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Ventilatory and Analgesic Effects of Dezocine in Humans

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The respiratory depressant and analgesic effects of intravenous dezocine were evaluated in six healthy volunteers. Single 0.15 mg/kg doses were compared with identical amounts of morphine, and the two drugs were given in combination. Five successive 0.15 mg/kg doses of dezocine also were given to identify dose–effect relationships. Respiratory center sensitivity was monitored by carbon dioxide (CO_2) rebreathing and mouth occlusion pressure ($P_{0.1}$) measurements, while analgesia to experimental pain was tested with submaximal tourniquet ischemia. Single 0.15 mg/kg doses of dezocine produced significantly more tolerance to experimental pain and greater respiratory depression than a comparable dose of morphine in the first hour, but effects of both drugs were similar thereafter. Multiple doses of dezocine progressively increased pain tolerance from 46 ± 14% above control with the first dose to 70 ± 18% above control with the second dose (cumulative total 0.30 mg/kg). Additional dezocine doses did not result in significantly more analgesia. Depression of CO_2 sensitivity followed a similar pattern. Morphine 0.15 mg/kg, when given to subjects who had received a prior dose of dezocine, produced no additional effect beyond that observed with dezocine. With the reverse sequence, dezocine increased the respiratory depression of morphine but also produced a dramatic increment in analgesia, which suggested an additive action. Dezocine is therefore an effective analgesic with morphine-like effects. In human subjects it appears to be a slightly more potent analgesic than morphine in identical clinical doses (0.15 mg/kg). Dezocine is similar to other agonist–antagonist analgesics in that it exhibits a ceiling effect for respiratory depression that parallels its analgesic activity. (Key words: Analgesics: dezocine; morphine. Carbon dioxide: ventilatory response. Pain: experimental; measurement. Ventilation: airway occlusion pressure; carbon dioxide response.)

OPIOIDS WITH A COMBINED agonist–antagonist activity are of interest because of their ability to produce analgesia, decreased liability to addiction, and limited depression of respiration compared with the classical opioid, morphine. This limited or ceiling effect for respiratory depression has been demonstrated for nalorphine,[1] pentazocine,[2] and a more recent drug of this type, nalbuphine.[3] These compounds have been developed with the hope of providing the benefits of increasing analgesic effects while retaining these limited respiratory effects. With nalubphine, however, the limited respiratory effect with increasing dose was paralleled by a low ceiling for analgesia to experimental pain[4] and ability to reduce anesthetic requirements.[5]

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Dezocine (WY 16225), a newer opioid with agonist–antagonist properties, appears to produce dose-related reductions of anesthetic requirements in rats over a wider range of dosage while demonstrating a plateau effect on respiration near the low end of this dose range.[6] Observations in patients suggest that analgesic efficacy of dezocine is similar to that of morphine and is enhanced by increasing dosage.[7,8] However, these studies were based on subjective observations over a very limited dosage range and did not include any objective assessments of respiratory function.

This study was performed to compare directly the respiratory depressant and analgesic effects of dezocine and morphine in common clinical doses (0.15 mg/kg) in a group of healthy subjects and to determine if the effects of incremental doses of dezocine were similar to those seen with increasing doses of morphine.[4] In addition, the clinical doses of dezocine were administered in combination with similar amounts of morphine to assess the interactions of the two drugs, since many clinical situations may arise in which multiple opioid drugs are used.

Methods

Subjects for the study were six healthy nonsmoking male volunteers (ages 23–29 yr) with normal baseline pulmonary function. Each subject gave informed consent for the protocol, which was approved by the Human Studies Committee of the University of Virginia. All testing was performed while subjects were in the supine position. A modification of the submaximal tourniquet ischemia test[9] was used to produce experimental pain. Exsanguination of the subject's upper arm was accomplished by application of an Esmarch Bandage® and maintained by inflating tourniquet to 250 mmHg. Following 1 min of ischemia, the subject performed submaximal exercise by compressing a hand-held rubber ball, once each second for an additional minute, and then placed the arm at his side. The pain response was assessed by recording the time from tourniquet inflation to that at which the pain became unbearable (tolerance). Three such trials were performed prior to drug administration, and the average value served as the control for each experiment.

