Title: THE PHARMACOKINETICS AND PHARMACODYNAMICS OF 4-AMINOPYRIDINE IN ANESTHETIZED DOGS

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Introduction. 4-Aminopyridine (4AP) has been used to antagonize many types of neuromuscular blockades including those from nondepolarizing muscle relaxants and antibiotics. To determine the pharmacokinetics and pharmacodynamics of 4AP, we under took this study.

Methods. Seven fasted, mongrel dogs were anesthetized with acetylpromazine, 0.1 mg/kg, and pentobarbital, 25-35 mg/kg IV. After endotracheal intubation, ventilation was controlled with room air. Cannulation of both external jugular veins, the urethra and common bile duct was performed. The force of contraction of the anterior tibialis muscle in response to indirect stimulation was measured by a Grass FT03 force displacement transducer and recorded on a polygraph. After recording stable twitch tension for 20 min, pancuronium was infused at a rate sufficient to reduce twitch tension to 10-20 percent of control. After 20 min of unchanged twitch tension and a steady state pancuronium infusion, 4AP, 1 mg/kg, was administered as an IV bolus. Venous blood was sampled 5 min before and 2, 4, 6, 8, 10, 15, 20, 25, 30, 45, 60, 90, 120, 150, 180, 210, 240, 270, 300, 360, 420, 480, 540 and 600 min after 4AP. Urine and bile were sampled before and then every 1/2 half hour after 4AP until ten hours. 4AP levels were measured using the ion-pair HPLC assay, as described previously (1). Serum concentration data were analysed with a weighted nonlinear least squares regression analysis and best fit a three compartment open pharmacokinetic model. Volume of distribution (V_1), volume of distribution at steady state (VDss), distribution half-lives ($t\pi 1/2$ and $t\alpha 1/2$), elimination half-life ($t\beta 1/2$), and clearance (Cl) were determined. Renal clearance was calculated to be equal to the product of total clearance and the fraction of injected dose recovered in the urine in ten hours. The pharmacodynamic effect of 4AP was expressed as percent of pancuronium-induced depression of twitch tension that was antagonized.

Results. Pharmacokinetic parameters (mean ± S.D.) are shown below.

V_1	412 ± 352 ml/kg
V_{Dss}	2517 ± 363 ml/kg
$t\pi 1/2$	1.1 ± 0.7 min
$t\alpha 1/2$	25.4 ± 11 min
$t\beta 1/2$	125 ± 23 min
Cl	21 ± 4 ml/kg/min

The renal clearance was calculated to be 12.4 ml/kg/min. Over half of the unchanged drug was eliminated in the urine (60 ± 9 percent of the injected dose) in ten hours whereas very little appeared in the bile (0.01 ± 0.01 percent of injected dose). The onset time (time from injection to peak effect) was 14 ± 3 min; peak antagonism = 97 ± 27 percent and duration (time from injection to 50 percent of peak antagonism remaining) = 219 ± 54 min.

Discussion. From the comparison of renal clearance to normal GFR in a fasted dog (3 ml/kg/min), we conclude that 4AP must be actively secreted at the site of the renal tubule. The $t\beta 1/2$ of 4AP is nearly three times longer than the $t\beta 1/2$ of neostigmine and pyridostigmine.(2) This may represent a pharmacokinetic basis for the longer duration of action of 4AP over neostigmine and pyridostigmine.(3) However, the relationship between serum concentration and effect of all antagonists of neuromuscular blockade is still unknown.

References.

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