Title: DOUBLE-BLIND POST-OPERATIVE STUDY COMPARING MULTIPLE DOSES OF DEZOCINE (WY16225) WITH MORPHINE AND PLACEBO

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INTRODUCTION: Dezocine is a new synthetic analgesic of the agonist-antagonist type, (amino-octahydro methyl methanobenxzocyclodecen). This study was designed to test the efficacy and safety of dezocine in post-operative patients with moderate to severe pain over 48 hours.

METHODS: One hundred sixty one ASA 1 and 2 consenting patients scheduled for elective surgery were enrolled in a double blind, multiple dose, controlled study of randomized parallel design approved by the Institutional Review Board. Four treatment groups compared dezocine 10 mg/, 15 mg, with morphine 10 mg, and placebo given intramuscularly. General anesthesia was the same in all patients. Post-operative pain was assessed by a blinded nurse observer using scales for: pain intensity, pain relief, and pain visual analog (line 100 mm long). Numerical values were assigned to each scale. All observations were made 15 minutes, 30 minutes, 1, 2, 3, 4, 5, and 6 hours after injection, and repeated after each subsequent dose. A maximum of six doses were to be allowed over 48 hours with a minimum interval of 3 hours. If pain relief was inadequate after 30 minutes, the patient dropped out of the study and conventional pain relief medications were substituted. The formal statistical analysis of efficiency was restricted to the first dose given. Analysis of the scores was made by the non-parametric Kruskal-Wallis test. Effective relief and premedication rate was tested by a Chi-square procedure plus Fischer's exact test for pair-wise comparisons. The randomization produced groups of equal age, gender, race, weight and type of operation, except for the placebo group who were younger (32.7 vs 40.7 years).

RESULTS: At all observation times in the intial dose period, the mean score on each of three efficacy scores was lower ($p < .05$) in the placebo group than in any of the active therapy groups. A slight, but consistent advantage for dezocine 15 mg over dezocine 10 mg was seen throughout the dose period; the two dezocine groups both showed somewhat higher scores than the morphine 10 mg group during the first 3 hours (particularly during the first hour), with the scores of the three active therapy groups all falling within a narrow range beyond that point. The cumulative 6 hour sum of pain intensity as well as the peak pain relief scores, were all at the highest level in the dezocine 15 mg group, followed by the dezocine 10 mg group, the morphine 10 mg group and then the placebo group. Each of the active therapy groups showed statistically significant ($p < .05$) advantages over the placebo in the cumulative 6 hour scores, as well as in the peak relief scores. The advantage for dezocine 15 mg over dezocine 10 mg was seen mainly in the first 30 or 60 minutes. The advantages of dezocine 15 mg over morphine 10 mg were mainly in a more rapid onset and a higher peak affect, up to 2 hours. Morphine duration of action appeared to be slightly longer than that of either dose of dezocine. An analysis of discontinuation of medication (Table) provides further information as to whether the patient is deriving overall subjective benefit from the tested drugs. Placebo is significantly inferior to active medications. Forty percent of the patients denied adequate relief with morphine 10 mg after the first dose. This increased to 45% over the total period. Discontinuations with dezocine 15 mg 6 hour period was 22% and 38% with dezocine 10 mg. Nausea and vomiting was between 16% and 18% for the active therapeutic groups. A rash occurred in 12% of the morphine patients and none of the dezocine patients. There were statistically significant differences in the respiratory rates from the baseline with dezocine 10 mg and dezocine 15 mg. Both dezocine 10 mg and dezocine 15 mg were shown to decrease respiratory rate more than morphine 10 mg between 1 and 3 hours post treatment; however, these were clinically unimportant. Only one case of severe respiratory depression occurred in the dezocine 15 mg group in which respirations were reduced to between 7 and 8 per minute after the second dose of the drug. This was reversed with naloxone.

DISCUSSION: Dezocine is a safe and efficacious potent narcotic agonist-antagonist similar in analgesic efficacy to morphine, but with a more rapid onset and a slightly shorter duration. Dezocine has the propensity for respiratory depression and should not be considered different from morphine in the clinical dosages used. Up to 60% of the morphine patients elected alternative or extra medication because of unsatisfactory pain relief and adverse experiences. At 2½ hours after injection, only 50% of the patients reported moderate to greater relief. This high percentage of dissatisfaction may be attributed to the close attention paid to their analgesic needs by the nurse observers. Dezocine in the higher dosages showed a tendency to better analgesia that also produced increased incidence of nausea and vomiting. Greater or more frequent doses may be tried in the future if the side effects could be controlled without producing a synergistic sedation.

REASONS FOR DISCONTINUATION OF PAIN MEDICATIONS

| | P | D10 | D15 | M10 |
|---|---|---|---|---|
| Unsatisfactory Pain Relief (%) | 85 | 38 | 22 | 45 |
| Adverse Reaction (%)* | 3 | 10 | 22 | 15 |
| Total Discontinuation (%)+ | 98 | 83 | 80 | 93 |

Where P= placebo, D10= Dezocine 10mg, D15= Dezocine 15mg, M= Morphine 10mg.

* - nausea, vomiting
+ - preferred oral medication, no analgesia required, administrative problems, etc.