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Midazolam Does Not Influence Intravenous Fentanyl-Induced Analgesia in Healthy Volunteers

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ZACNY, J. P., D. W. COALSON, J. M. KLAFTA, P. A. KLOCK, R. ALESSI, G. RUPANI, C. J. YOUNG, P. G. PATIL AND J. L. APFELBAUM. *Midazolam does not influence intravenous fentanyl-induced analgesia in healthy volunteers.* PHARMACOL BIOCHEM BEHAV **55**(2) 275–280, 1996.—The effects of saline and intravenous midazolam (0.5, 1, and 2 mg per 70 kg) in combination with intravenous fentanyl (0.1 mg/70 kg) were examined on pain induced by a cold pressor test. Healthy volunteers (six females, six males) were enrolled in a prospective, double-blind, randomized, crossover trial in which mood and psychomotor performance were also examined. Five minutes and 135 min postinjection subjects immersed their forearm in ice cold water for 3 min while assessments of pain were recorded. During the first immersion, subjects reported significantly lower pain intensity and bothersomeness ratings after having been injected with fentanyl, relative to the saline condition, but the addition of midazolam neither increased nor decreased pain reports. During the second immersion (approximately 2.5 h postinjection) pain ratings did not differ between the drug and saline conditions. Mood-altering and psychomotor-impairing effects of the drug combination were dose related. We conclude that midazolam at the doses and route of administration tested neither potentiates nor decreases the analgesia produced by fentanyl in a cold-pressor pain assay. **Copyright © 1996 Elsevier Science Inc.**

Anesthetics: intravenous, midazolam Analgesics: intravenous, fentanyl Analgesia
McGill Pain Questionnaire, visual analog scale Brain: psychomotor performance Mood

THERE is an abundant literature on the interaction between opioids and benzodiazepines on anesthesia and analgesia. A majority of infrahuman and human studies indicate that the relationship between benzodiazepines and opioids in inducing hypnosis or anesthesia is either additive (15,44) or synergistic (7,14,16,46). The relationship between the two classes of drugs is more complex when analgesia is considered, and appears to depend largely on the route of benzodiazepine administration. Potentiated analgesia or antinociception has been reported when benzodiazepines are administered in the spine (intrathecally) and opioids are administered systemically or in the spine (17,18,23,33,49). An antagonistic effect by benzodiazepines on opioid-induced analgesia has been obtained in a number of studies in which the benzodiazepines were administered supraspinally or systemically (1,5,6,18,20,28,29,32,35,48). However, there are studies that have demonstrated a potentiating effect of benzodiazepines on opioid-induced analgesia when the benzodiazepine is administered systemically (7,41,52), and at least two studies did not detect an antagonistic (or potentiating) effect of systemically administered benzodiazepines on opioid-induced antinociception (1,39).

The research conducted to date on the interaction between opioids and benzodiazepines on analgesia (antinociception) has been conducted primarily with infrahumans. The scant literature involving humans have come primarily from clinical and case reports, and these studies have indicated that systemically administered benzodiazepines ameliorate opioid-induced analgesia (19,21,40). No laboratory investigation on the relationship between these two classes of drugs and analgesia has been conducted to our knowledge. Such studies would

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have clear clinical relevance, because opioids and benzodiazepines are often coadministered in both general anesthetic and conscious sedation procedures (26). The infrahuman and human studies to date would suggest that benzodiazepines actually work against opioids in the achievement of a satisfactory level of analgesia. Accordingly, we undertook the present study to examine the effects of different midazolam doses on fentanyl-induced analgesia, using the cold pressor test as our pain-inducing assay. We hypothesized that there would be a midazolam dose-related antagonism of fentanyl's analgesic effects in the range of commonly administered clinical doses. A secondary aim of the study was to characterize the mood-altering and psychomotor and cognitive effects of the drug combination of fentanyl and midazolam. Fentanyl and midazolam are often given together in conscious sedation procedures, and although each drug has been studied by itself, no studies have examined the psychotropic effects of the drug combination.