The ventilatory response to carbon dioxide was assessed by Read's Rebreathing Method.[10] Progressive hyperoxic hypercapnia was produced as subjects rebreathed a mixture of 7% CO_2 93% O_2 from an electronic spirometer (Model 840, Ohio Medical Prod-

ucts) that measured flow and volume. The spirometer was filled with a volume of gas equal to the subjects' forced vital capacity plus 1 l. End-tidal carbon dioxide tension ($P_{ET}CO_2$) was measured by an infrared analyzer (Beckman® LB-2). Subjects breathed through a circuit divided into inspiratory and expiratory limbs by two low-resistance unidirectional valves (Hans Rudolf, Inc.). The circuit resistance was 1.0 $cmH_2O \cdot l^{-1} \cdot s$ linear to a flow of 4 $l \cdot s^{-1}$. During rebreathing runs that lasted 5–6 min, airway occlusion was accomplished at the rate of about one every 20 s by silently closing a valve on the inspiratory side of the circuit as subjects breathed out through the expiratory limb. This allowed occluded inspirations to begin at functional residual capacity.

The pressure generated by the respiratory muscles during the first 0.1 s of occlusion ($P_{0.1}$) was measured at the mouth with a differential pressure transducer (Validyne® MP −45, range ± 50 cmH_2O) and recorded at a paper speed of 50 mm/s. This occlusion pressure represents a mechanical transform of respiratory center output that increases with CO_2 but, unlike minute ventilation, is not affected by the mechanical characteristics of the respiratory system.[11] Minute ventilation ($\dot{V}_E$) was calculated from the average of tidal volume (V_T) and frequency (f) for the three breaths preceding such occlusion. Since f is related inversely to total respiratory cycle duration (T_{tot}), it was calculated as the reciprocal of the total cycle duration times 60 (*i.e.*, $f = 1/T_{tot} \times 60$). Other indices of respiratory timing calculated from the three breaths preceding each occlusion included the duration of inspiration (T_i) and the mean inspiratory flow rate (V_T/T_i).

Ventilatory responses were analyzed by computing by least-squares linear regression the slope responses relating changes in $\dot{V}_E$ to $P_{ET}CO_2$ ($\dot{V}_E/P_{CO_2}$) and changes in occlusion pressure to $P_{ET}CO_2$ ($P_{0.1}/P_{CO_2}$). To detect changes in CO_2 sensitivity not reflected by a change in slope, but rather by a shift in position of the response curves, we also recorded changes in $\dot{V}_E$ and $P_{0.1}$ during rebreathing at a fixed increased level of CO_2 ($P_{ET}CO_2$ = 60 mmHg). This point was chosen because it was encompassed by the linear portion of the response curves in all subjects so that $\dot{V}_E60$ and $P_{0.1}60$ could be derived by interpolation rather than extrapolation. Control measurements of CO_2 response were made in duplicate and their average used to compute control values.

During all experiments, ECG and heart rate were monitored continuously and blood pressure was checked intermittently. Subjects were asked to describe any subjective effects after each drug administration. To provide a route for drug infusion, a 20-gauge catheter was placed in a vein in the arm opposite the tourniquet.

To observe the effects of a single low drug dose, subjects were studied on each of three separate days (at least 4 days apart) and received blindly by random allocation either placebo, morphine 0.15 mg/kg, or dezocine 0.15 mg/kg intravenously. Subjects were tested before drug administration (control), 30 min after each drug, and then hourly for 4 h.

The effects of larger cumulative dezocine doses were evaluated in a multiple-dose study on another separate day. Subjects received dezocine intravenously as five successive doses 0.15 mg/kg each (total dose 0.75 mg/kg) at 30–40-min intervals. Subjects were tested before drug administration and after each incremental drug dose. The testing sequence was begun 10 min after each dose and consisted of measurement of analgesia, followed by CO_2 rebreathing. Naloxone 0.4 mg was administered intravenously to subjects 15 min after completing measurements with the final analgesic dose. Additional naloxone doses (0.4 mg im and 0.4 mg iv) were administered before subjects' departure from the laboratory.

The interaction between dezocine and morphine was assessed on two additional separate days. Subjects received randomly either dezocine 0.15 mg/kg followed by morphine 0.15 mg/kg, or the reverse sequence. The pattern of drug administration was reversed on the second day for each subject. Measurements of analgesia and CO_2 response were begun 10 min after each drug and 10 min after reversal with 0.4 mg naloxone iv.

Results are expressed as mean value ± SEM. Analysis of variance was performed to test for significant differences among groups and the differences isolated by the modified *t* test according to the method of Bonferroni.[12] Differences with a $P < 0.05$ were considered significant.

