Intravenous Dezocine for Postoperative Pain: A Double-Blind, Placebo-Controlled Comparison With Morphine

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Dezocine, a new mixed agonist-antagonist opioid analgesic, and morphine were compared in a double-blind study in 206 patients with postoperative pain. The analgesic efficacy of single intravenous injections of dezocine (2.5, 5.0, and 10.0 mg), morphine (5.0 mg), and placebo was assessed by verbal and visual scales at regular intervals for six hours after administration. All active treatments provided greater pain relief than placebo. Pain relief with dezocine 5 and 10 mg was significantly greater ($P < .05$) than with placebo for up to four and five hours, respectively, and with morphine up to one hour. Pain relief scores were significantly higher ($P < .05$) with morphine than with placebo at all observations except that of the fifth hour, and higher with dezocine 2.5 mg than with placebo for the first 30 minutes. Doses of 5 and 10 mg of dezocine produced approximately the same peak analgesic effect, with the larger dose having a longer duration of effect. All active treatments produced mild to moderate sedation. Side effects were few and mild or moderate with all of the treatments. The physician's and the patients' evaluations favored dezocine in a dose-dependent order, with morphine 5 mg rated lower than dezocine 5 mg and higher than dezocine 2.5 mg.

The need for a potent analgesic with few side effects and a low dependence liability has led to the introduction of the mixed agonist-antagonist opioid analgesics for clinical use. Dezocine, a synthetic bridged aminotetralin (Figure 1) with structural similarities to the benzomorphan compounds, is such an agent. In standard animal analgesic tests, it was seven to 18 times as potent as morphine with a therapeutic index greater than 1,000.[1,2] In tests for dependence liability, dezocine did not substitute for morphine or produce dependence when chronically administered to monkeys.[2] In dogs, dezocine produced substantially less bronchoconstriction, respiratory depression, hypotension, and histamine release than did morphine or pentazocine.[3]

In humans, dezocine 10 mg has been reported to be equipotent to morphine 10 mg[4] and meperidine 50 to 100 mg[5] after intramuscular administration. A ceiling effect for respiratory depression was found at a dose of dezocine 30 mg/70 kg.[6]

This study was designed to compare the safety and efficacy of single intravenous injections of dezocine (2.5, 5, or 10 mg), morphine (5.0 mg), and placebo in patients with moderate to severe postoperative pain.

PATIENTS AND METHODS

A total of 206 patients with moderate or severe pain participated in this study. The protocol and the consent form were approved by the Committee to Review Grants for Clinical Research and Investigation Involving Human Beings at the University of Michigan Medical Center. All patients gave written informed consent. Pregnant women, patients sensitive to opioid analgesics, and those with a history of abuse of these agents were excluded. All patients were in

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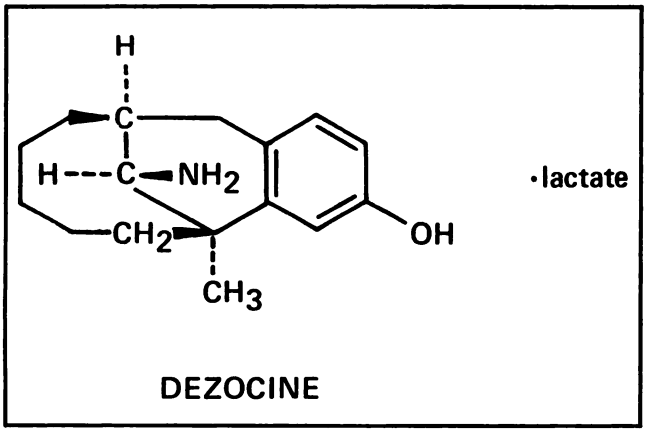

Figure 1. Chemical structure of dezocine.

American Society of Anesthesiologists physical status I or II[7] and underwent general surgical, gynecologic, or orthopedic procedures under general anesthesia. There was no restriction in the choice of anesthetic agents; however, patients who had received an analgesic within three hours or a psychotropic drug within six hours were excluded from the study.