METHOD

Subjects

Twelve healthy volunteers were recruited. Candidates aged 21–39 years old who consumed at least one alcoholic drink per week were scheduled for a screening interview with one of the research personnel and a physician. Prospective volunteers were excluded if they had a history of drug or alcohol abuse, or had any significant psychiatric or medical problems. Females who were pregnant or were planning to become pregnant during the course of the study were excluded; pregnancy tests were administered as a screening procedure in females once a week throughout the study. Subjects were paid for their participation upon completion of the study. The study was approved by the local institutional review board. Written informed consent was obtained during a practice session. To keep subjects blinded as to the compounds being studied, subjects were told and it was stated in the consent form that the agents being studied might come from one of several classes: sedative, stimulant, general anesthetic (at subanesthetic concentrations), opiate, alcohol, or placebo. Subjects were also informed in the consent form that during each of the five sessions they would receive two injections of drugs that may approach but not exceed clinically relevant doses. Six females and six males participated in the study. Their mean (± SD) age was 26.1 ± 3.8 years (range: 21–32). Four subjects smoked cigarettes (less than eight per day), and three subjects smoked marijuana (range: 0.25–2 joints/week). All subjects consumed alcohol within the last 30 days [mean (± SD) number of drinks consumed/week: 4.3 ± 3.3].

Experimental Design

A randomized, placebo-controlled, double-blind, crossover trial was conducted in which saline, fentanyl, and fentanyl in combination with different doses of midazolam were studied. Subjects were first injected intravenously with 0, 0.5, 1, or 2 mg of midazolam, and were then injected intravenously with saline or 0.1 mg fentanyl (all doses per 70 kg body weight). The five conditions were: 0 mg midazolam, 0 mg fentanyl; 0 mg midazolam, 0.1 mg fentanyl; 0.5 mg midazolam, 0.1 mg fentanyl; 1.0 mg midazolam, 0.1 mg fentanyl; 2.0 mg midazolam, 0.1 mg fentanyl. Each injection was done over a 15-s interval. The doses of midazolam and fentanyl tested are within the range of clinical doses given for conscious sedation and/or pain relief. Mood, psychomotor performance, and physiological status were assessed before and at periodic intervals after the injection in each of the five sessions of the experiment.

Experimental Procedures

There were five sessions in this experiment, and sessions were separated from each other by at least 72 h. Subjects were instructed to abstain from all drugs (excluding their normal amounts of caffeine and nicotine) for 24 h prior to sessions. In addition, the subjects were instructed not to consume food or full liquids for 4 h prior to the session and not to consume clear liquids for 2 h before the session. Upon arrival in the laboratory on each session, an intravenous catheter was inserted into one of the subject's upper extremity veins for drug administration. Noninvasive monitoring apparati were placed on the subject so that pulse, blood pressure, and arterial oxygen saturation could be measured during the session. After the vital signs were recorded, the subject was given a battery of subjective and psychomotor tests that took approximately 2.5 min to complete (see below). A dose of saline or midazolam was administered intravenously over 15 s, followed by a 15-s injection of saline or fentanyl. During the injections and for 15 min thereafter the vital signs of the subject were continuously monitored. At 2, 15, 30, 60, 90, 120, 150, and 180 min after the last injection, the battery of subjective and psychomotor tests was initiated. Five and 135 min after the last injection, the cold pressor test (see below) was initiated.

Cold Pressor Test

The cold pressor apparatus consisted of a standard ice chest divided into two compartments by a wire screen. The tank was filled with water, and ice was added to one side of the screen. A cradle for the subject's forearm was positioned in the side of the chest with no ice, which allowed the subject to rest the forearm while immersing it into the cold water. The water in the ice chest was constantly circulated by an aquarium pump and maintained at 2.0 ± 0.5°C. Each immersion of the nondominant arm lasted for 180 s. The cold pressor test is considered to be a valid method of inducing tonic pain (4), and is sensitive to the analgesic effects of different drugs including opioids and nitrous oxide (30,31).

