

# THE EFFECT OF SODIUM SUCCINATE AND SOME OF ITS DERIVATIVES ON THIOPENTAL ANESTHESIA \* †

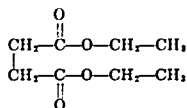
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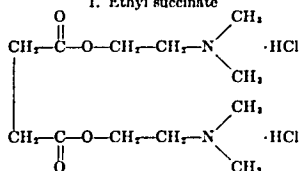
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THE widespread use of the barbiturates as sedative, hypnotic and anesthetic agents has led many investigators into a search for substances which might alter their duration of action. The greatest efforts have been directed toward finding antagonistic substances which might be useful as antidotes for the toxic effects of the barbiturates or for shortening the recovery period following barbiturate anesthesia. Numerous conflicting reports have appeared concerning the activity of sodium succinate as such an antagonist (1-7).

The purpose of this work has been twofold: (1) to reinvestigate the reported antagonistic action of sodium succinate on barbiturate depression, and (2) to study any similar antagonistic action produced by two derivatives of succinic acid, which were thought to represent forms of succinate with higher oil-water partition coefficients, and, consequently, with a greater tendency to become deposited in the central nervous system (approximately 20 per cent lipid). The two substances chosen for this study were the simple ethyl ester of succinic acid (I) and bis-dimethylaminoethyl succinate (II), which was synthesized by one of us (R. P. R.), using a method reported by Fusco *et al.* (8). This latter compound is the tertiary analogue of the neuromuscular blocking agent, succinylcholine (anectine®).



I. Ethyl succinate



II. Bis-dimethylaminoethyl succinate dihydrochloride

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## METHODS

Adult, male albino mice (Carworth), weighing about 25 Gm. were used in this study. These animals were anesthetized with 40 mg. of thiopental § per kilogram of body weight, injected into one of the lateral tail veins. The thiopental solutions were freshly prepared, in a concentration of 2 per cent, before each experiment. The duration of anesthesia was recorded in minutes from the end of the thiopental injection, when the animal was placed in a supine position, to the moment the righting reflex was regained.

The chemical substances under investigation were administered in varying doses by one of two methods: (1) intra-abdominally, five minutes before the intravenous injection of thiopental, and (2) intravenously, immediately following the induction of anesthesia by the thiopental.

The sodium succinate was used throughout in a 5 per cent aqueous solution. Since ethyl succinate is insoluble in water it was necessary to prepare a 5 per cent emulsion in 1 per cent aqueous polyvinyl alcohol. This latter substance was shown to have no effect on the mean duration of anesthesia. The bis-dimethylaminoethyl succinate dihydrochloride was used in 2 per cent aqueous solution for intra-abdominal injections, and in 4 per cent aqueous solution for intravenous injections.

## RESULTS

1. *Controls.* All of the data are presented in table 1. From 6 to 12 control animals (that is, those receiving 40 mg. per kilogram of thiopental alone) were used with each experiment. For the pooled group of 86 controls the mean duration of anesthesia  $\pm$  the 95 per cent confidence limits was  $6.88 \pm 0.45$  minutes.

2. *Sodium succinate, ethyl succinate, bis-dimethylaminoethyl succinate.* The substances under investigation, when administered alone in the dosages subsequently used, produced no signs of depression of the central nervous system, which might obscure the end point of recovery from the barbiturate. It may be observed (table 1) that sodium succinate, when given intra-abdominally in a dose of 500 mg. per kilogram, had no effect on the duration of anesthesia. However, when sodium succinate was administered intravenously in a dose of 125 mg. per kilogram, the mean anesthesia time was significantly increased rather than decreased. Isotonic saline solution, given intravenously in the same volume as the sodium succinate, had no influence on the duration of anesthesia.

Ethyl succinate, in a dose of 500 mg. per kilogram given intra-abdominally, was found to produce a highly significant prolongation of thiopental anesthesia, roughly twofold.

§ We are indebted to the Abbott Laboratories, North Chicago, for generously supplying us with the thiopental (pentothal® sodium) used in this study.

Finally, the bis-dimethylaminoethyl succinate in a dose of 200 mg. per kilogram given intra-abdominally, significantly prolonged thiopental anesthesia, while the same dose, administered intravenously, had no influence on the duration of anesthesia.

### DISCUSSION

In general, those reports in the literature tending to substantiate Soskin and Taubenhaus' original finding on the antagonism between succinate and barbiturates have indicated that the antagonism is less striking than previously stated (2, 4). In those studies on human beings and experimental animals, concerning the influence of succinate on the duration of hypnosis produced by the barbiturates or on the

TABLE 1

INFLUENCE OF SODIUM SUCCINATE AND TWO ANALOGUES ON THE DURATION OF ANESTHESIA INDUCED BY 40 MG. PER KILOGRAM OF THIOPENTAL (INTRAVENOUSLY) IN MICE

Treatment	Dose mg./kg.	Route of Adminis- tration	Number of Animals	Mean Duration of Anesthesia $\pm$ 95% Confidence Limits	P*
Controls (40 mg./kg. of thio- pental alone)	—	—	86	6.88 $\pm$ 0.45 min.	—
Sodium succinate	500	IP†	12	7.28 $\pm$ 1.74	> .5
Sodium succinate	125	IV‡	12	13.57 $\pm$ 4.82	.01 > p > .001
Isotonic saline	0.0025 cc./gm.	IV	18	6.65 $\pm$ 1.42	> .5
Ethyl succinate	500	IP	19	14.07 $\pm$ 3.72	< .001
Polyvinyl alcohol	0.01 cc./gm.	IP	6	6.23 $\pm$ 1.06	> .5
Bis-dimethylamino- ethyl succinate	200	IP	15	12.57 $\pm$ 4.39	.01 > p > .001
Bis-dimethylamino- ethyl succinate	200	IV	11	5.85 $\pm$ 1.87	> .5

\* P = probability of chance occurrence calculated from Student's t. Values less than 0.05 are considered statistically significant, that is, respective treatments are considered significantly different from the controls.

† Intra-abdominal administration.

‡ Intravenous administration.

rate of disappearance of the barbiturates from the bloodstream, either no antagonism was observed or, in certain instances, equivocal results were obtained (5, 6, 7). In this investigation, it was obvious not only that no antagonism exists between succinate and thiopental, but that a significant potentiation of anesthesia is produced when succinate is administered intravenously immediately after the thiopental. Furthermore, it has been found in this work that derivatives of succinate which, conceivably, would accumulate in the central nervous system in greater concentration than sodium succinate, are devoid of any antagonism for thiopental anesthesia, and demonstrate a significant potentiation of this anesthesia.

On theoretical grounds, it has been possible to postulate that suc-

inate would antagonize barbiturate action. Thus, Quastel (9) has pointed out that if succinate oxidation could give rise to adenosine triphosphate formation, the depressed state of the central nervous system attributable to narcotics, in general, would be lifted. On the other hand, Bain (10) has suggested that the failure of succinate as an analeptic for barbiturates may be explained by the demonstration of an uncoupling action (by the barbiturates) on the uptake of inorganic phosphate associated with the oxidation of succinate (and other substrates). This, however, would hardly aid in an understanding of the potentiating action observed. This phenomenon requires further study in regard to the metabolism and distribution of thiopental.

#### SUMMARY

Sodium succinate, ethyl succinate, and bis-dimethylaminoethyl succinate were investigated for possible antagonistic effects on the duration of anesthesia induced by thiopental in mice. No such antagonism was observed, but rather, in certain doses and by certain routes of administration, all three of these succinate derivatives significantly prolonged the thiopental anesthesia.

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