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The expectorant action of cephaeline, emetine and 2-dehydroemetine

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Cephaeline, emetine and 2-dehydroemetine were administered, as the dihydrochlorides, in doses from 0·1 to 81 mg/kg body weight, orally and subcutaneously to 135 rabbits and 92 cats arranged for the collection of respiratory tract fluid. To the extent that comparisons were made, the effects of the three alkaloids were identical. The volume output of respiratory tract fluid was increasingly augmented by doses of from 0·1 to 1·0 mg/kg. No further increase followed administration of higher doses up to the highest non-lethal dose. Doses of from 9·0 to 81 mg/kg were increasingly lethal and increasingly depressed the output of respiratory tract fluid, probably through their cardiotoxic action. Lethal doses were similar for all three alkaloids and by both routes of administration. It is concluded that the expectorant action of ipecacuanha is due in whole or in major part to its content of emetine and cephaeline. The expectorant action of synthetic 2-dehydroemetine is essentially similar to that of emetine and cephaeline.

IPECAC syrup, U.S.P. XVI (1960), is classified as an emetic and expectorant. Boyd (1954) has defined an expectorant as a drug which augments the output of respiratory tract fluid. Oral administration of ipecacuanha has been reported to augment the output of respiratory tract fluid in cats (Van Dongen & Leusink, 1953), rabbits and cats (Perry & Boyd, 1941), and albino rats (Boyd, Palmer & Pearson, 1946), and to lower its viscosity (Basch, Holinger & Poncher, 1941). These results indicate that ipecacuanha could be of expectorant value in the treatment of cough due to irritation of the respiratory airway below the epiglottis from insufficient production of demulcent respiratory tract fluid (Boyd, 1954; Beckman, 1961).

Effects of the alkaloids of ipecacuanha upon the output of respiratory tract fluid have not been previously reported. Assuming that augmentation of the output of respiratory tract fluid by galenical preparations of ipecacuanha was due, in whole or in part, to their content of emetine and cephaeline, it may be estimated from the data of Perry & Boyd (1941) and of Boyd, Palmer & Pearson (1946), that doses of these alkaloids of 1 to 20 mg/kg could have a similar effect. The higher doses in this range could also inhibit the output of respiratory tract fluid through their cardiotoxic and hypotensive actions (Boyd & Scherf, 1941).

We have set out to determine the effect of administration of cephaeline and emetine, two natural alkaloids of ipecacuanha and 2-dehydroemetine (2,3-dehydroemetine, Mebadin), a synthetic alkaloid, prepared by Brossi & others (1959) as the racemic mixture, upon the output of respiratory tract fluid in rabbits and cats.

Methods

The animals used were healthy CBL female cats and male rabbits of 2 to 3 kg weight. Food was withdrawn for 16 hr before intragastric, but not subcutaneous, administration of the alkaloids. The animals

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were anaesthetised with urethane at an average dose of 1·00 g/kg, given intraperitoneally as 4·00 ml/kg of a 25% (w/v) solution in distilled water, with supplementary local procaine as required during the tracheotomy.

The animals were arranged for the collection of respiratory tract fluid by a modification of the technique of Boyd & Perry (1963). The modification consisted of enlarging to 1·25 c.ft the reservoir of conditioned air. This eliminated temporary fluctuations in the temperature and humidity of air inhaled by the animals under study. Air in the reservoir was maintained at 100° F and 99 to 100% relative humidity as read from a built-in wet and dry bulb thermometer. Maintenance of conditioned air was arranged through a thermostat connected with a heater under a vessel partially filled with distilled water, the warm vapour from which was piped into and circulated through the reservoir by a blower.

The volume output of respiratory tract fluid was recorded hourly for a period of 3 hr before, and 4 hr after, drug administration. The output was measured in ml and expressed as ml/kg body weight per 24 hr. Output during the 2 hr immediately preceding drug administration was considered as the control output. This was subtracted from the output each hr after drug administration to obtain a difference. The mean and standard error of these hourly differences were calculated and the mean difference subjected to a "*t*" test of significance (Croxton, 1953).

