THE EFFECT OF QUINIDINE AND PROCAINAMIDE ON THE NEUROMUSCULAR BLOCKING ACTION OF SUXAMETHONIUM

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SUMMARY

Previous workers have shown that under certain clinical and experimental conditions, quinidine potentiates the neuromuscular blocking action of suxamethonium. This effect of quinidine has been demonstrated experimentally in a nerve-muscle preparation in vivo while another antifibrillatory drug, procainamide, has also been shown to potentiate suxamethonium. Possible explanations of these drug interactions are discussed. Since quinidine is known to cause respiratory paralysis in man when administered intravenously during the recovery phase from suxamethonium block, it is suggested that procainamide may produce similar effects in this situation.

Quinidine, the dextrorotatory isomer of quinine, is a drug which has proved of value in the treatment of certain cardiac arrhythmias, notably in auricular fibrillation and ventricular tachycardia. Although quinine and the related cinchona alkaloids have been studied largely for their cardiac and anti-malarial actions these drugs have also been shown to exert effects on skeletal muscle.

In 1936, Wolf made the observation that dystrophia myotonica can be relieved symptomatically by quinine. In an investigation of the action of quinine on skeletal muscle, Harvey (1939) demonstrated that quinine increases the tension response to single maximal stimuli applied directly to the muscle but diminishes the effect of tetanic stimulation by increasing the refractory period. Quinine was also shown to interfere with neuromuscular transmission by increasing the threshold of excitability of the motor endplate, this being a curare-like effect. In isolated phrenic nerve-diaphragm preparations, quinidine initially increases the effect of both nerve and muscle stimulation, and depresses in high doses (Stephenson, 1948; Dutta, 1949).

Recent observations have drawn attention to an interaction of quinidine with neuromuscular blocking drugs. Schmidt, Vick and Sadove (1962) found that the administration of quinidine to a patient, just after emergence from anaesthesia involving dimethyl tubocurarine, caused signs of respiratory paralysis to reappear. In experiments in rabbits quinidine was found to have no effect on the amount of muscle relaxant required to produce a flaccid paralysis of the neck muscles, but when quinidine was given after recovery from tubocurarine, decamethonium or suxamethonium, paralysis recurred. More recently, Grogono (1963) has reported the return of respiratory paralysis in two patients when quinidine was injected intravenously during recovery from suxamethonium.

Procainamide is an antifibrillatory drug which has similar indications to those of quinidine, but no reports have appeared suggesting an interaction between procainamide and neuromuscular blocking agents.

In this communication the interaction between quinidine and suxamethonium is demonstrated in the sciatic nerve-tibialis anterior muscle preparation of the anaesthetized cat, and a similar interaction is shown to occur between procainamide and suxamethonium.

METHODS

Cats weighing 2.0–3.75 kg were anaesthetized with intravenous pentobarbitone sodium. The contractions of the tibialis anterior muscle in response to supramaximal shocks applied to the peripheral end of the cut sciatic nerve (5–7 shocks/min, 0.5 m.sec duration) were recorded as described by Paton and Zaimis (1951). In some experiments
the electrocardiogram and arterial blood pressure were monitored using a Devices 4-channel pen-writing recorder.

**Drugs.**

The following compounds were used: quinidine sulphate, procainamide hydrochloride (Pronestyl), suxamethonium bromide (Brevidil-M) and gallamine triethiodide (Flaxedil). All drugs were injected into the cannulated external jugular vein. Solutions of quinidine sulphate and procainamide hydrochloride in 0.9 per cent saline were infused over a period of 15–30 seconds.

**RESULTS**

**Quinidine.**

Intravenous infusion of quinidine sulphate 2–5 mg/kg had no neuromuscular blocking effect. A dose of 10 mg/kg caused a small potentiation of the muscle twitch. When 5 mg/kg of quinidine sulphate was infused intravenously during the recovery phase following neuromuscular blockade with suxamethonium, recovery was interrupted by a phase of increased block (fig. 1). In two similar experiments with gallamine triethiodide, quinidine sulphate 10 mg/kg intravenously had little effect on the recovery of neuromuscular transmission (fig. 2). No effect was seen when 1 ml/kg 0.9 per cent saline was injected intravenously during the recovery phase from suxamethonium (fig. 3) or from gallamine.

**Procainamide.**

Intravenous infusion of procainamide hydrochloride (2–20 mg/kg) had no neuromuscular blocking effect. In four experiments procainamide hydrochloride (15–20 mg/kg) was infused intravenously during the recovery phase following suxamethonium; a phase of increased block comparable to that seen with quinidine delayed recovery in three of the experiments. This is illustrated in figure 4. In two similar experiments with gallamine triethiodide, procainamide hydrochloride 15 mg/kg intravenously caused a transient interruption in the recovery of neuromuscular transmission (fig. 5).

When procainamide hydrochloride (10–15 mg/kg) was infused intravenously, either shortly before the injection of suxamethonium or during the phase of complete neuromuscular blockade following suxamethonium, the neuromuscular blocking action of the latter drug was enhanced.

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**Fig. 1**

Cat, 2.5 kg, pentobarbitone anaesthesia. Record of the contractions of the tibialis anterior muscle produced by stimulation of the peripheral end of the cut sciatic nerve (supramaximal shocks at 7 shocks/min, pulse duration 0.5 m/sec). Sux = suxamethonium; Quinid = quinidine. Drugs injected intravenously (doses/kg). Time marks, 30 sec.

Note the phase of increased neuromuscular block caused by quinidine when infused during recovery from suxamethonium.
FIG. 2
Cat, 2.0 kg, pentobarbitone anaesthesia. Experimental details as in fig. 1. Gall = gallamine; Quinid = quinidine.
Quinidine had little effect on the recovery of neuromuscular transmission following gallamine.

