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Comparison of the Sedative Effects of Butorphanol and Midazolam

Mark Dershwitz, M.D., Ph.D.,* Carl E. Rosow, M.D., Ph.D.,†
Patricia M. DiBiase, R.N., B.S.N.,‡ Alan Zaslavsky, Ph.D.§

Although kappa opioid agonists and certain agonist–antagonists are known to be sedating, this effect has not been well characterized in a drug-naive population. We compared the sedative properties of intravenous butorphanol with those of midazolam or the combination in 126 healthy preoperative patients. Subjects were randomly assigned to receive one of nine treatments in a double-blind fashion: 7.1, 22.5, or 71.4 μg/kg butorphanol; 4.3, 13.6, or 42.9 μg/kg midazolam; or 3.6 + 2.2, 11.3 + 6.8, or 35.7 + 21.5 μg/kg butorphanol and midazolam in combination. Eight visual analogue scales (VAS) were completed by the subject and an observer. The subject then performed two psychomotor tests (the Trieger dot test and the Halstead trail-making test) and was shown two playing cards in order to assess memory. The test drug was administered, and 5 min later the evaluations were repeated and two more cards were shown. On the following day the subjects were asked to recall the names of the playing cards. Butorphanol, midazolam, and their combination produced dose-related changes in VAS scores that were significant and qualitatively similar: subjects became sleepy, less nervous, weak, and less clear-thinking. There was no significant euphoria or dysphoria. The sedative and depressant effects on respiratory rate of the high-dose combination were significantly greater than those predicted by simple additivity: 14 of 14 subjects receiving the high dose of the butorphanol/midazolam combination had lid droop and marked sedation, and 2 of 14 subjects had respiratory rates of less than 4 breaths per min. All three drug treatments caused significant, dose-dependent impairment of psychomotor function. Subjects usually remembered cards seen prior to drug treatment, but not those seen afterward. The amnesic effects of midazolam were dose-related, profound, and much greater than those of butorphanol. In a 70-kg subject, a dose as low as 0.5 mg butorphanol (lower than the usual analgesic dose) provided clinically useful sedative effects. At this dose, however, butorphanol caused no significant amnesic effect or psychomotor impairment. (Key words: Analgesics, intravenous: butorphanol. Antagonists: opioid. Hypnotics, intravenous: midazolam. Interaction, drug. Premedication. Toxicity: drug.)

BUTORPHANOL is an agonist–antagonist opioid that is believed to have agonist activity at kappa and some mu opioid receptors.[1] It produces opioid effects, such as analgesia and respiratory depression, but these effects plateau at clinically used doses. Martin *et al.*[2] first demonstrated that kappa-type opioids produce sedation in animals, and this has subsequently been confirmed by others. In humans, an analgesic dose of butorphanol given by the intramuscular, intravenous, or epidural route often produces marked sedation.[3,4] Intravenous butorphanol has been evaluated as a sedative for gastrointestinal endoscopy and facial plastic surgery, but this effect has not been well characterized.[5,6] Little has been published regarding the doses needed or the quality of the sedation (*e.g.*, regarding amnesia, anxiolysis, dysphoria, or psychomotor impairment). This study was designed to compare the sedative effects of intravenous butorphanol and midazolam. Because of the frequency with which opioids and benzodiazepines are combined for intravenous sedation, we also investigated the effects of a butorphanol–midazolam mixture.

Materials and Methods

The study was approved by the Subcommittee on Human Studies and the Pharmacy Committee of the Massachusetts General Hospital. Each of the 126 subjects gave written, informed consent to participate. The subjects were between 18 and 64 yr old and ASA physical status 1 or 2 and were scheduled for elective surgery under general anesthesia of anticipated duration of 4 h or less. All operations had an anticipated blood loss of <1 l, and each patient was scheduled to remain in the hospital for at least one postoperative day. No patient was taking any psychoactive, sedating, opioid analgesic, or autonomic agonist or antagonist medication in the 2 weeks prior to surgery.

The study included nine treatment groups (three doses in each of three drug groups). Subjects were randomly assigned to receive butorphanol, midazolam, or the combination in a low, medium, or high dose, as described in table 1. The doses were selected to encompass the sedative dosage range of midazolam and the analgesic dosage range of butorphanol. For example, a 70-kg subject randomized to a high-dose group received either 5 mg butorphanol, 3 mg midazolam, or 2.5 mg butorphanol plus 1.5 mg midazolam. The low-dose group received a dose that was one tenth that used in the high-dose group. The medium-dose group received a dose midway between the low and

* Assistant Professor of Anaesthesia, Harvard Medical School.
† Associate Professor of Anaesthesia, Harvard Medical School.
‡ Clinical Research Nurse, Anesthesia Services of Massachusetts General Hospital.
§ Assistant Professor of Statistics, Harvard University.