The three alkaloids were used as dihydrochlorides. Cephaeline, emetine and 2-dehydroemetine were each given by intragastric tube to rabbits in doses of 0·0, 0·1, 0·3, 1·0, 3·0, 9·0, 27·0 and 81·0 mg/kg weight, using 4 to 11 animals per dose and 135 rabbits in all. The same range of doses of 2-dehydroemetine and doses of 0·1 and 0·3 mg/kg of emetine were given orally to 62 cats. An additional 30 cats and 30 rabbits received 2-dehydroemetine subcutaneously in doses of 0·0, 1·0, 3·0, 9·0, 27·0 and 81·0 mg/kg weight. Each dose was dissolved in distilled water and administered in a volume of 1·00 ml/kg except for the highest dose (81 mg/kg) which was given in a volume of 4·00 ml/kg. In animals given distilled water containing no drug, the volume used was 1·00 ml/kg.

Results

All three alkaloids augmented the output of respiratory tract fluid when given by mouth to rabbits in the lower range of doses. Representative data from doses of 1·0 mg/kg of emetine and cephaeline and 3·0 mg/kg of 2-dehydroemetine are illustrated in Fig. 1. The responses to doses of 0·1, 0·3, 1·0 and 3·0 mg/kg did not differ, per dose, amongst the three alkaloids. The mean percentage augmentation of output of respiratory tract fluid by all three alkaloids has been plotted against dosage in Fig. 2. There was a significant positive correlation with log dose over this range.

Oral doses higher than 3·0 mg/kg did not produce a further increase in the output of respiratory tract fluid in the rabbit but rather produced a plateau effect. This extended to and included a dose of 9·0 mg/kg of cephaeline and 2-dehydroemetine and of 3·0 mg/kg of emetine. Higher

doses were within the lethal range and depressed the output of respiratory tract fluid. The regression of effect over the complete range of doses, therefore, was quadratic and represented by the equation

$$Y = a + bX + cX^2,$$

where b is plus and c is minus.

Oral administration of 2-dehydroemetine to cats produced an increase in the output of respiratory tract fluid which was statistically significant at a dose of 1·0 mg/kg (Fig. 3), but not at higher doses. Doses in the lethal range depressed the volume output. Emetine significantly ($P = 0{\cdot}02$) augmented the output of respiratory tract fluid in cats at a dose of 0·3 mg/kg by mouth.

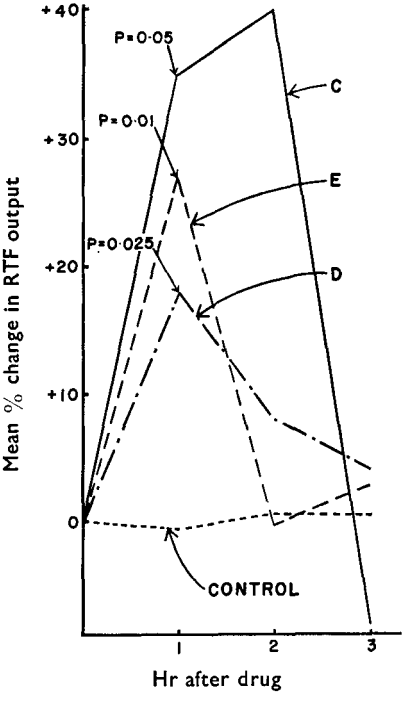

FIG. 1. The effect of representative low oral doses of ipecacuanha alkaloids on the output of respiratory tract fluid in rabbits. C, cephaeline, 1 mg/kg. D, dehydroemetine, 3 mg/kg. E, emetine, 1 mg/kg.

Subcutaneous injection of 2-dehydroemetine augmented the output of respiratory tract fluid at doses of 1·0 and 3·0 mg/kg as shown in Fig. 3. Larger doses had either no significant effect or produced a decrease.

The effect of lethal doses upon the output of respiratory tract fluid was similar for all three alkaloids given orally or subcutaneously to rabbits or cats. The results were averaged and are shown in Fig. 4. The mortality rate from a dose of 9·0 mg/kg was 4%. This figure was due to the death of 1 rabbit at 4 hr after receiving emetine at a dose of 9·0 mg/kg which significantly depressed the volume output of respiratory tract fluid

in the remaining rabbits. A dose of 27 mg/kg killed 42% of animals at 3 to 4 hr and death was preceded by a significant fall in the output of respiratory tract fluid. A similar result was obtained from a dose of 81 mg/kg which killed 75% of animals at 2 to 4 hr after administration.