FIG. 3
Cat, 2.7 kg, pentobarbitone anaesthesia. Experimental details as in fig. 1. Sux = suxamethonium; Sal = 0.9 per cent saline solution.

FIG. 4
Cat, 2.0 kg, pentobarbitone anaesthesia. Experimental details as in fig. 1 except stimulation at 5 shocks/min. Sux = suxamethonium; Proc. A = procainamide. Note the phase of increased neuromuscular block caused by procainamide when infused during recovery from suxamethonium.

FIG. 5
Cat, 3.0 kg, pentobarbitone anaesthesia. Experimental details as in fig. 1. Gall = gallamine; Proc. A = procainamide. Infusion of procainamide caused a transient interruption in the recovery of neuromuscular transmission after gallamine.
This effect appeared predominantly as an increase in the potency of suxamethonium.

**DISCUSSION**

Suxamethonium (bis-2-dimethylaminoethyl succinate) produces its neuromuscular blocking effect partly by depolarization and by decreasing the sensitivity of the endplate to the transmitter substance (Thesleff, 1955); its short action is due to rapid hydrolysis by pseudocholinesterase (Bourne, Collier and Somers, 1952). The latter occurs in two stages: the di-ester is broken down by pseudocholinesterase to a mono-ester (2-dimethylaminoethyl succinate), and then hydrolysis converts the mono-ester into succinic acid and choline; the second stage involves both pseudocholinesterase and acetylcholinesterase (Whittaker and Wijesundera, 1952). Suxamethonium itself has some anti-cholinesterase activity but this is not considered to contribute significantly to its neuromuscular blocking action (Paton, 1952).

Evans et al. (1952) have suggested that the degree of muscular relaxation produced by suxamethonium is determined by the pseudocholinesterase level, and some anticholinesterase agents, such as eserine iodide, are known to depress serum pseudocholinesterase levels (Leopold, Krishna and Lehman, 1959; de Roetth et al., 1965; McGavin, 1965) and also to cause prolonged apnoea when suxamethonium is administered (Pantuck, 1966; Gesztes, 1966). The possibility must be considered that the potentiation of suxamethonium by quinidine and procainamide is due to the inhibition of pseudocholinesterase by these compounds. This is supported by our observation that both quinidine and procainamide failed to show similar effects when infused during recovery from gallamine, a neuromuscular blocking agent of the non-depolarizing type. Although inhibition of pseudocholinesterase might account for a prolongation of the action of suxamethonium, this mechanism cannot be held responsible for an increase in neuromuscular block as was observed in the present experiments. Schmidt, Vick and Sadove (1962) found that quinidine potentiated the neuromuscular blocking effect of decamethonium and tubocurarine, as well as that of suxamethonium, thus suggesting a non-specific mechanism, but the present results do not support this view.

The local anaesthetic, procaine, has been shown to potentiate the neuromuscular blocking effect of suxamethonium in man and in experimental animals (Foldes et al., 1953; Salgado, 1961). Foldes and his colleagues have suggested that this potentiation is due to substrate competition, since both compounds are hydrolyzed by pseudocholinesterase; procainamide may similarly be hydrolyzed by this enzyme. Both quinidine and procainamide are known to have local anaesthetic activity (de Elio, 1948; Goodman and Gilman, 1955) and quinidine has been shown to depress the effect of direct muscle stimulation (Stephenson, 1948; Dutta, 1949). Neither mechanism would appear to account for the present results, since, if local anaesthetic activity or a depressant action on skeletal muscle is responsible, similar results would be expected with both suxamethonium and gallamine.

Procainamide has recently been shown to reduce the release of acetylcholine from preganglionic nerve endings in autonomic ganglia, (Paton and Thompson, 1964) and there is also evidence from studies on cardiac muscle that quinidine and other anti-arrhythmic agents depress depolarization by interfering with the mechanism by which cations enter the fibre (Vaughan-Williams, 1964). Although the mechanism by which quinidine and procainamide potentiate the effect of suxamethonium is obscure, interference with the release of acetylcholine or interference with transport of cations at the neuromuscular junction may be involved. It is possible that the interaction observed between quinidine or procainamide and suxamethonium is common to all drugs with quinidine-like activity. This may be of particular interest in respect to the sympathetic β-receptor antagonists, pronethalol and propranolol, which are known to possess quinidine-like activity (Sekiya and Vaughan-Williams, 1963; Morales-Aguilera and Vaughan-Williams, 1965), since these compounds may be used to reverse arrhythmias occurring during anaesthesia.

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REFERENCES


EFFETS DE LA QUINIDINE ET DE LA PROCAINAMIDE SUR LE BLOCAGE NEUROMUSCULAIRE PRODUIT PAR LE SUXAMETHONIUM

SOMMAIRE

D'autres auteurs ont montré que dans certaines conditions cliniques et expérimentales, la quinidine renforçait le blocage neuromusculaire produit par le suxamethonium. Nous avons démontré expérimentalement cette propriété de la quinidine, in vivo, sur une préparation nerf-muscle et avons constaté par ailleurs que la procainamide, autre médicament anti fibrillaire, potentialisait elle aussi le suxamethonium. Nous discutons les explications possibles de ces interactions médicamenteuses. Puisque la quinidine peut provoquer une paralysie respiratoire chez l'homme si on l'administre par voie intraveineuse pendant la phase de récupération du blocage au suxamethonium, nous pensons que la procainamide pourrait avoir des effets analogues dans ces mêmes circonstances.

DIE WIRKUNG VON CHINIDIN UND PROCAINAMID AUF DIE NEUROMUSKULÄRE BLOCKBILDUNG DURCH SUXAMETHONIUM

ZUSAMMENFASSUNG