Title: THE ANALGESIC EFFICACY OF A3508 COMPARED TO FENTANYL

Authors: J. Lu, M.D., P.S.A. Glass, M.D., E.M. Camporesi, M.D., M.S. Afifi, M.D., T.J. Quill, M.D.
Affiliation: Department of Anesthesiology,Duke University Medical Center,Durham, North Carolina, 27710

This study evaluated the analgesic, respiratory and hemodynamic effects of increasing doses of A3508 (a new piperidine derivative analgesic) and fentanyl in humans. In animals studies, A3508 produced dose dependent changes in analgesia but with a "ceiling effect" on ventilatory depression, perhaps due to differing affinity of A3508 for opiate receptor subtypes.

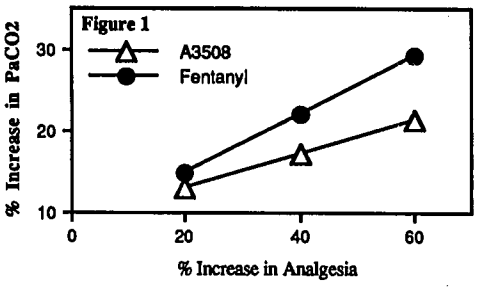
42 healthy adult male volunteers entered this ascending-dose double-blind study. Four subjects received A3508 at each of six dose levels with one volunteer receiving placebo. The initial dose group received 12.5 µg/kg of A3508 and this was doubled for each subsequent group. In the 100, 200 and 400 µg/kg dose groups, an additional 4 subjects in each group received 0.75, 1.5 and 3 µg/kg fentanyl, respectively. Arterial blood gas samples were taken prior to, and at 1, 3, 5, 10, 20, 40 and 60 min following drug administration. Analgesia was asssessed by the maximal tolerance (average of 2 readings) to periosteal pressure over the tibia and manubrium using a spring loaded rod. Readings were obtained prior to drug administration and repeated at 3, 6, 10, 15, 20, 30, 45 and 60 minutes after drug injection. All placebo subjects were combined as a single group. All values were calculated as a percentage change from baseline (prior to drug). The dose response for maximal changes in analgesic tolerance, respiratory and hemodynamic parameters was evaluated using linear regression.

A3508 showed both analgesic and respiratory dose-response effects. The ED50 dose calculated from the linear regression to produce a 20%, 40%, and 60% increase in analgesic tolerance, 20% increase in PaCO2 and 20% decrease in PaO2 are given in Table 1. The calculated increase in PaCO2 produced by doses of fentanyl or A3508 to provide a 20%, 40%, and 60% increase in analgesic tolerance is shown in Fig. 1. There was no significant change in systolic - diastolic blood pressure or heart rate at any time interval or dosage level.

The increasing potency ratio between A3508 and fentanyl for increasing analgesic efficacy implies the analgesic dose response curve for A3508 is flatter than that of fentanyl (Table 1 potency ratio). However, increasing equianalgesic doses of A3508 appeared to depress ventilation less than fentanyl (Figure 1). Thus, A3508 may be worthy of further investigation.

Table 1:

Variable	ED50 3508 (µg/kg)	ED50 Fentanyl (µg/kg)	Potency Ratio
+20% Analgesia	11.4	0.4	28
+40% Analgesia	79.2	1.1	47
+60% Analgesia	545.1	7.2	76
+20% PaCO2	294.2	1.1	261
-20% PaO2	29.7	0.8	40



A836

Title: Assesment of the analgesic efficacy of pentamorphone to morhine.

Authors: B. Ginsberg MD, M. Muir R.N., M Damask MD, T.J. Quill MD,P.S.A Glass MD.
Affiliation: Department of Anesthesiology Duke University Medical Center and Anaquest.

The establishment of the relative analgesic potency of opioids is difficult due to the inherent differences in pharmacokinetics between drugs and the variable pharmacodynamic response to opioids between patients. Patient controlled analgesia (PCA) enables patients to self titrate to their own analgesic endpoint thus compensating for any differences in pharmacokinetics or pharmacodynamics. In this study PCA was used in patients recovering from a lower abdominal incision to determine the potency and safety of pentamorhone (P), a new opiate analgesic, relative to morphine (M).

Forty eight patients entered in a randomized double blinded study into two unequal sized groups to receive either M (33%) or P (66%). Estimated equipotent doses of M (1mg/ml) and P (5mcg/ml) were prepared.[1] Anesthesia was standardized to include thiopental, N2O-oxygen-isoflurane and less than 6 mcg/kg of fentanyl. Post operatively when the visual analogue scale > 5 cm(VAS), a loading dose of 0.04 ml/kg of the analgesic was given via an Abbott Lifecare PCA™. Three loading doses could be given if the VAS exceeded 5 cm. The maintenance dose was 0.02 mls/kg with a lockout interval of 8 min. A VAS, sedation scale and side effects, were recorded at 10, 20 and 30 minutes, 1, 4, 8, 12, 16, 20, and 24 hours. Analysis of variance was used for comparison between the groups. The Mann Whitney was used for comparison of non parametric data. A $p < 0.05$ was considered significant. Results are given as a mean ± SD.

There was no statistical difference between the groups with respect to the age, weight, duration of procedure and total amount of fentanyl used. VAS scores were equal prior to (P 81±18 vs. 82.7±18) and immediately following the initial loading dose (P 51±31 vs M 63±32) but were lower at 20, 30 and 60 minutes in the P group ($p < 0.05$). After the first hour equianalgesic levels were obtained. The total dose of P was 0.315±.14 mg and M 54±29 mg. No differences in sedation or side-effects were noted between the 2 groups.

Thus utilizing PCA the relative analgesic potency of P to M once an equianalgesic level had been obtained was established as 170:1. P tended to produce a more rapid onset of effective analgesia eventhough patients self titrated their own analgesic requirements. P appears to be a safe and effective analgesic

Reference: 1)Anesth Analg 68: 302-307, 1989