Title : RENAL ELIMINATION OF ORG-NC45 AND PANCURONIUM

Authors : N. N. Durant, Ph.D.*, M.C. Houwertjes, and S. Agoston, M.D., Ph.D.

Affiliation : Institute of Clinical Pharmacology, University of Groningen, Groningen, The Netherlands. *Present address: Department of Anesthesiology UCLA Medical Center, Los Angeles, California 90024

Introduction. The renal elimination of a muscle relaxant is of clinical importance since patients with impaired renal function may exhibit a prolonged neuromuscular block[1]. ORG-NC45 (3α, 17β-diacetoxy-2-dipiperidino-5α-androstane 16-N-mono-methobromide) 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 monkey[2]. In contrast to pancuronium, however, ORG-NC45 lacks a cardioselective atropine-like action at neuromuscular blocking doses, in the cat[2], consequently ORG-NC45 may be of potential clinical use. The aim of the present study was to determine the effect of kidney exclusion on the intensity and the time course of action of ORG-NC45 in the cat. Pancuronium was included in the study for comparison.

Methods. The sciatic nerve-tibialis anterior muscle preparation of ten anesthetised cats was used to determine neuromuscular block. The kidneys were excluded from the circulation by means of clamps placed on the renal veins and arteries. Doses of ORG-NC45 (25 to 40 μg/kg iv) and pancuronium (22 μg/kg iv) were used which produced an approximately 80% reduction of twitch tension. The effects of kidney exclusion were quantified by changes in the depth and time course of the neuromuscular block during temporary (ten minutes) and permanent exclusion compared to control. Neuromuscular block was produced at least five times in each cat with bolus administrations of either muscle relaxant, during the third of which the kidneys were temporarily excluded and during the fifth the kidneys were 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 ± SEM of five observations.

Results. Temporary exclusion of the kidneys only slightly but not significantly ($P > 0.05$) increased the depth of the neuromuscular block produced by ORG-NC45, from its control value of 79 ± 8% to 86 ± 8%. The time from injection to 50% recovery of twitch tension was not significantly ($P > 0.05$) affected, 10 ± 2 minutes vs. 9 ± 2 minutes. By comparison the depth of the neuromuscular block produced by pancuronium was also only slightly but not significantly ($P > 0.05$) increased from 85 ± 7% to 98 ± 1% by temporary kidney exclusion. Similarly the time from injection to 50% recovery of twitch tension increased only slightly but not significantly ($P > 0.05$), from 15 ± 3 minutes to 17 ± 1 minutes.

Permanent exclusion of the kidneys also only slightly but not significantly ($P > 0.05$) increased the depth of the neuromuscular block produced by ORG-NC45, from its control value of 78 ± 11% to 85 ± 8%. The time from injection to 50% recovery of twitch tension was not significantly ($P > 0.05$) affected, 10 ± 2 minutes vs. 8 ± 2 minutes. In contrast to ORG-NC45, permanent exclusion of the kidneys did significantly increase ($P < 0.05$) the depth of the neuromuscular block produced by pancuronium, from its control value 96 ± 2% to 100%. Also the time from injection to 50% recovery of the twitch tension was significantly ($P < 0.05$) increased from 17 ± 3 minutes to 27 ± 6 minutes.

Discussion. The results of the present study clearly demonstrate that, in contrast to pancuronium, the renal elimination of ORG-NC45 is low. Previous workers have demonstrated that in the cat the renal and hepatic routes contribute equally to the elimination of pancuronium[3], whilst in man renal excreation of the drug is the main route of elimination[4]. It is not possible to postulate whether the renal elimination of ORG-NC45 in man will be low, as in the cat. However, if such should be the case ORG-NC45 might be of clinical advantage over pancuronium in patients with renal failure. It is concluded that the low renal elimination of ORG-NC45 and the drug's lack of autonomic side effects in the cat[2] suggest that the drug may possibly have potential clinical use.

References:

1. Miller R D, Stevens W C, Way W L: The effect of renal failure and hyperkalemia on the duration of pancuronium neuromuscular blockade in man. Anesth Analg (Cleve) 52: 661-665, 1973

2. Durant N N: A comparison in the anaesthetised cat and monkey, of pancuronium with a monoquaternary analogue. Excerpta Medica, International Congress Series No. 452, 1978, p.240

3. Agoston S, Kersten U W, Meijer D K F: The fate of pancuronium bromide in the cat. Acta Anesthesiol Scand 17:129-135, 1973

4. Agoston S, Vermeer G A, Kersten U W, Meijer D K F: The fate of pancuronium in man. Acta Anesthesiol Scand 17: 267-275, 1973

ORG-NC45 and pancuronium were supplied by Organon International Scientific Development Group, Oss, The Netherlands.