USE OF A SUCCINYLCHOLINE EXTENDER *†‡

JOHN ANTONETTI, M.D., ROBERTO OTTOLENGHI, M.D., AND ROBERT D. DRIPPS, M.D.

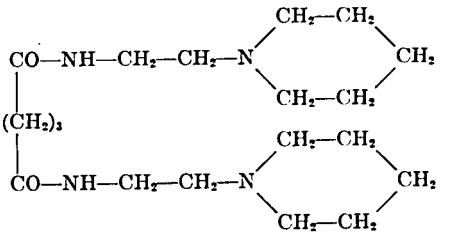
Philadelphia, Pennsylvania

ANECTINE® (succinylcholine chloride) has become established as a useful drug. Its brevity of action is one of its assets, yet, on occasions, so brief is the period of muscular relaxation during intubation of the trachea, for example, that the patient coughs, strains, or "bucks" following introduction of the endotracheal tube. This Valsalva-like response can be harmful to an individual with poor circulatory reserve. A few more minutes of relaxation, therefore, might be desirable.

Ellis and co-workers (1, 2) have synthesized certain amide analogs of succinylcholine which appear capable of prolonging the neuromuscular blocking action of succinylcholine. This report deals with a clinical evaluation of one of these compounds, No. 50–354.§ Our results indicate that the substance can double or triple the duration of anectine in anesthetized man. Its effects have been studied in a series of 77 patients.

CHEMISTRY AND PHARMACOLOGY

The structural formula for compound 50-354 is:



It is a white, crystalline solid, extremely soluble in water and alcohol, not destroyed by autoclaving at 15 lbs. for 20 minutes, M.W. = 352.2, M.P. 134 to 135 C.

* From the Department of Anesthesiology, Hospital of the University of Pennsylvania, and the Harrison Department of Surgical Research, University of Pennsylvania School of Medicine.

† This study was supported (in part) by the Wellcome Research Laboratories.

‡ Accepted for publication September 21, 1954.

According to laboratory data obtained from anesthetized dogs and rabbits: (1) it intensifies and prolongs the skeletal muscle paralysis produced by anectine; (2) it potentiates the neuromuscular blocking action of decamethonium but in doses 10 to 100 times larger than those required to prolong anectine; (3) it has an anticurare action similar to that of prostigmine® and tensilon, although this effect amounts only to one third or one fifth the activity of the former compounds. (4) At high dosage levels, it shows a transient neuromuscular blocking action of its own.

Anticholinesterase drugs can produce all of the above. One discrepancy in this explanation, however, is the failure to find potentiation of the muscarinic actions of acteylcholine in the intact cat and dog.

METHODS

Forty-one anesthetized patients received 20 mg. of anectine intravenously. The duration of apnea was determined. Ten to thirty minutes later, and with every effort made to maintain the same plane of anesthesia, 20 mg. of anectine plus varying amounts (20 to 60 mg.) of compound 50-354 were injected intravenously. Again, the duration of apnea was recorded. Changes in blood pressure and pulse rate were noted. The age range of the patients was from 19 to 69 years; 35 were females. All but 1 of the group were classed as physical status 1 or 2, according to the American Society of Anesthesiologists' criteria. All but 2 of the patients received morphine sulfate or meperidine hydrochloride together with atropine sulfate or scopolamine hydrobromide, intramuscularly, approximately 1 hour prior to induction of anesthesia. Twenty-three cases received ethyl ether as the primary anesthetic agent; in 7, cyclopropane was administered; 8 received thiopental and nitrous oxide-oxygen and 3 received a cyclopropane-ethyl ether mixture. Depth of anesthesia varied from plane 1 of the third stage to plane 3, with only 2 patients in the third plane of surgical anesthesia.

To test the possibility of a cumulative action of anectine, 2 identical doses of this drug were administered to 17 patients at ten minute intervals. Again the period of apnea was measured. Paired doses of 20, 30, and 40 mg. of anectine were administered in this fashion. The duration of apnea from a 20 mg. dose of anectine appears greater in our series than one might anticipate from current clinical reports on this drug. Use of controlled respiration during the period of apnea can cause reduction in arterial blood pCO_2 and prolongation of apnea can result. Excessive ventilation, therefore, may offer a partial explanation for the duration of apnea reported.

A group of 19 additional anesthetized patients received compound 50-354 alone in an effort to determine the effects of this drug on respiration, blood pressure, and pulse rate.

RESULTS

Table 1 indicates the effect of various doses of compound 50-354 on the duration of apnea produced by 20 mg. of anectine administered intravenously. With each patient serving as his own control, it is evident that compound 50-354 potentiated the respiratory effect of anectine. The larger the dosage of compound 50-354, the greater was this potentiation until 50 to 60 mg. doses were reached. A plateau effect was noted at this dosage range. There did not appear to be any striking effect of the anesthetic agent on the duration of apnea.

