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In vitro response of neuromuscular blockers after chronic carbamazepine treatment in rats

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Chronic carbamazepine treatment, induces resistance to non-depolarising neuromuscular blockers like atracurium, pancuronium and vecuronium [1–3] and to the depolarising blocker succinylcholine [4]. Chronic phenytoin displays similar resistance [5–7] which is more pronounced when patients receive multiple anti-convulsant therapy [8]. Resistance has been postulated to be either pharmacokinetic and/or pharmacodynamic in nature [4, 9]. The objective of this work was to elucidate whether the observed resistance with chronic carbamazepine had a pharmacokinetic or pharmacodynamic origin. In particular, the effects of a non-depolarising blocker (atracurium) and a depolarising blocker (succinylcholine) were determined after chronic carbamazepine treatment in rats.

Carbamazepine serum concentrations of 4.4 ± 0.64, 2.3 ± 0.18 and 0.45 ± 0.09 μg/ml (range: 18.6 to 1.9 μM) were achieved after 7, 14 and 21 days. Carbamazepine induces its own metabolism hence these concentrations declined over the 21 day dosing interval ($P < 0.01$).

Neuromuscular paralysis-concentration curves for atracurium and succinylcholine did not differ between the carbamazepine and placebo groups; the curves were superimposable (Fig.). Thus C_{50} values for atracurium (18 ± 1 versus 20 ± 3 μM) and succinylcholine (8.6 ± 0.5 versus 8.0 ± 0.6 μM) did not differ between the carbamazepine and placebo groups.

Neuromuscular junction sensitivity to atracurium and succinylcholine was not altered by chronic carbamazepine treatment. Thus, the primary reason for the observed resistance to neuromuscular blockers during chronic anti-convulsant therapy in patients seems to be due to pharmacokinetic effects related to an increased metabolism of the neuromuscular blockers resulting in sub-effective concentrations.

Experimental

Two groups (n = 6) of male Sprague-Dawley rats were studied: carbamazepine group received four 200 mg subcutaneous pellets (Innovative Research of America, USA) to achieve carbamazepine concentration of 5 μg/ml for 21 days. Control group received four placebo pellets. Serum carbamazepine was assayed using HPLC 7, 14 and 21 days after pellet insertion [10]. Hemi-diaphragms with their attached phrenic nerves were dissected on day 21 under urethane anaesthesia and mounted in organ baths with oxygenated Kreb's buffer, pH 7.4 at 37 °C. The nerve was stimulated supramaximally (2 volts, 0.1 Hz and 0.2 ms duration) and muscle twitches were recorded using force-displacement transducer. These 12 preparations from both groups were used to generate paralysis-concentration curves for atracurium and succinylcholine; six preparations for atracurium first followed by washout and then for succinylcholine in a crossover design. Paralysis-concentration relationships for atracurium and succinylcholine were fitted to sigmoid E_{max} equations and concentration of each blocker eliciting 50% paralysis (C_{50}) in the carbamazepine and placebo groups were compared using unpaired Student's t-test. Mean ± S.E.M. of the results are presented and $P < 0.05$ was considered significant.

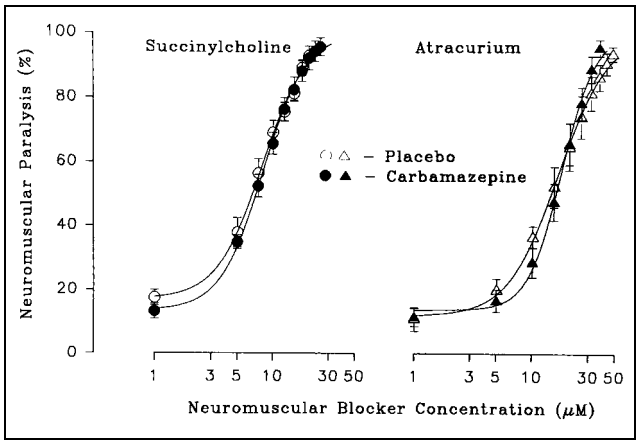

Fig.: *In vitro* paralysis-concentration relationships for atracurium and succinylcholine following chronic *in vivo* treatment with carbamazepine or placebo for 21 days

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