Results

Tolerance to experimental pain prior to morphine (13.9 ± 1.4 min) and dezocine (13.3 ± 1.3 min) was increased significantly for 2 h after either drug was given in a single 0.15 mg/kg dose (fig. 1). Tolerance in the placebo group did not vary significantly from control (13 ± 1.4 min) throughout the experiment. At both 1/2 and 1 h after drug injection, the mean increases in tolerance with dezocine (55 and 58%) were significantly greater ($P < 0.01$) than those with the same dose of morphine (36 and 24%). The analgesic effects were similar for both drugs at 2 h and beyond.

The respiratory depression associated with the single 0.15 mg/kg doses followed a time course approximating the analgesia (fig. 2). Again, during the first hour, the ventilatory effects of dezocine reflected by $\dot{V}_E$ and $P_{0.1}$ at P_{CO_2} of 60 mmHg were significantly greater ($P < 0.01$) than those of morphine. In addition, the slopes of the ventilatory response ($\dot{V}_E/P_{CO_2}$) were decreased significantly ($P < 0.01$) from control for 2 h after dezocine but unaffected by morphine.

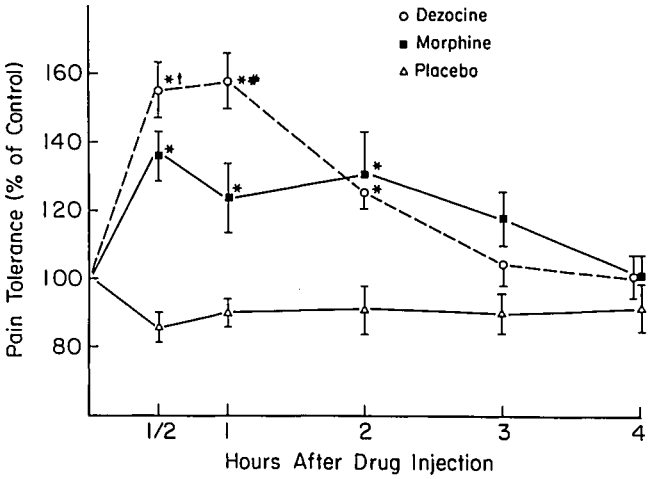

FIG. 1. Time-related changes in tolerance to experimental pain after single 0.15 mg/kg doses of drug. Mean values ± SEM for six subjects are plotted as a percent of control. *$P < 0.01$ denotes values significantly different from placebo. †$P < 0.05$, #$P < 0.01$ denote values significantly different from morphine.

When dezocine was administered in multiple doses of 0.15 mg/kg, pain tolerance increased 46 ± 14% above control with the first dose (fig. 3). The second dezocine dose (cumulative total 0.3 mg/kg) produced a further increase in pain tolerance to 70 ± 18% above control. This was significantly greater ($P < 0.05$) than the analgesia with the first dose. Subsequent doses of dezocine failed to produce additional tolerance to pain. The responses among the subjects were highly variable with the larger doses.

The slope of the ventilatory response to CO_2 ($\dot{V}_E/P_{CO_2}$) was decreased significantly ($P < 0.01$) from its control value of 4.0 ± 0.5 $l \cdot min^{-1} \cdot mmHg^{-1}$ with the initial 0.15 mg dezocine dose (fig. 4). With each subsequent dezocine dose, response slopes remained significantly below control. However, there were no significant differences among these postdrug slopes. The mean slope changes for the occlusion pressure response ($P_{0.1}/P_{CO_2}$) followed a similar pattern, but postdrug changes were not significantly different from control. Shifts in the position of CO_2 response curves with repeated dezocine administration were more dramatic. Control $\dot{V}_E60$ (53 ± 7 $l \cdot min^{-1}$) decreased to 57 ± 7% of control ($P < 0.01$) with the initial dezocine dose and underwent a further significant decrease to 39 ± 6% of control ($P < 0.01$) with the second dezocine dose (cumulative total 0.30 mg/kg). Additional dezocine administration produced no further decrements in $\dot{V}_E60$. Similarly, $P_{0.1}60$ decreased significantly to 72 ± 9% of control with the first dezocine dose, decreased further to 50 ± 7% of control with the second, and showed no further significant decreases with additional dezocine.

The alterations in the respiratory pattern that contributed to the decreased ventilation after dezocine are shown in figure 5. Although the mean respiratory rate (f) during hypercapnic rebreathing ($P_{CO_2}60$ mmHg) decreased slightly after dezocine, the change was not significant. Progressive reductions in V_T were noted with each of the first two dezocine doses, but none occurred thereafter. These reduced V_T values were not the result of a decreased duration of inspiration (T_i) but rather were rather a result of reductions in mean inspiratory flow (V_T/T_i).

