Title: ARE INFANTS SENSITIVE TO RESPIRATORY DEPRESSION FROM FENTANYL?

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Introduction. It is commonly believed, based on a study of morphine in neonates,[1] that neonates and infants are "sensitive" to the respiratory depressant effects of all narcotics. However, there are no published data regarding the respiratory effects of fentanyl in these patients. Because clearance of fentanyl is higher in infants than in adults,[2] infants would be "sensitive" to fentanyl only if there were marked pharmacodynamic differences between them and adults, *i.e.*, they developed respiratory depression at a lower plasma concentration of fentanyl. To evaluate this issue, we determined the relationship between plasma concentration of fentanyl and respiratory depression in infants, children, adults, and the elderly recovering from anesthesia.

Methods. After approval from our Committee on Human Research, we studied 35 subjects [13 infants (1-12 months), 10 children (1-5 yr), 8 adults (23-31 yr), and 4 elderly (70-85 yr)] undergoing elective surgery. All subjects were ASA PS I. Exclusion criteria included tobacco use > 10 pack-years, ethanol use > 30 ml/day, regular use of sedative or narcotic medications, and thoracic or abdominal surgery. No premedication was given. Anesthesia was induced with N_2O and halothane following which pancuronium and fentanyl (8-15 μg/kg) were administered and halothane was discontinued. Anesthesia was maintained with N_2O, fentanyl, and pancuronium. Halothane was administered for 10-20 min; end-tidal halothane concentrations at the end of surgery were < 0.02%. At the end of surgery, N_2O was discontinued, muscle relaxation antagonized, and mechanical ventilation slowed until spontaneous ventilation resumed. The trachea was extubated when clinically appropriate. We recorded skin-surface PCO_2 (P_sCO_2) (SensorMedics Transend™ Cutaneous Gas System) from the end of surgery until a stable control value was obtained during recovery. If P_sCO_2 exceeded 65 mmHg, naloxone was administered until ventilation was adequate. We defined peak P_sCO_2 resulting from fentanyl as the value obtained when we believed that N_2O would no longer contribute to respiratory depression (defined as $P_{et}N_2O$ < 6%). Plasma samples were obtained at this time for the determination of fentanyl concentrations by radioimmunoassay. The difference between peak P_sCO_2 and the control value was plotted against fentanyl concentration. Ventilatory pattern was monitored in the recovery room using a Hewlett-Packard 78202C impedance pneumogram. Minor apnea was defined as an absence of respiratory effort for a period of time exceeding two baseline respiratory intervals; major apnea exceeded three respiratory intervals (*e.g.*, if respiratory rate was 20/min, minor and major apnea were defined as pauses > 6 and 9 s, respectively). Values for the four groups were compared using χ^2 analysis.

Results. P_sCO_2 elevation at the time that $P_{et}N_2O$ was < 6% increased with increasing fentanyl concentrations (figure); there were no differences between groups. Six subjects — 2 infants, 1 child, 1 adult and 2 elderly — required naloxone. Five of these subjects had similar fentanyl concentrations, 3.3-5.5 ng/ml; one infant aged six weeks (the only infant younger than three months) required naloxone at a relatively low fentanyl concentration, 2.2 ng/ml.

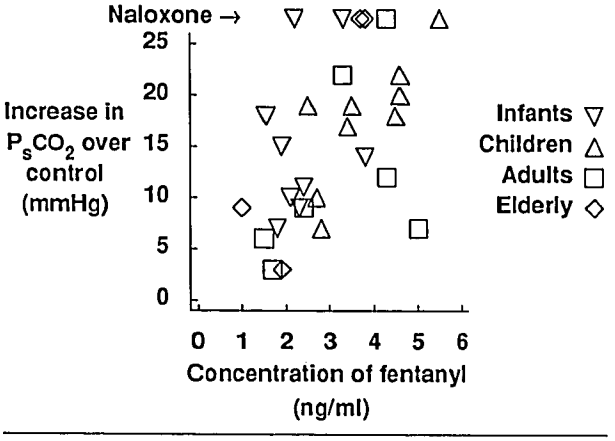
Incidence of apnea increased progressively with age (table). In addition, the number of episodes of apnea per subject increased with age: for example, infants greater than three months of age had 2-4 episodes and children had 1-6 episodes whereas adult and elderly subjects averaged 21 and 11 episodes, respectively. In infants, apnea occurred only with fentanyl concentrations exceeding 1.6 ng/ml whereas adult and elderly subjects demonstrated apnea with fentanyl concentrations as low as 0.8 ng/ml.

Table. Incidence of postoperative apnea in four age groups.

	Infants	Children	Adults	Elderly
Major apnea*	2/13	2/9	5/7	3/4
Minor apnea*	3/13	6/9	7/7	4/4

* Incidence increases with age ($P < 0.05$ by χ^2 analysis).

Figure. Elevation in P_sCO_2 above control value is plotted against concentration of fentanyl for four age groups. Six subjects, shown at top of figure, required naloxone because P_sCO_2 exceeded 65 mmHg.



Discussion. In neonates, depression of the ventilatory response to CO_2 following morphine, 0.05 mg/kg, exceeds that seen in adults.[1] This has been attributed to greater permeability of the neonatal blood-brain barrier. The results of that study have been extrapolated to the belief that not only neonates, but also infants, are "sensitive" to all narcotics.[3,4] In contrast, we found that pediatric patients older than three months are similar, or possibly "resistant", in the magnitude of their ventilatory depression following fentanyl, compared to adults. In addition, the elderly appear to be "sensitive" to the effects of fentanyl, as defined by the high incidence of apnea in these subjects. A similar finding has been reported for morphine in the elderly.[5] Of note is our finding that the subject in whom naloxone was required at a comparatively low fentanyl level was the only subject younger than three months of age; this infant also had the most apnea of any infant. Our results demonstrate that pediatric patients aged three months to five years are not "sensitive" to, and may be "resistant" to, the respiratory depressant effects of fentanyl.

References.

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