Neuromuscular and cardiovascular studies with dimethyl tubocurarine in anaesthetized cats, rhesus monkeys and man

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The pharmacological properties of dimethyl tubocurarine were first described by Collier, Paris & Woolf (1948). Although it was more potent, caused less ganglion blockade and released less histamine than tubocurarine, it never gained popularity because it was difficult then to prepare batches of consistent potency (Mogey & Trevan, 1950). Recently, we found that neuromuscular paralysing doses of dimethyl tubocurarine, unlike those of most non-depolarizing agents, did not cause vagal blockade (Hughes & Chapple, 1975). These interesting properties merit further investigation.

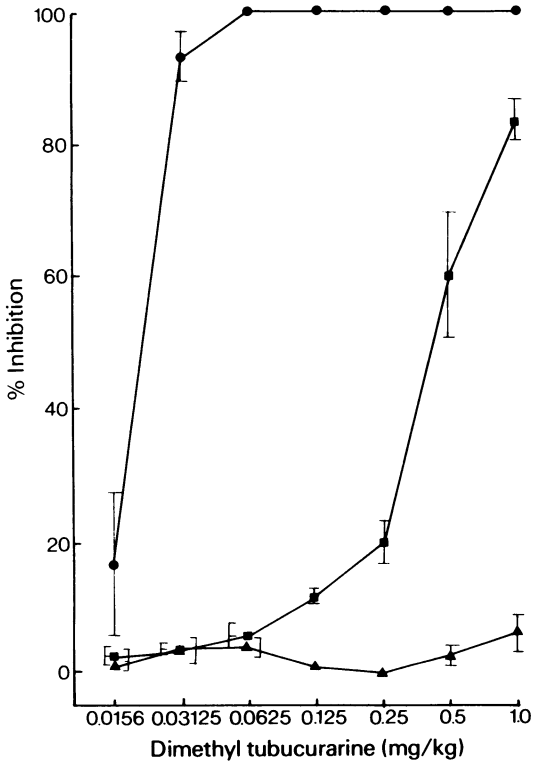

Figure 1 Dose-response curves showing blockade of neuromuscular and autonomic mechanisms by dimethyl tubocurarine given intravenously to cats anaesthetized with chloralose (each point represents the mean of 4 observations). (●) Percentage inhibition of the twitch response of the gastrocnemius muscle to indirect stimulation at 0.1 Hz. (■) Percentage inhibition of the bradycardia response to vagal stimulation at 10-20 Hz per 10 seconds. (▲) Percentage, inhibition of the response of the nicitating membrane to sympathetic nerve stimulation at 10-20 Hz for 60 seconds. Vertical lines indicate standard errors.

Intravenous doses of dimethyl tubocurarine required for complete neuromuscular paralysis of the twitches of the gastrocnemius muscle were 0.0625 mg/kg for each of 4 cats (Figure 1) and 0.125 mg/kg for 4 monkeys. Vagal blockade only became appreciable at 8-16 times these respective doses; heart rate was unchanged. Sympathetic function was unimpaired in cats (Figure 1) and in monkeys the vasopressor response to carotid occlusion was only reduced (about 10-40%) by supramaximal doses of 0.5-2 mg/kg i.v.; these doses lowered mean blood pressure by 35-46 mmHg in cats and 14-20 mmHg in monkeys. The drug was long acting in cats and monkeys—more than 60 min was required for recovery from complete neuromuscular paralysis.

Preliminary studies, using techniques described previously (Sugai, Hughes & Payne, 1975), were carried out in patients who had given their informed consent before undergoing urological surgery. In 6 anaesthetized patients, intravenous doses of 0.16-0.32 mg/kg dimethyl tubocurarine were required to cause complete neuromuscular paralysis of the twitches of the adductor pollicis muscle, its potency in man corresponded more to that in monkeys than cats. Disturbances in arterial blood pressure and heart rate were minimal. The drug was also long acting in man, more than 60 min was required for recovery, but neuromuscular paralysis was well antagonized by neostigmine.

Thus, dimethyl tubocurarine has desirable clinical properties but the ideal non-depolarizing neuromuscular blocking agent would need to be shorter acting.

