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In vitro neuromuscular effects of droperidol in rats

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Droperidol is used as anaesthetic pre-medication, for induction of anaesthesia and as a part of neuroleptanaesthesia [1]. Droperidol, 33 and 26 μM, induced 90% depression of diaphragm muscle response during direct (muscle) or indirect (nerve) stimulation; neostigmine did not alter this response [2]. Droperidol may thus produce neuromuscular effects and interact with neuromuscular blockers. The present study examined the *in vitro* neuromuscular effects of droperidol and its interactions with two blockers, suxamethonium and atracurium, using rat phrenic nerve-hemidiaphragm muscle preparation.

Droperidol induced neuromuscular paralysis when the phrenic nerve was stimulated; its concentration at 50% paralysis (C_{50}) after 5 min of exposure (31.8 ± 1.4 μM, $n = 12$) was higher ($P < 0.001$) compared to that after the 10 (22.7 ± 0.9 μM, $n = 12$) or 20 min (20.6 ± 1.2 μM, $n = 12$) exposure. Droperidol also suppressed muscle response in curarised preparations during direct muscle stimulation, C_{50} for this for 5 min of exposure was 39.6 ± 2.5 μM ($n = 8$).

Neostigmine (2 μM), caused $14 \pm 3\%$ reversal of $45 \pm 3\%$ droperidol paralysis ($P < 0.001$, $n = 4$) but intense paralysis ($89 \pm 1\%$, $n = 4$) was not reversed, consistent with a non-depolarizing (curare-like) effect. Droperidol (20 μM) increased d-tubocurarine (3 μM) paralysis from $53 \pm 7\%$ to $86 \pm 2\%$ ($P < 0.001$, $n = 4$). Similarly, droperidol (30 μM) paralysis was increased from $44 \pm 3\%$ to $85 \pm 5\%$ by 3 μM d-tubocurarine ($P < 0.001$, $n = 4$), consistent with a non-depolarizing action. Reduction in Ca^{2+} from 2.5 to 1.25 mM did not alter droperidol paralysis (C_{50}: 34.4 ± 2.3 vs 38.5 ± 2.2 μM, $P > 0.05$, $n = 4$), indicating that acetylcholine release was unaffected.

Droperidol 5, 10 or 20 μM reduced suxamethonium and atracurium C_{50}; inverse linear relationships were noted between C_{50} of each blocker and droperidol concentrations (Fig.). This effect was greater with atracurium than with suxamethonium (slope 0.251 vs 0.133).

Droperidol paralysis was slow in onset and was mediated via direct effect on the muscle as well as depolarizing and non-depolarizing components. It also enhanced suxamethonium and atracurium response, in contrast to a previous report with suxamethonium [3]. Droperiol's effect was similar to haloperidol in the rat phrenic nerve-diaphragm preparation [4]. Droperidol concentrations that produced these effects were higher than those noted in patients but care needs to be taken when droperidol is used with neuromuscular blockers.

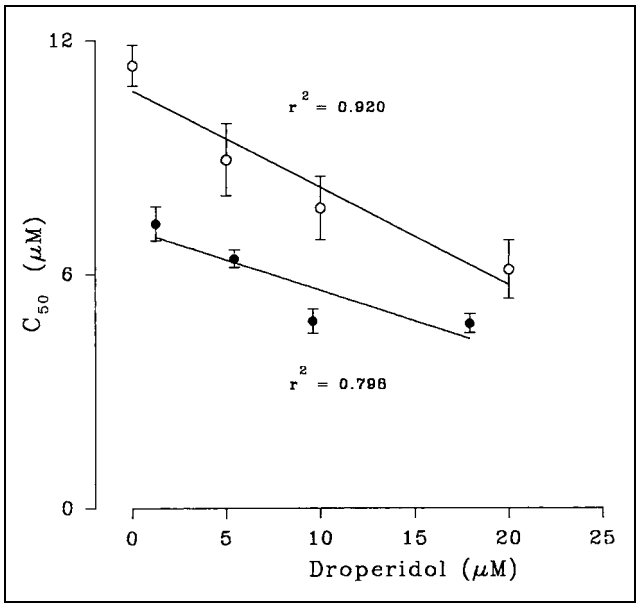

Fig.: Effect on droperidol on the C_{50} for, suxamethonium (●) and atracurium (○)

Experimental

Rat hemi-diaphragms with attached phrenic nerves were mounted in organ bath containing Krebs solution (pH 7.4) at 37 °C [5]. Supramaximal electrical stimuli were delivered to the nerve (0.1 Hz, 0.2 ms duration) or the muscle (0.1 Hz, 2 ms duration) and muscle response-droperidol concentration relationships were generated. Three sets of preparations were stimulated via the nerve with 5, 10 or 20 min of droperidol exposure; responses were also generated in another experiment using direct muscle stimulation after d-tubocurarine (3 μM) pretreatment. Mechanisms of droperidol action were also examined, 50% d-tubocurarine (3 μM) paralysis was produced and 5 min later, droperidol (20 μM) was added. Alternatively 50% paralysis was induced with droperidol and then of d-tubocurarine (3 μM) was added. Droperidol's effect was also evaluated after neostigmine (2 μM) or when Ca^{2+} was reduced from 2.5 to 1.25 mM. Effect of 5, 10 or 20 μM droperidol on suxamethonium or atracurium actions were examined; pharmacodynamic relationships were derived for each blocker alone or in the presence of droperidol added 5 min before each blocker. Muscle response-concentration relationships were fitted to Hill-type equations. Mean ± s.e.m. data are presented, $P < 0.05$ (ANOVA or Student's t-test) was considered significant.

References

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