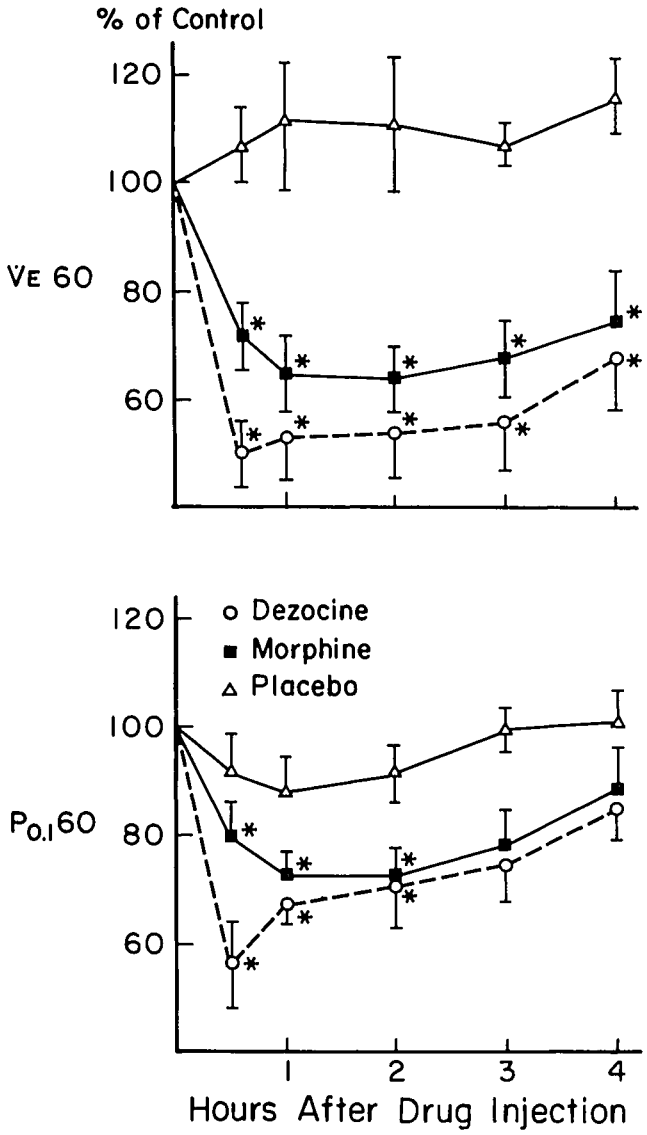

FIG. 2. Time-related changes in respiratory depression after single 0.15 mg/kg drug doses. Mean values ± SEM for six subjects are plotted as per cent of control. Minute ventilation ($\dot{V}_E$) and mouth occlusion pressure ($P_{0.1}$) were measured at P_{CO_2} 60 mmHg during rebreathing. *$P < 0.01$ denotes values significantly different from placebo.

The respiratory and analgesic effects of dezocine morphine combinations are displayed in figure 6. Dezocine 0.15 mg/kg produced a 44 ± 9% increase in tolerance and a 54 ± 8% decrease in $\dot{V}_E60$. A similar dose of morphine, when added to this dezocine dose, produced no significant changes in these variables. When morphine 0.15 mg/kg was administered first, tolerance increased 46 ± 5% above control and $\dot{V}_E60$ decreased by 42 ± 7%. When dezocine was added, $\dot{V}_E60$ decreased significantly more ($P < 0.05$) to 58 ± 6% below control. The analgesic effects also were increased significantly ($P < 0.01$). This increase in pain tolerance (75 ± 8%) was also significantly greater ($P < 0.05$) than that seen with dezocine alone and dezocine followed by morphine. The respiratory and analgesic effects of both morphine–dezocine combinations were reversed easily and promptly by naloxone administration.

Morphine injection in all subjects was followed by a sense of warmth and some tightness in chest and shoulders, which then progressed to a relaxed comfortable state. Dezocine's onset was more subtle but rapidly produced marked sedation and drowsiness that was reversed readily with naloxone at the end of the study. Only one subject experienced nausea, which was present with both morphine and dezocine and persisted in the period following reversal with naloxone.

