Oral Ciramadol: A New Analgesic for Postoperative Pain

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Ciramadol, a new synthetic narcotic agonist-antagonist analgesic, was compared in 30 and 60 mg doses with pentazocine 50 mg, aspirin 650 mg, and placebo in the treatment of 153 patients with postoperative pain. All drugs were administered between six and 72 hours after surgery. Analgesic efficacy was assessed for six hours after study drug administration using verbal pain intensity, analog pain intensity, and verbal pain relief scales. Significantly ($P < .05$) higher analgesic efficacy scores were seen with ciramadol 30 mg than with pentazocine 50 mg and placebo at most of the evaluation points. Doses of ciramadol 30 mg were significantly ($P < .05$) more effective than aspirin 650 mg at several time periods, and ciramadol 60 mg was better than pentazocine and placebo at several evaluation times. The 30-mg dose of ciramadol was generally more effective than the 60-mg dose. The mean six-hour cumulative sum of pain intensity difference scores, total pain relief scores, and sum of pain analog intensity difference scores showed that the best analgesic response occurred in the ciramadol 30 mg group, followed by the ciramadol 60 mg, aspirin 650 mg, pentazocine 50 mg, and placebo groups. Side effects were rare and mild. There were no medically important changes in vital signs in any treatment group.

Ciramadol (Wy-15,705) is a new synthetic opioid agonist-antagonist analgesic with a benzylamine structure (phenol, 3-[1α(R*), 2α]]-3-[(dimethylamino)-(2-hydroxycyclohexyl)methyl) (Figure 1). The results of animal experiments have shown that parenterally administered ciramadol approaches morphine sulfate in analgesic activity, and it has a wide margin of safety.[1]

In clinical trials, intravenous ciramadol 20 mg has provided good analgesia for patients with renal colic,[2] and oral ciramadol 20 mg has been effective in treating gynecologic and orthopedic postoperative pain[3,4] and chronic pain from cancer.[5] The incidences of side effects in these studies were relatively low.

The present study was performed to compare the analgesic efficacy and safety of single oral doses of ciramadol 30 or 60 mg, pentazocine 50 mg, aspirin 650 mg, and placebo in the treatment of patients with postoperative pain.

PATIENTS AND METHODS

Patients between 18 and 66 years of age who had been classified before surgery as American Society of Anesthesiology (ASA) physical status I or II[6] and who were having moderate to severe postoperative pain were included in the study. Excluded were patients sensitive to narcotics; those with a history of drug or alcohol abuse or psychiatric disorders; patients receiving psychotropic drugs; pregnant or lactating women; and patients taking interfering or potentially interacting medication. All patients signed informed consent forms before surgery. The study was approved by the Medical University of South Carolina institutional review board. Minimum time lapses of six hours after administration of a tranquilizing agent and three hours after ingestion of an analgesic were required. The patients must have been able to take oral fluids after surgery.

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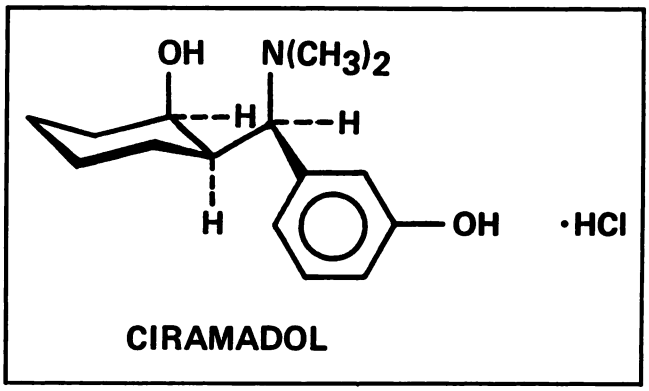

Figure 1. Chemical structure of ciramadol.

Patients underwent intra-abdominal, orthopedic, and general surgical procedures under general anesthesia. After surgery, the patients were randomized in a double-blind fashion into five groups: ciramadol 30 mg, ciramadol 60 mg, pentazocine 50 mg, aspirin 650 mg, and placebo. The test medications were given between six and 72 hours after surgery as the first oral pain medication. Data were collected at 30 minutes and one, two, three, four, five, and six hours after medication was given.

Efficacy data were based on the patients' responses on verbal pain intensity (four-point) and pain relief (six-point) scales as well as on a visual pain analog scale. Pain intensity was reported as none (0), mild (1), moderate (2), or severe (3). Pain relief was rated as complete (4), alot of (3), moderate (2), little (1), none (0), or worse (−1). The analog scale was a 100-mm line with the extremes representing "no pain" on the left and "worst pain I've ever felt" on the right. Patients were asked to mark the line to indicate their pain intensity.