Dependent Measures

Pain Ratings. At 30, 70, 110, and 170 s after the onset of the cold-water immersion the subject verbally reported how much pain they felt on a scale of 0 (not at all painful) to 10 (extremely painful) and how much the pain bothered them on a scale of 0 (not at all bothersome) to 10 (extremely bothersome). The subject was asked to fill out the short-form McGill Pain Questionnaire (SF-MPQ) (22) 80 s after the onset of immersion. The SF-MPQ consists of 15 descriptors (throbbing, shooting, stabbing, sharp, cramping, gnawing, hot–burning, aching, heavy, tender, splitting, tiring–exhausting, sickening, fearful, punishing–cruel), which represent the sensory, affective, and evaluative dimensions of the pain experience. Each descriptor is ranked on an intensity scale from 0–3 (0 = none, 1 = mild, 2 = moderate, 3 = severe).

Subjective and Psychomotor/Cognitive Effects. Mood states were measured on a visual analog scale (VAS) form that had 20 100-mm lines, each labeled with an adjective (e.g., high, sedated, dizzy, elated, coasting, in control of body, in control of thoughts). Subjects were instructed to place a mark on each line indicating how they felt at the moment, ranging from "not

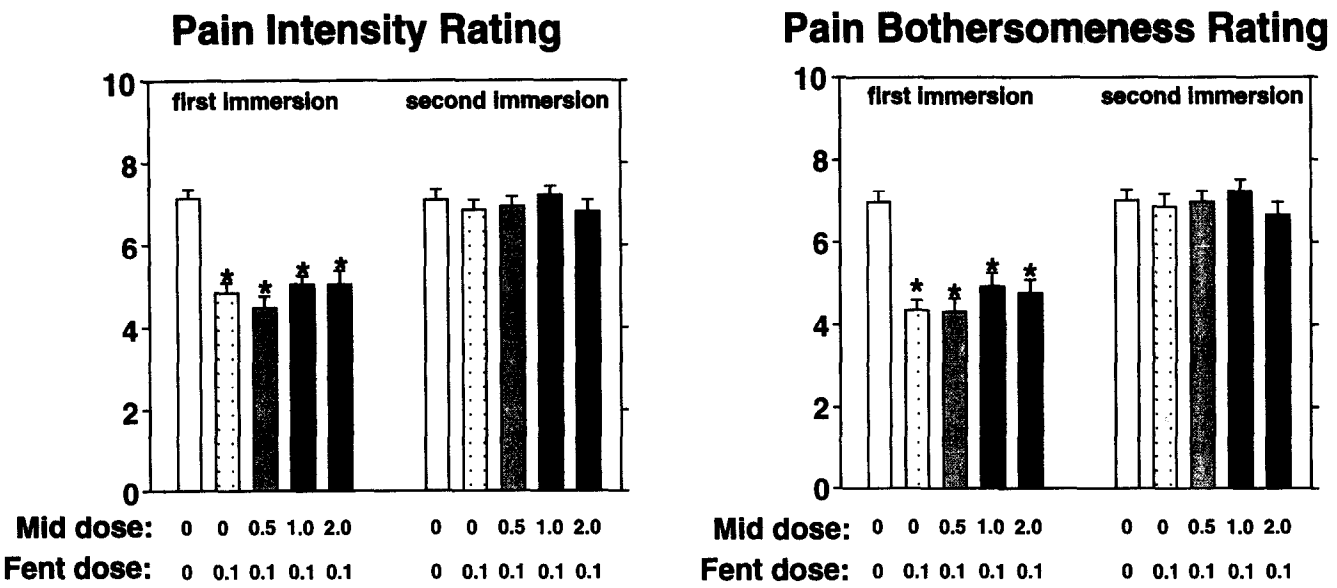

FIG. 1. Effects of the five different drug conditions on pain intensity (left frame) and pain bothersomeness ratings (right frame) as a function of immersion trial [first (5–8 min postinjection) vs. second (135–138 min postinjection)]. Brackets indicate SEMs and asterisks indicate that a given condition is significantly different from the saline condition, as determined by post hoc testing.

at all" to "extremely." On a locally developed Drug Effects/Liking questionnaire, subjects were asked to rate the intensity of the agent's effect as they were currently feeling it on a scale of 1–5 (from 1 = "I feel no effect at all" to 5 = "I feel a very strong effect"), and to indicate their current degree of liking of the drug effects on a 100-mm line (0 = dislike a lot; 50 = neutral; 100 = like a lot).

