DRUG DISPOSITION III — OPIOIDS

A320

TITLE: THE PHARMACOKINETICS OF ALFENTANIL ADMINISTERED BY MULTIPLE BOLUS AND CONTINUOUS INFUSION IN THE PRESENCE OF EITHER NITROUS OXIDE OR PROPOFOL

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A recent report suggested that the pharmacokinetics of alfentanil is altered in the presence of an infusion of propofol and recommended lower doses of alfentanil be used concomitantly with propofol.[1] The present report compares the pharmacokinetics of alfentanil administered as a combined multiple bolus/continuous infusion regimen to supplement either hypnosis produced by a propofol infusion or maintenance of anesthesia with nitrous oxide.

METHODS: Twenty-four ASA PS 1 or 2 patients scheduled for peripheral surgery participated in this study after providing institutionally approved written informed consent. They were randomly assigned to receive either propofol (2 mg/kg over 2 min, 0.2 mg/kg/min for 20 min, and 0.060 mg/kg/min until 5 min before the end of surgery) or nitrous oxide (67% in O_2) after induction of anesthesia with propofol (2 mg/kg over 2 min). All patients received vecuronium, 0.06 mg/kg, followed by an infusion of 1 ug/kg/min adjusted to suppress twitch 80% or less. Alfentanil was administered to all patients at 30 ug/kg/min for 5 min then 50 ug/kg/hr with 1 mg boluses and 25 ug/kg/hr infusion rate increases or 12.5 ug/kg/hr infusion rate decreases according to somatic or autonomic response or lack of response to surgical stimuli. Plasma alfentanil concentrations were measured by RIA. The disposition of alfentanil was modelled with CONSAM. Statistical comparisons were made with the unpaired t-test using $P<0.05$ as the criterion for rejection of the null hypothesis.

RESULTS: The pharmacokinetics of alfentanil in the present study are summarized in the Table. No differences between the groups were detected.

TABLE Alfentanil Pharmacokinetics ($\bar{x}$±SD)

GROUP	V_{ss} (L)	Cl_E (L/min)	$t_{1/2\beta}$(min)
N_2O	30.5±6.5	0.21±0.07	126±50
Propofol	31.4±6.9	0.26±0.09	100±23

DISCUSSION: This randomized, prospective study failed to detect a difference in the disposition of alfentanil in the presence of either nitrous oxide or propofol. These kinetics are similar to those reported elsewhere.[2] Differences in alfentanil requirements and concentrations to supplement hypnosis with a propofol infusion or maintenance with nitrous oxide are unlikely to have a pharmacokinetic basis.

REFERENCES:

1. Gepts E, Jonckheer K, Maes V, Sonck W, Camu F: Disposition kinetics of propofol during alfentanil anaesthesia. Anaesthesia 43 (Suppl): 8-13, 1988.

2. Bower S, Hull CJ: Comparative pharmacokinetics of fentanyl and alfentanil. Br J Anaesth 54:871-877, 1982.

A321

TITLE: ONDANSETRON DOES NOT AFFECT ALFENTANIL-INDUCED VENTILATORY DEPRESSION

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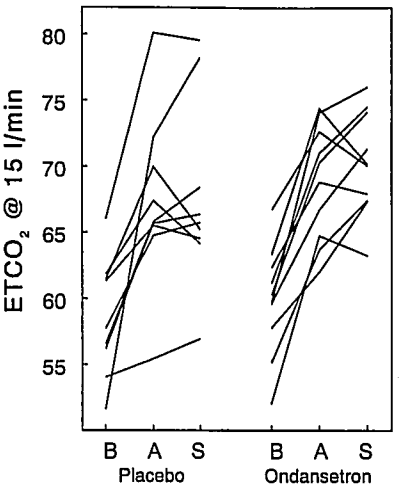
Ondansetron is a selective 5-HT_3 receptor antagonist recently approved for the management of cancer chemotherapy-induced nausea and vomiting. We have previously demonstrated its efficacy in the prophylaxis of postoperative nausea and vomiting.[1] In that study, ondansetron was found to have no effect on the time to awaken from general anesthesia. The 5-HT_3 receptor was formerly referred to as the serotonin "M" receptor because morphine antagonized serotonin-mediated contraction of the guinea pig ileum. Thus it is reasonable to predict that ondansetron may affect mu-opioid receptor-mediated effects such as ventilatory depression or analgesia. The present study is designed to determine if ondansetron interacts with alfentanil to affect opioid-induced ventilatory depression.

The study was approved by the MGH Subcommittee on Human Studies and each of the 29 healthy, male volunteers gave written, informed consent. Ventilatory drive was determined by a modification of the Read rebreathing method. Each subject sat in a semi-recumbant position and was fitted with an airtight mask 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). 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 valve to a 13 l reservoir bag which had been filled with 10 l of a mixture of 5.24% CO_2, 50% O_2, balance N_2. 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 PC-based program TIDAL was used for data acquisition and provided breath by breath analysis of minute ventilation and end-tidal CO_2.[2] TIDAL was kindly supplied by Dr. D.S. Ward. Linear regression analysis was applied to yield the best-fit line for the minute ventilation vs. end-tidal CO_2 data. The end-tidal CO_2 value corresponding to a minute ventilation of 15 l/min was used as a measure of ventilatory drive; an increasing value for this 15 l/min intercept was taken to indicate a blunted ventilatory response to CO_2 stimulation.

Each subject was evaluated in the following way. Three determinations of baseline ventilatory drive were made, each beginning at 30 min intervals. The subject was then administered alfentanil as a 5 mcg/kg bolus followed by an infusion of 0.25 mcg/kg/min. Subsequent measurements of ventilatory drive were made at 30 min intervals, and the infusion rate was adjusted upward if necessary to produce a measurable increase in the 15 l/min intercept value. All subjects manifested ventilatory depression by this criterion with alfentanil infusion rates of 0.25-0.75 mcg/kg/min. After two consecutive 15 l/min intercept values were similar, each subject was administered study medication (ondansetron 8 mg or 16 mg or saline placebo) in a random, double-blind fashion. Another determination of ventilatory drive was made, the alfentanil infusion was terminated, and three additional determinations of ventilatory drive were made at 30 min intervals.

The mean value for the 15 l/min intercept prior to alfentanil administration was 59.62 ± 0.56 torr (mean ± S.E.M.). The figure shows the 15 l/min intercept values during baseline (B), alfentanil infusion (A), and after study medication (S) in the placebo and 16 mg ondansetron groups. The 15 l/min intercept values were significantly higher during the alfentanil infusion as compared to the baseline values ($P < 0.0001$, Student's t test for paired data), indicating that an unequivocal ventilatory-depressant effect of alfentanil was present. The 15 l/min intercept was unchanged in all three groups after study medication ($P = 0.72$, one-way ANOVA) indicating that ondansetron had no effect on alfentanil-induced ventilatory depression. The rate of recovery from alfentanil-induced ventilatory depression after the discontinuation of the alfentanil infusion was also identical in all three groups ($P > 0.3$ at all time points; ANOVA for repeated measurements).

These data indicate that ondansetron does not interact with alfentanil to potentiate or antagonize narcotic-induced ventilatory depression. Ondansetron may therefore be safely administered to patients receiving narcotic analgesics without fear of potentiating ventilatory depression. Although pain threshold was not determined in the present study, it seems unlikely that ondansetron would potentiate or antagonize analgesia caused by mu-receptor agonists. [The study was supported in part by a grant from Glaxo, Inc.]



References

1. Clin. Pharm. Ther. 1991; 49:187.

2. Ann. Biomed. Eng. 1989; 17:93-108.