Reciprocal potentiation of neuromuscular blocking agents

SIR,—When the rat phrenic nerve diaphragm preparation is used for quantitative work, the washout period, after the application of a neuromuscular blocking agent, is adjusted so that the subsequent addition of an equal concentration of the same agent will cause a similar response. We have already noted that a rat phrenic nerve diaphragm preparation, previously treated with tubocurarine and washed out as described, was unexpectedly sensitive to diallylnortoxiferine (Pleuvry & Hunter, 1967). Some further investigations have now been made.

Approximately equipotent concentrations of two neuromuscular blocking agents were applied, for 3 min to a rat phrenic nerve diaphragm preparation. Blocking agent A was applied first and the percentage reduction in lever movement measured. The preparation was then washed in the appropriate manner and then blocking agent B was added for 3 min. After a washout period appropriate for blocking agent B, blocking agent A was repeated and the percentage increase in response over the initial response was measured.

TABLE 1. RECIPROCAL POTENTIATION OF NEUROMUSCULAR BLOCKING AGENTS

Drug A	Drug B	% Potentiation of Drug A (± s.e.)
Diallylnortoxiferine	Tubocurarine	119 (±21·2) (6)*
Tubocurarine	Diallylnortoxiferine	22·3 (±3·70) (6)*
Tubocurarine	Toxiferine	67·0 (±8·66) (5)*
Diallylnortoxiferine	Toxiferine	80·7 (±10·4) (6)*
Gallamine	Toxiferine	1·2 (±5·59) (6)*

* Number of experiments from which the standard errors were calculated.

TABLE 2. EFFECT OF ANTICHOLINESTERASES AGENTS ON RECIPROCAL POTENTIATION

Anticholinesterase agents	Increase (%) in response to diallylnortoxiferine on a tissue sensitized by tubocurarine (± s.e.)	No. of experiments
Neostigmine	132·4 (±15·64)	6
Physostigmine	13·1 (±5·94)	7
Edrophonium	67·1 (±16·04)	6
Ambenonium	71·6 (±19·54)	5
Dyflos	26·9 (±19·54)	7

The neuromuscular blocking agents used were gallamine, diallylnortoxiferine, toxiferine and (+)-tubocurarine. The results (Table 1) show that treatment of the preparation with toxiferine and tubocurarine potentiated diallylnortoxiferine. Toxiferine also potentiated tubocurarine and to a lesser, but still significant, extent diallylnortoxiferine potentiated tubocurarine. Only gallamine was not significantly potentiated by toxiferine.

The effect of anticholinesterases was investigated only on the potentiation of diallylnortoxiferine by tubocurarine. Edrophonium, ambenonium, physostigmine and neostigmine were used in approximately equipotent concentrations, and each agent was added to the preparation 1 min before each administration of neuromuscular blocking agent. The results (Table 2) showed that only physostigmine reduced the potentiation to insignificant levels. Complete

inhibition of cholinesterase with di-isopropylfluorophosphonate (dyflos, DFP, 20 μg/ml for 1 hr) also inhibited the potentiation. It is interesting to note that physostigmine and dyflos have by far the highest lipid solubility and this may be related to their ability to inhibit this potentiation.

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Reference

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The influence of hypoxia upon toxicity of a nucleotoxic agent, mustine hydrochloride

SIR,—Although many radioprotective substances also provide protection against nucleotoxic agents (Scarborough & Thomas, 1962), this is not so for 5-hydroxytryptamine (5-HT) which is a powerful chemical radioprotector (Uroić, Rabadjija & Supek, 1964) but enhances the toxicity of a typical representative of radiomimetic poisons—mustine hydrochloride (nitrogen mustard).

Tissue hypoxia provides protection against ionizing radiation (Brues & Patt, 1953). According to van den Brenk & Haas (1961) 5-HT exerts its radioprotective effect in terms of pharmacologically-induced hypoxia. If this is true then hypoxia alone should not protect against mustine hydrochloride. To test this assumption we have examined the influence of acute hypoxia upon the chronic toxicity of mustine hydrochloride in rats. Hypoxia was produced by administering 55 mg/kg of hydroxylamine hydrochloride intraperitoneally. This dose does not change the toxicity of mustine, but exerts a strong methaemoglobinaemia (40–50%) with consequent anaemic hypoxia.

Two groups of 34 albino rats were injected intravenously with mustine hydrochloride (0·8 mg/kg). The first group received saline and the second group hydroxylamine hydrochloride (55 mg/kg) intraperitoneally 30 min before mustine. The survival of rats was observed every 12 hr during 30 days. The mortality (%) and the mean survival time (days $\pm$s.e.m.) were: 64·7 and 13·7 $\pm$ 2·09 for the saline group and 30·3 and 22·4 $\pm$ 2·04 for the group treated with hydroxylamine hydrochloride.

A decrease in mortality rate (χ^2-test; $P < 0.01$) and increase in mean survival itme (t-test; $P < 0.01$) was observed. It is evident that hypoxia in our experimental conditions significantly reduces the toxicity of mustine hydrochloride.

The present finding does not seem to be consistent with the hypothesis that 5-HT exerts its radioprotective action by means of cellular hypoxia.

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