

Title : HEPATIC ELIMINATION OF ORG-NC45 AND PANCURONIUM
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Introduction. ORG-NC45 is a monoquaternary analogue of pancuronium which possesses a similar neuromuscular blocking potency and time course of action to pancuronium in the cat and rhesus monkey¹. In contrast to pancuronium, ORG-NC45 lacks a cardioselective atropine-like action at neuromuscular blocking doses in the cat¹, and consequently ORG-NC45 may be of potential clinical use. The hepatic uptake of a neuromuscular blocking drug with potential clinical use is of importance with regard to duration of action. For example, ORG. 6368, a 3 α -monoacetoxy congener of pancuronium, is short acting in the cat because of rapid hepatic uptake, but not in man. The aim of the present study was to determine the role of the liver on the intensity and time course of the neuromuscular block produced by ORG-NC45 in the cat. Pancuronium was included for comparison.

Methods. The sciatic nerve-tibialis anterior muscle preparation of ten anesthetized cats was used to determine neuromuscular block. The liver was prepared for exclusion by the insertion of a T-piece in the vena cava and another in the portal vein. The two T-pieces were connected via a bypass through which the blood flow could be permitted by the deflation of two small intraluminal balloons. When the circulation to the liver was clamped off, the bypass was opened. A cannula in the portal vein T-piece permitted intraportal injection of drugs. Doses of ORG-NC45 (25 μ g/kg iv) and pancuronium (22 μ g/kg iv) were used which produced an approximately 80% reduction of twitch tension. At least six administrations of either muscle relaxant were made to each cat. During the third administration the liver was temporarily (ten minutes) excluded. The fourth administration was made intraportally. During the sixth administration the liver was permanently excluded. The other administrations served as controls. To prevent cumulation, one hour was left between administrations of ORG-NC45 and two hours between administrations of pancuronium. All results are presented as the mean \pm SEM of five observations.

Results. Temporary exclusion of the liver significantly ($P < 0.05$) increased the depth of the neuromuscular block produced by ORG-NC45, from its control value of 82 \pm 7% to 100%. Also the time from injection to 50% recovery of twitch tension was significantly ($P < 0.05$) increased from 10 \pm 2 minutes to 19 \pm 1 minutes. Similarly, temporary liver exclusion also increased, although not significantly ($P > 0.05$) the depth of the neuromuscular block produced by pancuronium from

92 \pm 7% to 100%. The time from injection to 50% recovery of twitch tension was also significantly ($P < 0.05$) increased from 15 \pm 4 to 26 \pm 2 minutes.

Permanent exclusion of the liver also significantly ($P < 0.05$) increased the depth of the neuromuscular block produced by ORG-NC45, from 98 \pm 1% to 100%. Also the time from injection to 50% recovery of twitch tension was significantly ($P < 0.05$) increased, from 12 \pm 1 minutes to 28 \pm 9 minutes. The depth of the neuromuscular block produced by pancuronium was slightly but not significantly ($P > 0.05$) increased, from 98 \pm 2% to 100%. However, the time from injection to 50% recovery of twitch tension was significantly ($P < 0.05$) increased from 17 \pm 2 minutes to at least 45 minutes. Administration of ORG-NC45 but not pancuronium intraportally produced a neuromuscular block of 63 \pm 12% which was slightly but not significantly ($P > 0.05$) less than the control value of 82 \pm 7%.

Discussion. The results of the present study clearly demonstrate that the neuromuscular block produced by ORG-NC45 and pancuronium are both similarly affected by temporary and permanent liver exclusion in the cat. Previous workers have found that the hepatic elimination of pancuronium is significant in the cat², and the results of the present study suggest the same to be so for ORG-NC45. It is unlikely that the slight hepatic uptake of ORG-NC45 observed in the present study totally accounts for the drug's slightly shorter time course of action compared to pancuronium. Since, even when the liver is permanently excluded the time from injection to 50% recovery of twitch tension after ORG-NC45, is still shorter than after pancuronium. It is more likely that ORG-NC45 has a slightly lower affinity for the neuromuscular receptor than pancuronium, or that the metabolites of ORG-NC45 are less potent neuromuscular blocking agents than those of pancuronium. It is concluded that, in the cat, the hepatic elimination of ORG-NC45 is similar to pancuronium, and that the slight hepatic uptake of ORG-NC45 does not greatly influence the time course of action of the drug.

References:

1. Durant NN: A comparison in the anesthetized cat and monkey, of pancuronium with a monoquaternary analogue. *Excerpta Medica, International Congress Series No. 452, 1978, p.240.*
2. Agoston S, Kersten UW, Meijer DKF: The fate of pancuronium bromide in the cat. *Acta Anaesthesiol Scand 17:129-135, 1973*

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