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Effect on the Electrocardiogram of Coumingine Hydrochloride, a New Alkaloid with Digitalis-like Action.

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Many substances have been found to have a digitalis-like action on the heart. However, until a few years ago, the only known alkaloid showing this effect was erythrophleine. Recently Chen[1] and his colleagues published observations on the potency of a series of natural cardiac *erythrophleum* alkaloids and one derivative. Based on the data in frogs and cats, coumingine hydrochloride, a salt of a new crystalline alkaloid of *Erythrophleum coumingo*,[2] proved to be the most potent of the whole group. Since the effects on the electrocardiogram of this alkaloid have not been studied, they have been made the subject of this investigation. A preliminary report of this study has appeared.[4]

The following experiments were performed: (A) Coumingine hydrochloride* was standardized by the Hatcher and Brody method[3] in 15 adult cats. (B) Electrocardiographic changes recorded during this procedure and also in 4 dogs were studied as well as those taken in another series of 23 dogs following daily intramuscular injections of various fractions of the cat unit per kilogram of body weight. In this latter group, injections were stopped after the onset of P-R prolongation and the daily EKG tracings continued until normal records were obtained. The electrocardiograms obtained in both the intravenous and intramuscular experiments were then compared with control records following injections of a standardized digitalis preparation in 6 cats and 7 dogs under similar conditions. (C) Toxic symptoms which appeared before the conclusion of experiments were noted throughout this study.

All animals showed normal EKG tracings before injections were started. Lead 2 was uniformly used although in many instances

1 Chen, K. K., Hargreaves, C. C., and Winchester, W. T., *J. Am. Ph. A.*, 1938, **27**, 9.

2 Dalma, G., *Boll. Soc. ital. biol. sper.*, 1936, **11**, 791.

3 Hatcher, R. A., and Brody, J. G., *Am. J. Pharm.*, 1910, **82**, 360.

4 Martin, S. J., and Cominole, B., *Am. J. Physiol.*, 1938, **123**, 141.

* Our sample was courteously supplied by Dr. K. K. Chen, the Lilly Research Laboratories, Indianapolis.

leads 1 to 4 were also employed. Dogs used in the intramuscular experiments were trained to lie quietly during EKG recording.

For the cat unit determination, a solution of coumingine hydrochloride crystals 1:100,000 was prepared in warm saline and injected intravenously in cats at a rate of about 0.5 to 1.0 cc per minute. In dogs the strength of the solution for intravenous administration was 1:50,000 and the rate of injection 2 cc per minute. Electrocardiograms were taken at various intervals during a 90-minute period of injection, an average number of 15 readings being recorded for each animal. For daily intramuscular injections, a 1:1000 solution was administered in order to keep the volume of injections small. Electrocardiograms were taken before and in many cases 1 to 4 hours after each daily injection until the end of the experiment. An average number of 20 tracings was recorded on each dog.

Results. A. *Determination of Cat Unit*—The cat unit of coumingine hydrochloride was found to be 0.159 mg per kg of body weight (range 0.102 to 0.184). This figure, which is in close agreement with that reported by Chen,[1] was used as a basis for the doses given in experiments on daily intramuscular injections. Emesis during intravenous injection of coumingine was noted in only 4 of 15 cats.

B. *Changes in the Electrocardiogram*—Electrocardiographic tracings taken every few minutes during the determination of the cat unit of coumingine hydrochloride closely simulated those obtained from digitalized preparations. In order, the following changes in lead 2 were noted in almost all animals studied (Fig. 1): a widening and increase in height of T wave or commonly an absence or inversion of the wave, a progressive slowing of the S-A rhythm, bradycardia, P-R prolongation, intermittent absence of P waves, A-V dissociation, decrease in the height of the R complex with slurring and notching, showers of extraventricular systoles, ventricular tachycardia, and fatal ventricular fibrillation. Occasionally, there were noted extraäuricular systoles and rarely, a widening of QRS_2, and elevation of $S\text{-}T_2$. In the other leads, a slight occasional increase in Q_4 was found.

In the 15 cats and 4 dogs at the rate of intravenous injection of coumingine hydrochloride of about 0.007 to 0.02 mg per kg per minute, definite T-wave changes, P-R prolongation and A-V dissociation appeared on the average of 22, 44, and 53 minutes, respectively. Corresponding changes occurred more rapidly following digitalis injection.

The disturbances in the electrocardiogram of dogs receiving daily intramuscular injections of coumingine hydrochloride were similar