When the patients complained of moderate to severe pain in the recovery room, they were randomly assigned to one of five treatment groups and given a single intravenous injection of either dezocine 2.5, 5, or 10 mg; morphine 5 mg, or placebo (normal saline) in a double-blind fashion. Pain intensity was assessed at baseline, and both pain intensity and pain relief were assessed at 15, 30, and 60 minutes and then hourly for six hours after drug administration.

Three analgesic efficacy scales were employed at each observation time. Pain intensity was assessed verbally and rated as none (0), mild (1), moderate (2), or severe (3). Pain relief was rated as complete (4), alot (3), moderate (2), little (1), none (0), or worse (−1). A visual analogue pain intensity scale, a 100-mm line whose terminal points represented "no pain" and "worst pain I've ever felt," also was used to evaluate pain intensity. Patients who did not receive at least moderate pain relief within 30 minutes were offered a standard rescue analgesic (morphine) and were withdrawn from the study. These patients were considered treatment failures and were assigned scores corresponding to the baseline pain intensity and to no relief for the observations beyond the point of remedication.

Several analgesic measures were derived from the patients' subjective assessments. Differences from baseline in verbal pain intensity (PID scores) and analogue pain intensity (PAID scores) were determined at each observation time. Weighted PID and PAID scores (i.e., each score multiplied by the proportion of an hour since the last reading) were added to determine cumulative efficacy measures (SPID and SPAID scores, respectively). Individual total pain relief (TOTPAR) scores were calculated by adding weighted pain relief scores in a similar fashion.

Vital signs (arterial blood pressure, pulse, and respiratory rate) and degree of sedation (marked [3], moderate [2], mild [1], and none [0] were recorded at all observation times. Adverse effects were recorded, and their relation to the study medication was determined. Discomfort at the site of injection was also noted.

At the end of the study, the investigator provided an overall clinical judgment as to whether the treatment was satisfactory on the basis of the degree and duration of pain relief (at least 50% pain relief for at least 60 minutes) and the presence or absence of adverse reactions. Each patient also gave a global assessment (excellent [4], good [3], fair [2], and poor [1]) of his or her treatment.

Statistical Analysis

The treatment groups were compared with respect to age, weight, and baseline pain analogue scores, using a one-way analysis of variance, with pairwise comparisons made using the Newman-Keuls procedure. Sex. race, and the baseline distributions of pain and sedation scores were compared among the groups using the chi-square test; Fisher's exact test was used for pairwise comparisons when appropriate.

Pain relief and PID scores, at each observation time and cumulatively, were analyzed by means of the generalized Cochran-Mantel-Haenszel procedure, using marginal ridit scores. This approach also was used to analyze the proportions of patients with effective (at least moderate) pain relief, peak pain relief scores, sedation scores, cumulative remedication rates, and overall evaluations by the patients and physician. Comparisons of PAID and SPAID scores among the treatment groups were made using the analysis of covariance.

The frequencies of adverse effects were compared among treatment groups using the chi-square test, supplemented by Fisher's exact test for pairwise comparisons. Vital signs and laboratory determina-

tions were examined for changes within groups from baseline using a paired t test, and comparisons among the groups were made by analysis of covariance.

RESULTS

Patient Attributes

The overall study population consisted of 69 men (33%) and 137 women (67%); the mean age was 36 years (range, 18 to 69 years) and the mean weight was 152 lb (range, 100 to 210 lb). Prior to receiving study medication, 69 (33%) patients had moderate pain, and 137 (67%) patients had severe pain.

With the exception of race, there were no statistically significant differences among the five treatment groups with respect to demographic characteristics or initial pain intensity (both verbal and analogue). There were significantly ($P < .05$) more white patients in the 5-mg morphine (95%) and placebo (98%) groups than in the 2.5-mg dezocine group (75%). Of the 206 patient enrolled, eight were excluded from the efficacy analysis because they had received fentanyl within three hours of dosing; all patients were included in the safety analysis.