Multiple doses of dezocine were associated with mild truncal itching. Drowsiness was most marked after the second dose (total 0.30 mg/kg); most subjects appeared more alert after the final dose. None of the subjects experienced unpleasant psychic effects with the higher doses of dezocine. Reversal with naloxone eliminated the drowsiness and produced a sense of fullness in the head, which most subjects likened to a mild headache. Four of the six subjects also experienced waves of mild nausea. Similar mild discomfort was observed following reversal of high doses of morphine in a previous study.[4]

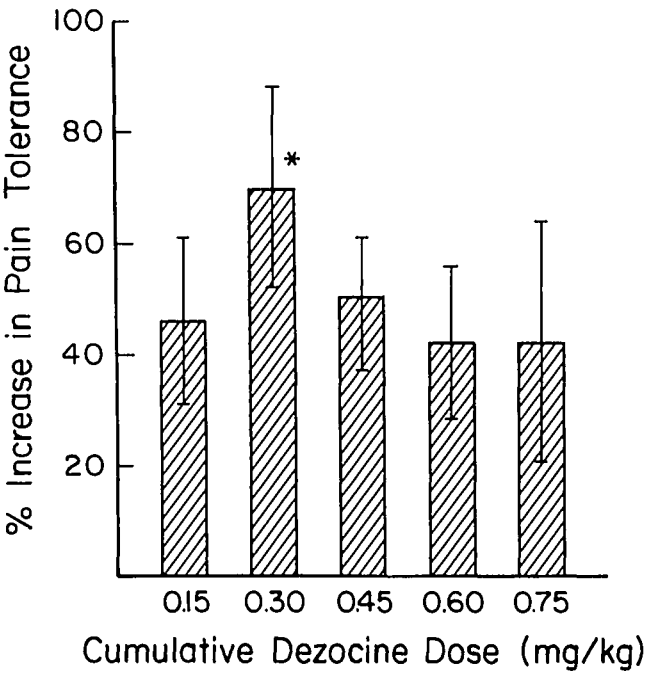

FIG. 3. Altered responses to experimental pain after each of five successive 0.15 mg/kg doses of dezocine. Values are mean ± SEM for six subjects expressed as per cent change from control. *$P < 0.05$ denotes value significantly greater than previous dose.

Discussion

The results of this study demonstrate that dezocine alters the response to experimental pain in a fashion similar to morphine[4] and other nonopioid analgesics.[13] The pattern of response after administration of 0.15 mg/kg doses of dezocine and morphine was an increase in pain tolerance (fig. 1), which persisted for at least 2 h. Although the time courses for both dezocine and morphine were roughly similar, the analgesic effects of dezocine were significantly greater during the first hour after intravenous injection. This same pronounced early effect was seen in patients given intramuscular dezocine for postoperative analgesia.[8]

Increasing the dezocine dosage appeared to increase analgesia in a dose-related fashion only up to cumulative doses of 0.30 mg/kg. Continued administration of the drug to doses as high as 0.75 mg/kg failed to produce additional analgesia, and in some subjects the tolerance to pain appeared to decrease. Respiratory depression likewise reached its peak with 0.30 mg/kg of dezocine, which therefore appears to be the optimum effective dose. This optimum or ceiling effect of dezocine is associated with relatively more analgesia and respiratory depression than is the celing effect of nalbuphine.[4] Respiratory data with other agonist–antagonist compounds such as butorphanol[14,15] and pentazocine[16] also suggest a more profound ceiling effect for dezocine.

Observations with other opioids such as morphine and meperidine[17] suggest that altered respiratory system mechanics, in the form of increased respiratory impedance, may play a role in the decreased ventilatory responses. In healthy subjects, changes in $\dot{V}_E$ ordinarily can be utilized to reflect respiratory center activity. Discrepancies between respiratory center output measured by $P_{0.1}$ and that measured by $\dot{V}_E$ suggest the possibility of altered respiratory mechanics, since the measurement of $P_{0.1}$ reflects respiratory center output essentially independent of respiratory mechanics. Such a discrepancy is suggested after the initial dezocine dose (fig. 4). At this point the reductions in $\dot{V}_E60$ and $\dot{V}_E/P_{CO_2}$ appear to be more dramatic than those of $P_{0.1}60$ and $P_{0.1}/P_{CO_2}$.

