PHARMACOLOGICAL STUDIES OF THE IPECAC ALKALOIDS AND SOME SYNTHETIC DERIVATIVES OF CEPHAELINE

II. STUDIES ON EMETIC EFFECT AND IRRITANT ACTION

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Received for publication July 19, 1917

A. EMETIC EFFECT

Both emetine and cephaeline are known to be emetic in small doses when taken by mouth. Since emetine is cephaeline methyl ether and is less emetic than cephaeline, it was of interest to determine the relative emetic power of some of the higher homologues of this series. The following ethers of cephaeline were prepared and their emetic action compared with that of cephaeline and emetine: ethyl, propyl, butyl, iso-amyl and allyl. Cats were chosen as suitable animals for these emetic tests. Full grown cats were fed milk about 7.30 a.m. At 10.00 a.m. each cat received 1 ounce of fresh raw beef, finely cut. Between 11.30 and 12.00 the alkaloidal salt was given in solution by stomach tube, the solution with the washings amounting to 20 cc. The animals were kept under observation until 5.30 p.m. The same animal could not be used satisfactorily oftener than once a week. After continued use the animals became more susceptible to the emetic effect of the drug. As different cats varied considerably as to the amount of drug required to produce emesis, it was necessary to give at least two of the alkaloids to the same animal in order to obtain a correct comparison. This difference in reaction and the increasing susceptibility on repeated dosage necessitated the use of a large

number of animals. In the experiments summarized here, fifty-six cats were used and the period of experimentation extended over several months. The following protocols illustrate the method pursued, but conclusions must be based on a series of such tests.

Protocols

ANIMAL	DRUG	DOSE PER CAT	RESULT
		gram	
92	Cephaeline hydrochloride	0.002	Vomited
	Cephaeline hydrochloride	0.002	Vomited
	Emetine hydrochloride	0.004	Did not vomit
	Emetine hydrochloride	0.004	Did not vomit
86	Cephaeline hydrochloride	0.002	Vomited
	Cephaeline hydrochloride	0.002	Did not vomit
	Cephaeline hydrochloride	0.002	Did not vomit
	Emetine hydrochloride	0.005	Vomited
	Emetine hydrochloride	0.004	Did not vomit
	Emetine hydrochloride	0.004	Did not vomit
12	Cephaeline hydrochloride	0.004	Vomited
	Cephaeline hydrochloride	0.003	Did not vomit
	Cephaeline hydrochloride	0.003	Did not vomit
	Cephaeline hydrochloride	0.002	Did not vomit
	Cephaeline propyl ether hydrobromide	0.016	Vomited
	Cephaeline propyl ether hydrobromide	0.012	Did not vomit
	Cephaeline propyl ether hydrobromide	0.010	Did not vomit
	Cephaeline ethyl ether hydrobromide	0.012	Vomited
	Cephaeline butyl ether hydrobromide	0.012	Vomited
	Emetine hydrochloride	0.010	Vomited
85	Emetine hydrochloride	0.008	Did not vomit
	Emetine hydrochloride	0.012	Vomited
	Cephaeline propyl ether phosphate	0.012	Did not vomit
	Cephaeline propyl ether phosphate	0.016	Did not vomit
	Cephaeline propyl ether phosphate	0.020	Vomited
13	Emetine hydrochloride	0.008	Did not vomit
	Emetine hydrochloride	0.010	Did not vomit
	Emetine hydrochloride	0.012	Vomited
	Cephaeline iso-amyl ether hydrobromide	0.024	Did not vomit
	Cephaeline iso-amyl ether hydrobromide	0.030	Did not vomit
	Cephaeline iso-amyl ether hydrobromide	0.036	Vomited

Protocols—Continued

ANIMAL	DRUG	DOSE PER CAT	RESULT
		gram	
31	Cephaeline allyl ether phosphate	0.015	Did not vomit
	Cephaeline allyl ether phosphate	0.020	Vomited
	Emetine phosphate	0.010	Did not vomit
	Emetine phosphate	0.012	Vomited
	Psychotrine hydrochloride	0.075	Did not vomit
	Psychotrine hydrochloride	0.100	Vomited
	Pyschotrine hydrochloride	0.100	Did not vomit
	Pyschotrine hydrochloride	0.120	Did not vomit
	Psychotrine hydrochloride	0.130	Did not vomit

A total of 290 doses were given and from an analysis of the several experiments the following comparative figures were compiled, the emetic dose of cephaeline having been taken as 1.

