Title : PIPECURONIUM DOSE REQUIREMENTS FOR MAINTENANCE OF STEADY STATE NEUROMUSCULAR BLOCKADE DURING ORTHOTOPIC LIVER TRANSPLANTATION IN PIGS

Authors : J.F. Pittet, M.D., P. Leemann. M.D., D.R. Morel, M.D. G. Mentha, M.D., E. Tassonyi, M.D.

Affiliations : Laboratory of Experimental Surgery, Department of Anesthesiology and Surgery, Centre Médical Universitaire, 1211 Geneva, Switzerland.

Introduction: Pipecuronium (PIP) is a new long acting nondepolarizing steroid muscle relaxant, which has been found to have a pharmacodynamic and pharmacokinetic profile similar to pancuronium, but without producing tachycardia (1). In patients with severe renal failure, the plasma clearance of PIP remains at 60% of normal values, suggesting that only 40% of the injected dose of PIP is dependent on the kidneys for its elimination (2). The duration of the neuromuscular (NM) block after a single i.v. dose of PIP is primarily dependent on a redistribution from active to inactive sites (3), whereas during a continuous administration, the renal and hepatic clearance determine the duration of NM blockade. To test the contribution of the liver on the duration of PIP-induced NM blockade, we compared the perfusion rates of PIP producing a NM block of equal intensity with and without liver function during liver transplantation in pigs.

Materials and Methods: Eight pigs (suus scrofa domesticus), weighing 22 to 25 kg, were premedicated with azaperon 4 mg/kg, ketamine 7.5 mg/kg and fentanyl 2 ug/kg i.m. and anesthetized with isoflurane 2-3%. The trachea was intubated without use of a muscle relaxant and anesthesia was maintained with isoflurane (0.5% in oxygen) and fentanyl (2 ug/kg/hr). Ventilation was controlled to keep end-tidal PCO_2 at 30-40 mm Hg; body temperature was maintained at 35-37°C with thermoblankets. Normal saline was infused intravenously through the jugular vein at 6 ml/kg/hr. Mean systemic arterial pressure and central venous pressure were measured using a carotid arterial cannula and a central venous catheter, respectively, connected to calibrated quartz pressure tranducers (1290A HP), positionned at the mid-axillary line, and recorded on a chart recorder (78172A HP). During the whole investigation, arterial pH was maintained within the range of 7.30-7.45 with a $NaHCO_3$ infusion. The sciatic nerve was surgically prepared, isolated, and directly stimulated with a nerve stimulator Laubscher P1 NS-2B delivering a single twitch at 0.1 Hz with 0.2 msec duration, at supramaximal stimulation. The corresponding evoked muscle contraction was continuously recorded by a Grass FT-10 force-displacement transducer on a one-channel recorder. Cumulative i.v. doses of PIP were given during the first ten minutes until a 90% twitch depression was obtained, followed five minutes later by a constant rate intravenous perfusion of PIP adjusted to maintain a constant 90% twitch depression during the whole investigation. The perfusion of PIP was stopped at crossclamping of liver vessels and reinstituted if the NM block decreased below 90% twitch depression. Mean ± SE values of data at different predetermined time intervals were calculated. Statistical comparison over time was conducted by a one-way analysis of variance, followed by a Duncan's test, taking a P value of < 0.05 as statistically significant.

Results: Pharmacodynamic data of PIP are summarized in Table 1. The cumulative ED_{90} of PIP was 120 ± 20 ug/kg. The perfusion rate for maintenance of the NM block was significantly lower ($P<0.001$) during the anhepatic phase of liver transplantation as well as after restoration of the circulation to the transplanted liver than during the preclamping period. Temperature, mean systemic arterial pressure and hematocrit remained within 15% of baseline values, and arterial pH was maintained within the range of 7.30-7.45 during the whole study.

Discussion: The results of this study demonstrate that in pigs the absence of liver function produces a significant decrease in the requirement of PIP necessary to maintain a constant NM block, indicating that the liver plays a major role in the clearance of this muscle relaxant in pigs. These results confirm the human data reported by Caldwell and colleagues (2) demonstrating that PIP is largely independent of the kidney for its elimination. In conclusion, the duration of the NM block induced by PIP is greatly dependent on the liver and may therefore be significantly increased in patients with severe hepatic or multiorgan failure.

References: 1. Caldwell S, et al. *Anesthesiology* 67: A611, 1987
2. Caldwell S et al. *Anesthesiology* :67: A612, 1987
3. Nagashima H, et al. *Anesthesiology* 59: A264, 1983

Table 1: Pharmacodynamic Data of Pipecuronium

	Before Crossclamping	During Crossclamping	After Recirculation
Duration of surgical period (min)	119 ± 11	90 ± 19	163 ± 22
Perfusion rate (µg/kg/min)	7.1 ± 1.2	1.1 ± 0.5*	2.7 ± 0.3*
Total dose of PIP (mg/kg)	9.2 ± 1.2	0.9 ± 0.6*	2.4 ± 0.7*
Duration of PIP perfusion (min)	119 ± 11	42 ± 18*	92 ± 16

$\bar{x}$ ± SE, n=8
* $P < 0.05$ from before crossclamping values