TITLE: THE INFLUENCE OF HALOTHANE ON FENTANYL PHARMACOKINETICS

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Introduction. Recently, both Borel et al.[1] and Hug et al.[2] have reported fentanyl pharmacokinetics in dogs concomitantly given N_2O and muscle relaxants. The pharmacokinetic parameters reported by these investigators were very similar. However, fentanyl pharmacokinetics in these two studies were markedly different than those previously reported by Murphy et al. in dogs anesthetized with enflurane and nitrous oxide.[3] Seemingly, the only significant difference between these studies was the use of a volatile anesthetic agent in the latter study. To investigate this, we compared fentanyl pharmacokinetics in dogs with and without concomitant halothane administration.

Methods. Five healthy mongrel dogs were studied two times as members of two groups, control (C) and fentanyl-halothane (FH). Each dog was rested a minimum of 2 weeks between studies. Use or nonuse of halothane for the initial study was randomized. Each dog was given intravenous pancuronium while breathing 50% nitrous oxide by mask. After topical lidocaine administration to the trachea, a cuffed oral endotracheal tube was placed. Halothane anesthesia .2-.5% was provided during forarm leg placement of an intravenous catheter and groin cutdown for femoral artery catheter insertion in the control dogs. Halothane administration did not exceed 30 minutes and was discontinued at least 20 minutes prior to the injection of narcotic in this group. During the same time interval, halothane administration to the FH group was adjusted to maintain end-tidal concentrations at 1.25%. Each dog was then administered 100 µg/kg of fentanyl as an IV bolus. Arterial blood samples for serum concentration determinations were collected for 7 hours after fentanyl administration. In addition to fentanyl, anesthesia was maintained with 60% nitrous oxide in oxygen and supplemental pancuronium. Ventilation was mechanically controlled to maintain $PaCO_2$ at 40 ± 5 torr as confirmed by periodic arterial blood gas analysis. Serum fentanyl concentrations were analyzed by the method of Gillespie et al. The model independent method of Benet and Galeazzi was used to determine pharmacokinetic parameters. Students t-test was used to compare group means. Significance was chosen at $p < .05$.

Results. Weight and correspondingly, fentanyl dose were similar in the C and FH groups of dogs. Despite this, mean serum concentrations of fentanyl were clearly higher in the FH dogs (Figure). This resulted from a prolonged terminal elimination half-life ($t_{\frac{1}{2}}$) in these dogs compared to C (Table). Volume of distribution steady state (Vdss) was similar in the two groups of dogs but fentanyl clearance (Cl) was significantly decreased in the FH group compared to the C dogs.

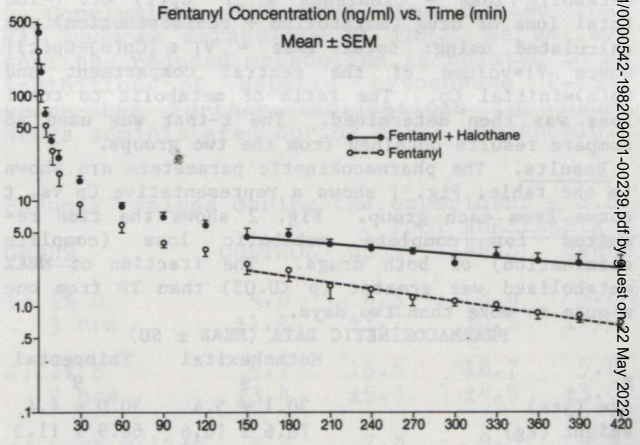
Discussion. This study clearly demonstrates that halothane can alter the disposition of fentanyl. The prolonged fentanyl $t_{\frac{1}{2}}$ in this study was due to alteration of fentanyl Cl in dogs anesthetized with halothane. Altered fentanyl hepatic Cl can be a result of changes in drug protein binding, liver blood flow, or the ability of the liver to metabolize fentanyl. Halothane alteration of drug protein binding has not been investigated. However, halothane has been shown to inhibit the hepatic p450 metabolism of many compounds and also has been shown to decrease liver blood flow. Both of these effects would lead to decreased drug clearance.

The clinical significance of these findings remains to be proven since this study was performed in dogs and halothane was administered for the entire 7 hours of the study. Certainly, this study suggests that a prolonged fentanyl terminal elimination half-life may occur in association with protracted halothane administration. Whether the same is true with short-term halothane administration (less than 2 hrs) remains to be determined.

TABLE: CONTROL VS. HALOTHANE (MEAN)

	Wt (kg)	Dose (µg)	$t_{\frac{1}{2}}$ (min)	Vdss (l)	Cl (ml/min)
C	21.4	2134	141	116	1070
FH	21.4	2144	235*	103	515**

Significantly different, *$p < .05$, **$p < .02$.



References

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