Cephaeline hydrochloride	1.
Cephaeline methyl ether (emetine) hydrochloride	2.
Cephaeline ethyl ether hydrobromide	2.4
Cephaeline propyl ether hydrobromide	3.6
Cephaeline propyl ether phosphate	3.8
Cephaeline butyl ether hydrobromide	3.6
Cephaeline iso-amyl ether hydrobromide	5.0
Cephaeline ailyl ether phosphate	2.5

The results are only approximately correct at best, but they show that the emetic power of this series of compounds diminishes much in the same order as does their toxicity (1) and that emetine hydrochloride is about one-half as emetic as cephaeline hydrochloride and that cephaeline iso-amyl ether hydrobromide is only one-fifth as emetic as cephaeline hydrochloride.

It was noted that some salts of these cephaeline compounds were more emetic than others, and accordingly the hydroiodides of the methyl, propyl and iso-amyl derivatives were tried in a manner similar to that above detailed, with the exception that the alkaloidal salts were all given in capsules instead of in solution.

The following tables are two of a series of seven and demonstrate the greatly diminished emetic power of the difficultly soluble hydroiodides of the cephaeline propyl and iso-amyl

ethers. Emetine hydroiodide was not appreciably weaker as an emetic than emetine hydrochloride.

Cat 14; weight, 3086 grams

DATE	DRUG	DOSE PER CAT	RESULTS
		gram	
April 5, 1916	Cephaeline propyl ether hydroiodide	0.020	Vomited
April 12, 1916	Cephaeline propyl ether hydroiodide	0.015	Did not vomit
April 19, 1916	Cephaeline propyl ether hydroiodide	0.020	Vomited
April 27, 1916	Cephaeline propyl ether hydroiodide	0.015	Did not vomit
May 5, 1916	Emetine hydrochloride	0.010	Vomited
May 12, 1916	Emetine hydrochloride	0.007	Vomited
May 19, 1916	Emetine hydrochloride	0.005	Did not vomit
May 26, 1916	Emetine hydrochloride	0.005	Vomited
June 2, 1916	Emetine hydroiodide	0.007	Vomited

Cat 18; weight, 2484 grams

March 30, 1916	Cephaeline iso-amyl ether hydroiodide	0.040	Did not vomit
April 14, 1916	Cephaeline iso-amyl ether hydroiodide	0.050	Did not vomit
April 21, 1916	Cephaeline iso-amyl ether hydroiodide	0.060	Did not vomit
April 28, 1916	Cephaeline iso-amyl ether hydroiodide	0.060	Did not vomit
May 5, 1916	Cephaline iso-amyl ether hydroiodide	0.065	Did not vomit
May 12, 1916	Cephaeline iso-amyl ether hydroiodide	0.070	Did not vomit
May 19, 1916	Cephaeline iso-amyl ether hydroiodide	0.075	Did not vomit
May 26, 1916	Emetine hydrochloride	0.010	Did not vomit
June 2, 1916	Emetine hydrochloride	0.012	Vomited
June 15, 1916	Cephaeline iso-amyl ether hydroiodide	0.080	Did not vomit
June 23, 1916	Cephaeline iso-amyl ether hydroiodide	0.085	Did not vomit
July 7, 1916	Cephaeline iso-amyl ether hydroiodide	0.090	Did not vomit
July 21, 1916	Cephaeline iso-amyl ether hydroiodide	0.095	Vomited

A summary of the results with these seven cats is given below.

