NALOXONAZINE BLOCKS ALFENTANIL-INDUCED ANALGESIA BUT NOT MUSCLE RIGIDITY IN THE RAT.

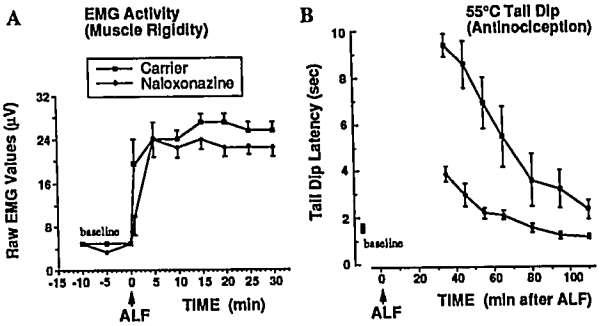
MB Weinger MD, JB Bronson, SR Furst MD, G Pasternak PhD.
Depts. of Anesthesiology, UCSD and the San Diego VAMC; Dept. of Neurology, Sloan-Kettering Cancer Center, New York City.

Opiate-induced muscle rigidity has become a significant clinical problem with the introduction of potent, selective mu (μ) agonists like alfentanil (ALF). Rigidity appears to be mediated by the μ rather than the kappa or delta receptor [1]. Naloxonazine (NAZ), an irreversible opiate antagonist, is able to discriminate two subtypes of μ receptors, μ1 and μ2, which mediate different opiate effects [2]. For example, NAZ pretreatment blocked morphine-induced analgesia, but not respiratory depression [3]. The present study examined the effects of NAZ pretreatment on ALF-induced muscle rigidity and analgesia.

Methods. After Animal Care Committee approval, anesthetized male Wistar rats were injected intravenously with 1 ml/kg of either NAZ (n=7; 15 mg/ml dissolved in 1% acetic acid) or carrier (n=7) in a randomized, blinded fashion. 24 hr later, baseline tail dip latencies were obtained by dipping the distal 3.5 cm of the tail into 55.0±0.5°C water and recording the time required for withdrawal. Rigidity was then assessed using electromyographic (EMG) activity from the left gastrocnemius muscle [4]. After a 15 min baseline, the rats were injected with ALF (0.5mg/kg sc) and EMG data were collected at 1 min and every 5 min for 30 min. Tail dip latencies were then measured at 35, 45, 55, 65, 80, 95, and 110 min after ALF. Statistical differences ($P<0.05$) were assessed using 2-way ANOVA followed by Newman-Keuls tests with data expressed as mean±SEM.

Results. Pretreatment with NAZ had no effect on baseline tail dip latency or EMG activity (Figures). ALF injection resulted in the rapid onset of significant rigidity which persisted for 30 min (A) and was similar in the two treatment groups. In contrast, ALF-induced analgesia was significantly greater in the placebo group until the 110 min measurement (B). The NAZ-pretreated group did have a small but significant increase in tail dip latency at 35 min after ALF but not thereafter.

Discussion. This study demonstrates that NAZ differentially blocks two effects of high-dose ALF administration in the rat; muscle rigidity and analgesia. Analgesia is mediated by μ1 receptors [2,3] while rigidity appears to be a μ2 effect. Thus, it may be possible to develop opioid receptor subtype-selective drugs which produce analgesia and anesthesia without muscle rigidity or respiratory depression.



References. [1] Bronson JB, Weinger MB: Anesthesiology 71: A600, 1989, [2] Pasternak GW, Wood PJ: Life Sci 38: 1889, 1986, [3] Ling GSF, et al: J Pharmacol Exp Ther 232: 149, 1985, [4] Weinger MB, et al: Pharmacol Biochem Behav 29: 573, 1988.

A332

TITLE: PROGRAMMED INFUSION OF ALFENTANIL BASED ON LEAN BODY MASS

AUTHORS: D.P. Crankshaw, FFARACS, Ph.D., D.J. Morgan, Ph.D., G.H. Beemer, FFARACS, F. Karasawa, M.D.

AFFILIATION: Dept. Anaesth., Royal Melbourne Hospital & University of Melbourne, Parkville, Vic. 3052, Australia.

Infusion of anesthetic agents to achieve a constant arterial concentration permits evaluation of clinical efficacy, minimizes the risk of over- and under-dosing and can achieve cost savings.

Infusions to achieve a target concentration based on pharmacokinetic parameters of alfentanil and on patient total body weight have generally shown considerable variability[1]. A method for generating infusion profiles using an error-correcting approach and calculated lean body mass (LBM) for the highly lipophilic drugs thiopental and methohexital has been described[2].

This abstract reports an evaluation of the error-correcting method for the considerably less lipid soluble opioid alfentanil.

With the approval of the Hospital Board of Medical Research and informed consent, cardiac surgical patients were studied in the period from induction of anesthesia until the start of cardiopulmonary bypass. In the first group of five patients, a 10μg/min/kgLBM infusion of alfentanil for one minute was followed by a maintenance infusion of 1μg/min/kgLBM. Radial arterial blood was sampled frequently. Total plasma concentrations of alfentanil were determined by HPLC (Figure 1).

Subsequent groups were infused with successively corrected infusion profiles evaluating slope and bias about a target concentration of 100 ng/ml.

The results show a precision considerably improved over previous studies of alfentanil infusions and support the value of the error-correcting approach, combined with the use of calculated LBM, in optimizing infusion profiles.

This study was supported by the National Health and Medical Research Council of Australia and by Janssen Cilag Pty Ltd.

References
1. Anesthesiology 66:1-2, 1987.
2. Anesthesiology 67:32-41, 1897.

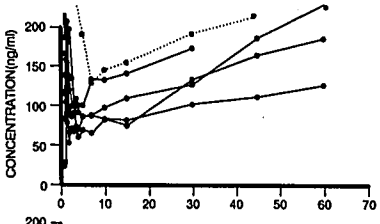


Figure 1. Plasma concentrations of alfentanil following a two stepped infusion.

Figure 2. Plasma concentrations of alfentanil in the final iteration of a programmed infusion to a target of 100 ng/ml and based on patient LTM.