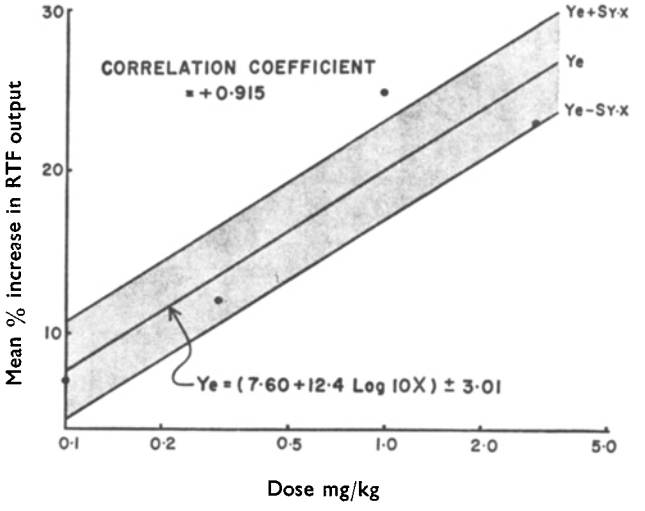

FIG. 2. The regression on dose of mean percentage increases in the output of respiratory tract fluid at 1 hr after oral administration of ipecacuanha alkaloids to rabbits.

The immediate cause of death in animals so observed was cardiac arrest, preceded by tachypnoea, tremors and struggling. Death rates have been collected in Table 1. The incidence of deaths from 2-dehydroemetine given orally to cats and rabbits was essentially similar to that given subcutaneously, the median lethal dose lying between 27 and 81 mg/kg.

TABLE 1. DEATH RATES (% MORTALITY) FOLLOWING ADMINISTRATION OF LETHAL DOSES OF IPECACUANHA ALKALOIDS

Alkaloid	Dose (mg/kg)	Species	Route	Mortailty %
Cephaeline	27	Rabbit	oral	33
Emetine	9	Rabbit	oral	25
Emetine	27	Rabbit	oral	50
Emetine	81	Rabbit	oral	100
2-Dehydroemetine	27	Rabbit	oral	75
2-Dehydroemetine	81	Rabbit	oral	100
2-Dehydroemetine	81	Cat	oral	50
2-Dehydroemetine	27	Rabbit	s.c.	50
2-Dehydroemetine	81	Rabbit	s.c.	75
2-Dehydroemetine	27	Cat	s.c.	25
2-Dehydroemetine	81	Cat	s.c.	50

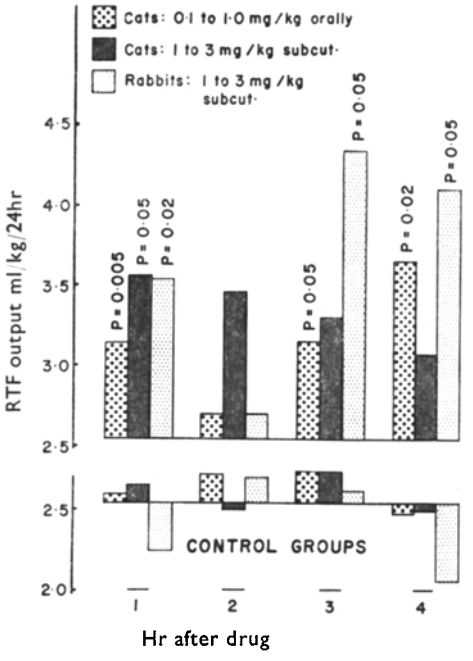

FIG. 3. The mean volume output of respiratory tract fluid after administration of 2-dehydroemetine dihydrochloride to cats and rabbits. The results are shown as changes from a common weighted mean output before drug administration. Mean changes significant at P = 0·05 or less are so indicated. Controls received distilled water only.

Discussion

Perry & Boyd (1941) reported that powdered ipecacuanha, given by stomach tube as a suspension, produced an increase in the output of respiratory tract fluid after administration in a dose of 1 g/kg to cats under urethane anaesthesia. This dose corresponded to 20 mg/kg of total alkaloids calculated as emetine. Doses up to 3–9 mg/kg of the three alkaloids of ipecacuanha herein studied were found to augment the output of respiratory tract fluid. The expectorant action of ipecacuanha, therefore, is due in whole or in part to its content of cephaeline and emetine.