Efficacy Assessment

Results from the three methods of efficacy assessment were similar. The pain relief scores, which are representative of the scores for all three efficacy measures, are shown in Figure 2. Higher pain relief scores were observed in the 5- and 10-mg dezocine groups and the morphine group than in the 2.5-mg dezocine and placebo groups. Doses of 5 and 10 mg of dezocine provided significantly ($P < .05$) greater pain relief than placebo for up to four and five hours, respectively. The 5- and 10-mg doses of dezocine also provided significantly greater ($P < .05$) pain relief than 2.5 mg of dezocine for two and three hours, respectively. Significantly ($P < .05$) greater pain relief scores were observed at 15 minutes through one hour after administration of both 5 and 10 mg of dezocine than for morphine. Similar peak effects were seen with 5 and 10 mg of dezocine, but 10 mg of dezocine provided longer lasting analgesia. Significantly ($P < .05$) higher pain relief scores were seen in the morphine 5 mg group than in the dezocine 2.5 mg group at two hours. The 2.5-mg dose of dezocine provided greater ($P < .05$) pain relief than placebo for the first 30 minutes.

As shown in Table I, the proportions of patients who required remedication with standard analgesics were significantly ($P < .05$) lower in the dezocine 5 and 10 mg and morphine groups than in the placebo group at most evaluations through five hours. In addition, the cumulative remedication rates for the dezocine 2.5 mg group were significantly ($P < .05$) higher than those in the dezocine 5 mg group at one and two hours, the dezocine 10 mg group at one, two, three, and five hours, and the morphine group at one through three hours, and lower than those in the placebo group at 15 and 30 minutes.

The maximal percentage of patients with effective

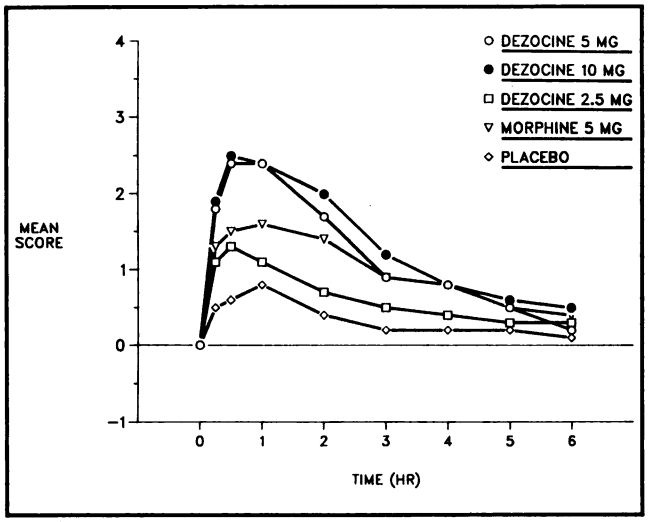

Figure 2. Mean pain relief scores during the six-hour evaluation period. Higher scores indicate greater pain relief.

TABLE I

Cumulative Remedication Rates (% of Patients)

Time	Dezocine 2.5 mg	Dezocine 5 mg	Dezocine 10 mg	Morphine 5 mg	Placebo
15 min	0*	0*	0*	0*	7%
30 min	21%*	10%*	11%*	8%*	51%
1 hr	46%	21%*†	16%*†	24%*†	61%
2 hr	64%	40%*†	29%*†	39%*†	85%
3 hr	77%	62%*	50%*†	55%*†	93%
4 hr	85%	69%*	66%*	74%*	95%
5 hr	90%	79%*	71%*†	79%	95%
6 hr	90%	83%	74%*	79%*	95%

**Significantly lower than placebo ($P < .05$); †significantly lower than 2.5 mg of dezocine ($P < .05$).*

pain relief was highest in the dezocine 10 mg group (82%), followed by the dezocine 5 mg group (79%), the morphine 5 mg group (63%), the dezocine 2.5 mg group (49%), and the placebo group (27%).

The cumulative SPID, SPAID, and TOTPAR scores for the six-hour study period are shown in Table II. The 10-mg dose of dezocine was the most effective, followed by 5 mg of dezocine and 5 mg of morphine, then 2.5 mg of dezocine, and placebo. Both the 5- and 10-mg doses of dezocine showed a significant ($P < .05$) advantage over 2.5 mg of dezocine and placebo as measured by SPID and TOTPAR scores. Morphine showed a significant ($P < .05$) advantage over 2.5 mg of dezocine and placebo as measured by SPAID and TOTPAR scores.

