Ondansetron Does Not Affect Alfentanil-induced Ventilatory Depression or Sedation

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Ondansetron is a selective 5-hydroxytryptamine type 3 receptor antagonist effective as an antiemetic in patients experiencing postoperative or cancer chemotherapy–induced nausea and vomiting. Currently, no information is available regarding the interaction of ondansetron with opioids, although a serotonin antagonist might be expected to modify some opioid actions. This study was designed to measure the effects of ondansetron on alfentanil-induced ventilatory depression and sedation in healthy male volunteers. Ventilatory drive (measured as the end-tidal CO_2 necessary to produce a minute ventilation of 15 l/min) was determined in 29 subjects using a modification of the Read rebreathing technique. Sedation was measured by asking the subjects to complete visual analog scales. Alfentanil was administered as a bolus (5 µg/kg) followed by a continuous infusion (0.25–0.75 $\mu g \cdot kg^{-1} \cdot min^{-1}$) for at least 90 min. Study medication (ondansetron 8 or 16 mg or vehicle placebo) was then administered in a randomized, double-blind manner, and the alfentanil was infused for an additional 15 min. Measurements of ventilatory drive and sedation were made at baseline, during alfentanil infusion, after study medication, and at 30-min intervals after alfentanil was discontinued. Alfentanil produced significant ventilatory depression ($P < 0.001$) and sedation ($P < 0.001$) in all three groups. Neither placebo nor ondansetron produced further change in the intensity of either alfentanil effect. After discontinuation of the opioid, both ventilatory depression and sedation decreased, and the rate of recovery was not significantly different between groups. The data indicate that alfentanil-induced sedation and ventilatory depression are not significantly affected by the subsequent administration of ondansetron. (Key words: Analgesics, opioids: alfentanil. Antiemetics: ondansetron. Antagonists, serotonin: ondansetron. Ventilation.)

ONDANSETRON is a selective 5-hydroxytryptamine type 3 (5-HT_3) receptor antagonist recently approved in the United States for the management of cancer chemotherapy–induced nausea and vomiting. We have previously demonstrated its efficacy in the prophylaxis of postoperative nausea and vomiting,[1] and others have demonstrated the efficacy of ondansetron in the treatment of postoperative nausea and vomiting.[2,3] Although this agent is likely to be administered together with opioids and sedatives, its interactions with these drugs have not been studied specifically.

In the nomenclature of the older literature on serotonin receptor pharmacology, the 5-HT_3 receptor was called the serotonin "M" receptor because morphine antagonized serotonin-mediated contraction of the guinea pig ileum.[4] Inhibition of electrically induced contraction of the guinea pig ileum is a relatively specific bioassay for opioid alkaloids and peptides acting via µ-opioid receptors. Thus, it is reasonable to predict that ondansetron may interact with µ-opioid agonists like fentanyl, alfentanil, or sufentanil. The present study was designed to determine if ondansetron alters the intensity or duration of alfentanil-induced ventilatory depression or sedation.

Materials and Methods

The study was approved by the Massachusetts General Hospital Subcommittee on Human Studies. Each of the 29 healthy male volunteers gave written, informed consent. They took nothing by mouth for the 8 h before the study and reported to the hospital in the early morning on the day of the study. An intravenous catheter was inserted in an upper extremity for drug administration. All subjects were continuously monitored with ECG and pulse oximetry (Nellcor 2500) to ensure that they did not become hypoxic or experience hypercapnia-induced cardiac arrhythmias.

Ventilatory drive was determined by a modification of the Read rebreathing method.[5] Each subject sat in a semirecumbent position and was fitted with an air-tight mask (Hans Rudolph 7910) equipped with a turbine to measure expired tidal volume (Interface Associates model VMM-2) and a side port for measurement of expired CO_2 by infrared spectroscopy (Datex model PB253). They were asked to watch a television program of their choice and to listen to it using headphones during rebreathing sessions. To maintain a closed breathing system, sampled gas was returned to the system after analysis. After a 10-min equilibration period of breathing room air, the mask was switched via a two-way Collins valve to a 13-l reservoir bag that had been prefilled with 10 l of a mixture of 5.24%

CO_2, 50% O_2, and balance N_2. This initial gas volume was chosen to ensure an adequate supply of O_2 during the period of rebreathing. The subject's respiratory rate, tidal volume, and end-tidal CO_2 were then measured for the next 5 min as the minute ventilation increased in response to increasing end-tidal CO_2.