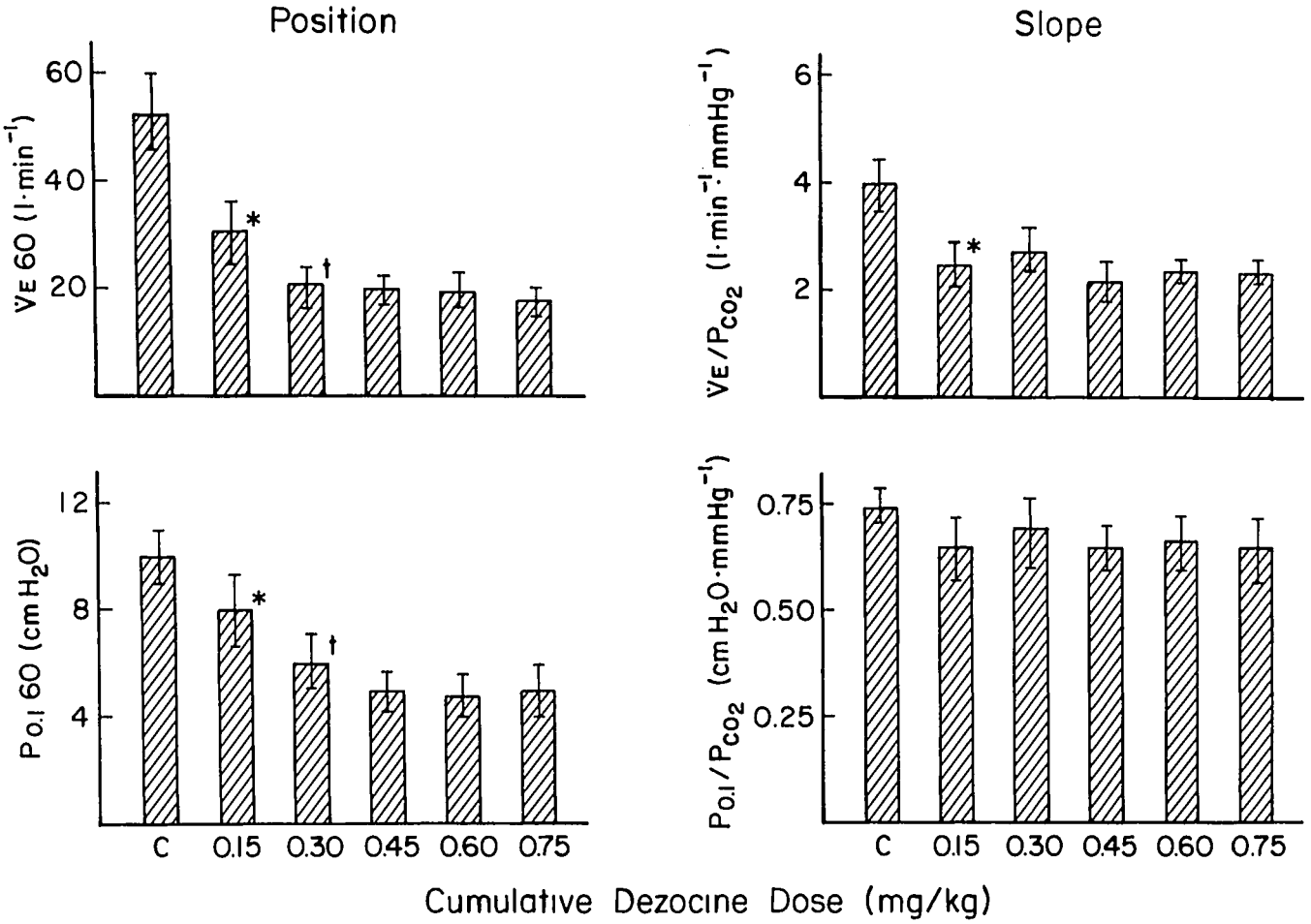

FIG. 4. Changes in responses to CO_2 rebreathing after each of five successive 0.15 mg/kg doses of dezocine. Mean values ± SEM for six subjects are plotted for the slopes of the ventilatory ($\dot{V}_E P_{CO_2}$) and occlusion pressure ($P_{0.1}/P_{CO_2}$) responses. Changes in position of the response curves are indicated by minute ventilation ($\dot{V}_E 60$) and occlusion pressure ($P_{0.1}$) were measured at P_{CO_2} 60 mmHg during rebreathing. *$P < 0.01$, †$P < 0.05$ denote values significantly different from preceding measurement.

Respiratory impedance, which includes both respiratory system resistance and compliance, can be estimated from the ratio of $P_{0.1}$ and mean inspiratory flow (V_T/T_i).[18] We, therefore, compared values of $P_{0.1}$ and V_T/T_i obtained at an increased level of P_{CO_2} (60 mmHg) during rebreathing. We also compared $P_{0.1}$ values that were associated with identical mean inspiratory flow rates (1 l·s^{-1}) both before and after dezocine so that the pressure components related to flow would be similar.[16] In neither case did the postdezocine values for $P_{0.1}$ and $P_{0.1}/(V_T/T_i)$ differ significantly from baseline. Thus increased respiratory impedance does not appear to play a significant role in the decreased ventilatory responses. In this respect, dezocine is similar to other agonist–antagonists such as nalbuphine[4] and pentazocine.[16] Data obtained under similar circumstances with morphine[4] also tend to discount a significant role for altered respiratory mechanics.