TABLE II

Six-Hour Cumulative Efficacy Scores*

Treatment	Mean Score		
	SPID	SPAID	TOTPAR
Dezocine 2.5 mg	1.5	60.5	3.3†
Dezocine 5 mg	3.5†‡	106.3†	6.4†‡
Dezocine 10 mg	3.6†‡	138.1†‡	7.3†‡
Morphine 5 mg	3.0†	109.9†‡	5.5†‡
Placebo	0.8	22.7	1.4

**Higher scores indicate greater pain relief; †significantly better than placebo ($P < .05$); ‡significantly better than 2.5 mg of dezocine ($P < .05$). SPID = sum of pain intensity difference scores; SPAID = sum of pain analogue intensity difference scores; TOTPAR = total pain relief scores.*

Sedation

The distribution of sedation at baseline differed significantly ($P < .05$) among the groups, with moderate sedation being more frequent in the dezocine 2.5 mg group (28%) than in the dezocine 10 mg, morphine 5 mg, and placebo groups (3%, 3%, and 5%, respectively). Significantly ($P < .05$) more sedation was noted in each of the four active therapy gorups than in the placebo group at two or more time periods through two hours, with the highest mean sedation scores generally occurring in the dezocine 10 mg group. For all groups, however, the peak mean scores during therapy ranged between "mild" and "moderate."

Vital Signs

With the exception of one patient in dezocine 10-mg group who became hypotensive (see below), clinically significant changes in vital signs were not apparent.

Adverse Effects

The most commonly reported adverse effects related to the study medications were nausea and vomiting; one or both of these effects occurred in two of 40 patients (5%) in the dezocine 2.5 mg group, two of 42 (5%) in the dezocine 5-mg group, one of 41 (2%) in the dezocine 10-mg group, one of 41 (2%) in the morphine group, and two of 42 (5%) in the placebo group. One additional patient became hypotensive (blood pressure fell from 108/60 to 80/50 mm Hg) after receiving dezocine 10 mg and was treated successfully with intravenous bolus injections of fluid. Another patient developed a skin rash after receiving morphine 5 mg. Three patients had discomfort at the injection site (one patient in the dezocine 5 mg group and two patients in the morphine 5 mg group). No one was withdrawn from the study because of adverse effects. There were no statistically significant differences in the incidence of adverse effects among the groups.

Overall Evaluation

The physician's and patients' overall evaluations are presented in Table III. The physician's evaluations favored dezocine in a dose-dependent order, with morphine 5 mg rated between 2.5 and 5 mg of dezocine. Both the 5- and 10-mg doses of dezocine showed a significant ($P < .05$) advantage over 2.5 mg of dezocine, 5 mg of morphine, and placebo. The patient evaluations of treatment showed a similar order of preference, although the differences between 5 mg of dezocine and 5 mg of morphine were not statistically significant. Morphine showed a significant ($P < .05$) advantage over placebo for both evaluations.

DISCUSSION

Acute or chronic pain is often inadequately treated because of unrealistic fear of the respiratory depression and dependence liability of opioid analgesics, which include morphine and meperidine.[8,9] Physicians and nurses have been blamed by the medical and lay press for treating pain inadequately.[10] In response to these reports, research efforts have been aimed toward alternative methods of administering

TABLE III

Physician's and Patients' Overall Evaluations

Evaluation	Dezocine 2.5 mg	Dezocine 5 mg	Dezocine 10 mg	Morphine 5 mg	Placebo
Physician Evaluation					
unsatisfactory	26* (67%)	10 (24%)	7 (18%)	18 (47%)	32 (78%)
satisfactory	13 (33%)	32 (76%)	31 (82%)	20 (53%)	9 (22%)
Patient Evaluation					
poor (1)	16 (52%)	7 (17%)	2 (6%)	9 (26%)	18 (51%)
fair (2)	2 (6%)	5 (12%)	7 (21%)	9 (26%)	7 (20%)
good (3)	11 (35%)	22 (52%)	15 (45%)	13 (37%)	9 (26%)
excellent (4)	2 (6%)	8 (19%)	9 (27%)	4 (11%)	1 (3%)
Mean Score	2.0	2.7	2.9	2.3	1.8