The analog outputs of the ventilation monitor and the capnometer were connected to an analog-to-digital converter (Data Translation DT2821) installed in an AT-class personal computer. The personal computer program TIDAL†† was used for data acquisition and provided breath-by-breath analysis of minute ventilation and end-tidal CO_2.[6] Immediately after each CO_2 rebreathing trial, linear regression analysis was applied to yield the best-fit line for the minute ventilation *versus* end-tidal CO_2 data. The slope, x-intercept, correlation coefficient, the end-tidal CO_2 value corresponding to a minute ventilation of 15 l/min (the "15-l/min intercept"), and the minute ventilation value corresponding to an end-tidal CO_2 of 60-mmHg (the "60-mmHg intercept") were calculated. The 15-l/min intercept was used as a measure of ventilatory drive; an increasing value signified a blunted ventilatory response to CO_2 stimulation. This information was available immediately after each rebreathing session and could be used, as described below, to adjust the rate of opioid infusion. After each determination of ventilatory drive, the subject completed a visual analog scale with the words "not sleepy" and "very sleepy" at opposite ends of a 100-mm line.

To confirm that ventilatory drive did not change during the study period (as long as 6 h) and that the response to hypercapnia did not fatigue, three subjects were given no alfentanil or study medication. Their treatment was otherwise identical to that of the other subjects.

Each subject was evaluated in the following way. Three determinations of baseline ventilatory drive were made at 30-min intervals. This interval was chosen to allow arterial CO_2 tension to return to baseline values and thus prevent cerebrospinal fluid acidosis. The subject was then given intravenous alfentanil HCl (Alfenta®, Janssen). An infusion pump (Infus OR®, Bard) was set to deliver a 5-µg/kg bolus followed by an infusion of 0.25-µg·kg^{-1}·min^{-1}. Subsequent measurements of ventilatory drive were made at 30-min intervals, and the infusion rate was adjusted upward if necessary to produce an increase in the 15-l/min intercept value. The goal was to produce a 10-mmHg increase in the 15-l/min intercept value in each subject. All subjects manifested ventilatory depression by this criterion with alfentanil infusion rates of 0.25–0.75 µg·kg^{-1}·min^{-1}. After two consecutive 15-l/min intercept values had been obtained at the final in-

fusion rate, end-tidal CO_2 was recorded continuously for 15 min while the subjects breathed room air. The subjects received study medication in a random, double-blind manner; end-tidal CO_2 was recorded for another 15 min; and the next determination of ventilatory drive was made. Study medication for each subject consisted of two coded vials containing ondansetron 2 mg/ml (Zofran®, Glaxo) or vehicle placebo. Four milliliters were withdrawn from each vial, and the total was diluted to 20 ml with normal saline for injection. Study medication was administered over 5 min. Subjects in the three groups received ondansetron 8 or 16 mg or vehicle placebo. After the first determination of ventilatory drive after study drug administration, the alfentanil infusion was terminated, and three or four additional determinations of ventilatory drive were made at 30-min intervals.

Statistical significance was assessed using Student's *t* test for paired data or analysis of variance for repeated measurements, as appropriate. A *P* value less than 0.05 was deemed significant.

Results

SUBJECT DEMOGRAPHICS

The subjects ranged in age from 18 to 52 yr, in height from 165 to 193 cm, and in weight from 63 to 107 kg. There were no significant differences between the groups in terms of age, height, or weight by analysis of variance.