The unique actions of agonist–antagonist opioids have been utilized clinically[19,20] and experimentally[21] to reverse the respiratory depression associated with high doses of agonist type narcotics with the hope of maintaining satisfactory levels of analgesia. The interactions of such drugs at lower dose levels as used clinically for analgesia are far less understood. The addition of morphine to dezocine-treated animals produced an additional decrease in anesthetic requirement, which suggested that morphine would be an effective supplement to dezocine analgesia.[6] However, our results indicate that this may not be the case in humans. When subjects were given dezocine 0.15 mg/kg and then a similar dose of morphine, the morphine appeared to have no additional effect (fig. 6). The respiratory and analgesic effects appeared to be those of the prior dose of dezocine.

The addition of dezocine to morphine in our subjects produced strikingly different results. With this combination the respiratory depression was significantly greater than that of morphine alone but not unlike that of dezocine alone or dezocine followed by morphine. Additive respiratory effects between the two drugs, there-

fore, do not appear likely. Rather, one might speculate that the effects merely reflect dezocine's greater potency as seen with the single dose (fig. 2).

In contrast to the respiratory effects, the analgesic action of dezocine appeared to be somewhat additive to those of morphine. In all subjects there was a dramatic increase in ability to tolerate experimental pain when dezocine was added to morphine. The analgesia not only exceeded that produced by morphine but was significantly greater ($P < 0.05$) than that of dezocine alone or dezocine and morphine administered in the reverse sequence. The 75% increase in tolerance was very similar to the effects of two doses (cumulative total 0.30 mg/kg) of dezocine (fig. 3).

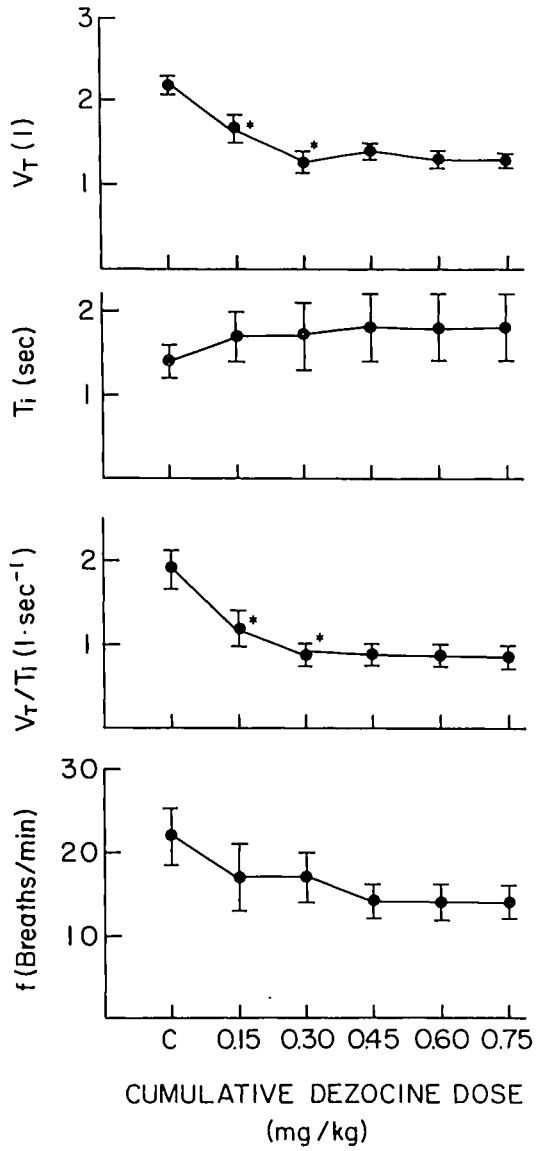

FIG. 5. Respiratory patterns during rebreathing after each of five successive 0.15 mg/kg doses of dezocine. Values are mean ± SEM for six subjects measured at end-tidal CO_2 tension of 60 mmHg during rebreathing. V_T = tidal volume; T_i = duration of inspiration; V_T/T_i = mean inspiratory flow rate; f = respiratory rate. *$P < 0.01$ denotes value significantly different from preceding measurement.