The three alkaloids, after oral administration, had almost identical ability to augment the output of respiratory tract fluid. Over the dosage range 0·1 to 3·0 mg/kg, increase in the output of respiratory tract fluid was positively correlated with log dose. The smallest and largest doses producing an individually significant increase in rabbits were 1 and 9 mg/kg for cephaeline, 3 and 9 for 2-dehydroemetine, and 1 and 3 for emetine. Radomski & others (1952) reported that cephaeline was slightly more potent than emetine as an emetic in dogs, while Herrero & others (1960) found 2-dehydroemetine slightly less potent than emetine in similar

circumstances. The oral emetic dose of all three alkaloids in dogs is about 1 mg/kg, which is similar to the dose which augmented output of respiratory tract fluid in rabbits. Boyd, Daicar & Middleton (1956) have noted that vomiting in cats and dogs is not necessarily accompanied by an increase in the output of respiratory tract fluid. Schwartz & Rieder (1961) found that 2-dehydroemetine is eliminated from tissues of the rabbit more rapidly than emetine.

Doses of all three alkaloids within the lethal range decreased the output of respiratory tract fluid by decreasing the volume of the pulmonary circulation. Cephaeline in an oral dose of 27 mg/kg killed 33% of rabbits, emetine 50% and 2-dehydroemetine 75% with no statistically significant difference between the death rates. The oral MLD of emetine in rabbits has been reported to be between 15 and 20 mg/kg (Spector, 1956). The single intraperitoneal LD50 of cephaeline in the rat is similar to that of emetine (Radomski & others, 1952), while single oral, subcutaneous and intravenous median lethal doses of 2-dehydroemetine in mice are higher than those of emetine (Herrero & others, 1960).

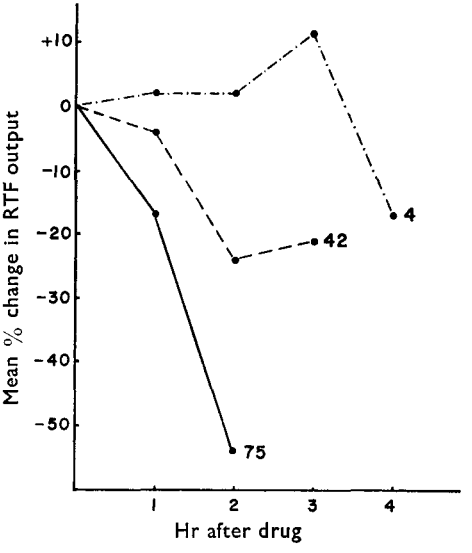

FIG. 4. The mean percentage change in the output of respiratory tract fluid in cats and rabbits after oral and subcutaneous administration of lethal doses of ipecacuanha alkaloids. Figures on the graph are % dead from 9 mg/kg (4%), 27 mg/kg (42%) and 81 mg/kg (75%).

Under the conditions of our experiments cats were more resistant than rabbits to the lethal effect of 2-dehydroemetine. For example, an oral dose of 27 mg/kg killed 75% of rabbits and no cats. The total mortality rate in 16 rabbits given doses of 27 and 81 mg/kg orally or subcutaneously was 75% and in 16 cats 31%, the difference being significant at $P = 0{\cdot}02$. Comparable data for emetine reviewed by Spector (1956) suggests that the rabbit and cat are about equally susceptible to its lethal action.

The death rate to 2-dehydroemetine given subcutaneously to rabbits and cats was insignificantly different from that when given orally. Spector (1956) indicated that the same relationship holds for emetine in frogs, guinea-pigs, rabbits, cats and dogs.

The cause of death from 2-dehydroemetine appeared to be similar to that from emetine, namely a cardiotoxic action. The cardiotoxic action of emetine has been related to an inhibition of oxidation of various substrates by heart homogenates (Marino & Magliulo, 1961). Heim, Froede & Erwin (1962), however, have provided the interesting information that emetine in lower doses, comparable to those which kill intact animals, actually stimulates the cardiac succinate oxidase system in a manner similar to that of thyroxine.

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