PRELIMINARY STUDIES ON THE MUSCLE RELAXING PROPERTIES OF CHLORPROMAZINE

SHELDON KOTKIN, M.D., ERWIN LEAR, M.D., ALBERT E. CHIRON, M.D.
IRVING M. PALLIN, M.D., DONALD DICKLER, M.D.

During the early investigative work on chlorpromazine, French authors reported a muscle relaxing effect of this drug on laboratory animals (1). In their study, the French used Flaxedil®, a curare-like preparation, and showed that chlorpromazine enhanced its muscle relaxing effect. These data, however, were based upon a limited series of experiments in non-standardized animals. It was felt that further study of any possible muscle relaxing properties of chlorpromazine was indicated. This was undertaken in our laboratory. Succinylcholine chloride was substituted for Flaxedil® in our studies because we had a number of well-standardized animals available.

TECHNIQUE

The head drop test, as described by Varney, Linegar and Holaday, (2) was employed in this experiment. Male adult rabbits which had received almost daily injections of succinylcholine for several months prior to this study were used. Rabbits will frequently show erratic responses to succinylcholine and other muscle relaxants when first exposed to them; hence we found that well-standardized animals were necessary for the experiment.

Succinylcholine chloride (Sucostrin®) was diluted to a uniform strength of 0.6 mg. per milliliter in normal saline solution. The solution was placed in a microburette, and titrated into the ear vein of a rabbit at the rate of 0.1 ml. of solution per 15 seconds, as suggested by Varney (3) of the Squibb Laboratories. The rabbits were lightly restrained to prevent dislodgement of the cannula. The solution was titrated into the rabbit until it was unable to lift its head when gently stimulated. When his test was inconclusive, the appearance of complete flaccidity of the neck muscles was taken as the end point. The needle was then removed from the vein, and the animal was untied and turned on its side. The ability of the animal to right itself from the lateral position was considered to be the recovery end point.

In the course of each individual experiment the procedure was as follows:

1. A selected rabbit was placed on an animal board, restrained, and given a titrated dose of succinylcholine solution until head drop

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was produced. The dosage of relaxant required to produce this effect was recorded. The animal was then turned on its side and the recovery time was determined.

2. An injection of chlorpromazine (Thorazine®) was administered intramuscularly at this time. The dose depended upon the individual experiment, being either 2.5 mg., 5 mg. or 10 mg. per kilogram of body weight.

3. One-half hour after the first experimental run, procedure 1 (above) was repeated upon the same animal, the dosage and recovery time being recorded.

4. At half-hour intervals thereafter, until the conclusion of the experiment, procedure 1 was repeated.

5. The data collected were plotted as time against milligrams of succinylcholine required to produce head drop, as shown in figures 1 and 2.

![Graph](image)

**Fig. 1.** Amount of succinylcholine required to produce head drop is plotted against time. "0" minutes is the time of the first head drop determination. At "5" minutes (as indicated by the arrow) 2.5 mm. per kg. of Thorazine® was injected intramuscularly. At half-hour intervals thereafter, head drop determinations were repeated. The broad striped band indicates the trend of the average values for the complete run. Note the slight potentiation of succinylcholine by chlorpromazine.

Earlier workers had reported that succinylcholine has no cumulative effect (4), and that repeated head drop tests could be done on the same animal almost as frequently as one desired. This statement was checked and found to be not completely true. At intervals of less than twenty minutes between test runs there is apparently some accumulation of drug. At intervals of more than twenty minutes there is no evidence of accumulation, as will be seen in figure 3. The thirty minute interval used in this experiment was chosen with this point in mind.
Results

Examination of figures 1 and 2 shows that there is a definite reduction in the dose of succinylcholine necessary to produce head drop in rabbits treated with chlorpromazine. This is particularly true in the higher dose range of 5 mg. per kilogram of body weight. Similar studies made on rabbits not treated with chlorpromazine showed that the dose of succinylcholine necessary to produce head drop remained relatively constant throughout three hours of repeated tests at half-hour intervals (fig. 3). On the other hand, animals receiving chlorpromazine can be divided into two classes, depending upon their reaction to varying doses of chlorpromazine.