Psychomotor and cognitive performance was measured with the Digit Symbol Substitution Test (DSST) (47), the Maddox Wing (MW) test (12), and a memory test (50). On the paper-and-pencil DSST, subjects replaced digits with an appropriate symbol during a 1-min period. Different forms of the DSST were used at the different time points. The score was the number of symbols correctly drawn by the subject. The MW test measures relative position of the eyes in prism diopters. Some drugs cause extraocular muscles of the eye to diverge (exophoria), and this divergence is considered to be an indicator of psychomotor impairment (12). In the memory test, subjects were shown 15 words sequentially on a computer screen, each word presented for 2 s. To assess immediate recall, for 2 min after the last word was presented, subjects were instructed to write down as many words as they could remember from the list, in any order. To assess delayed recall, subjects at the 180-min postinjection time point were given 2 min to write down as many words as they could remember from the original list. Different lists of words were used across sessions, and the words were selected from established norms (27,43).

Physiological Effects. Systolic and diastolic blood pressure were measured at baseline (preinjection) and during both cold-water immersions (40 s intraimmersion).

Data Analysis

Repeated measures analysis of variance (ANOVA) was used for statistical treatment of the data. In the pain intensity and bothersomeness analyses, factors were drug condition (0 mg midazolam, 0 mg fentanyl; 0 mg midazolam, 0.1 mg fentanyl; 0.5 mg midazolam, 0.1 mg fentanyl; 1.0 mg midazolam, 0.1 mg fentanyl; 2.0 mg midazolam, 0.1 mg fentanyl), trial (5 min and 135 min postinjection), and time (30, 70, 110, 170 s intraimmersion). In the SF-MPQ rating analyses, factors were drug condition and trial (7 min and 137 min postinjection). In the other analyses (e.g., mood), factors were drug condition and time (4–11 levels) as the factors. F-Values were considered significant for $p < 0.05$ with adjustments of within-factors degrees of freedom (Huynh-Feldt) to protect against violations of symmetry. When significant drug, drug × trial, or drug × time interactions were obtained, Tukey post hoc tests were done.

RESULTS

Pain Ratings

A significant drug condition × trial effect was obtained on both pain intensity, $F(4, 44) = 7.0$, $p < 0.001$, and pain bothersomeness, $F(4, 44) = 6.9$, $p < 0.001$, ratings. Pain ratings in the four active drug conditions were significantly lower than in the saline condition during the first cold-water immersion, but active drug condition pain ratings did not differ significantly from each other (Fig. 1). By the second cold-water immersion, pain ratings in the active drug conditions were not different from that of saline.

Of the 15 SF-MPQ adjectives, there were seven adjectives in which drug and/or drug × trial effects were obtained (aching, gnawing, shooting, splitting, stabbing, tender, throbbing). With few exceptions, reductions in the SF-MPQ ratings were obtained during the first immersion and not with the second, and did not differ between the four active drug conditions.

Subjective Effects

Significant drug and/or drug × time effects were obtained on the following VAS ratings: "anxious," "carefree," "coasting," "confused," "dizzy," "drunk," "feeling in control of

