AN EXPERIMENTAL STUDY OF THE ACTION OF SUXAMETHONIUM ON THE CIRCULATORY SYSTEM

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SUMMARY

The cardiovascular actions of suxamethonium were studied in spinal cat preparations, and in cats with intact central nervous systems anaesthetized with a thiopentone, nitrous-oxide and oxygen sequence. Mechanical artificial ventilation of the lungs was maintained throughout. Intra-arterial pressure, standard limb lead electrocardiograms and respiratory movements were recorded. Under these conditions suxamethonium was shown to have nicotine-like and muscarine-like activity. It is suggested that suxamethonium produces similar effects in other animals and in man.

Experimental work relating to the action of suxamethonium on the circulatory system appears to have led to conflicting results. Bovet et al., (1949) and Bovet et al., (1951) working with dogs, found that small doses (1 mg/kg) caused a slight fall in blood pressure and bradycardia, while large doses (10 mg/kg) produced a nicotinic type of hypertension. Thesleff (1952) demonstrated a slight depolarization at autonomic ganglia and suggested that this could explain the nicotinic response; he failed to observe any fall in blood pressure except when enormous doses (100 mg/kg) were administered. More detailed investigations by Paton (1953) showed that large doses of suxamethonium caused a fall in blood pressure, while after atropine they produced a rise due to stimulation of autonomic ganglia. Somers (1953) failed to demonstrate any muscarinic effect of the drug in cats under chloralose anaesthesia and was unable to produce hypotension in either cats or dogs, thus supporting the observations of Castillo and de Beer (1950) who concluded from their experiments that in cats and dogs any blood pressure changes after the administration of suxamethonium were the result of asphyxia. Beretervide (1955) also concluded that the drug had no effect on the heart or circulation, but as many of his experiments were carried out on conscious animals without artificial ventilation of the lungs, his results may be suspect. Reports in the veterinary literature concerning the effects of suxamethonium in conscious horses leave very little doubt that in these animals the drug produces severe cardiovascular disturbances (Stowe, 1955; Larsen, 1958; Neal and Wright, 1959; Tavernor, 1959; Hofmeyr, 1960).

Discrepancies are also apparent in reports of the action of suxamethonium in man. Phillips (1954) recorded that suxamethonium produced cardiovascular side effects, but in some patients the relaxant was given prior to barbiturate anaesthesia and doubt exists about the adequacy of oxygenation in such cases. Under these circumstances he found marked muscle fasciculation accompanied by a rise in blood pressure which was maintained during the period of apnoea produced by the drug. An initial bradycardia was followed by tachycardia as relaxation of the skeletal muscles occurred. Cardiac arrhythmias such as ventricular extrasystoles, atrial standstill and nodal rhythm were common during the period of bradycardia. When the barbiturate was given before the relaxant, similar though less pronounced blood pressure changes were observed, but arrhythmias were not seen during the period of bradycardia. Continuous drip infusion of suxamethonium produced no change in pulse rate but was associated with a sustained rise in
blood pressure. Calvert and Morgan (1954) found a rise in blood pressure after the administration of suxamethonium but considered that it was due to hypercapnia and could be abolished by improving the pulmonary ventilation. Martin (1958) demonstrated that suxamethonium can induce cardiac arrhythmias and these findings have been confirmed by Bullough (1959) and Lupprian and Churchill-Davidson (1960) under reasonably controlled conditions.

In view of the confusion arising from all these conflicting reports it was decided to carry out an experimental and clinical investigation into the effects of suxamethonium on the cardiovascular system in animals and in man. The results of the initial experimental work in cats are reported below and details of the other investigations will be reported later.