CAT	DRUG	EMETIC DOSE	DRUG	EMETIC DOSE
		mgm.		*mgm.*
14	Cephaeline propyl ether hydroiodide	15–20	Emetine hydrochloride	5
17	Cephaeline propyl ether hydroiodide	35–40	Emetine hydrochloride	10–12
19	Cephaeline propyl ether hydroiodide	35–40	Emetine hydrochloride	10–12
15	Cephaeline iso-amyl ether hydroiodide	55–60	Emetine hydrochloride	7–10
16	Cephaeline iso-amyl ether hydroiodide	75–80	Emetine hydrochloride	10–12
18	Cephaeline iso-amyl ether hydroiodide	90–95	Emetine hydrochloride	10–12
20	Cephaeline iso-amyl ether hydroiodide	60–65	Emetine hydrochloride	12–15

From these tests made on seven animals, cephaeline propyl ether hydroiodide is not more than one-third as emetic for cats as is emetine hydrochloride, and cephaeline iso-amyl ether hydroiodide is not more than one-sixth as emetic as emetine hydrochloride or one-twelfth as emetic as cephaeline hydrochloride, the mother substance.

A few tests on persons showed an individual variation in susceptibility to the ipecac alkaloids. As a rule one-eighth grain of cephaeline hydrochloride and one-fourth grain of emetine hydrochloride proved emetic. One-sixth grain of cephaeline iso-amyl ether hydrochloride caused slight nausea but no emesis in two persons and no noticeable effect in four others; one-third grain caused slight nausea in one case and no effect in another, and one person, a boy of sixteen years, took one-sixth grain three times a day for fourteen days without any symptoms of vomiting or nausea. The cephaeline iso-amyl ether hydroiodide was given in single doses of three-fourths of a grain without producing nausea. One person took one-fourth grain of this hydroiodide three times a day for fourteen days without nausea resulting. Larger doses than the above were not given.

B. IRRITANT ACTION

The irritant action of emetine hydrochloride when injected hypodermatically has been noted by all who have used this alkaloidal salt. Its irritant effect has also been evident where accidentally solutions of it have come in contact with the conjunctiva or with the mucous membrane of the oral cavity. Furthermore, workers employed in the manufacture of emetine or in handling powdered ipecac root not infrequently develop a cutaneous eruption as a result of the local action of the drug. A noticeable feature of this irritating action is the slowness of its onset. When injected hypodermatically the pain or soreness does not develop for several hours, sometimes not until the second day. When solutions of emetine hydrochloride, or even particles of the alkaloid itself, come into contact with the conjunctiva, pain is not felt for six or eight hours and severe inflammation does not set in previous to this time.

Conjunctival tests

In order to determine the relative irritating effects of cephaeline and some of its derivatives, solutions of these alkaloidal salts were instilled into the eyes of rabbits. It was determined that one-tenth per cent solutions were well suited for this purpose. The alkaloidal salts were dissolved in 0.85 per cent sodium chloride solutions and the right conjunctival sac was filled with the fluid to be tested. This was held in the sac for one minute and then allowed to flow out naturally. The left eye was treated in a similar manner with 0.85 per cent salt solution and was used as a control. The condition of the ocular and palpebral conjunctiva was observed from time to time over several days. The following protocol illustrates this method.

Thirty-two tests of this nature were made using cephaeline hydrochloride, emetine hydrochloride, cephaeline propyl ether phosphate, cephaeline iso-propyl ether hydrochloride and hydrobromide, cephaeline iso-amyl ether hydrochloride and hydrobromide, and cephaeline allyl ether hydrobromide. Of these substances cephaeline hydrochloride and emetine hydrochloride

TIME	RABBIT	AGENT	PALPEBRAL CONJUNCTIVA	OCULAR CONJUNCTIVA
9.43	1	0.1 per cent cephaeline propyl ether phosphate	Normal appearance	Normal appearance
9.45	2	0.1 per cent emetine hydrochloride	Normal appearance	Normal appearance
After 3 hours	1		Injected	Injected
	2		Injected	Injected
After 7 hours	1		Injected	Injected
	2		Injection greater than rabbit 1	Injected
After 23 hours	1		Injection slight	Normal
	2		Marked injection and increased secretion. Edges of lids reddened. Much worse than rabbit 1	Injected
After 49 hours	1		Normal	Normal
	2		Still markedly injected, less than at 23 hours	Injected
After 97 hours	1		Normal	Normal
	2		Injection still present	Normal
After 121 hours	1		Normal	Normal
	2		Normal	Normal

were undoubtedly the most irritating to the conjunctiva. The irritation was intense and long lasting. Of the other substances the cephaeline iso-amyl ether was the least irritating, although the difference among these was not very great.

