POSTER SESSION XII

A360

Title: **PHARMACOKINETICS OF A NEW OPIOID ANTAGONIST: METHYLNALTREXONE**

Authors: J.F. Foss, MD, M.F. Roizen, MD, J. Moss, MD, PhD, M.B. Murphy, MD, C. Seals, MS
Affiliation: Committee on Clinical Pharmacology and the Department of Anesthesia and Critical Care, University of Chicago, Chicago, IL 60637

Methylnaltrexone (MNTX) is a quaternary narcotic antagonist with limited ability to cross the blood brain barrier. In animals, it antagonizes the peripherally mediated effects of opioids such as emesis, ileus, cough, and biliary spasm.[1] Our study was designed to determine the pharmacokinetics of intravenous MNTX in humans.

Methods All protocols were approved by the IRB. Eight male volunteers in good health were studied on six or seven visits. Screening physical exams, Chem-17, CBC and UA were normal. On each visit, baseline vital signs and blood samples were taken followed by administration of placebo or MNTX at 0.04, 0.08, 0.16, 0.32 and 0.64 mg/kg i.v. over 10 min. The sequence was ascending with the placebo randomly inserted into the order. Five of the subjects also received an additional dose of 1.25 mg/kg i.v. Blood samples were obtained at 0, 10, 12, 14, 16, 20, 40, 60, 120, 240, 480, and 720 min. These samples were centrifuged and stored at -20° C until analysis. Sample analysis (by HPLC with electrochemical detection) was done after adding a standard amount of naltrexone as an internal control. The lower limit of sensitivity is 100 ng/ml and pharmacokinetic values are based on data from the 0.64 and 1.25 mg/kg doses.

Plasma concentration-time data were fit by the biexponential equation $C = Ae^{-at} + Be^{-\beta t}$ where C is the plasma concentration and A and B are coefficients for the distribution (a) and elimination (β) phases, respectively. A non-linear regression program, NONLIN (Systat 5.0), run on a Macintosh computer was used to fit the data.

Terminal elimination $t_{1/2}$ ($t_{1/2\beta}$) is calculated as: $t_{1/2\beta} = 0.693/\beta$, plasma area under curve as: $AUC = A/a + B/\beta$, total body clearance as: CL = dose/AUC and instantaneous volume of distribution as: Vc = dose/(A+B). Vc and CL are normalized for body weight.

Results After a 10 min iv infusion, MNTX plasma concentration declined in a biphasic fashion and the data were well fit by the biexponential equation (fig). The pharmacokinetic parameters are

AUC	181181.0	± 107884.6	ng-min/ml
$t_{1/2a}$	4.5	± 1.1	min
$t_{1/2\beta}$	103.3	± 56.9	min
Vc	78.7	± 31.8	L/kg
CL	6.5	± 2.7	ml/min/kg

Reference 1. Neuropharmacology 24:181, 1985.

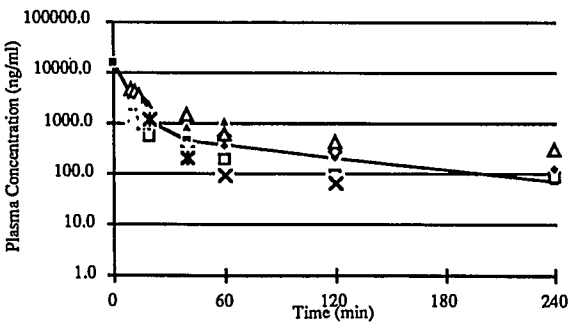

Fig. 1: Fitted pharmacokinetic plot of plasma concentration-time curve for MNTX overlayed on scattergram of raw values.

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TITLE: HALOTHANE ANESTHESIA DURING PERFLUOROCHEMICAL VENTILATION

AUTHOR: D.B.Kimless-Garber, M.D.,M.R.Wolfson,Ph.D., C.Carlsson,M.D.,T.H. Shaffer, Ph.D.
AFFILIATION: Departs. of Physiology and Anesthesiology, Temple Univ Sch.of Med and Hospital, Phila, PA 19140

Perfluorochemical (PFC) liquid ventilation (LV) has been successfully employed to reduce surface tension, insufflate the lung at lower alveolar pressures than gas ventilation, support gas exchange, and deliver biological agents in premature, newborn, and adult animals with respiratory distress. A recent clinical study demonstrated the feasibility of LV treatment in human premature neonates with respiratory distress. Because the PFC liquid can be homogeneously distributed throughout the lung at low inflation pressures, PFC LV techniques may also provide an effective means of inducing anesthesia while supporting gas exchange at lower risk of barotrauma. Therefore, the objective of this study was to test the hypothesis that PFC LV can be used as a vehicle to deliver halothane and induce anesthesia.

Following surgical instrumentation (carotid arterial and femoral venous catheters; tracheostomy) 7 hamsters were paralyzed and stabilized with mechanical gas ventilation. The animals were then ventilated in alternating cycles with gas and either oxygenated neat PFC liquid or PFC liquid mixed with liquid halothane (PFC:hal) in concentrations equivalent to 1.5%; arterial blood pressure and blood gases were monitored throughout the protocol. After each cycle the animal was stimulated with a foot clamp for 2 seconds. Mean arterial pressure (MAP: mm Hg) response to this stimulation (expressed as the % change from the resting MAP during the cycle) was used as an index of anesthesia. One animal was ventilated with neat PFC for four cycles, one animal was ventilated with PFC:hal for two cycles, and the remaining 5 hamsters were ventilated for one cycle with neat PFC and then one to four cycles of PFC:hal. Statistical analysis using single factor analysis of variance was used to determine differences in MAP as a function of anesthesia. Significance was accepted at the $p < 0.05$ level.

MAP was reduced during ventilation with PFC:hal as compared to MAP during neat PFC or gas ventilation. Statistical analysis indicated a significant reduction in resting MAP = 73 ± SE during PFC:hal as compared to MAP during neat PFC ventilation (113 ± 5 SE) and gas ventilation (107 ± 5 SE). MAP response (% change in MAP from baseline) to foot clamp stimulation was significantly attenuated with PFC:hal ventilation (+12 ± 5% SE) as compared with neat PFC (+28 ± 8% SE) and gas ventilation (29 ± 9% SE). There was no statistically significant difference in resting MAP or MAP response to foot clamp stimulation between four cycles of ventilation with neat PFC alone. In addition, blood gases were not significantly different between modes of ventilation or anesthesia.

This study has shown that resting MAP and MAP response to foot clamp stimulation is attenuated following LV with halothane when compared to these indices during gas ventilation or LV with neat PFC. Neither resting MAP or MAP response to foot clamp were significantly different during LV ventilation as compared to gas ventilation.

These data indicate that PFC LV with halothane can induce anesthesia while supporting cardiopulmonary function. As such, this study demonstrates the feasibility and potential of simultaneously inducing and maintaining anesthesia while using PFC LV techniques.