Title: HEPATO-SPLANCHNIC SUFENTANIL EXTRACTION AND URINARY/BILIARY EXCRETION RATES IN PIGS: COMPARISON WITH HUMANS

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Introduction: Metabolic and physiologic similarities between swine and humans have been well established. Therefore, having studied sufentanil (S) pharmacokinetics in humans, we have in the present study investigated a similar surgical model in the pig with the intent: a) to assess whether narcotic pharmacokinetics are sufficiently similar in humans and swine to derive clinically useful information from the pig model and b) to expand upon earlier S-research by investigating urinary/biliary excretion patterns.

Materials and Methods: Six pigs (4M/2F) of similar weight (18 kg) and length (43 cm) were kept NPO overnight. Following anesthetic induction by a standard medication of intramuscular ketamine 500 mg, xylazine 24 mg and glycopyrrolate 0.2 mg, the animals underwent orotracheal intubation on the morning of surgery. A peripheral (ear) venous catheter was inserted and the animals were paralyzed by atracurium infusion. Mechanical ventilation was maintained with 40% O_2 in N_2O. The estimated overnight fluid deficit was replaced by the infusion of Ringer's Lactate, 500 cc during the first hour of anesthesia. Anesthesia was maintained by S-infusion, averaging 4-6 ug/kg/hr. Indwelling catheters were inserted into the following anatomical sites: 1) femoral artery (FA); 2) portal vein (PV); 3) hepatic vein (HV); 4) gall bladder and 5) urinary bladder. A triple lumen catheter was inserted into the PV via splenic venous access, following midline laparotomy. HV catheter insertion was performed under fluoroscopy using an internal jugular venous access. The position of PV and HV catheter ports was verified angiographically before and after study. The quantitative collection of all bile produced was achieved by choledochal ligation distal to the indwelling catheter. The urinary Foley catheter was inserted by transabdominal cystostomy and all urine produced was collected into an urometer. Hepatic blood flow (HBF) was assessed using continuous indocyanine green (ICG) infusion via ear vein catheter. Following 10 minutes of ICG infusion ($\leq$428 ug/min), simultaneous EDTA blood specimens were obtained from the HV, PV and FA for determination of plasma S and ICG concentrations. During the next 20 minutes, 3 additional sets of specimens were drawn in order to verify steady state conditions of plasma S and ICG concentrations. In addition, baseline urine and bile specimens were obtained and the urinary and gall bladders were evacuated prior to the injection of ^{3}H-S at time zero. 10^7 CPM (#200 ng) of immunoreactive ^{3}H-S were mixed with 50 ug (1 ml) of non-radioactive S and injected into the distal tip of the PV catheter. 10 ml of the animal's own blood, collected previously, were used to purge the ^{3}H-S bolus over 1 minute. Subsequent sets of blood specimens were obtained at 2.5, 5, 10, 20, 30, 40, 60, 90, and 120 minutes following the completion of purge. PV blood specimens were collected from the proximal ports of the triple lumen catheter in order to minimize the chance of ^{3}H-S contamination. Urine and bile specimens were collected 10 minutes after the ^{3}H-S bolus injection and simultaneously with blood specimens, thereafter. Plasma ICG concentrations were determined by a highly sensitive HPLC technique with a lower limit of detection of 50 ng/ml; plasma A-concentrations were determined by RIA using a double antibody precipitation technique with a lower limit of sensitivity of 50 pg/ml.

Results and Discussion: Preliminary results obtained in 6 animals suggest that, under steady state conditions, the mean hepato-splanchnic S-extraction ratio is 69 $\pm$ 9%, about 80% of which is contributed by the liver vs 20% by the intestine. The portal injection of a large S-bolus (50 ug) did not result in an appreciable increase in plasma S-concentrations in the HV in 2 pigs, although it did produce a marked increase (50-400%) in HV S-concentrations in the remaining 4 pigs. Peak S-concentrations in these animals occurred at 2.5 min p.i., followed by a gradual decline toward baseline concentrations over 60-90 minutes. The HV elution pattern of the portal ^{3}H-S pulse dose closely followed the elution pattern of unlabelled S. No ^{3}H-S peak, but a shallow plateau of radioactivity eluting in the HV was demonstrable in those 2 animals which had failed to show appreciable increases of unlabelled S in the HV. Biliary excretion of ^{3}H-S metabolites over 1 1/2 hours averaged 5%, but urinary excretion accounted for 25-30% of the total dose of radioactivity injected into the PV. Appreciable amounts of radioactivity in bile or urine did not appear until 10 minutes after ^{3}H-S bolus injection. Hepatic ICG extraction rates showed marked variability among animals, ranging from 12-41%. These findings suggest that ICG clearance in pigs is limited by hepatic metabolism and may not serve as a reliable indicator of HBF.

Summary: S-metabolism and excretion in swine and humans show patterns of remarkable similarity. In both species, the hepato-splanchnic S-extraction ratio averages70%.Urinary excretion of S-metabolites far outweighs biliary excretion and appears to follow similar time curves. These findings suggest that the study of pigs provides a useful research model to investigate the metabolism of fentanyl-like narcotics and derive clinically meaningful information.

^{3}H-S tracer was kindly provided by Dr. Jos Heykants, Janssen Pharmaceutica, Beerse, Belgium.

This study was supported in part by funds from Janssen Pharmaceutica.