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Address reprint requests to Dr. Rosow: Department of Anesthesia, Massachusetts General Hospital, Boston Massachusetts 02114.

TABLE 1. Doses of Test Drugs Administered

Drug Treatment Group	Dose (μg/kg)		
	Low	Medium	High
Butorphanol	7.1	22.6	71.4
Midazolam	4.3	13.6	42.9
Butorphanol + midazolam	3.6 + 2.1	11.3 + 6.8	35.7 + 21.4

high doses on a logarithmic scale. Neither the subjects nor the investigators knew the drug or dose assignment.

The pharmaceutical preparations used were midazolam hydrochloride (Versed®, Roche) and butorphanol tartrate (Stadol®, Bristol). Midazolam was diluted in saline with the final *p*H adjusted to 3. Butorphanol was diluted in isotonic citrate buffer. Neither pharmaceutical supplier possessed stability data on very dilute solutions of their drug. Since we anticipated that the study would take place over several months, we were concerned about the stability of the most dilute solutions we used (36 μg/ml butorphanol and 21 μg/ml midazolam). To verify that these solutions did not deteriorate over the duration of the study period (5 months), samples of these solutions were analyzed by high-performance liquid chromatography (National Medical Services, Willow Grove, PA). The assays have an accuracy of 1 μg/ml and a coefficient of variation of 7%. No measurable decrease in the concentration of either drug occurred during the study period.

For each subject, two coded vials were prepared by the hospital pharmacy. The subject received 0.1 ml/kg of study drug from each vial. For subjects receiving butorphanol or midazolam alone, one vial contained active drug, and the second vial contained saline.

Each subject was evaluated in the following manner. Vital signs (blood pressure by cuff and auscultation; pulse and respiration by palpation) were recorded, and then a series of visual analogue scales (VAS) were completed by the subject and the investigator. The subject then performed two psychomotor tests (described below). Finally, the subject was shown two playing cards (from a deck consisting of the 36 numbered cards) and was told to read the names of the cards out loud. An intravenous catheter was inserted, and the study drug was administered intravenously over 90 s. Vital signs were recorded immediately after drug administration and again after 5 min. Five minutes after drug administration, the VAS again were completed by subject and investigator; the psychomotor tests were performed; and two different playing cards were shown to the subject. The presence or absence of dysarthria and lid droop also were assessed 5 min after drug administration. This time point corresponds approximately to the peak EEG effect of midazolam[7] and the peak analgesic effect of butorphanol.[3] All subjects were evaluated by the same investigator.

The subjects then underwent their scheduled surgeries. No limitations were placed on the agents used for general anesthesia except that no scopolamine and no benzodiazepines were administered. On the first postoperative day, the subjects were asked to name the playing cards they had been shown.

VISUAL ANALOGUE SCALES

The subjects were given a single sheet of paper with a series of six 100-mm lines, labeled as shown in table 2; the first three lines were designed to assess somatic perception and the latter three to assess mood. The subject was told to make a mark somewhere along each line reflecting how he or she felt at that moment. Two VAS were simultaneously and independently completed by the investigator. These scales are also shown in table 2. The VAS were scored as an integer from 0 to 100 corresponding to the position of the mark in millimeters to the right of the origin of the line.

PSYCHOMOTOR TESTS

The Trieger dot test is a well-described test of visual and motor coordination.[8] It consists of a series of dots that need to be connected by two discontinuous lines. The score is the number of dots missed. Practice is believed to have little effect on this test. Our modification of the Halstead trail-making test consisted of a sheet of paper marked with the numbers 1–13 and the letters A–L enclosed in circles.[9] To perform the test, the subject used a pen to connect the circles as follows: 1–A–2–B–3–C, and so forth. Thirty seconds were allowed to complete the test, and no subject was able to complete all 24 correct connections. A shortened version of the test is

TABLE 2. The Subject-Rated and Observer-Rated VAS

Subject-rated VAS	
0	100
Not thinking clearly at all	Thinking very clearly
Not sleepy at all	Very sleepy
Not weak at all	Very weak
Terrible	Terrific
Not nervous at all	Very nervous
Not depressed at all	Very depressed
Observer-rated VAS	
0	100
Awake	Somnolent
Not nervous at all	Very nervous

East set of VAS consisted of these phrase pairs at opposite ends of 100-mm lines.

administered once for practice and instruction prior to the timed test. The score is the number of correct connecting lines. This test is believed to reflect a subject's ability to concentrate and his or her susceptibility to interference by competing stimuli in the environment.[9]

Memory Tests

To evaluate the possible amnesic effects of the test drugs, the subjects were shown playing cards both before and after drug administration. They were not asked to recall the names of the cards until the first postoperative day. The subject was given one point for recalling the number and one point for recalling the suit of each card. For each pair of cards, the subject could therefore receive from zero to four points. Inability to remember cards shown before and after drug administration was considered evidence of retrograde and anterograde amnesia, respectively.