STUDY DRUG–MEDIATED VENTILATORY DEPRESSION

A typical ventilatory response to rebreathing CO_2 is shown in figure 1. The same subject's ventilatory response while receiving an alfentanil infusion at 0.25 µg·kg^{-1}·min^{-1} is shown in figure 2. The best-fit line in figure 2 is shifted to the right, and the 15-l/min intercept value has increased as a result of alfentanil-induced ventilatory depression. At the alfentanil infusion rates used in this study (0.25–0.75 µg·kg^{-1}·min^{-1}), a few subjects did not manifest a decreased slope in the minute ventilation *versus* end-tidal CO_2 curve, and for this reason, an increase in the 15-l/min intercept value was used as an indicator of ventilatory depression. The data also were evaluated in terms of the effects of alfentanil and study medication on the 60-mmHg intercept. Although the data are not shown, the results would have been the same had the 60-mmHg intercept been used as an indicator of ventilatory depression instead of the 15-l/min intercept.

The slopes of the CO_2 response curves in the various groups are listed in table 1. There was wide variation in the slopes before the administration of any medication; however, infusion of alfentanil produced a significant decrease in the slopes in all groups. The additional admin-
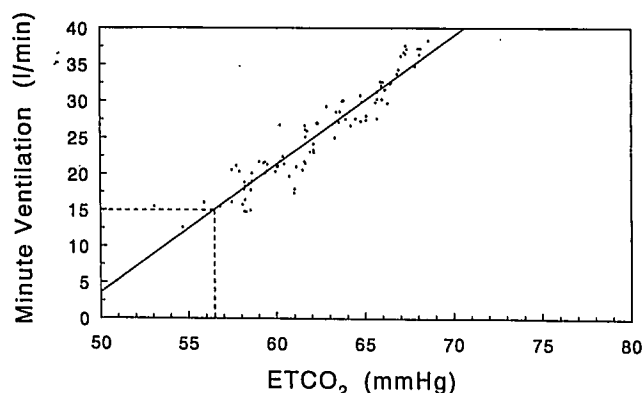
FIG. 1. The minute ventilation *versus* end-tidal CO_2 curve for one subject. Each dot represents one breath. The solid line is the best-fit line provided by least squares analysis. The dashed lines indicate the 15-l/min intercept, in this subject 56.5 mmHg.
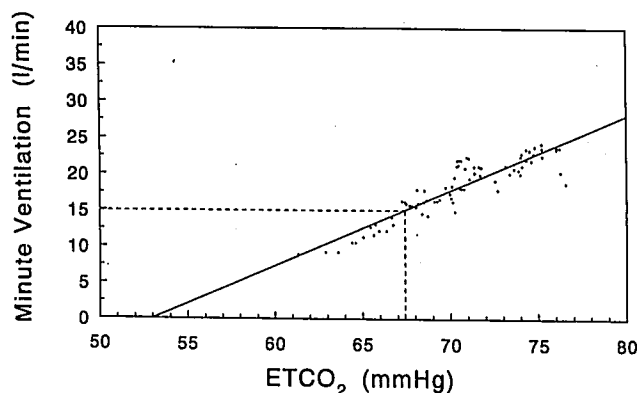

FIG. 2. The minute ventilation *versus* end-tidal CO_2 curve for the same subject as in figure 1 while the subject was receiving an alfentanil infusion at 0.25 $\mu g \cdot kg^{-1} \cdot min^{-1}$. In comparison to figure 1, the slope of the best-fit line through the points is decreased, and the line is shifted to the right. The 15-l/min intercept value is 67.4 mmHg.

istration of study medication had no significant effect on the slopes of the CO_2 response curves.

A decrease in the slope of the CO_2 response curve may increase the 15-l/min intercept value and thus produce an apparent shift in the response curve to the right. To confirm that the increases in the 15-l/min intercept values we observed were a result of the actual displacement of the curve to the right, the x-intercept values (*i.e.*, the end-tidal CO_2 at 0 l/min ventilation by extrapolation) are also listed in table 1. Again, alfentanil caused a significant increase in this value as compared to baseline, whereas no additional effect occurred after study drug administration.