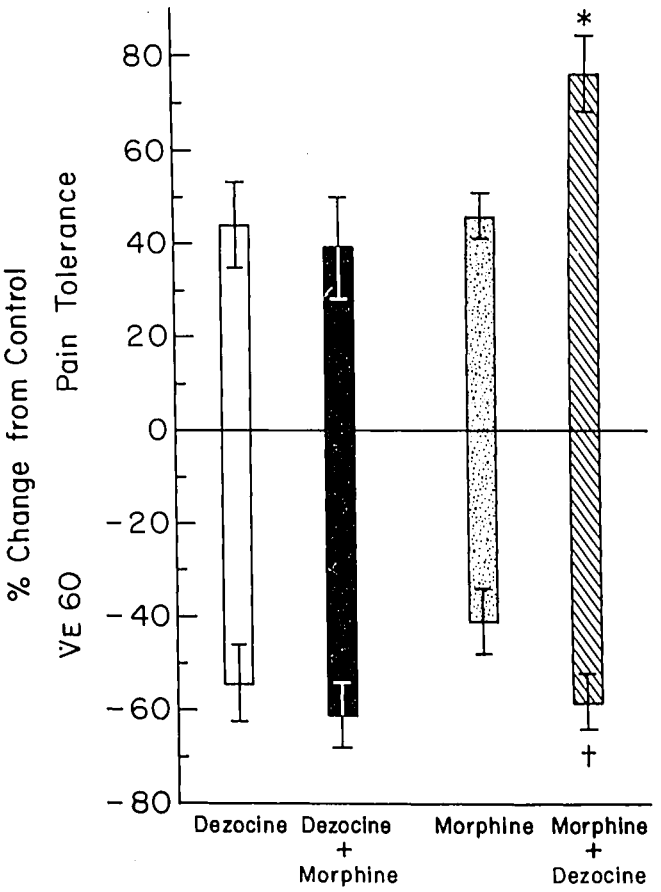

FIG. 6. Changes in tolerance to experimental pain and ventilation following 0.15 mg/kg doses of dezocine and morphine administered alone and in combination. Values are mean ± SEM for six subjects expressed as percent change from control. $\dot{V}_E60$ = minute ventilation at P_{CO_2} = 60 mmHg during rebreathing. *$P < 0.01$ denotes value significantly different from all other treatments. †$P < 0.05$ denotes value significantly different from morphine.

The interpretation of the effects of incremental dezocine doses, as well as dezocine in combination with morphine, provides some framework for postulating the nature and site of dezocine's action on specific opioid receptors. When given alone, dezocine has morphine-like effects and thus is a partial agonist at the morphine or mu receptor. If less than maximum morphine effect is present, such as with 0.15 mg/kg, the addition of dezocine may increase the effect as seen in this study. This may result from dezocine's action at the mu receptor where its affinity may be equal to or greater than morphine. Alternately, the actions of morphine at the mu receptor may be modulated and enhanced by an action of dezocine on the delta receptors, which influence the activity of the mu receptors.[22] The incre-

mental analgesia seen with the addition of dezocine to morphine also may result from dezocine's action at kappa receptors. The analgesia and prominent sedation indicate that dezocine has a significant affinity and efficacy at the kappa receptors.[23]

Undesirable psychologic reactions are common after administration of pentazocine[24] and may occur with large doses of nalbuphine.[4] Despite the obvious structural relationships to pentazocine, dezocine produced no psychotomimetic effects, even at the high doses used in this study. Thus, unlike other agonist–antagonist compounds, such as nalorphine, pentazocine, butorphanol, and nalbuphine, dezocine does not appear to possess any affinity for the sigma receptor.[24] As such, the spectrum of dezocine's activity most closely resembles that of buprenorphine with perhaps one major exception. Buprenorphine is reputedly very resistant to reversal with naloxone.[24] In this study, we found dezocine to be essentially similar in its response to naloxone reversal, as were morphine and nalbuphine in a previous study.[4] The data of Romagnoli and Keats also indicate that dezocine and morphine respond similarly to naloxone.[25]

In conclusion, this study demonstrates that dezocine is an effective analgesic with morphine-like effects in human subjects in usual clinical doses of 0.15 mg/kg. At this dosage level, dezocine appears to be slightly more potent than morphine in both its respiratory depressant and analgesic effects. Such doses of dezocine also appear capable of producing significant postoperative analgesia in patients who have received morphine-type drugs preoperatively or even intraoperatively.

The actions of dezocine appear to be dose related up to 0.30 mg/kg; beyond this dose a ceiling effect results. This ceiling effect is qualitatively similar to the actions of other agonist–antagonist compounds, but the analgesia and respiratory depression of dezocine seem to be more profound. Large doses of dezocine do not cause undesirable psychotomimetic effects but are associated with limited analgesic effects. Whether this limited analgesic efficacy will constrain dezocine's usefulness as an adjunct to general anesthesia remains to be seen.

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