*Number of patients.

opioid analgesics (e.g., patient-controlled analgesia) and toward the use of newer agents that have fewer side effects than those currently in use (e.g., mixed agonist-antagonist analgesics). Agonist-antagonist analgesics have a ceiling effect for respiratory depression and a low abuse potential. However, some of these agents (e.g., pentazocine) cause psychotomimetic effects, presumably because they bind to sigma-opiate receptors in the central nervous system. Dezocine, a synthetic mixed agonist-antagonist opioid analgesic, has been characterized as a partial mu agonist with some delta-receptor activity but is virtually devoid of kappa- or sigma-receptor activity (personal communication, S. H. Snyder, Department of Neuroscience, Pharmacology and Experimental Therapeutics, Johns Hopkins University School of Medicine, 1984). With such an opiate-receptor binding profile, dezocine may have less propensity to produce psychotomimetic effects than other agonist-antagonist agents.

In the present study, all the active treatment groups produced more effective pain relief than did placebo. Moreover, remedication rates after drug administration were consistently lower among patients who received active treatment than among those who received a placebo. Dezocine produced greater pain relief than did similar doses of morphine (rated satisfactory by the physician in 76% vs 53% of the patients) with a quicker onset of action. These properties could be very useful in clinical practice whether dezocine is used in either incremental intravenous injections (i.e., patient-controlled analgesia) or continuous intravenous infusion for postoperative pain. Both 5- and 10-mg doses of dezocine were more effective than 5 mg of morphine; however, whether 5- and 10-mg doses of dezocine would also be more effective than larger doses of morphine is impossible to ascertain, as only one dose of morphine was used for comparison. Because this was a double-blind study, we were reluctant to administer larger doses of morphine intravenously.

Some patients, who were excluded from the efficacy analysis, received fentanyl or morphine within three hours of receiving dezocine and experienced good analgesia, which suggests that the antagonist properties of dezocine were not prominent in these patients. Further studies are required to evaluate the interaction of dezocine with opiates and other psychotropic drugs used during anesthesia.

Thus, the results of this study indicate that dezocine is a safe and promising analgesic that is significantly more effective than placebo and perhaps more potent than equal doses of morphine for the relief of acute postoperative pain. Its rapid onset of analgesia after intravenous administration may offer an additional advantage.

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REFERENCES

1. Malis JL, Rosenthale ME, Gluckman MI: Animal pharmacology of Wy-16,225, a new analgesic agent. *J Pharmacol Exp Ther* 1975;194:488–498.

2. Swain HH, Seevers MH: Evaluation of new compounds for morphine-like physical dependence in the rhesus monkeys, in *Proceedings of the 36th Annual Scientific Meeting Committee on Problems of Drug Dependence.* Washington, DC, National Academy of Sciences, 1974; 27–28.
3. Lewis AJ, Kirchner T: A comparison of the cardiorespiratory effects of ciramadol, dezocine, morphine and pentazocine in the anesthetized dog. *Arch Int Pharmacodyn Ther* 1981;250:73–83.
4. Downing JW, Brock-Utne JG, Barclay A, et al: Wy-16,225 (dezocine), a new synthetic opiate agonist-antagonist and potent analgesic: Comparison with morphne for relief of pain after lower abdominal surgery. *Br J Anaesth* 1981; 53:59–63.
5. Fragen RJ, Caldwell W: Comparison of dezocine (Wy-16,225) and meperidine as postoperative analgesics. *Anesth Analg* 1978;57:563–566.
6. Romagnoli A, Keats AS: Ceiling respiratory depression by dezocine. *Clin Pharmacol Ther* 1984;35:367–373.
7. Owens WD, Felts JA, Spitznagel EL: ASA physical status classifications: A study of consistency ratings. *Anesthesiology* 1978;49:239–243.
8. Torda TA: Management of acute and postoperative pain. *Int Anesthesiol Clin* 1983;21:27–46.
9. Andrews IC: Management of postoperative pain. *Int Anesthesiol Clin* 1982;21:31–42.
10. Utting JE, Smith JM: Postoperative analgesia. *Anaesthesia* 1979;34:320–332.