The overall ventilatory depression data are shown in figure 3. The mean value for the 15-l/min intercept before alfentanil administration was 59.62 ± 0.56 mmHg (mean ± SEM). The 15-l/min intercept values for the three groups that were given alfentanil increased in response to alfentanil administration ($P < 0.001$). In each case, the value was not significantly different after study medication. These data indicate that ondansetron had no measurable effect on preexisting alfentanil-induced ven-

tilatory depression. There also was no effect of study medication on resting ventilation or end-tidal CO_2 during the 15 min after administration of study medication and before CO_2 challenge.

The rate of recovery from alfentanil-induced ventilatory depression is shown in figure 4. After discontinuation of the alfentanil infusion, the displacement of the CO_2 response curve returned toward baseline at approximately the same rate in all three groups. The differences were not statistically significant, but the variance in these measurements was large, and a type II error cannot be ruled out.

The three control subjects (figs. 3 and 4) who received no alfentanil or study medication had 15-l/min intercept values determined every 30 min, and these remained stable for 6 hr.

STUDY DRUG-MEDIATED SEDATION

The overall sedation data are shown in figure 5. The sedation scores for all three groups increased in response

TABLE 1. Slope and X-intercept Values

	Baseline	Alfentanil	Study Drug
Slope ($l \cdot min^{-1} \cdot mmHg^{-1}$)			
Placebo	1.76 ± 0.29	1.07 ± 0.15*	1.21 ± 0.17†
Low	1.28 ± 0.13	0.82 ± 0.08*	0.81 ± 0.09†
High	1.48 ± 0.17	1.09 ± 0.08*	1.09 ± 0.11†
X-intercept (mmHg)			
Placebo	48.31 ± 1.65	51.81 ± 2.32*	51.85 ± 3.27†
Low	46.41 ± 1.10	50.95 ± 1.67*	51.75 ± 1.00†
High	48.13 ± 1.57	55.05 ± 0.91*	54.63 ± 1.60†

Each value is the mean ± SEM.

* $P < 0.001$ compared to baseline measurement. Data from the three groups of subjects were pooled for this statistical calculation.

† Not significant compared to the measurement made during the alfentanil infusion.
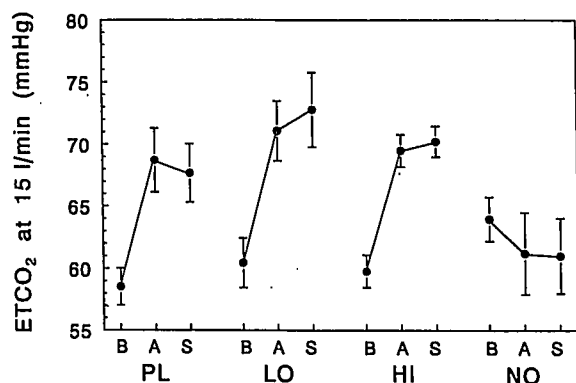
FIG. 3. The four panels indicate the four subject groups: PL represents subjects given placebo (9 subjects), and LO (10 subjects) and HI (10 subjects) represent subjects given 8- and 16-mg ondansetron, respectively. Within each panel the 15-l/min intercepts are shown during baseline (B, three determinations), alfentanil infusion (A, two determinations), and after study medication (S, one determination). The control group (NO, 3 subjects) was given no alfentanil infusion or study medication, and measurements were made at comparable times. Each value is the mean ± SEM.
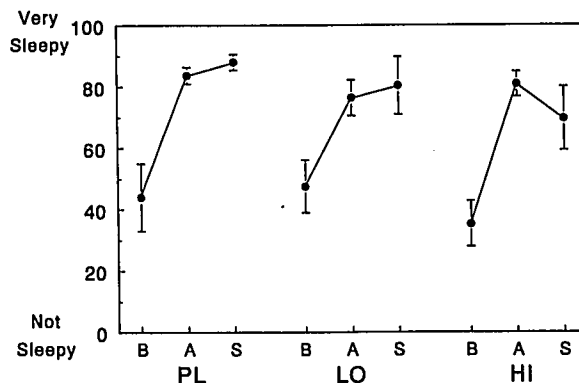

FIG. 5. The visual analog scale values measuring sedation (0 = "not sleepy," 100 = "very sleepy.") The three panels indicate the three subject groups: PL represents subjects given placebo (9 subjects), and LO (10 subjects) and HI (10 subjects) represent subjects given 8- and 16-mg ondansetron, respectively. Within each panel the 15-l/min intercepts are shown during baseline (B, three determinations), alfentanil infusion (A, two determinations), and after study medication (S, one determination). The subjects in the control group (group NO) did not perform the visual analog scale. Each value is the mean ± SEM.

to alfentanil administration ($P < 0.001$) and did not increase further after study medication. These data indicate that ondansetron had no measurable effect on preexisting alfentanil-induced sedation.

