TITLE: DOSE REQUIREMENTS AND PLASMA LEVELS OF PIPECURONIUM DURING RENAL EXCLUSION AND ORTHOTOPIC LIVER TRANSPLANTATION IN PIGS

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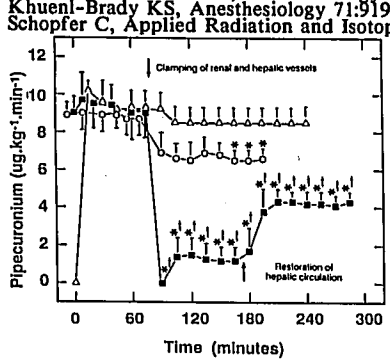
Plasma clearance of pipecuronium (PIP), a new steroidal nondepolarizing muscle relaxant remains unclear since previous reports are contradictory. In patients undergoing cadaver renal transplantation, a 34% reduction of plasma clearance of PIP has been reported (1), whereas in dogs with bilateral renal exclusion, a 85% reduction of PIP plasma clearance has been observed (2). Moreover, the role of the liver on plasma clearance of PIP has not been investigated. To evaluate the respective roles of the kidney and the liver on the plasma clearance of PIP, we studied 5 pigs undergoing bilateral renal exclusion, 7 pigs undergoing orthotopic liver transplantation, and 3 control animals without surgery.

Animals were premedicated with azaperon 4mg/kg, ketamine 7.5 mg/kg and fentanyl 2 ug/kg i.m. and anesthetized with isoflurane (0.5% in oxygen) and fentanyl (2 ug/kg/hr). Body temperature was maintained at 35.5-37 °C with thermoblankets and arterial pH within the range of 7.30-7.45 with a $NaHCO_3$ infusion, if necessary. The right sciatic nerve was continuously stimulated with supramaximal stimuli at 0.1 Hz. The force of the corresponding evoked isometric muscle contraction was continuously recorded. An i.v. infusion of PIP adjusted to maintain a constant 90 to 95% twitch depression was administered throughout the entire investigation. Plasma concentrations of PIP were determined by a new technique using iodine-labelled bengal rose (3). The detection limit was 5 ng/ml. This technique does not measure metabolites of PIP. Statistical comparison between the three animal groups were made using an ANOVA followed by a Duncan's multiple comparisons test.

Control pigs needed an infusion rate of PIP between 8.0 to 10.7 ug/kg/min. In the renal exclusion group, it was necessary to reduce the infusion rate of PIP by about 25% after clamping both renal vascular pedicles (from 8.9 to 6.9 ug/kg/min, $P < 0.05$ from controls). In pigs undergoing liver transplantation, it was necessary to reduce the infusion rate of PIP by approximately 80% after clamping hepatic vessels (from 9.3 to 1.2 ug/kg/min, $P < 0.05$ from controls and from the period after clamping of renal vessels). After hepatic recirculation, the infusion rate of PIP was progressively increased to a rate which corresponded to 50% of baseline values (from 1.5 to 4.3 ug/kg/min, $P < 0.05$ from the anhepatic phase and from controls). Mean plasma concentrations of PIP were 1460 (range:1241-1677), 1783 (range:1416-2098), and 1988 (range:1332-2513) ng/ml in the renal exclusion group, controls, and liver transplantation group, respectively, and were not significantly different between the three animal groups. These values did not change significantly during the entire study, despite a 90-minute and 120-minute exclusion period of the liver and of the kidneys, respectively.

The results of the present study demonstrate that the liver plays a more important role than the kidney in the plasma clearance of PIP in pigs. These results also indicate that the renal elimination of PIP in pigs, but not in dogs, is comparable to that measured in humans, suggesting that the pig is a better animal model than the dog to study the plasma clearance of muscle relaxants.

References: 1. Caldwell JE, Anesthesiology 70:7-12,1989
2. Khuenl-Brady KS, Anesthesiology 71:919, 1989
3. Schopfer C, Applied Radiation and Isotopes 39:771,1988



Mean infusion rate of PIP adjusted to maintain a stable 90 to 95% twitch depression in 3 control pigs (△), in 7 pigs undergoing liver transplantation (■), and in 5 pigs undergoing a bilateral renal exclusion (○). Data points represent mean ± SE of values measured every 15 minutes. † * $P < 0.05$ from control. † $P < 0.05$ from pigs with bilateral renal exclusion.

VECURONIUM NEUROMUSCULAR BLOCKADE AT THE VOCAL CORDS AND ADDUCTOR POLLICIS IN HUMANS

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Wide variations in the intensity and time course of neuromuscular blockade may exist between different muscles. This study was designed to compare the effects of vecuronium at the adductors of the vocal cords and the commonly monitored adductor pollicis.

METHODS : The protocol was approved by the Hospital Ethics Committee. After informed consent, sixteen ASA I and II women, aged 20-65 yr were anesthetized with propofol, 2-4 mg/kg, and fentanyl, 3-5 ug/kg. Tracheal intubation was performed without neuromuscular blocking drugs, and the inflatable cuff of the tube was positioned between the cords under direct vision. The pressure inside the cuff was measured with an air-filled transducer. Mechanical ventilation was instituted, and anesthesia was maintained with propofol, 10-20 mg/kg/hr, and fentanyl. No nitrous oxide or volatile agent was given. Supramaximal train-of-four stimulation was applied to the thyroid cartilage notch. This was found in pilot studies to produce bilateral adduction of the vocal cords. The ulnar nerve was stimulated and the force of contraction of the adductor pollicis muscle was measured. Vecuronium, 0.04 mg/kg or 0.07 mg/kg was given. First twitch height (T1) was measured.

RESULTS : In unparalyzed patients, single stimulation of the vocal cords produced consistent, reproducible increases in cuff pressure, in the range 5-10 mmHg. Direct muscle stimulation was ruled out because the response was abolished with large doses of vecuronium. Vocal cord neuromuscular blockade occured sooner, was less intense and recovered more rapidly than simulateneously measured adductor pollicis blockade (Table).

DISCUSSION : Vocal cords adductors require larger doses for complete relaxation than the adductor pollicis, but maximum blockade occurs sooner, within 3-3.5 min. Complete adductor pollicis recovery indicates no residual paralysis of vocal cord adductor muscles.

TABLE :
(Mean ± SEM)

Variable	Dose	Vocal cords	Add. poll.	
Max block (%)	0.04	54 ± 10	89 ± 3	*
	0.07	88 ± 5	97 ± 2	
Onset (min)	0.04	3.3 ± 0.1	5.8 ± 0.2	*
	0.07	3.4 ± 0.2	5.7 ± 0.4	*
Rec. 90 % (min)	0.04	11 ± 2	27 ± 2	*
	0.07	24 ± 2	40 ± 4	*.

* $P < 0.05$ between both muscles.