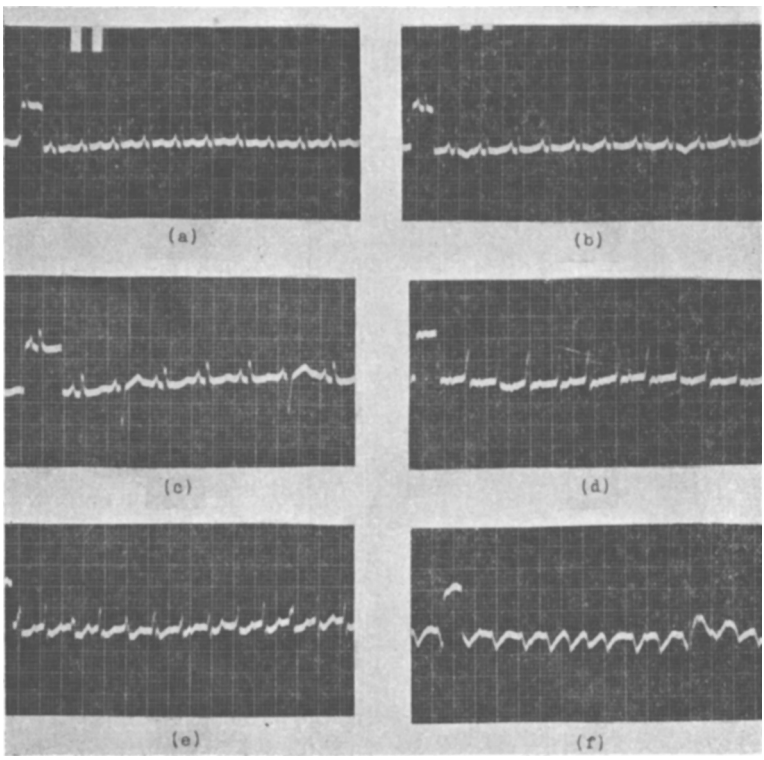

FIG. 1.

Successive electrocardiographic changes recorded on cat 14 during the determination of a unit of coumingine hydrochloride by the Hatcher and Brody method. Lead II: (a) control, (b) disappearance or inversion of the T waves (19 min.), (c) ventricular extrasystoles (25 min.), (d) P-R prolongation and splintering of R wave (46 min.), (e) complete A-V dissociation (50 min.), (f) ventricular fibrillation (67 min.).

to those noted after comparable doses of digitalis. However, there were differences in time of onset and disappearance of effects upon cessation of injection. On the whole, depression of the S-A mechanism and interference of nodal conduction was not as prompt with coumingine hydrochloride as with digitalis (Table I). With the large dose (1 cat unit per kg), P-R prolongation was generally noted within 2 hours when either drug was administered intramuscularly. With smaller doses, however, digitalis effects appeared predominantly earlier. This is true also for the appearance of widened and inverted T waves. After injections were stopped, the return of normal nodal conduction was not significantly faster in dogs given digitalis. The restoration of the T waves, however, was definitely more rapid in those receiving coumingine hydrochloride.

TABLE I.
Comparative Effects of Intramuscular Injections of Coumingine Hydrochloride and Digitalis on Electrocardiogram of the Dog.

Drug injected	No. of dogs used	Dose, cat unit per kg	No. daily injections Avg	Avg time before P-R prolongation, Days	Hr	Avg days required for return to normal of EKG after cessation of injections: P-R prolongation	Avg days required for return to normal of EKG after cessation of injections: T wave changes	Remarks
Coumingine HCl	3	1.0	1		1-2	1.8	16	Total dose given in 2 equal injections 6-8 hr apart. Marked upper gastrointestinal symptoms after first administration.
Digitalis	3	1.0	1		1-2	2.0	22.5	One dog found dead third day after injection.
Coumingine HCl	6	0.3	5.2	5.2		5.1	13.3	Salivation and emesis after 2-5 daily injections. One dog found dead seventh day.
Digitalis	3	0.3	3.6	3.6		5.6	15.6	Nausea and emesis more marked in this group of dogs.
Coumingine HCl	3	0.2	9	9		7.7	14.7	Salivation and emesis only occasionally seen during end of injection period.
Coumingine HCl	3	0.1	16.7	21		4.0	15.6	Diarrhea in 2 dogs after eighth day.
Digitalis	2	0.1	10	11		3.5	21	Occasional emesis seen near end of injection period.

C. *Toxic Symptoms*—Muscular weakness of the leg probably due to pain resulted immediately after intramuscular injection of doses greater than 1 mg per kg. In 24 to 48 hours swelling of the thigh appeared with inflammation and subsequent serosanguinous discharge. Upon cessation of administration, all irritation subsided with no induration. None of the control dogs receiving digitalis intramuscularly in equivalent doses showed local reactions.

Evidence of general toxicity following daily intramuscular injections of coumingine hydrochloride consisted essentially of upper gastro-intestinal irritation manifested by salivation, anorexia, retching, and emesis. Other symptoms, less commonly noted, were transient tachypnoea 1 to 2 hours after injection, mild diarrhea and a variable loss in body weight. The onset of symptoms depended directly upon dosage. They were shown by all dogs receiving sufficient coumingine hydrochloride to induce definite P-R prolongation and were of milder character than those noted in control digitalized dogs.

The cardiac effects of erythrophleum alkaloids at present are merely of academic interest. Our data indicate that in addition to the pharmacological findings of Chen[1] coumingine hydrochloride can induce electrocardiographic changes similar to those of digitalis.

The similarity in these changes may possibly be accounted for by the presence of the sterol ring system in both compounds. However, it will require further chemical research to demonstrate the intimate structural relationship of coumingine hydrochloride to digitalis glucosides.

Conclusions. 1. The parenteral administration of coumingine hydrochloride, a new alkaloid, produced electrocardiographic disturbances in dogs and cats similar to those of digitalis. 2. The cat unit by the Hatcher and Brody method was found to be 0.159 mg per kg, confirming the result of Chen. 3. Daily intramuscular injections in dogs of variable sublethal doses of coumingine hydrochloride revealed that the onset of electrocardiographic disturbances was slower than after comparable doses of digitalis. The rate of disappearance of P.R prolongation after injections were discontinued, was essentially the same. However, the myocardial irritation of coumingine hydrochloride indicated by T-wave changes, was less persistent than after digitalis administration. 4. Toxic symptoms were essentially similar to those noted in digitalized controls but were milder in character. 5. Local inflammatory reaction following intramuscular injection of moderate or large doses of coumingine hydrochloride was marked.