The rate of recovery from alfentanil-induced sedation after the discontinuation of the alfentanil infusion is shown in figure 6. These data show no significant differences among the groups in the rate of recovery from alfentanil-induced sedation.

Discussion

Ondansetron is an effective antiemetic when it is used prophylactically before the induction of general anesthesia[1,7-9] or when it is administered in the postanesthesia care unit to treat nausea or vomiting.[2,3] Ondansetron does not increase postoperative sedation or psychomotor impairment,[10,11] and when it is given prophylactically before induction of general anesthesia, patients
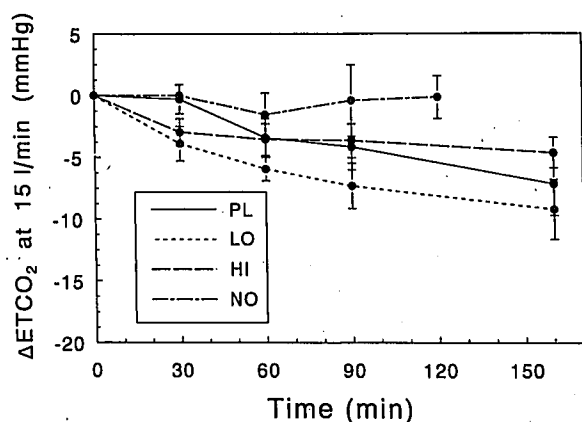

FIG. 4. The change in the 15-l/min intercept values as a function of time after discontinuation of the alfentanil infusion in the placebo (PL, 9 subjects) and 8-mg (LO, 10 subjects) and 16-mg (HI, 10 subjects) ondansetron groups. For comparison, results are also shown for the control group (NO, 3 subjects) who received neither alfentanil nor study medication. Zero time on this figure is 15 min after study medication administration and is immediately prior to discontinuation of the alfentanil infusion. Each value is the mean ± SEM.
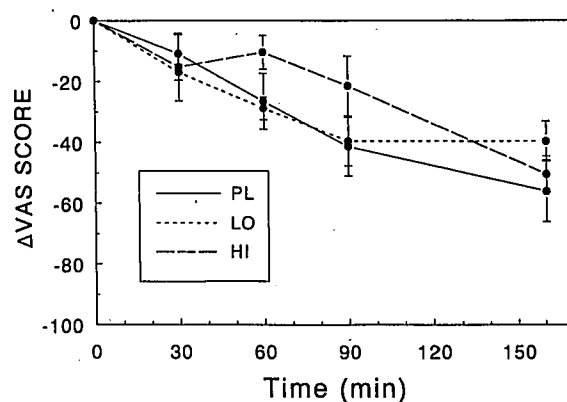

FIG. 6. The change in the sedation visual analog scale (VAS) values as a function of time after discontinuation of the alfentanil infusion in the placebo (PL, 9 subjects) and 8-mg (LO, 10 subjects) and 16-mg (HI, 10 subjects) ondansetron groups. A more negative value on this scale indicates a lesser degree of sedation as the subject recovers. Zero time on this figure is 15 min after study medication administration and is immediately prior to discontinuation of the alfentanil infusion. Each value is the mean ± SEM.

take no longer to awaken in comparison to patients given placebo.[1] Thus, it appears that ondansetron is less sedating than the commonly used antiemetics that act as dopamine$_2$ or cholinergic receptor antagonists (droperidol, prochlorperazine, metoclopramide, hydroxyzine, or scopolamine).

