Title : COMPARISON OF NALTREXONE AND NALOXONE IN MAN

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No direct study of the time course of the pure competative opioid antagonists Naloxone and Naltrexone has been published, despite the importance of this information in planning emergence from opioid supplemented anesthesia. A loading dose and constant infusion of fentanyl achieved a constant ventilatory depression permitting study of the time course and dose response of reversal.

The method uses Lambertsen's alveolar P_{CO_2} control concept, maintaining a constant ventilatory stimulus, so that changes in respiratory minute volume ($\dot{V}_E$) directly reflect drug effect. The closed spirometer circuit has flow meters for O_2, CO_2, N_2 and vacuum and a variable CO_2 absorption to permit control of gas mixture. Airway O_2 & CO_2 spirometer volume, and the EKG are recorded continuously. The subject has a knee pad for notes and a spittoon for emesis. A sigmamotor pump provides a constant infusion of fentanyl. IRB approval was given.

In a preliminary study a loading dose of 0.4 mg fentanyl and an infusion of 4 mg/hr gave a stable depression within 30 minutes in three subjects. A dose response study of the antagonists, given double blind, gave a log-linear response with slopes of 11 l/m $\dot{V}_E$ per doubling of either antagonist. The half effect doses were 5 micrograms/kg Naloxone and 3 micrograms/kg Naltrexone.

Five informed consenting volunteers completed studies with both antagonists. Their initial ventilatory response to CO_2 was high, 3.6 $\pm$ 1.1 l/min/torr, but fell to normal after fentanyl, 2.1 $\pm$ 0.6. This slope did not change during the 3 hours after the antagonist. In the Naloxone study, at a P_{CO_2} of 56 torr, $\dot{V}_E$ fell from 47.1 $\pm$ 4.9 to 20.7 $\pm$ 5.6 l/m after fentanyl. Naloxone caused a prompt recovery and equally prompt emesis, which tended to recur in waves over the next 4-6 hours. Fifteen minutes after Naloxone, V_E was 39.9 $\pm$ 7.9 l/min. and fell as shown in the figure to stabilize at 17.1 $\pm$ 1.4. A single exponential decay with a half time of 20 $\pm$ 2 minutes fitted the data.

Naltrexone, studied at 60 torr, caused a similar prompt reversal, with waves of emesis, and then a fall as shown in the figure. Again a mono-exponential fit the data giving a half life of 49 $\pm$ 3 minutes, significantly longer than Naloxone by a two tailed non-paired t test.

Naltrexone given alone in 4 volunteers, in a dose of 8 mg produced no change in breathing or heart rate, and a slight queasy sensation lasting 3-5 hours.

Introduction of Naloxone offered a new possibility to anesthetists: that of terminating an opioid-anesthetic at will, much as anti-cholinesterase drugs terminate a paralysant supplemented anesthetic. However, multiple reports soon showed that Naloxone's duration was too short to permit a single reversing injection. A longer acting antagonist would be preferred. Studies in animals and man suggested that Naltrexone might be such a drug. It has little or no intrinsic effect but can block heroin effects for 24 hours after one large oral dose. The clinical impression of rapid dissapation of Naloxone effect is confirmed by a half life of 22 minutes. Naltrexone is more than 2 times as long lasting. While this is an improvement, permitting in theory the single dose reversal of fentanyl supplemented anesthesia, one can still predict the need for careful observations and repeated doses of Naltrexone following other opioid anesthetics, e.g., meperidine or morphine.