ANTICHOLINESTERASES AND MUSCLE RELAXANTS

BY

B. G. B. LUCAS, F.F.A.R.C.S., M.R.C.S., D.A.

AND

S. MILES, M.B., M.Sc., D.T.M.&H.

(From the Chemical Defence Experimental Establishment,
Porton)

The muscle relaxants commonly used in anaesthesia achieve their action either by competing with acetylcholine at the motor end-plate—for example, gallamine and tubocurarine—or by persistently depolarizing the motor end-plate and rendering it inexcitable to acetylcholine—for example, succinylcholine and decamethonium iodide (Paton, 1953). Normal neuromuscular transmission is dependent upon the liberation of acetylcholine, which transmits the stimulus to the muscle and is thereafter immediately neutralized by the enzyme cholinesterase, which is normally present in excess. If neutralization does not take place the accumulation of acetylcholine permanently depolarizes the motor end-plate, so preventing the passage of further impulses, and produces a paralysis (Feldberg, 1951). The competitive blocking agents gallamine and tubocurarine antagonize the action of acetylcholine, whereas succinylcholine acts in the same way as an accumulation of acetylcholine, and its hydrolysis is similarly dependent upon the presence of cholinesterase, though at a slower rate (Bovet *et al.*, 1951). Decamethonium iodide, although also achieving its effect by depolarization, is not dependent upon the presence of cholinesterase for its removal (Paton and Zaimis, 1949).

The amount of cholinesterase in the body may alter the duration of action of some relaxants, and it would therefore seem that when using these drugs in cases in which the blood cholinesterase has been lowered by previous exposure to anticholinesterase substances—for example, certain insecticides—varying modifications of dosage might be needed. To determine whether in fact such modifications were necessary a comparison has been made of the periods of respiratory paralysis following intravenous injection of comparable dosages of tubocurarine, gallamine, decamethonium iodide, and succinylcholine in Rhesus monkeys before and after they received a standard dose of a known anticholinesterase. The chosen compound was sarin (*iso*-propyl-methyl-phosphono-fluoridate), which was given subcutaneously in a dose of two-thirds of the LD_{50} (the LD_{50} being the dose which is lethal to 50% of monkeys of the same species in a given series). This dosage was sufficient to cause marked symptoms of miosis, salivation, respiratory distress, and muscular fibrillation.

Technique

Rhesus monkeys of approximately 4 kg. were anaesthetized with thiopentone, 0.1 g. intravenously, and intratracheal intubation was performed with a close-fitting polythene cannula, through which the animal was ventilated at a rate of 18 a minute and a stroke volume of 50 ml. by means of a standard respiratory pump. A pneumograph was attached to the chest and a continuous record of respiratory movement obtained. The relaxant under investigation was then injected, after which 1 ml. of blood was withdrawn for plasma cholinesterase estimation. At five-minute intervals the respiration pump was disconnected for 30 seconds to

ascertain whether spontaneous respiration had returned. The time of respiratory paralysis in all experiments was taken as the time from the injection of the relaxant to the re-establishment of effective natural respiration—that is, a rate and an amplitude of respiration which would lead to recovery without further application of the pump. At the end of each experiment a second 1-ml. sample of blood was withdrawn for plasma cholinesterase estimation.

The relaxants were investigated in pairs—namely, tubocurarine and decamethonium iodide, gallamine and succinylcholine—on two groups of 10 monkeys as follows:

1st week	..	Gallamine	}	5 monkeys
2nd "	..	Succinylcholine		
Monkeys then	given	sarin		
3rd week	..	Gallamine		
4th "	..	Succinylcholine	}	5 monkeys
1st week	..	Succinylcholine		
2nd "	..	Gallamine		
Monkeys then	given	sarin		
3rd week	..	Succinylcholine	}	
4th "	..	Gallamine		

Similarly, a further 10 monkeys were used for the remaining pair of relaxants.

The dosages of relaxants used were as follows: tubocurarine, 1 mg./kg.; gallamine, 4 mg./kg.; decamethonium iodide, 0.75 mg./kg.; succinylcholine, 60 mg./kg. These dosages were selected, after preliminary investigations, to give 30 to 90 minutes' respiratory paralysis.

Immediately after the completion of each experiment the plasma cholinesterase estimations were carried out by Ammon's modification of Warburg's manometric method (Ammon, 1933).

Results

The results showed that there was no influence of one relaxant upon another in any experiment, and the four agents could therefore be considered independently. As

Table of Results

Monkey	Period of Respiratory Paralysis before Exposure (min.)	Days after Exposure	Period of Respiratory Paralysis after Exposure (min.)	Change (min.)
<i>Tubocurarine</i>				
1	85	2	70	-15
2	115	3	75	-40
3	75	4	40	-35
4	90	4	65	-25
5	85	4	55	-30
6	75	7	100	+25
7	65	7	75	+10
8	85	8	70	-15
9	85	8	75	-10
10	75	10	70	-5
<i>Decamethonium Iodide*</i>				
11	30	3	25	-5
12	35	3	35	0
13	15	3	10	-5
14	30	4	40	+10
15	30	4	25	-5
<i>Gallamine,†</i>				
16	95	2	80	-15
17	85	3	75	-10
18	100	4	65	-35
19	110	5	95	-15
20	95	6	75	-20
21	75	10	75	0
22	105	12	90	-15
23	110	13	90	-20
24	105	13	90	-15
25	80	14	85	+5
<i>Succinylcholine</i>				
26	55	3	70	+15
27	35	3	55	+20
28	40	4	55	+15
29	35	5	55	+20
30	35	7	65	+30
31	35	7	45	+10
32	50	11	55	+5
33	35	11	35	0
34	35	12	35	0
35	30	13	30	0