Both peripheral and central serotonergic pathways are known to be involved in the action of μ-opioid agonists. For example, activation of brain stem raphé nuclei by morphine modulates the transmission of pain information.[12] Similarly, substantial older literature shows that nonspecific manipulation of serotonin neurotransmission (e.g., p-chlorophenylalanine, L-tryptophan) can profoundly alter many opioid effects. Gaddum originally designated serotonin receptors as "D" or "M" subtypes because certain effects could be blocked by Dibenzyline and morphine, respectively.[4] The serotonin receptor subtype, now designated 5-HT$_3$, is identical to the old M receptor classification and appears to mediate the neuronal depolarizing properties of serotonin. Blockade of the depolarizing effect of serotonin on vagal afferent fibers and in the chemoreceptor trigger zone is thought to be the mechanism for the antiemetic effects of ondansetron.[13,14] Considering the clinical settings in which ondansetron is likely to be used, it would be important to know whether this drug interacts with μ agonists to potentiate or antagonize their effects.

The data presented here show that ondansetron does not affect the intensity of steady-state alfentanil-induced ventilatory depression or sedation. Although not specifically investigated in this study, it seems improbable that ondansetron would affect the degree of analgesia produced by a μ agonist. In addition, our data did not show a measurable effect of ondansetron on the rate of recovery from alfentanil-induced ventilatory depression or sedation. Although the variability in our data on the recovery from alfentanil-induced ventilatory depression was large, a clinically important prolongation or shortening of opioid effects is quite unlikely.

The ventilatory depressant effect of alfentanil determined in this study is the same as that seen with other μ-opioid agonists. The low dosage range of alfentanil used in these normal volunteers caused a shift to the right in the CO_2 response curve (fig. 2) in all subjects but had no consistent effect on the slope of the CO_2 response curve. This is consistent with the fact that doses of morphine that do not result in sleep may also cause a displacement of the curve to the right without an alteration in slope.[15,16]

To confirm that the measured increases in the 15-l/min intercept values were indeed due to displacement of the CO_2 response curve to the right, we calculated the x-intercept values of the response curves by extrapolation. It is important to emphasize that the CO_2 response curve is not linear at low values for minute ventilation. Hence,

the values we determined for the x-intercept at baseline (46–48 mmHg) do *not* represent a determination of apneic threshold. That the x-intercept values increased as a result of alfentanil administration simply confirms that the simultaneous increase in the 15-l/min intercept values is a result of actual displacement of the CO_2 response curve and not simply a result of a drug-mediated decrease in the slope of the curve.

Several other methods are used to assess drug-induced ventilatory depression, the most common being the determination of minute ventilation at several steady-state values of end-tidal CO_2. The disadvantage of the rebreathing method, in contrast, is that it tends to underestimate drug-mediated decreases in slope and the magnitude of the rightward displacement of the curve.[16] The steady-state method, however, requires much more time to perform each CO_2 response curve. In the present study, as many as 12 determinations of ventilatory response were performed in a single subject. Because we wanted to allow sufficient time for the subject to rest and recover between trials, we believed that the rebreathing method was more practical.

Determination of the occlusion pressure response to CO_2 has also been applied to the study of drug-induced ventilatory depression. When this method has been used in combination with the minute ventilation response to CO_2, the results of the two methods have been similar. For example, the minute ventilation or occlusion pressure *versus* end-tidal CO_2 curves were similarly displaced to the right by fentanyl,[17] epidural buprenorphine,[18] nalbuphine,[19] and clonidine,[20] even in the absence of any significant drug effect on the slopes of the curves.[19,20]

Ondansetron is the first clinically available 5-HT$_3$ antagonist, and the pharmacology of this class of drugs has not been examined in most perioperative situations. Studies comparing ondansetron to conventional antiemetic agents are underway and will permit recommendations to be made concerning its role in perioperative antiemetic therapy. It will be important to determine in the perioperative patient population whether ondansetron interacts with volatile anesthetics, muscle relaxants, pressors, and other drugs. Based on the results presented here, it appears unlikely that ondansetron will be found to interact in a positive or negative way with μ-agonist opioids.

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