Table 2 presents data on the duration of apnea to be expected by the repeated injections of anectine alone. The comparability is reasonably good and justifies the belief that repetition of anectine as described in table 1 was not responsible for the increased period of apnea noted when compound 50-354 was added. To test this further,

TABLE 1

EFFECT OF COMPOUND 50-354 ON THE DURATION OF APNEA PRODUCED BY 20 MG. OF ANECTINE ®

I.V. Dose (mg.)	No. Patients	Average Age	Average Wt. (lbs.)	Average Duration of Apnea (sec.)			
				Anectine Alone		Anectine + 50-354	
					Range		Range
20	12	43	137	161	(0–435)	283	(0–504)
30	7	41.4	141	140	(60–195)	360	(240–485)
40	6	44.5	136	152	(90–200)	459	(230–665)
50	7	34.3	136	181	(100–265)	663	(420–1,190)
60	9	47	145	134	(0–270)	515	(375–805)

injections of 30 and 40 mg. of anectine were made. These resulted in comparable durations of apnea (table 2).

In 5 of the 41 patients, a transient (5 to 10 minutes) decrease in blood pressure was observed following the intravenous injection of compound 50-354 plus anectine. The dose of the former drug did not appear to play a part since 2 instances of hypotension were noted after 20 mg. of 50-354 while 2 patients receiving 60 mg. showed a similar decrease in blood pressure. The greatest decrease was from 118/80 to 70/40 in a 41 year old woman, the only patient whose hypotension caused concern. Six of the 41 individuals responded to the combination injection with a slowing of the cardiac rate. Again, dosage of compound 50-354 seemed unimportant. Bradycardia without hypotension occurred in 4 patients. The slowed rate persisted for 5 to 15 minutes. The anesthetic agent did not appear to influence either the hypotension or the heart rate response. The intravenous

injection of 0.4 mg. of atropine reversed the bradycardia in the 1 patient in which this was tried.

Since anectine *per se* rarely causes hypotension, compound 50–354 alone was injected intravenously. A marked decrease in blood pressure occurred in 3 of 19 individuals, with a moderate decline in 4 additional patients. Pulse rate decreased in 13 of the 19, a marked fall occurring in 6. The dosage range of 50–354 was 20 to 60 mg. Neither dosage of 50–354 nor type of anesthetic agent appeared to affect these responses, although thiopental was used in only 1 patient. Spontaneous recovery of blood pressure and pulse rate to control levels occurred within 5 to 20 minutes.

The duration of action of compound 50–354 so far as its ability to potentiate anectine was concerned was difficult to determine. Three patients received additional 20 mg. injections of anectine intravenously

TABLE 2

EFFECT OF REPEATED DOSES OF ANECTINE (10-MINUTE INTERVALS) ON THE DURATION OF APNEA PRODUCED BY THIS DRUG

	1st Injection	2nd Injection
(A) 20 mg. of Anectine I.V. (6 subjects)		
Average duration apnea (sec.)	208	182
Range (sec.)	0–515	0–390
(B) 30 mg. of Anectine I.V. (6 subjects)		
Average duration apnea (sec.)	265	312
Range (sec.)	180–510	215–510
(C) 40 mg. of Anectine I.V. (5 subjects)		
Average duration apnea (sec.)	324	365
Range (sec.)	200–550	210–745

at varying periods of time. Prolongation of action of anectine was noted at 15 minutes but not at 40 minutes after administration of compound 50–354.

SUMMARY AND CONCLUSIONS

Compound 50–354 can increase the duration of action of anectine at least so far as block of respiratory muscles is concerned. Whether the drug will have a place in clinical anesthesia is uncertain. In all probability, should a longer duration of action be desired from anectine, this could be accomplished as readily by increasing the dosage of anectine. The occasional hypotension and bradycardia observed to follow administration of compound 50–354 would also tend to mitigate against its clinical value. Of interest, however, is the ability of one closely related chemical to affect the action of another. Since, except in large doses, compound 50–354 *per se* does not appear to block conduction through the nerve-muscle junction, its potentiation of anectine is intriguing. Our observations in man, supporting those made pre-

viously in animals, may provide further insight into the mechanism of the transmission of impulses from nerve to skeletal muscle.

REFERENCE

1. Ellis, C. H.; Wnuck, A. L.; Fanelli, R. V., and de Beer, E. J.: Comparative Pharmacological Study of the Mono and Dicholine Esters of Succinic Acid, J. Pharm. & Exper. Therap. 109: 83 (Sept.) 1953.
2. Philipps, A. P.: Dicarboxylic Acid Bis-B-Terharyaminoalkyl Amides and Their Quaternary Ammonium Salts as Curare Substitutes, J. Am. Chem. Soc. 74: 4320 (Sept. 5) 1952.