* In this group, there being no significant changes in respiratory paralysis after sarin within 4 days of exposure, it was unnecessary to expose further animals.

can be seen from the Table, with tubocurarine and gallamine there was a significant decrease in the period of respiratory paralysis after sarin, whereas with succinylcholine there was a significant increase. This effect of sarin was temporary, the period of respiratory paralysis in general showing less change with a longer period of delay. Sarin had no appreciable effect on the respiratory paralysis following decamethonium iodide.

Cholinesterase Estimations.—The results obtained from the plasma cholinesterase estimations were so anomalous that no attempt was made to correlate them with the periods of respiratory paralysis. There was a wide variation between individual monkeys in their clinical response, as well as in the degree of blood cholinesterase reduction produced by sarin.

Discussion

The results of this investigation are in accordance with current theories of neuromuscular block (Paton, 1953). Tubocurarine and gallamine achieve their action by inhibiting acetylcholine at the neuromuscular junction, and this effect is antagonized by sarin. The duration of the block with succinylcholine is governed by the speed with which the drug is hydrolysed in the blood and at the end-plate; sarin, by preventing hydrolysis, prolongs the action. Since decamethonium iodide acts not by preventing the action of acetylcholine but by mimicking it, and is not destroyed by cholinesterase, anticholinesterases have no effect. The experiments showed that these changes were more marked when the relaxant was given soon after exposure to the anticholinesterase and diminished with the passage of time, presumably owing to the gradual regeneration of cholinesterase to effective physiological levels.

It is interesting to note the large dose of succinylcholine needed to produce respiratory paralysis in the monkey, approximately ten times the dose for man. There was much less species difference in the dosages of the other three drugs.

Conclusions

With the exception of decamethonium iodide, the duration of action of the relaxants commonly used in anaesthesia appears to be modified temporarily by the effects of anticholinesterase intoxication. With the extended use of these substances as insecticides the possibility of inadvertent poisoning must be considered (Barnes and Davies, 1951) if a relaxant has to be used. This may be of particular importance to Service medical officers and others who may be called upon, in the event of war, to anaesthetize casualties who have been exposed to sarin.

Summary

A description is given of a series of simple experiments designed to determine the effect of intoxication with sarin on the duration of muscular relaxation produced by tubocurarine, gallamine, succinylcholine, and decamethonium iodide.

The duration of the respiratory paralysis induced by tubocurarine and gallamine is decreased, that produced by succinylcholine is increased, and the effect of decamethonium iodide is unchanged following sarin.

The clinical implications of these results are discussed.

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FAMILIAL HYDRONEPHROSIS

BY

R. B. RAFFLE, M.D., M.R.C.P.

South Shields

The coincidence of more than one case of hydronephrosis in a family is rare enough to attract attention. The incidence of non-calculous hydronephrosis in the family here reported is remarkable, and in view of its bearing on the aetiology of non-calculous hydronephrosis in general this occurrence is worthy of record.

Details of Family.—The constitution of the family is shown in the accompanying diagram. All the members of the family other than the four patients here described are apparently healthy and no other congenital abnormalities are known. There was no consanguinity.

Genealogical tree of family, showing distribution of cases. Ages at time of writing in parentheses.

Case 1

An unmarried girl of 19 was first seen in April, 1951. Her only complaint was of embarrassment occasioned by a generalized and gradually progressive abdominal swelling, which she had first noticed three years previously. The rate of enlargement had been noticeably greater in the preceding three months. She had no other complaints, and, in particular, there was no history of pain or disturbance of micturition. There had been no previous illnesses.

Examination revealed abdominal enlargement almost to the size of a full-term pregnancy, and on palpation this appeared to be due to a cystic swelling, localized mainly in the lower abdomen and extending up over the whole of the right side of the abdomen.

Straight x-ray examination showed a complete absence of gas and bowel shadows in the right half of the abdomen, and the liver, renal, and psoas outlines were not visible. All the bowel shadows were displaced to the left, apparently by a large fluid-containing cyst which was thought to be probably ovarian.

Laparotomy on May 3 revealed the tumour to be a massive right-sided hydronephrosis which contained 11 pints (6.2 litres) of fluid. Practically nothing was left of the normal renal tissue. The tumour was removed. The ureter was not dilated. No cause for the hydronephrosis was discovered. Post-operative progress was satisfactory and the patient was discharged from hospital two weeks later, since when she has remained well.

Case 2

A female infant was delivered normally at full term in February, 1953. Her birth weight was 5 lb. 2 oz. (2.3 kg.).