opioid > placebo), which may understate the analgesic efficacy of opioids and opioid combinations for acute pain.

METHODS

Subjects

To qualify for these trials, patients had moderate or severe pain (≥5 on a 10-point visual analog scale) following extraction of ≥2 ipsilateral third molars requiring bone removal. Key inclusion criteria included ≥16 years

Anesth Prog 48:79–81 2001

ISSN 0003-3006/01/$9.50
SSDI 0003-3006(01)

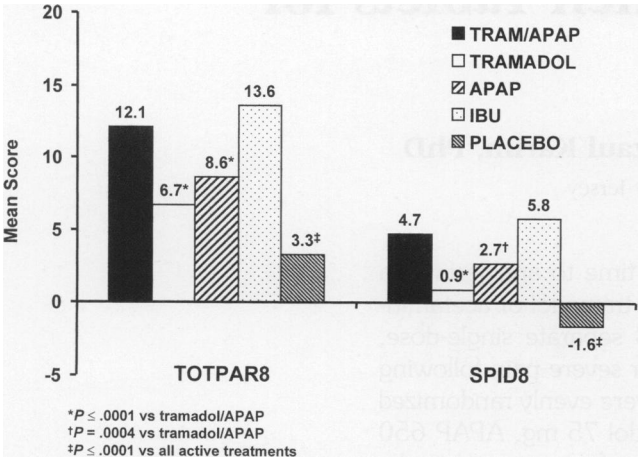

Figure 1. Pain relief and intensity.

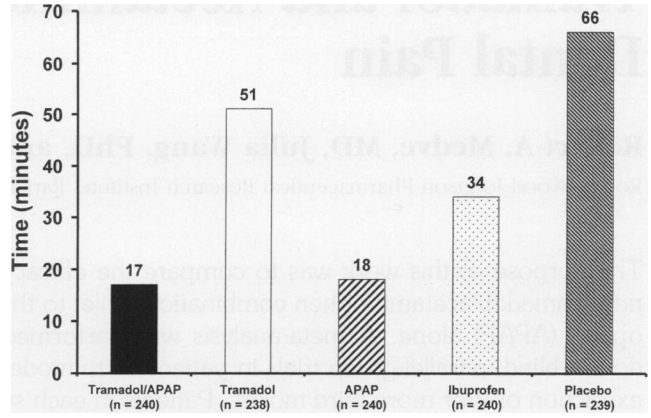

Figure 2. Estimated time to onset of pain relief.

Table 1. Outcome Measures—Patient Reported

Pain Relief	*Pain Intensity*	*Global Assessment*
0 = none	0 = none	1 = poor
1 = a little	1 = mild	2 = fair
2 = some	2 = moderate	3 = good
3 = a lot	3 = severe	4 = very good
4 = complete		5 = excellent

of age, weight <100 kg, and good physical health; women were required to be postmenopausal, surgically rendered incapable of having children, or not pregnant and using acceptable birth control. Exclusion criteria included receipt of experimental drugs/devices in the prior 30 days, receipt of an analgesic medication other than a short-acting preoperative or intraoperative anesthetic, use of an NSAID in the prior 3 days, history of seizures or substance abuse, current use of any medication known to reduce the seizure threshold (eg, selective serotonin reuptake inhibitors, monoamine oxidase inhibitors, tricyclic antidepressants, or neuroleptics), or history of sensitivity, allergy, precautions, warnings, or contraindications for tramadol, APAP, or ibuprofen.

Study Design

Three centers each performed a randomized, double-blind, parallel-group, active-controlled, single-dose trial with a placebo control. Twelve hundred patients were enrolled and 400 patients were randomized equally at each site, with 5 treatment groups per site; the active drugs were tramadol 37.5 mg with APAP 325 mg (in tablets), tramadol 37.5 mg (in capsules), APAP (325 mg in capsules), and ibuprofen 200 mg (in capsules). Active control with ibuprofen was used to determine model sensitivity. All trial drugs were packaged as a single dose consisting of 2 tablets and 2 capsules, using placebo capsules and/or tablets as necessary to maintain the double-blind. Patients took the 2 tablets and 2 capsules after surgery and were advised to wait at least 2 hours before taking supplemental analgesia.

Outcome Measures

Pain relief and pain intensity were reported on Likert scales (Table 1) at 30 minutes after the dose and then hourly for an 8-hour observation period. Total pain relief over 8 hours (TOTPAR8) and the sum of pain intensity differences (SPID8) were calculated from the hourly scores. Time to onset of pain relief was determined by the double-stopwatch technique. Time to remedication was defined as the time from dosing to the time patients remedicated. Patients reported their global assessment of study medication upon completion. Adverse events were recorded by each patient during the 8-hour observation period, even if supplemental analgesia was taken.