Statistical Analyses

For all continuous variables a covariance adjustment was performed to correct the posttreatment response for the pretreatment response.[10] Significant differences from baseline were calculated with Student's t test using a pooled estimate of variance. Quantal data were analyzed with Fisher's exact test. Statistical significance was defined as $P < 0.05$, unless a smaller P value is specified in the text or legend.

For each response, we compared the effect of the highest doses of midazolam, butorphanol, and the combination to test the hypothesis that the combination produced a supraadditive effect. We defined the effect as supraadditive when the effect of the highest combination dose was significantly larger than the average of the effect of the highest midazolam dose and the highest butorphanol dose. Significance was assessed using the following t statistic:

$$t = \frac{COM_{high} - 1/2(MID_{high} + BUTOR_{high})}{\sqrt{(SE_{COM})^2 + 1/4(SE_{MID})^2 + 1/4(SE_{BUTOR})^2}}$$

where SE = standard error of the mean for the designated group. Again, statistical significance is defined as $P < 0.05$, unless a smaller P value is specified in the text.

Results

Characteristics of the Study Groups

There were no protocol violations, and no data were discarded. The demographics of the nine groups are shown in table 3. The ratio of males to females was uneven, so covariance adjustments were made to correct for the effects of gender on responses. Because of the wide range of the ages of the subjects, covariance adjustments were made also to correct for the effects of age on responses. Since the results were not altered by either correction, we are reporting the data without these corrections. There were no significant differences between groups in the type or duration of surgery, anesthetic agents used, or intraoperative blood loss.

TABLE 3. Subject Demographics

Variable	Dose		
	Low	Medium	High
Sex (M/F)			
Butorphanol	2/12	3/11	5/9
Midazolam	9/5	8/6	3/11
Butorphanol + midazolam	6/8	9/5	4/10
Age (yr)			
Butorphanol	38.1 ± 3.2	31.6 ± 2.7	36.6 ± 2.9
Midazolam	32.4 ± 2.4	31.5 ± 3.2	34.9 ± 2.8
Butorphanol + midazolam	38.0 ± 3.7	40.6 ± 4.0	34.8 ± 4.0
Weight (kg)			
Butorphanol	59.9 ± 3.1	67.6 ± 3.0	71.9 ± 3.7
Midazolam	71.2 ± 3.2	77.5 ± 4.0	66.6 ± 4.4
Butorphanol + midazolam	73.6 ± 4.4	73.5 ± 4.7	67.4 ± 2.9

Subject-rated VAS

Before treatment, there were no significant differences among the nine groups. Therefore, baseline scores have been pooled for each scale and are indicated in the figures.

Somatic Perception

Results of these scales are shown in figure 1. At baseline, subjects did not perceive themselves to be sleepy or weak, and most believed they were thinking clearly. All treatments, except for the lowest dose of midazolam, produced significant sleepiness compared to baseline. Subjects receiving even the lowest dose of butorphanol had higher scores on the "sleepy/not sleepy" scale than did those receiving any dose of midazolam. In eight of the nine groups there was a significant increase in weakness, and in all groups there was a significant decrease in clear thinking. In each case, when midazolam and butorphanol were combined, the effect was significantly supraadditive.

Mood

Baseline scores on the three scales evaluating mood (fig. 2) were as follows. On the "not nervous/nervous" scale, they were at midpoint (50); on the "terrible/terrific" scale they were slightly elevated (64); and on the "not depressed/depressed" scale they were near the "not depressed" origin (16). Subjects receiving either butorphanol or midazolam became significantly less nervous, but the effect of the combination was not supraadditive.