![Key Image](image)

Fig. 2. At "5" minutes (as indicated by the arrow) 5.0 mg. per kg. of Thorazine® was injected intramuscularly. The broad striped band indicates the trend of the average values for the complete run. Note the marked potentiation of succinylcholine by chlorpromazine at this dosage.

In the first group, including most of the animals receiving 2.5 mg. per Kg., there was slight or no potentiation of succinylcholine by chlorpromazine. Any diminution in head drop dosage was fairly consistent but small.

In the second group, consisting largely of animals receiving doses of 5 mg. per kg., there was marked potentiation in all the animals. Succinylcholine required for head drop diminished rapidly within an hour of the intramuscular injection of chlorpromazine, and rose slowly over the next few hours as the effects of the chlorpromazine wore off.

An important point noted was that in those tests where there was no evidence of potentiation, the animals were not depressed by chlor-
promazine. They remained lively, alert, and uneasy throughout the experiment; showed clear, sharp, end points, and recovered within two to six minutes after the experiment had been terminated. Those animals which showed potentiation of the succinylcholine by chlorpromazine were lethargic shortly after the intramuscular injection was made, indifferent to their surroundings and tended to sleep if undisturbed. They were very somnolent and head drop was difficult to determine. We were compelled to depend mostly upon the appearance of flaccidity in the neck muscles for end points. Recovery was also delayed and difficult to determine because the animal, if undisturbed, would sleep on its side and make no attempt to right itself.

The original French research mentioned earlier in this paper had suggested doses as high as 10 mg. per kg. of body weight for potentia-

![Diagram](image)

**Fig. 3.** Four typical curves for head drop dosage of succinylcholine, each showing the effect of a different time interval between successive determinations. With a 10 minute interval there is rapid diminution in head drop dosage with each determination. With a 20 minute interval, there is slight diminution. With 30 and 60 minute intervals there is no diminution. Individual tests are indicated by the various symbols.

tion of Flaxedil® by chlorpromazine (1). In this series we attempted to use dosages of 10 mg. per kg. after the 2.5 and 5 mg. per kg. series had been completed. We found the animals to be so somnolent after this 10 mg. dose that, in most cases, head drop determinations were impossible. Further increase in the dosage of chlorpromazine was discontinued for this reason.

**Discussion**

The findings of this experiment appear to confirm the clinical impression of Lear, Chiron and Pallin (5) that premedication with chlorpromazine lessens the need for muscle relaxants. We have demonstrated a definite potentiation of succinylcholine by chlorpromazine.
This is not meant to imply that the potentiation seen is due to true synergism of the two drugs, since the modes and sites of action of chlorpromazine and succinylcholine are dissimilar. Succinylcholine is a muscle relaxant by virtue of its depolarizing effect upon the motor end plates of peripheral muscle (4, 6, 7). Chlorpromazine has some adrenolytic activity at the effector sites of the autonomic nervous system, but its major site of action is central, in the hypothalamus and/or the ascending reticular activation system (1, 8–11).

Dobkin (12) and his co-workers, using both frog and cat gastrocnemius-stiatic preparations, have shown that neither the competitive curare type of block nor the depolarizing block as seen with C10 are induced by chlorpromazine.

In other words, the potentiation of succinylcholine by chlorpromazine is probably more apparent than real, and is most likely the result of the generalized hypotonicity produced centrally, rather than by any peripheral effect. There seems to be little evidence to the contrary. The parallelism of peak muscle relaxant potentiation with peak generalized hypotonicity is clearly evident. No potentiation is seen in the absence of the sedated state produced by sufficient chlorpromazine. As the hypotonic state produced by chlorpromazine wanes, the muscle relaxant potentiation lessens until at the end of five or six hours, the succinylcholine requirements are close to those at the start of the experiment.

**Summary**

Chlorpromazine enhances the effects of the muscle relaxant succinylcholine. This effect is seen only when sufficient chlorpromazine has been administered to create a hypotonic state.

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**References**

3. Varney, R. F.: Personal communication to the authors.