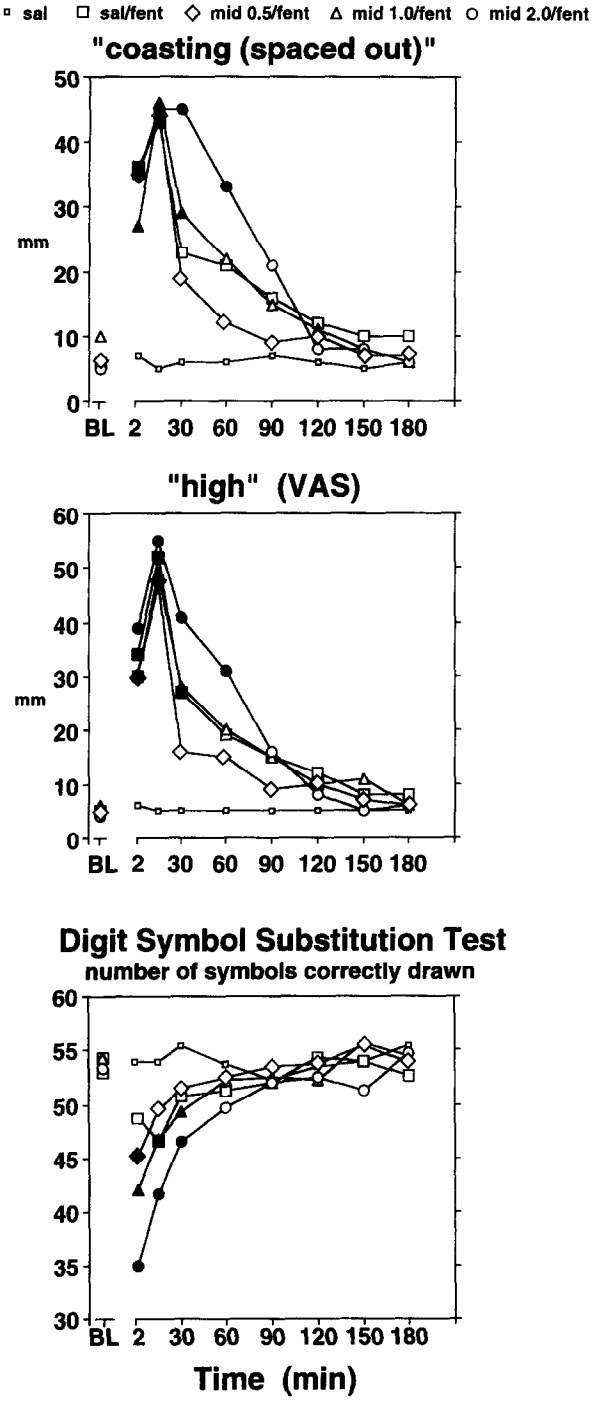

FIG. 2. Effects of the five drug conditions on VAS ratings of coasting (spaced out) (top frame) and high (middle frame), and number of symbols correctly drawn on the Digit Symbol Substitution Test (DSST) (bottom frame), as a function of time since injection. VAS ratings were made on a scale from 0 to 100 mm. Each point represents the mean of 12 subjects. Time point BL refers to the preinjection baseline. Solid symbols indicate that the dose is significantly different from placebo at a given time point (Tukey post hoc test; $p < 0.05$).

body," "feeling in control of thoughts," "high," "sedated," and "stimulated." With the exception of "feeling in control of body" and "feeling in control of thoughts," the VAS ratings were increased at one or more dose combinations. In general, midazolam increased or decreased fentanyl's subjective effects in a dose-related fashion by lengthening the duration, but not the peak, of effect. Figure 2 (top and middle frames) shows VAS ratings of "coasting (spaced out)," and "high," which shows the lengthening of drug effect as a function of midazolam dose. This pattern was also observed with the Feel Drug Effects question—fentanyl alone significantly increased ratings, and these ratings were potentiated by the addition of increasing doses of midazolam [drug × time: $F(32, 352) = 15.0, p < 0.001$. There was a significant drug × time effect on the rating of drug liking, $F(32, 352) = 2.1, p < 0.05$, but post hoc tests revealed that no drug liking ratings from any of the four active drug conditions differed significantly from saline at any of the postinjection time points.

Psychomotor and Physiological Effects

A significant drug × time interaction was obtained on performance of the DSST, $F(32, 352) = 6.8, p < 0.001$, the MW test, $F(32, 352) = 3.1, p < 0.001$, and the memory test, $F(4, 44) = 3.1, p < 0.05$. Fentanyl alone impaired performance on the DSST, and midazolam increased the magnitude and duration of this impairment (Fig. 2, bottom frame). MW performance and immediate recall were impaired by the two higher doses of midazolam in combination with fentanyl, and delayed recall was impaired by all three midazolam/fentanyl dose combinations. Systolic [time: $F(2, 22) = 9.7, p < 0.005$] and diastolic [time: $F(2, 22) = 11.7, p < 0.005$] blood pressures were significantly elevated during both cold water immersions relative to the baseline measure, in all five drug conditions (i.e., evidence of a pressor effect).