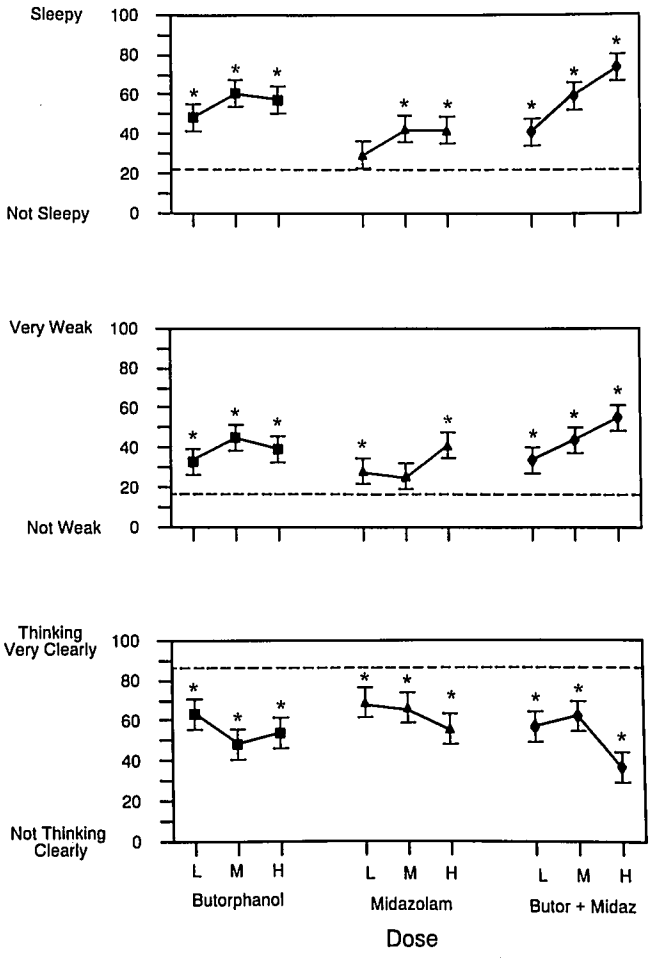

FIG. 1. The dose-response relationships for the three subject-rated VAS measuring somatic perception. Each point represents the mean ± SEM for the responses to butorphanol (squares), midazolam (triangles), or the combination (butor + midaz) (diamonds), administered in a low (L), medium (M), or high (H) dose, as described in table 1. The x-axis shows these doses plotted on a logarithmic scale. The dashed line indicates the mean pretreatment value for each VAS. Each point marked with an asterisk is significantly different from the pretreatment value ($P < 0.05$).

There were no consistent dose-related effects on the other two VAS.

OBSERVER-RATED VAS

The baseline scores on the "awake/somnolent" and "not nervous/nervous" scales (fig. 3) show that the investigator perceived the subjects as awake (5.8) and slightly nervous (65.6). All treatments, except for the lowest dose of midazolam, produced significant increases in somnolence and decreases in nervousness, and the responses were clearly dose-related. For both VAS, the combination of butorphanol and midazolam produced significant supraadditive effects ($P < 0.01$).

PSYCHOMOTOR TESTS

The subjects' performance on the Trieger and Halstead tests is shown in figure 4. The lowest dose of butorphanol produced a small improvement in performance, which for the Trieger test reached significance. Otherwise, all three drug treatments produced significant, dose-related decrements in performance. The effects of midazolam appeared to be larger than those of butorphanol, but these differences were not significant. The effect of the combination was not significantly supraadditive on either test.

DYSARTHRIA AND LID DROOP

Only 17 of the 126 subjects became dysarthric after drug administration, and 13 of them were in the high-dose groups (table 4). The frequency of dysarthria was not significantly different between drug treatments. The overall frequency of lid droop was 60 of 126 subjects.

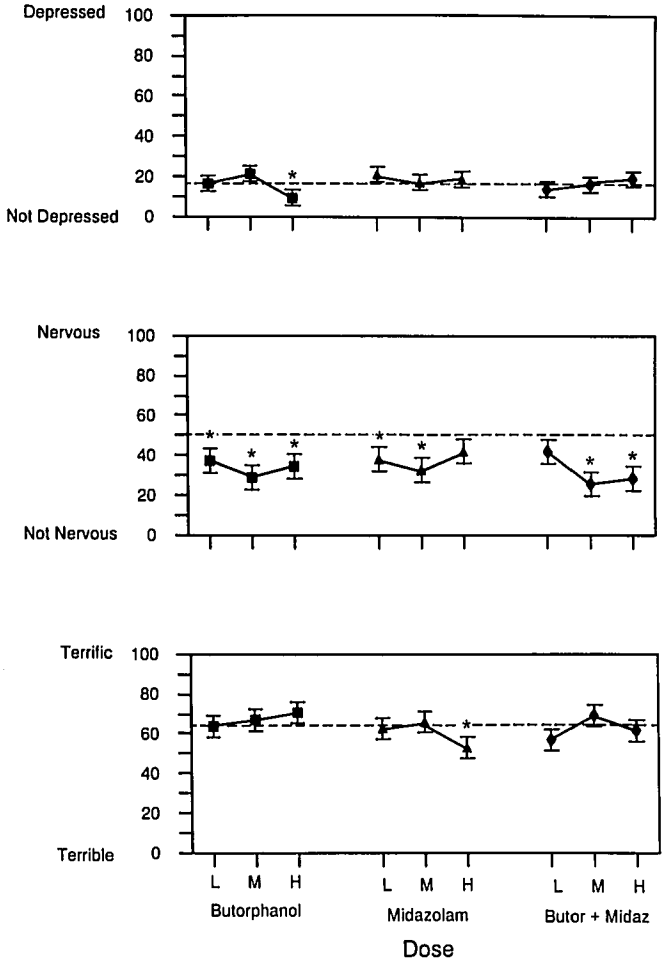

FIG. 2. The dose-response relationship for the three subject-rated VAS measuring mood. Legend symbols and abbreviations are as in figure 1.

