

**TITLE:** ORAL TRANSMUCOSAL PERMEABILITY OF FENTANYL AND ISOPROTERENOL IN A DOG MODEL: pH DEPENDENCE

**AUTHORS:** J. Zhang, Ph.D., C.D. Ebert, Ph.D., AJF. de Boer, drs., S. Niu, M.D., T.H. Stanley, M.D.

**AFFILIATION:** Department of Anesthesiology, University of Utah, Salt Lake City, Utah,

Recently, a collection of anesthetics and analgesics have been found to penetrate through oral mucosa tissues with sufficient speed to achieve analgesia and sedation in minutes. Oral transmucosal drug delivery is noninvasive, allows a rapid onset, is easy to titrate to a specific endpoint or effect, and avoids degradation in the GI tract and hepatic "first pass" metabolism. However, little is known about how ionization (as controlled by vehicle pH) affects the transmucosal permeability, although some investigators suggest only unionized molecules can permeate through the oral mucosa.

In this study, fentanyl and isoproterenol, both weak bases with PKa's of 8.3 and 8.6, respectively, were used in a dog model to evaluate the effect of ionization on transmucosal permeability. Both drugs were delivered via a diffusion cell [a device which, when attached to the inner side of the cheek of anesthetized dogs, allows the drug solution in it to directly contact the mucosa through a finite area (0.7-1.0 cm<sup>2</sup>)]. The permeability coefficient of isoproterenol was determined by comparing the steady state heart rate increase caused by transmucosal administration to that caused by IV infusions at different controlled rates. For fentanyl, the permeability coefficient was determined

by depletion kinetics of the drug from the solution in the diffusion cell.

The change of isoproterenol solution pH from 7.0 to 4.9 (corresponding to an 100-fold decrease in unionized molecule population) resulted in no significant change in the permeability coefficient (5.0 x 10<sup>-8</sup> cm/sec vs. 4.6 x 10<sup>-8</sup> cm/sec); while the change of fentanyl solution pH from 6.0 to 7.0, 8.0, and 9.0 resulted in dramatic increases in the permeability coefficient (from 9.3 to 34.1, 76.8, and 196.0 x 10<sup>-6</sup> cm/sec, respectively).

The reason for the different response of the permeability coefficient of the two drugs to the state of ionization is unknown and provocative. The authors postulate that the lack of pH dependence for isoproterenol may be attributable to the high hydrophilicity of its unionized species (the isoproterenol molecule has 3 OH groups). For a given concentration below saturation, the high hydrophilicity (low chemical activity) of the unionized molecule may reduce the chemical activity (tendency to leave the solution and penetrate into the mucosa) difference between the ionized and unionized species, resulting in a less pronounced pH dependence.

The results of this study suggest that hydrophilicity of both ionized and unionized species, as well as vehicle pH, are important factors in determining a drug's transmucosal permeability. They also suggest that it may be possible to control oral transmucosal drug delivery rates by manipulating vehicle pH in some but not all drugs.

A368

**TITLE:** AMNESIA AND UNCONSCIOUSNESS WITH FENTANYL INDUCED RIGIDITY IN HUMAN VOLUNTEERS: Incidence, Duration and Associated Plasma Levels

**AUTHORS:** J.B. Streisand, M.D., M.A. Ashburn, M.D., P.L. Bailey, M.D., S. Tarver, M.D., L. Le Maire, M.D.

**AFFILIATION:** Anesth. Dept., Univ. of Utah, Salt Lake City, Utah 84132

Narcotic induced muscular rigidity is a frequent, but poorly understood phenomenon observed when high doses of potent opioids are rapidly infused. Determining if unconsciousness occurs with rigidity is difficult in the clinical setting due to the concomitant administration of muscle relaxants and amnestic agents. In human volunteers given only intravenous fentanyl, we observed the incidence and duration of rigidity and the level of consciousness, as well as measured associated fentanyl plasma concentrations and hemodynamics.

Informed consent was obtained from 12 ASA-1 male volunteers after institutional approval of the investigation. After insertion of arterial and venous catheters under local anesthesia and placement of a pulse oximeter, fentanyl was infused at a rate of 150 ug/min until 15 ug/kg had been administered (6-8 min). Arterial samples for fentanyl assay were drawn and heart rate, systolic and diastolic blood pressures and respiratory rates were recorded at baseline, every 2 min during the infusion, and 1,2,3,4,6,8,10,15,30,45, and 60 min post infusion. If spontaneous ventilation became inadequate (O<sub>2</sub> saturation <90%; respirations <8), volunteers were prompted by verbal command to breathe. If rigidity occurred, positive pressure ventilation with bag and mask (100% O<sub>2</sub>) was instituted until spontaneous ventilation resumed. Plasma fentanyl concentrations were measured by radioimmunoassay with the lower limits of assay sensitive to 0.2 ng/ml.

The incidence of muscular rigidity (R) was 50% (6/12). Onset of R corresponded with apnea, loss of consciousness and unresponsiveness. No volunteer who became R recalled positive pressure ventilation. All volunteers who did not become rigid (NR) remained conscious and were able to respond to command throughout the study period. R was manifested by flexion of fingers, wrists, and elbows; extension of toes, ankles, and knees; stiffness of the neck muscles with flexion of the head; nystagmus; and rigidity of chest wall and abdominal musculature. Even when adjusted for a baseline (t=0) difference in HR (R=57, NR=67), R had lower HR while rigid than the corresponding times in the NR

group (p=0.08). No differences in systolic and diastolic blood pressures between groups (R vs NR) were detected. Mean group plasma fentanyl concentrations and the time of onset and duration of each episode of rigidity are shown in the figure. No significant differences in plasma fentanyl concentrations were found (R vs NR).

When rigidity occurred, it started 2.3 (range 1-4) min following the time of peak fentanyl concentration and lasted 11.5 (range 7-23) min before spontaneous ventilation resumed (see fig.). The mean plasma fentanyl concentration at which rigidity started was 21.5 (range 16-28) ng/ml and ended was 6.9 (range 5.2-8.7). Despite rigidity lasting up to 23 min muscle relaxant administration was never required to prevent desaturation (O<sub>2</sub> sat <90%).

These findings support the hypothesis that fentanyl, alone, can cause unconsciousness and amnesia and that the presence of rigidity indicates an anesthetized state. In addition, rigidity appears to be a self-limited phenomenon. The lack of difference between plasma fentanyl concentrations in rigid versus nonrigid volunteers suggests that a difference in pharmacodynamic susceptibility to fentanyl induced rigidity exists.