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The enterohepatic circulation of ^{3}H-phenolphthalein in the rat

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Many drugs are excreted in bile and, consequently, may undergo an enterohepatic circulation (EHC) (see Smith & Millburn, 1975). In the rat, phenolphthalein is conjugated with glucuronic acid and then extensively excreted in bile (Millburn, Smith & Williams, 1967). This paper reports on the EHC of phenolphthalein.

In bile-duct-cannulated rats injected with [^{3}H]-phenolphthalein (25 mg/kg i.p.), 89 ± 1.6% (n = 3) of the ^{3}H was excreted in bile in 3 h, whereas in intact rats four days are required for the elimination of 86 ± 3.9% (n = 3) in faeces. This delayed faecal excretion appears to be due to EHC.

Following intraduodenal infusion of [^{3}H]-phenolphthalein into bile-duct-cannulated rats, there is a rapid biliary excretion of radioactivity (Figure 1a). By contrast, on infusion of bile containing [^{3}H]-phenolphthalein glucuronide obtained from rats injected with [^{3}H]-phenolphthalein, there is a lag period of some 4 h before a comparable rate of excretion occurs (Figure 1a). This suggests that the glucuronide may require hydrolysis to the aglycone before significant absorption occurs, as is the case for stiboestrol glucuronide (Fischer, Millburn, Smith & Williams, 1966).

Rats were treated daily for 3 days with antibiotics to suppress the intestinal microflora. Figure 1b shows that this treatment did not inhibit the absorption of free phenolphthalein. However, on the intraduodenal infusion of bile containing [^{3}H]-phenolphthalein glucuronide the biliary excretion of ^{3}H (Figure 1b) was much lower than in untreated animals (Figure 1a). This indicates that hydrolysis of phenolphthalein glucuronide by bacterial β-glucuronidase is an important step in the EHC of phenolphthalein.

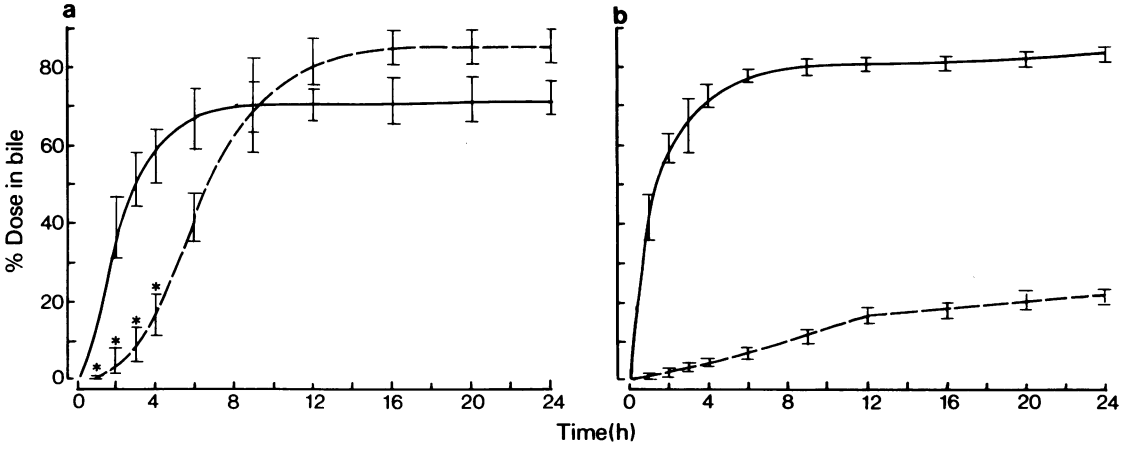

Figure 1 Biliary excretion of radioactivity after intraduodenal infusion of ^{3}H-phenolphthalein (——) or ^{3}H-phenolphthalein glucuronide (— — —) into bile-duct-cannulated female Wistar albino rats (200-250 g body weight). The dose was 79 μmol/kg. The vertical bars represent s.e. mean (n = 3).
a: without antibiotic treatment. *These values are significantly ($P < 0.05$) lower than the corresponding values for phenolphthalein.
b: after 3 days treatment with neomycin (100 mg kg^{-1} day^{-1}), tetracycline (50 mg kg^{-1} day^{-1}) and bacitracin (50 mg kg^{-1} day^{-1}).