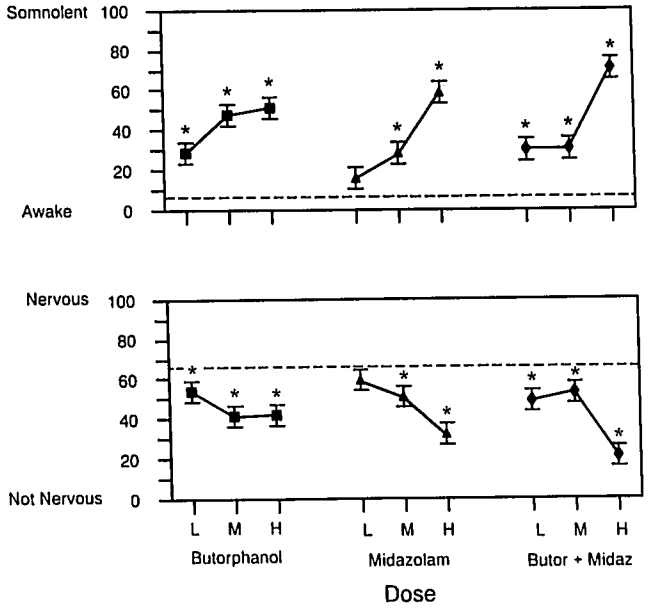

FIG. 3. The dose-response relationship for the two observer-rated VAS. Legend symbols and abbreviations are as in figure 1.

The incidence was dose-related for all three drug treatments, and the effects of the combination were significantly supraadditive. Lid droop occurred in 100% of subjects receiving the highest dose of the combination.

TABLE 4. Number of Subjects with Side Effects (n = 14)

Effect	Treatment Group		
	Low-dose	Medium-dose	High-dose
Dysarthria			
Butorphanol	0	2	3
Midazolam	0	0	4
Butorphanol + midazolam	1	1	6
Lid droop			
Butorphanol*	5	9	9
Midazolam*	0	3	10
Butorphanol + midazolam*	4	6	14‡
Respiratory rate <8 breaths per min			
Butorphanol†	2	4	4
Midazolam	1	0	1
Butorphanol + midazolam	0	3	6

* Significantly dose-related ($P < 0.001$).
† Significantly dose-related ($P < 0.005$).
‡ Significant supraadditive effect compared with the high dose of butorphanol or midazolam ($P < 0.05$).

MEMORY TEST

Memory assessment (fig. 5) could not be completed in 13 patients who were discharged early. There was no evidence that any treatment produced retrograde amnesia: subjects usually remembered both the names and suits of the playing cards shown prior to drug administration (mean score = 3.4 ± 0.4). Recall for cards shown after drug administration was impaired by both drugs. There was a small, but significant, anterograde amnesic effect with butorphanol, and a profound, dose-related amnesic effect with midazolam ($P < 0.001$). Eleven of 14 subjects receiving the highest dose of midazolam correctly recalled the cards seen before drug administration and remembered nothing about those seen after drug administration. The combination of butorphanol and midazolam had a significantly smaller effect on memory than did midazolam alone.

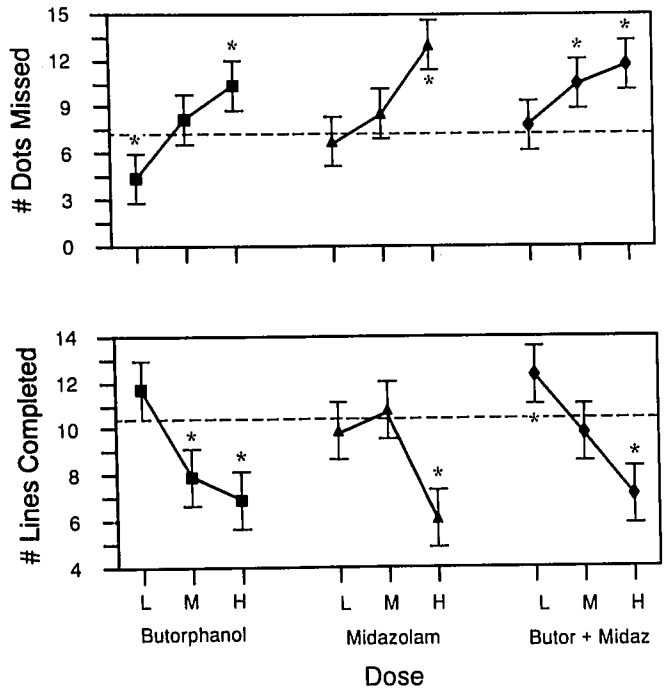

FIG. 4. The dose-response relationship for the two psychomotor tests. The tests were scored as described in Materials and Methods. Legend symbols and abbreviations are as in figure 1.