DISCUSSION

Our hypothesis that fentanyl-induced analgesia would be antagonized in a dose-dependent manner by midazolam was not supported by the data. Fentanyl indeed reduced self-reported pain ratings in the cold pressor test, but the degree of reduction was not affected by doses of midazolam up to those that are used in clinical situations. Fentanyl produced mood-altering effects, as measured by two locally developed questionnaires, and the addition of midazolam produced a longer duration of effect. Fentanyl had minimal impact on psychomotor performance, but midazolam in a dose-related manner impaired performance and impaired memory.

Our results concerning the lack of an effect of midazolam on opioid-induced analgesia runs counter to those studies conducted with infrahumans in which supraspinal or systemic administration of the two drug classes resulted in a lesser degree of analgesia or antinociception than the opioid alone (1,5,6,18,20,28,29,32,35,48). Several reasons might account for such a discrepancy. First, analgesia was tested at 5 min postinjection: the peak analgesic effect of fentanyl might be expected in 5–10 min postinjection (37), which formed the basis for our placement of the first immersion at that time point. However, perhaps midazolam did have an effect on opioid-induced analgesia, but an inappropriate sampling time (i.e., 5 min postinjection) was chosen. We think this is unlikely, though, because midazolam, like fentanyl, has a rapid onset of pharmacological effects—peak effect of sedation is reached within 2–3 min of an injection (34). Second, and relatedly, it is possible that had we taken multiple measurements of the pain response within the first 30 min postinjection, we may have found that the duration of fentanyl-induced analgesia was decreased by midazolam. We were not able to test this hypothesis, because the cold pressor test cannot be given repeatedly within such a

short interval of time (i.e., 30 min). Therefore, we cannot exclude the possibility that midazolam decreased (or increased) the duration of opioid-induced analgesia. Third, we placed a ceiling of the midazolam dose at 2 mg/70 kg. The rationale for the ceiling was that we wanted to ensure that subjects would be responsive during the first immersion (i.e., that they could fill out mood forms and report their level of pain), when drug effects were predicted to be at or close to peak levels. On the other hand, it may take higher systemic doses of midazolam before an effect is seen in humans. However, it should be pointed out that 2 mg of midazolam in addition to 0.1 mg of fentanyl is a typical dosing combination in conscious sedation medical procedures.

A secondary aim of this study was to characterize the effects of the fentanyl-midazolam combination on mood, and psychomotor/cognitive effects. Fentanyl alone produced a number of alterations in self-reported mood, and midazolam appeared to merely lengthen the duration that these effects were reported. The fact that fentanyl had minimal effects on psychomotor performance is in agreement with a number of other studies that have shown minimal impairment with this class of drugs at clinically relevant doses [e.g., (36)]. The dose-related degree of impairment when midazolam was added to fentanyl is consistent with other studies that have documented the psychomotor-impairing and amnestic effects of benzodiazepines [e.g., (38)].

The present study did not examine the analgesic effects of midazolam by itself. Numerous infrahuman studies have shown that benzodiazepines, such as midazolam and diazepam, are analgesic when administered spinally (intrathecally) (8,13,24,25,33,49), but one study (24) has shown that when administered systemically, it actually produces hyperalgesia in response to a nociceptive stimulus. Laboratory studies using humans as subjects have focused primarily on the systemic route of drug administration when investigating the relationship between benzodiazepines and the pain response. The predominant finding is that benzodiazepines have no effect on the sensory response to painful stimuli (3,9–11,42,45,51). The present finding demonstrating that intravenously administered midazolam did not decrease or potentiate fentanyl-induced analgesia, then, is consistent with those findings showing lack of an effect of benzodiazepines on the pain response in humans.

In conclusion, midazolam, administered intravenously, did not decrease (or potentiate) analgesia produced by fentanyl. These results are discordant with animal studies showing that systemic or supraspinally administered benzodiazepines reduce opioid-induced analgesia, and with those clinical and case reports suggesting an antagonist-like effect on opioid-induced analgesia in humans. The results are concordant, though, with the majority of studies showing a lack of effect of benzodiazepines on the pain response in humans. A clinical ramification of the present findings is that in surgical and medical procedures that produce pain, the addition of a benzodiazepine for its sedative and amnestic properties does not necessitate an increase in the amount of opioid administered for analgesia.

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