METHODS

For experiments on intact cats anaesthesia was induced by the intravenous injection of thiopentone sodium and the trachea cannulated. After cannulation apnoea was produced by the further intravenous injection of a small quantity of thiopentone sodium and maintained by slight hyperventilation of the lungs using a mechanically interrupted flow of a nitrous oxide and oxygen mixture. In most experiments carotid arterial blood pressure was recorded on a kymograph from a mercury manometer, but in the remainder an electromanometer was used and the arterial pressure recorded together with a standard limb electrocardiogram on a direct-writing instrument (Cambridge Instrument Company Ltd.). The respiratory movements were recorded from a stethograph-tambour system. The vagus nerves were exposed in the neck and when sectioned they were divided at the level of the cricoid cartilage of the larynx. The splanchnic nerves were exposed through an incision parallel to and about 1 cm ventral to the line of the transverse processes of the vertebrae. Stimulation of the peripheral ends of the splanchnic nerves was performed after dividing the nerves at the level of the diaphragm.

For spinal preparations anaesthesia was induced with ethyl chloride and maintained with ethyl ether. After section of the spinal cord at the level of the foramen magnum the anaesthetic was discontinued and the lungs ventilated with a mechanically interrupted flow of oxygen. The vagus and splanchnic nerves were prepared as in the intact anaesthetized cats.

In both the anaesthetized cats and in the spinal preparations all drugs administered after the induction of anaesthesia were given through a polyethylene catheter introduced into the posterior vena cava from an exposed femoral vein. Nerves were stimulated by means of an induction coil, the primary coil of which was connected to a 2-volt accumulator battery.

RESULTS

Injection of suxamethonium in anaesthetized cats.

The injection of 1 mg/kg of suxamethonium chloride produced a sharp fall in the arterial blood pressure which was immediately followed by an almost equally rapid rise to well above the pre-injection level (fig. 1). The blood pressure then fell and became stable at the pre-injection level 2 to 3 minutes after the injection of the drug. The initial fall in pressure coincided with the fasciculation of the muscles and was sometimes associated with a slight, transient decrease in the heart rate, but more commonly the heart rate was increased. Subsequent injections of 1 mg/kg of the drug, given at 5 to 10 minute
intervals, produced similar effects but the magnitude of the responses decreased until after five or six doses had been given only slight blood pressure changes were produced.

Similar results were obtained when suxamethonium was given in doses of 2 mg/kg and 4 mg/kg.

Division of the vagus nerves prior to the injection of suxamethonium had no effect on the nature of the responses obtained but the magnitude of the secondary rise in the blood pressure was increased.

The injection of 1 mg/kg of atropine sulphate was sufficient to block vagal conduction, as was shown by the absence of response to electrical stimulation of the peripheral end of the cut vagus. After this the initial sharp fall in the blood pressure produced by suxamethonium was abolished, but the secondary rise in pressure still occurred (fig. 2).

Hexamethonium bromide, when given before suxamethonium in doses large enough to abolish the blood pressure response to stimulation of the peripheral ends of the cut splanchnic nerves, caused the injection of the suxamethonium to be followed by a gradual decline in the blood pressure. It required up to 20 mg/kg of hexamethonium to produce the desired block. The fall in pressure was succeeded by a slow recovery (fig. 3).

The blood pressure changes produced by the injection of suxamethonium were completely abolished by the prior administration of both hexamethonium and atropine (fig. 4).

Injection of suxamethonium in spinal cat preparations.

The results obtained in the spinal cat preparations were similar to those obtained in the anaesthetized cats, but the magnitude of the various changes was not so great.

Effect of suxamethonium on the heart rate of anaesthetized cats.

Standard limb lead electrocardiograms were recorded from five anaesthetized cats and each animal was given seven doses of suxamethonium,
an interval of 5 minutes being allowed between each dose. It was found that the effect of suxamethonium on the heart rate was very variable. In three cats each injection of suxamethonium was followed by tachycardia, while one animal showed bradycardia after each dose of the drug. In the fifth animal the first four doses and the seventh dose were followed by tachycardia, while the fifth and sixth doses produced bradycardia.

DISCUSSION

The experiments described above demonstrate that, as might be expected from its close chemical relationship to acetylcholine, suxamethonium produces both nicotinic and muscarinic effects on the cardiovascular system of the cat. It has become obvious that much of the confusion arising from the reports of earlier workers (Bovet et al., 1949, 1951; Thesleff, 1952; Paton, 1953; Somers, 1953; Beretervide, 1955) is due to their failure to record whether the experimental animals used in their studies were or were not atropinized.