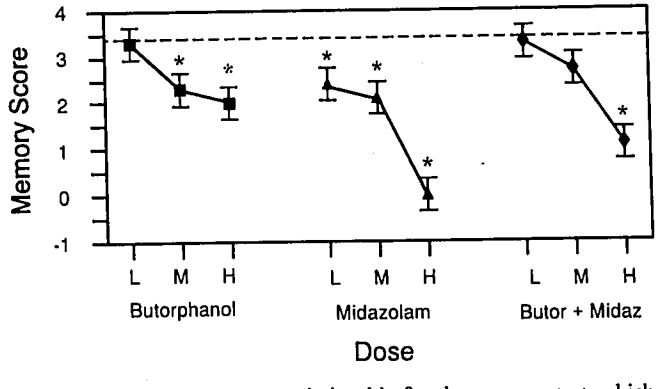

FIG. 5. The dose-response relationship for the memory test, which was scored as described in Materials and Methods. Legend symbols and abbreviations are as in figure 1.

VITAL SIGNS

Subjects receiving the highest dose of butorphanol had a significant rise in systolic blood pressure, of 10 ± 3 mmHg ($P < 0.01$). Otherwise, there were no significant changes in heart rate or blood pressure in these awake subjects. There were significant effects on respiratory rate, as shown in table 4. Midazolam produced a respiratory rate of less than 8 breaths per min in only 2 of 42 subjects. Butorphanol decreased respiratory rate significantly ($P < 0.001$), but there was no significant difference between dose groups. Six of 14 subjects receiving the highest dose of the combination had respiratory rates of less than 8 breaths per min. Two of these individuals had rates of less than 4 breaths per min and had to be encouraged to breathe. This severe depression of respiratory rate did not occur in subjects given midazolam or butorphanol alone. The decrease in respiratory rate produced by the combination was supraadditive ($P < 0.01$).

Discussion

Sedation is the most frequently observed side effect of butorphanol when the drug is given in recommended analgesic doses. In 1,440 patients with acute postoperative pain, doses of 0.5–4.0 mg butorphanol (intramuscular or intravenous) produced a 37% incidence of sedation.[3] DelPizzo found that 90 min after intramuscular injection of 2 mg butorphanol, 78% of patients had "moderate" or "marked" sedation. The amount of sedation was found to be greater than that produced by 80 mg meperidine.[11]

The mechanisms for this effect are not known. Butorphanol is believed to be a partial agonist at kappa opioid receptors, although animal studies indicate that some of its analgesic and endocrine effects may involve mu receptor mechanisms as well.[1] Compounds that are classified as specific kappa agonists (ethylketazocine, bremazocine, U-50,448) are known to produce "apathetic sedation" in animals. Goodman and Snyder suggested that this effect may be a consequence of the anatomic localization of kappa receptors in deep layers of the cerebral cortex.[12]

Whatever the mechanism, the subjective effects of butorphanol are unlike those of morphine, fentanyl, and other mu agonists. Animals trained to self-inject morphine sometimes generalize to butorphanol,[13] but human former addicts do not perceive the drug as morphinelike and sometimes confuse it with a barbiturate.[14] In individuals previously addicted to opioids, butorphanol does not produce mood elevation or drug-seeking behavior as does morphine.[14]

In only a few published studies has butorphanol been used primarily as a sedative. The specific effects on mood, memory, psychomotor performance, and so forth were not described. Recently, Bacon and Marshall completed a double-blind comparison of butorphanol and diazepam during upper gastrointestinal endoscopy.[6] They concluded that 4.8 ± 0.4 mg butorphanol and 12 ± 1 mg diazepam produced comparable sedative effects (patients were somnolent with eyelids closed, but they remained responsive to verbal commands). Our data indicate that adequate conscious sedation in the majority of cases can be achieved with lower doses of butorphanol. If a benzodiazepine is also administered, the sedative effect is greatly increased, and 4.8 mg butorphanol may be sufficient to produce unconsciousness.

Interestingly, Bacon and Marshall also reported that butorphanol produced a significant amnesic effect: 26 of their patients received only butorphanol, and 10 of them had total amnesia for the endoscopic examination. In contrast, we found that doses of butorphanol up to 0.07 mg/kg did not produce a large amount of anterograde amnesia. Since midazolam produced the expected effect on memory, we are confident that our test has sufficient sensitivity. The combination of butorphanol and midazolam actually had a smaller amnesic effect than did midazolam alone (probably because the midazolam doses were smaller in these groups).

