

**Title** : PHARMACOKINETICS AND PHARMACODYNAMICS OF ORG NC 45 IN PATIENTS WITH CIRRHOSIS

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**Introduction.** Org NC 45 is characterized by a short duration of neuromuscular blockade together with a rapid decline of the plasma concentration. Extensive hepatic uptake probably contributes to its rapid elimination<sup>1</sup> and therefore prolonged effect of Org NC 45 is expected in patients with liver cirrhosis. In the present study, we examined the pharmacokinetics and the pharmacodynamics of Org NC 45 in surgical patients with cirrhosis.

**Methods.** After obtaining informed consent and approval by Human studies Committee, nine adult patients with normal hepatic and renal function, aged (mean±SEM) 47±6 yrs and weighing 72±5 kg, and nine patients with cirrhosis, aged 53±5 yrs and weighing 67±5 kg were studied. All the patients underwent elective abdominal or orthopedic surgery. Patients were premedicated with diazepam (10 mg PO) and anesthetized with thiopental, fentanyl and 70% nitrous oxide in oxygen delivered by controlled ventilation. Tracheal intubation was performed after local anesthesia of the larynx with lidocaine. A bolus IV dose of Org NC 45 (0.2 mg/kg) was administered. Force of thumb adduction elicited by surpaximal ulnar nerve stimulation at a frequency of 0.1 Hz, was recorded. Venous blood samples were collected intermittently for three hours and immediately centrifuged and acidified to pH 6. The plasma concentration of Org NC 45 was determined using a minor modification of the Rose Bengale fluorimetric method for pancuronium assay.<sup>2</sup> The plasma concentration-time data were analysed using a two-compartment open model. The following pharmacokinetic parameters were calculated: the elimination half-life ( $t_{1/2\beta}$ ), the volume of the central compartment (Vc), the total apparent volume of distribution at steady state (Vdss) and the plasma clearance (Cl). The duration of the neuromuscular blockade was taken as the time from injection to 75% recovery and the recovery rate as the time elapsing between 25 and 75% of recovery. The plasma concentration corresponding to 50% recovery (Cp(50)) was also determined. The Mann and Whitney test ( $p < 0.05$ ) was used for statistical comparison.

### Results.

#### Pharmacokinetics.

	$t_{1/2\beta}$ (min)	Vc (l/kg)	Vdss (l/kg)	Cl (ml/min/kg)
Normal patients	55 +7	0.11 ±0.01	0.27 ±0.04	5.06 ±0.58
Cirrhotic patients	73* +7	0.08 ±0.02	0.23 ±0.04	2.71** ±0.47

#### Pharmacodynamics.

	Time to 75% recovery (min)	Recovery time (25-75%) (min)	Cp(50) (µg/ml)
Normal patients	75 +13	21 +4	0.21 ±0.02
Cirrhotic patients	137* +42	68* +34	0.30 ±0.08

\*  $p < 0.05$ ; \*\* $p < 0.01$ ; mean±SEM

**Discussion.** Patients with cirrhosis showed a 46% reduction in the Cl of Org NC 45 which resulted in a prolonged  $t_{1/2\beta}$ . The Cp(50) was not modified in patients with cirrhosis, suggesting that the prolonged duration of neuromuscular blockade was due only to delayed elimination of Org NC 45. In comparison with the present data, no pharmacokinetic alteration of Org NC 45 was observed in patients with renal failure. These findings suggest that the liver is the main route of elimination of Org NC 45 in humans.

#### References.

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