The degree of sedation was rated at baseline and at each observation time as none, mild, moderate, or marked, and vital signs also were recorded at these times. Adverse reactions were recorded as they occurred. Patients who were not relieved of pain after 30 minutes could receive their standard medication and be removed from the study. These patients were given efficacy scores corresponding to no relief or baseline pain intensity for the duration of the study period.

At the end of the study, each patient was asked to evaluate his or her treatment as excellent (4), good (3), fair (2), or poor (1). In addition, the investigator determined whether each patient's response to treatment was satisfactory based on safety and efficacy effects.

Pain relief was assessed at each evaluation period, and cumulative total pain relief (TOTPAR) scores were calculated as the sum of weighted pain relief scores, with weights being the proportion of time in hours between successive assessments. Pain intensity difference (PID) scores were derived at each evaluation period by subtracting the pain intensity score from that at baseline. The sum of pain intensity difference (SPID) scores were obtained by adding the weighted PID scores. Pain analog intensity difference (PAID) scores and sum of pain analog intensity difference (SPAID) scores were obtained from results on the pain analog scale and were determined in a manner analogous to that used in determining PID and SPID scores.

Statistical Analysis

Demographic, efficacy, and safety data were analyzed using a variety of statistical tests, depending on the type and distribution of the data. Continuous variables were analyzed using one-way analysis of variance, the Newman-Keuls procedure, paired *t* tests, and analysis of covariance,[7] whereas categorical data were analyzed using the chi-square test, Fisher's exact test, and the Cochran-Mantel-Haenszel test.[8,9]

RESULTS

One hundred fifty-three patients were studied. Two patients (one treated with placebo and one with pentazocine) were retrospectively found to be classified as ASA physical status III, and their data were excluded from the analyses of efficacy, sedation, and vital signs. One patient from the ciramadol 30 mg group received a narcotic (meperidine) 2.5 hours before the administration of the study drug and was subsequently excluded from the efficacy analysis.

The study population consisted of 66 (43%) men and 87 (57%) women, with a racial composition of 50 (33%) white and 103 (67%) black patients. Ages ranged from 18 to 66 years (mean, 34 years), and weight ranged from 45 to 99 kg (mean, 71 kg). There were no statistically significant differences in age, weight, race, sex, or baseline pain intensity among the groups.

Analyses of the efficacy assessment variables showed statistically significant differences among the groups at most or all of the observation times. Signif-

icantly higher mean pain relief scores ($P < .05$) (Figure 2) were seen with ciramadol 30 mg than with pentazocine 50 mg and placebo from two to six hours after administration. In addition, ciramadol 30 mg provided significantly greater ($P < .05$) pain relief than aspirin 650 mg at 0.5, three, and four hours. The 60-mg dose of ciramadol yielded more pain relief than pentazocine and placebo at several time periods. Although the differences between 30 and 60 mg of ciramadol were small, the highest responses were generally noted in the 30-mg group. Similar results were seen with the verbal and analog pain intensity scales.

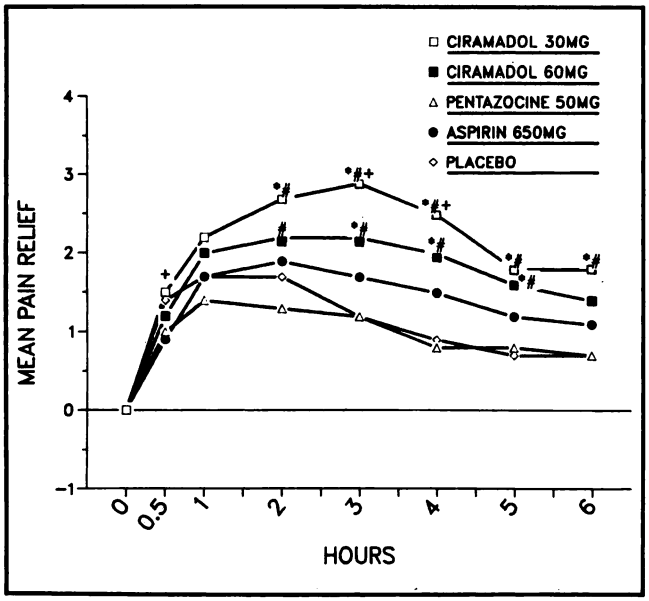

*Figure 2. Comparison of mean pain relief provided by the five treatments over time. Higher scores indicate greater pain relief. *Significantly ($P < .05$) different from placebo; †Significantly ($P < .05$) different from aspirin 650 mg; #Significantly ($P < .05$) different from pentazocine 50 mg.*

The Table presents the mean TOTPAR, SPID, and SPAID scores at six hours. These sixth-hour cumulative scores were highest for ciramadol 30 mg, followed in order by ciramadol 60 mg, aspirin, pentazocine, and placebo.