When butorphanol was given to our population of normal presurgical patients, it produced sedation that was qualitatively indistinguishable from that of midazolam. Patients obviously perceived a strong drug effect, and they appeared sleepy to the observer. Both drugs caused modest decreases in nervousness and very little change in other scales dealing with mood. Both drugs caused dose-related ptosis, dysarthria, and decreases in psychomotor performance.

We expected that the two drugs might differ in their effects on anxiety, but midazolam did not have demonstrable anxiolytic effects in our patients. This may be because at baseline these individuals were not very anxious. Benzodiazepines may not behave as predictably in normal surgical patients as in those with chronic anxiety states. Lichtor *et al.* have shown that midazolam may actually *increase* anxiety in preoperative patients.[15]

Patients receiving butorphanol for postoperative pain may experience dysphoria, whereas such reactions are quite infrequent with morphine or fentanyl.[16] Some of the older agonist–antagonists (*e.g.*, nalorphine or pentazocine) were reported in a large percentage of patients to produce unpleasant mental effects like depersonalization reactions or hallucinations.[17] None of our 126 patients had obvious euphoria or dysphoria, and there were no consistent changes on the relevant VAS (*e.g.*, on the "terrible/terrific" and "depressed/not depressed" scales). We did not seek specific information on mood

postoperatively, but there were no reports of dysphoria at the 24-h visit.

The measurement of respiratory rate as an indicator of drug-induced respiratory depression is not as sensitive as the determination of minute ventilation or response to carbon dioxide. Although we used respiratory rate rather than other measures of respiratory depression, our data are in agreement with those previously published for butorphanol. Approximately equivalent depression in carbon dioxide response is produced by 2 mg butorphanol and 10 mg morphine, but butorphanol-induced depression is reported to reach a "ceiling" at 2 mg in most individuals.[18] Respiratory depression and all of the other effects of butorphanol are reversible with the antagonist naloxone.[3] In our study, 10 of 42 patients given butorphanol alone had respiratory rates of <8 breaths per min, but none required intervention (table 4).

It was surprising that respiratory rate in our patients was generally unaffected by midazolam. Midazolam and other benzodiazepines are well known to depress the response to carbon dioxide and to cause apnea in certain individuals.[19] Our results may reflect the relative youth and good health of the population we studied or, possibly, the administration of the drug over 90 s.

When midazolam and opioid agonists are combined, they appear to produce a synergistic depression of respiration.[20] Many of the cases of respiratory arrest reported after the introduction of midazolam may actually have been attributable to interaction of the benzodiazepine with morphine, meperidine, or fentanyl.¶ It seems unlikely that the interaction between benzodiazepines and butorphanol is different. Cook reported an open trial of sedation with butorphanol plus diazepam which involved 417 outpatients undergoing facial plastic surgery.[5] Patients were given enormous doses of butorphanol (average 20.5 mg, intravenously; range 8–82 mg). All but 21 patients also received diazepam (5–15 mg, orally or intravenously or both). The author stated that verbal contact was maintained in all cases, and no patient required naloxone for respiratory depression (specific data were not presented). It is not possible for us to explain why Cook's patients needed—or tolerated—these doses, but our data indicate that much lower doses of butorphanol and midazolam in combination can cause very low respiratory rates. The interaction is supraadditive and therefore similar to the fentanyl–midazolam combination. Although the agonist–antagonists generally have an excellent safety record, their lack of toxicity should not be overstated.

Butorphanol has been in use as a parenteral analgesic for over 10 yr, although its place in anesthesia has not been well established. The mu opioid agonists produce more profound analgesia and greater depression of MAC for volatile anesthetics, so they continue to be preferred for many intraoperative indications.[21] However, the doses of fentanyl or morphine required to produce sedation are also large enough to produce substantial analgesia and depression of respiratory drive.[22] The current study suggests that butorphanol is more selective, since it is sedating at subanalgesic doses. Perhaps it is most accurate to describe the drug as a sedative with analgesic side effects.

In the current study, we confirmed the sedative properties of butorphanol and found them to be qualitatively similar to those of midazolam. Like fentanyl, butorphanol markedly potentiated the sedative effects of midazolam, and the butorphanol–midazolam combination appears to be a useful one. Significant sedation can also be produced by butorphanol alone at doses less than those usually used for analgesia, and such sedation is not accompanied by amnesia or impairment of psychomotor function. Butorphanol may therefore by useful in settings where profound anterograde amnesia is not desired and a lesser degree of psychomotor impairment is advantageous.