The electrocardiographic studies indicate that the response to suxamethonium, even in cats, may differ from one individual animal to another. Moreover, although every effort was made to keep the depth of anaesthesia and the ventilation constant throughout each experiment it is possible that variations in factors such as these may be responsible for variation in the response to the neuromuscular blocking drug.

The nicotinic and muscarinic actions of suxamethonium have been demonstrated both in spinal cat preparations and in cats anaesthetized with a thiopentone, nitrous oxide and oxygen sequence, so that it is likely that they occur whatever anaesthetic agents are employed although these agents may, of course, modify the response obtained.

The question of whether nicotinic and muscarinic effects are produced by suxamethonium in animals other than cats remains to be answered. However, available evidence suggests that these effects occur both in other species of animals and in man. Stevenson (1960) has shown that the rise in arterial blood pressure seen in dogs after the administration of suxamethonium is due to ganglionic stimulation and adrenaline release. Work in progress has shown that a similar rise in blood pressure is produced in horses (fig. 5) and can be prevented by the administration of hexamethonium before the injection of the suxamethonium (fig. 6). In man, the well-known bradycardia which may follow the injection of suxamethonium (Leigh et al., 1957; Bullough, 1959; Lupprian and Churchill-Davidson, 1960)

![Fig. 5](image_url)

**Fig. 5**

Effect of 0.15 mg/kg of suxamethonium chloride in a horse anaesthetized with thiopentone, cyclopropane and oxygen (tracings as in fig. 1). Spontaneous breathing throughout. Horizontal bar indicates injection of suxamethonium 80 mg. Vertical bar indicates fasciculation.
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FIG. 6
Effect of 0.15 mg/kg of suxamethonium chloride in the same horse as in fig. 5 after the administration of hexamethonium bromide. Horizontal bar indicates injection of suxamethonium 80 mg, 4 minutes after 2 g of hexamethonium bromide.

FIG. 7
Effect of stimulation of peripheral end of cut right vagus nerve in an anaesthetized cat.

may well be the result of a nicotinic and/or muscarinic action of the drug since the e.c.g. pattern produced can be imitated in cats (Adams and Hall, unpublished data, 1960) by electrical stimulation of the vagus nerve (fig. 7).

CONCLUSIONS
Under the experimental conditions of this study, suxamethonium was shown to have nicotine-like and muscarine-like activity in cats. It is suggested that suxamethonium produces similar effects in other animals and in man.

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REFERENCES

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SOMMAIRE


Sous ces conditions le suxaméthonium montre une action analogue à celles de la nicotine et de la muscarine. Les auteurs estiment que le suxaméthonium produit des effets similaires sur d'autres animaux et sur l'homme.

ZUSAMMENFASSUNG


Unter diesen Bedingungen zeigte Suxamethonium eine Nikotin- und Muskarin-ähnliche Wirkung. Es wird angenommen, dass Suxamethonium ähnliche Wirkungen bei anderen Tieren und beim Menschen hervorruft.

BOOK REVIEW


This book has been written primarily for the clinician and more specifically for postgraduate students studying for the Diploma in Psychological Medicine. It is mainly non-technical in its approach dealing only briefly with recording techniques. The normal and abnormal findings are supported by many typical records of eight-channel tracings and there are numerous references to the more detailed literature to allow follow-up of specific points of interest.

Anaesthetists will be disappointed to find only two references dealing specifically with the use of electroencephalography in anaesthesia. Its value in monitoring variations in levels of anaesthesia refers to a paper published twelve years ago. Also mentioned is the use of electroencephalography to indicate whether the blood supply of the brain is adequate during operations where whole body perfusion is being performed with extracorporeal circulation.

The principal value of this book is that it presents a brief but comprehensive survey of the clinical conditions in which electroencephalography is likely to prove of use in diagnosis. These indications are presented fairly and without undue enthusiasm. This book can be recommended to the anaesthetist who wishes to explore the value of electroencephalography before and after surgery, but other specialized books deal more specifically with anaesthetic agents and electroencephalography.

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