The physician's and patient's final global evaluations were highest for ciramadol 30 mg, followed by ciramadol 60 mg, aspirin, pentazocine, and placebo (Table). Both physician's and patient's evaluations showed a significant advantage ($P < .05$) for ciramadol 30 mg over pentazocine and placebo.

Baseline sedation was similar in the five groups. Only four patients reported mild sedation, and the others reported no sedation. Mean sedation scores remained low throughout the study. There were no significant differences among the groups.

Five patients (two from the ciramadol 30 mg group and one each from the ciramadol 60 mg, aspirin, and placebo groups) reported mild side effects of the gastrointestinal system, including nausea and vomiting, which were thought to be at least possibly related to therapy. One patient in the aspirin group reported alterations in taste, and one patient in the ciramadol 60 mg group experienced shortness of breath and pruritus. The latter adverse effect required symptomatic treatment with diphenhydramine; it was discovered that this patient had an allergy to narcotic analgesics that was not reported at the prestudy interview.

Statistically significant mean decreases from baseline in vital signs (heart beat, 3-9 beats/min; blood pressure, 6-11 mm Hg; and respiration rate, 1-2

TABLE

Mean Cumulative Sixth-hour Scores and Overall Evaluations*

Drug	Sixth-hour Mean Scores SPID	TOTPAR	SPAID	Physician Evaluation of Satisfactory	Patient Evaluation of Good or Excellent
Ciramadol 30 mg	(25)7.8†‡	(25)12.6†‡	(24)202.9†‡	77%†‡	70%†‡
Ciramadol 60 mg	(27)6.1	(27)10.5	(26)154.6	55%	55%
Pentazocine 50 mg	(29)3.3	(29)5.9	(29)76.5	38%	33%
Aspirin 650 mg	(30)5.0	(30)8.3	(30)134.1	53%	53%
Placebo	(26)3.1	(26)6.0	(26)74.3	38%	34%

**The number of patients with readings available is shown in parentheses; †Significantly ($P < .05$) different from placebo. ‡Significantly ($P < .05$) different from pentazocine.*
TOTPAR = total pain relief; SPID = sum of pain intensity differences; SPAID = sum of pain analog intensity differences.

breaths/min) were noted more often in the ciramadol groups than in the other groups. The differences among groups, however, were rarely statistically significant, and there were no medically important changes in individual or mean vital signs.

DISCUSSION

Mixed agonist-antagonist analgesics may represent an appropriate alternative to the pure opioid agonists for relief of postoperative pain as they generally have a lower addiction potential[10] and are associated with a low incidence of side effects. Pentazocine was chosen as an active control drug in the present study because it is a widely used opioid agonist-antagonist that produces pain relief comparable with that of codeine[11] but without the sedative effects of morphine. It is the only agonist-antagonist analgesic that is available as an oral formulation. The use of pentazocine has, however, been associated with acute dysphoric and psychotomimetic effects.[12] In addition, the analgesic efficacy of pentazocine after oral administration has been variable. In this study, pentazocine 50 mg was not significantly different than aspirin 650 mg. Similar results were reported in patients with chronic cancer pain.[12]

The present study demonstrates the efficacy of oral ciramadol (30 and 60 mg) given as a one-time dose in the immediate postoperative period for patients with moderate and severe pain. Ciramadol 30 mg gave better pain relief than pentazocine 50 mg, aspirin 650 mg, and placebo. Increasing the dose of ciramadol to 60 mg, however, did not increase analgesic efficacy. These findings are consistent with those of an earlier study in which there was an apparent analgesic ceiling reached with ciramadol 30 mg.[13] Among the hypothetic explanations for this phenomenon is the possibility that there is no dose-related analgesic response with ciramadol at doses above 30 mg because of predominating antagonistic properties at higher doses. Camu[3] and Fragen and Caldwell,[4] however, have shown 60 mg of ciramadol to be superior to 20- and 40-mg doses. The dissimilar results of these studies could be due to differences in surgical procedures, drugs used for anesthesia, pain intensity at baseline, and dosages of ciramadol evaluated.

Patients receiving ciramadol had side effects infrequently, and severe adverse reactions were not associated with the drug; especially noteworthy was the lack of sedation and psychotomimetic effects. The incidences of nausea and vomiting reported for ciramadol-treated patients were slightly lower than those reported in other clinical studies.[3,13]

Ciramadol in doses of 30 mg appears to be an effective and safe analgesic for the treatment of moderate to severe postoperative pain. Further studies will be necessary to determine its role as a parenteral postoperative analgesic medication and its relative efficacy.

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