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References

1. Wood PL, Sanschagrin D, Richard JW, Thakur M: Multiple opiate receptor affinities of kappa and agonist/antagonist analgesics: In vivo assessment. J Pharmacol Exp Ther 226:545–550, 1983
2. Martin WR, Eades CG, Thompson JA, Huppler RE, Gilbert PE: The effects of morphine- and nalorphine-like drugs in the nondependent and morphine-dependent chronic spinal dog. J Pharmacol Exp Ther 197:517–532, 1976
3. Caruso FS, Pircio AW, Madissoo H, Smyth RD, Pachter IJ: Butorphanol, Pharmacological and Biochemical Properties of Drug Substances. Vol. 2. Edited by Goldberg ME. Washington, American Pharmaceutical Association, Academy of Pharmaceutical Sciences, 1979, pp 19–57
4. Abboud TK, Moore M, Zhu J, Murakawa K, Minehart M, Longhitano M, Terrasi J, Klepper ID, Choi Y, Kimball S, Chu G: Epidural butorphanol or morphine for the relief of post-cesarean section pain: Ventilatory responses to carbon dioxide. Anesth Analg 66:887–893, 1987
5. Cook TA: Butorphanol tartrate: An intravenous analgesic for outpatient surgery. Otolaryngol Head Neck Surg 91:251–254, 1983
6. Bacon BR, Marshall JB: Randomized, prospective, double-blind clinical trial of butorphanol and diazepam in patients undergoing upper gastrointestinal endoscopy. Acute Care 12(suppl 1):57–62, 1988
7. Bührer M, Maitre PO, Ebling WF, Stanski DR: Electroencephalographic effects of benzodiazepines: II. Pharmacodynamic modeling of the electroencephalographic effects of midazolam and diazepam. Clin Pharmacol Ther 48:555–567, 1990

¶ Data on file. Hoffman-LaRoche, Nutley, New Jersey.

8. Newman MG, Trieger N, Miller JC: Measuring recovery from anesthesia: A simple test. Anesth Analg 48:136–140, 1969
9. Lezak MD: Neuropsychological Assessment. New York, Oxford University Press, 1976, pp 429–432
10. Cochran WS: Planning and Analysis of Observational Studies. New York, John Wiley and Sons, 1983, pp 108–109
11. DelPizzo A: Double-blind evaluation of butorphanol and meperidine given intramuscularly before anesthesia. Curr Ther Res 20:763–771, 1976
12. Goodman RR, Snyder SH: Autoradiographic localization of kappa opiate receptors to deep layers of the cerebral cortex may explain unique sedative and analgesic effects. Life Sci 31:1291–1294, 1982
13. Griffiths RR, Balster RL: Opioids: Similarity between evaluations of subjective effects and animal self-administration results. Clin Pharmacol Ther 25:611–617, 1979
14. Jasinski DR, Griffith JD, Pevnick JS, Clark SC: Progress report on studies from the clinical pharmacology section of the Addiction Research Center, National Institute on Drug Abuse, Problems of Drug Dependence 1975. Washington, D.C., National Academy of Sciences, Committee on Problems of Drug Dependence, 1976, pp 121–161
15. Lichtor JL, Korttila K, deWitt H, Ward J, Lane BS: Increased anxiety after intravenous midazolam (abstract). ANESTHESIOLOGY 69:A910, 1988
16. Houde RW: Analgesic effectiveness of the narcotic agonist–antagonists. Br J Clin Pharmacol 7:297S–308S, 1979
17. Lasagna L, Beecher HK: The analgesic effectiveness of nalorphine and nalorphine–morphine combinations in man. J Pharmacol Exp Ther 112:356–363, 1954
18. Nagashima H, Karamanian A, Malovany R, Radnay P, Ang M, Koerner S, Foldes FF: Respiratory and circulatory effects of intravenous butorphanol and morphine. Clin Pharmacol Ther 19:738–745, 1976
19. Forster A, Gardaz JP, Suter PM, Gemperle M: Respiratory depression by midazolam and diazepam. ANESTHESIOLOGY 53: 494–497, 1980
20. Bailey PL, Moll JWB, Pace NL, East KA, Stanley TH: Respiratory effects of midazolam and fentanyl: Potent interaction producing hypoxemia and apnea (abstract). ANESTHESIOLOGY 69:A813, 1988
21. Murphy MR, Hug CC, Jr: The enflurane sparing effect of morphine, butorphanol, and nalbuphine. ANESTHESIOLOGY 57: 489–492, 1982
22. Ben-Shlomo I, Abd-el-Khalim H, Ezry J, Sohar S, Tverskoy M: Midazolam acts synergistically with fentanyl for induction of anaesthesia. Br J Anaesth 64:45–47, 1990