TITLE: ORAL TRANSMUCOSAL FENTANYL CITRATE:
Oral Transmucosal Verses Gastrointestinal Absorption

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We previously determined the bioavailability and absorption character-istics of Oral Transmucosal Fentanyl Citrate (OTFC/"fentanyl lollipop")[1]. Since OTFC is exposed to the oral mucosal membranes, dissolved, swallowed and then exposed to gastrointestinal membranes, fentanyl (F) absorption could occur at either site. In this study, the bioavailability and absorption profile of a F solution swallowed directly into the stomach was established. By combining data from these two studies, a model was developed to quantify the fraction of F in OTFC absorbed through the oral mucosa and the gastrointestinal mucosa.

After institutional approval, informed consent was obtained from 8 ASA-I male volunteers from our previous study. Each volunteer had arterial and IV catheters inserted and a pulse oximeter attached. After the F solution (15μg/kg) of OTFC dissolved in sterile water to a total volume of 10cc) was swallowed, arterial samples were taken at specified intervals over 24-hr. Plasma F concentrations (PFC) were measured by radioimmunoassay. Bioavailability was calculated by the area-under-the-curve method from the PFC vs. time curve. F absorption was obtained by least squares deconvolution constrained to yield positive absorption rates. The model for OTFC absorption is as follows:

$$OTFC_{dose} \times OTFC_{bioavail} = O_{dose} \times O_{bioavail} + G_{dose} \times G_{bioavail}$$
$$OTFC_{dose} = O_{dose} + G_{dose}, \text{ then:}$$
$$O_{dose} = OTFC_{dose} \times (OTFC_{bioavail} - G_{bioavail}) / 1 - G_{bioavail}$$

$OTFC_{dose}$ = total dose of F in OTFC
O_{dose} = dose of F from OTFC absorbed in the mouth
G_{dose} = dose of F from OTFC that is swallowed
$OTFC_{bioavail}$ = overall bioavailability of OTFC
O_{dose} = bioavailability of F absorbed from the oral mucosa (assumed=100%)
$G_{bioavail}$ = bioavailability of F absorbed from the gastrointestinal tract

The figure shows the PFC vs time for the swallowed F solution and OTFC. Peak PFC were greater (2.6±0.3 vs 1.1±0.2 ng/ml)(mean ±SEM) and occured sooner (25 vs 80 min) with OTFC than after the swallowed F solution. The maximal rate of F absorption was also more rapid and occurred sooner after OTFC (12.5μg/min, 17 min) than after the swallowed solution (2.0ug/min, 80 min). The bioavailability of the swallowed solution was significantly lower than that of OTFC (0.33±0.10 vs 0.52±0.11)(mean ±SEM). Approximately 50% of the plasma F after OTFC administration results from oral transmucosal absorbtion, whereas the other 50% results from gastrointestinal absorption.

This study confirms that absorption of F occurs across the oral mucosa and that absorption by this route is faster and produces higher PFC than via the lower gastrointestinal tract. Hepatic clearance and delayed gastrointestinal motility are the most likely explanation of these findings.
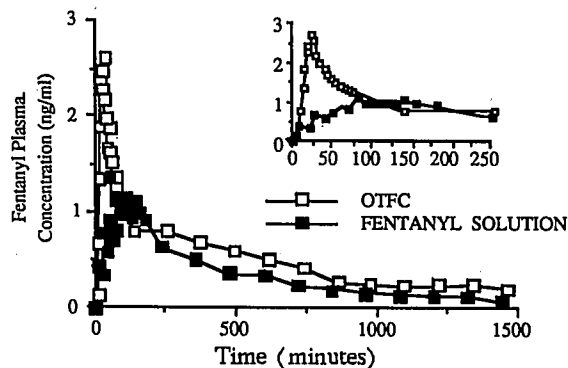
Anesthesiology, Vol 71: A 230, 1989

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TITLE: HALOTHANE DEPRESSES GALLOPOMIL (D600) BINDING TO BOVINE HEART SARCOLEMMA
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Volatile anesthetics (VA) exert their negative inotropic effect by interfering with Ca²⁺ homeostasis in the myocardial cell. The mechanism of this dose-dependent action is uncertain. [³H] Gallopomil ([³H]D600), a Ca²⁺ channel antagonist (CCA), binds to the voltage sensitive Ca²⁺ channels (VSCC) in a specific, saturable, and reversible manner. We used this ligand to study the effect of halothane (H) on the binding characteristics of the VSCC in purified bovine heart sarcolemma (SL).

Bovine heart was obtained from a local slaughter-house and SL membranes were isolated by a modification of the method of Jones (1) and Caroni (2). The binding assays were carried out with 50-100 μg protein in 5 cc sealed glass vials at 25°C with 5, 25, 50, and 100 nM [³H]D600 in 50 mM Tris HCl (pH 7.5, total volume – 1 ml), in the presence or absence of 1.0 mM unlabeled D600 as displacer, to determine total and non-specific binding. Sixty min incubations were carried out in control samples and with the addition of 0.4 μl and 0.8 μl H (equivalent to H concentrations of 1.3 and 2.5 v/v% in the vapor phase respectively as measured by UV spectroscopy 3). Samples were then filtered under vacuum and counted in a scintillation counter. In a fourth set of samples 0.8 μl of H were added, but the vial caps were removed 30 min prior to filtration to allow evaporation of the H. Three experiments were performed in triplicate on each of four different SL preparations.

H produced a significant (p<.05 by paired t-

test) dose-dependant and reversible depression of [³H]D600 specific-binding in bovine heart SL. Depression was completely reversed when H had evaporated from the samples prior to filtration. Addition of 0.4 μl H (1.75 xMAC in cows) produced a 40% reduction in B_{max}. K_d was not affected by H.

This study supports the hypothesis that one mechanism by which the VA induce negative inotropism is through the reduction of functional VSCCs in the heart, leading to reduction of Ca²⁺ entry. We have previously shown that H depresses the binding of [³H] nitrendipine, a separate class of CCA, in bovine heart SL (4). These two studies argue that VA do not interact with the VSCC at a specific site of action but may interact in a general way on the structural status of the membrane or protein.

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