Table 2. Baseline Demographics

	Tramadol/APAP (n = 240)	*Tramadol (n = 238)*	*APAP (n = 240)*	*Ibuprofen (n = 240)*	*Placebo (n = 239)*
Male : female	107:133	85:153	97:143	98:142	89:150
Age, mean (SD)	21.8 (5.6)	21.2 (4.7)	22.1 (5.6)	20.9 (4.7)	21.2 (4.6)
Baseline pain, mean (SD)	2.3 (0.5)	2.3 (0.5)	2.3 (0.5)	2.3 (0.5)	2.3 (0.5)

Table 3. Patient Global Assessment of Study Medication

Treatment	n	*Mean (SD)*	*P vs Tramadol/APAP*
Tramadol/APAP	240	3.0 (1.31)	—
Tramadol	238	2.0 (1.27)	.0001
APAP	240	2.7 (1.26)	.0040
Ibuprofen	240	3.0 (1.36)	.8342
Placebo	238*	1.6 (0.98)	.0001

* Data were not available for 1 patient.

Statistical Analyses

For the TOTPAR8 and SPID8 summary calculations, scores at 30 minutes and 1 hour after the dose were averaged to yield a composite value for hour 1. Two-sample *t* tests were performed on TOTPAR8 and SPID8 to compare all medications with placebo and to compare tramadol/APAP with its components. A 2-way ANOVA with interaction was used to assess the consistency of treatment effects across levels of baseline pain intensity. Mean pain relief and intensity difference scores (PRID) were calculated for each group and extrapolated to the point at which PRID = 1, and this point was used as the estimated time to onset of pain relief; 95% confidence limits were also calculated. Duration of pain relief was defined as the earliest time when half of the patients in a treatment group remedicated; 95% confidence limits were also calculated.

RESULTS

In all, 1197 patients (age range, 16–46 years) were evaluable for efficacy; treatment groups in each study were similar at baseline (Table 2). Pain relief and improvements in pain intensity were superior to placebo for all treatments (Figure 1). The superiority of ibuprofen to placebo confirmed the model sensitivity. Overall pain relief was significantly higher after 8 hours (TOTPAR8) in the tramadol/APAP group than in the tramadol or APAP groups (Figure 1). Mean overall changes in pain intensity (SPID8) in the tramadol/APAP group were significantly greater than those in the tramadol or APAP groups (Figure 1). Estimated onset of pain relief was 17 minutes (95% CI, 15–20 minutes) for tramadol/APAP, compared with 51 minutes (95% CI, 40–70 minutes) for tramadol, 18 minutes (95% CI, 16–21 minutes) for APAP, and 34 minutes (95% CI, 28–44 minutes) for ibuprofen (Figure 2). Median time to supplemental analgesia in the tramadol/APAP group was longer than in the tramadol or APAP monotherapy groups and comparable with that of the ibuprofen group (Figure 3).

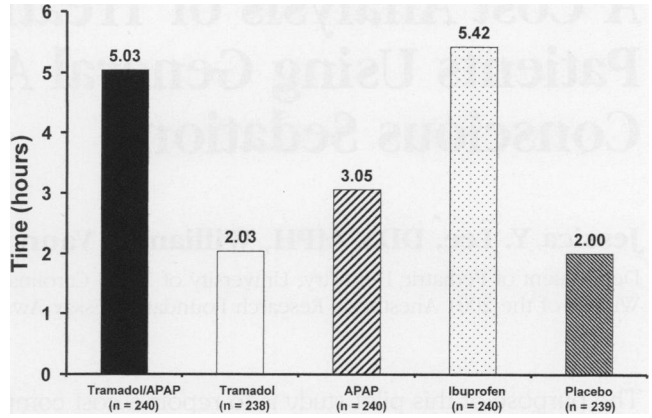

Figure 3. Duration of pain relief (time to remedication).

Mean overall assessment of study medication was higher in the tramadol/APAP group than in the tramadol or APAP monotherapy groups and equal to that of the ibuprofen group (Table 3). Treatment-emergent adverse events were generally transient, mild to moderate in severity, and were comparable in incidence between the tramadol/APAP and tramadol groups (Table 4).

CONCLUSIONS

All treatments were superior to placebo, confirming the sensitivity of the model. Tramadol/APAP was superior to tramadol or APAP alone with respect to pain relief and intensity and duration of analgesia in the treatment of dental pain. Tramadol/APAP was also superior to tramadol alone with respect to onset of pain relief. Adverse events in the tramadol/APAP group were generally transient, mild to moderate in severity, and comparable to those in the tramadol monotherapy group. Tramadol/APAP is a rapidly acting, long-duration analgesic that is effective and well tolerated for the treatment of acute pain.

Table 4. Adverse Events Reported by ≥5% of Patients, n (%)

	Tramadol/APAP (n = 240)	*Tramadol (n = 238)*	*APAP (n = 240)*	*Ibuprofen (n = 240)*	*Placebo (n = 239)*
Nausea	56 (23)	56 (24)	22 (9)	23 (10)	38 (16)
Vomiting	51 (21)	49 (21)	17 (7)	16 (7)	23 (10)
Dizziness	11 (5)	12 (5)	10 (4)	7 (3)	9 (4)