These experiments were not carried further as at this time the fallacy of the results was discovered. On the assumption that cephaeline iso-amyl ether hydrochloride was considerably less irritating than emetine hydrochloride, $\frac{1}{2}$ grain of this substance in 1 cc. of sterile water was injected subcutaneously into the

deltoid region of one of the laboratory workers. This injection was followed by a similar one on each of the two succeeding days and on the fourth day a deep intramuscular injection of ½ grain was given. The intramuscular injection gave rise to only a mild reaction. The injections given subcutaneously gave rise to considerable local reaction which consisted of a reddening of the skin and a soreness which developed during the first twenty-four hours. These effects increased during the following forty-eight hours at the end of which time there was also some induration. Objectively from seventy-two to ninety-six hours there was improvement though subjectively the condition was said to be worse. At the end of ninety-six hours the soreness decreased too. The reaction gradually decreased and was practically cleared up at the end of two weeks, although a small indurated subcutaneous nodule could still be palpated at the site of one of the injections.

Injections of ½ grain cephaeline iso-amyl ether hydrochloride were made intramuscularly in a second individual. The left arm received an injection into the triceps on the first day and was only slightly tender on the second day, was swollen, tender and painful on the third day, and the inflammation was rapidly subsiding on the fourth day. On the second day, an injection was made into the right triceps. This showed only slight tenderness on the following day and another injection was made into the left arm, this time into the deltoid. This last injection gave only slight evidence of irritation. The right arm was not sore on the day following the injection nor on the second day, but on the morning of the third day the patient wakened with a very sore arm and felt ill. This being Sunday the patient was not seen until the fourth day when he presented a swollen, slightly reddened and very tender right arm. The swelling began at the point of injection just above the deltoid insertion and extended over the triceps and outer aspect of the arm to the elbow. There was no soreness or swelling above the point of injection. The patient could not raise the arm. The swelling gradually subsided and the pain decreased so that the arm was practically normal at the end of the tenth day following the injection.

Three other patients who received injections of this preparation for amebic dysentery complained of considerable soreness at the sites of the injections.

These clinical tests seemed to conclusively prove that the conjunctival tests for irritation as carried out were not a reliable measure of the irritation afforded by hypodermatic injections. While emetine hydrochloride often causes severe local reaction when injected, we have never seen it cause as severe reactions as were produced by the cephaeline iso-amyl ether hydrochloride. Further laboratory tests which will now be described have substantiated the clinical findings, or rather have disproved the findings based on the conjunctival tests.

Intramuscular tests

Solution of the phosphate of each alkaloid was compared with a like solution of emetine phosphate. The emetine phosphate was injected deep into the right lumbar muscles of a rabbit and the substance to be tested into the left. These solutions in different experiments were given in amounts of either 0.25 cc. or 0.5 cc. The amount of alkaloid injected varied from 2 mgm. to 32.4 mgm. The injection of 32.4 mgm. into each side was occasionally fatal. The usual dilution was 16.2 mgm. in 0.5 cc., this being the concentration most commonly employed in clinical practice. The rabbits were chloroformed on the fourth day following the injection and the subcutaneous and intramuscular reactions of the two sides were carefully compared macroscopically. In these experiments the phosphates of the following cephaeline ethers were tested: methyl, ethyl, propyl, isopropyl, butyl, iso-butyl, tertiary butyl, iso-amyl, and allyl.

Without going into detail to describe the differences in the intensity of reaction, the comparative irritating effects may be indicated as follows:

DOSE	EMETINE PHOSPHATE	
		Cephaeline phosphate
16.2 mgm. in 0.5 cc.	+++	+++
		Cephaeline ethyl ether phosphate
16.2 mgm. in 0.5 cc.	++	++
32.4 mgm. in 0.5 cc.	++	++ died during night
		Cephaeline propyl ether phosphate
32.4 mgm. in 0.5 cc.	++	+++
32.4 mgm. in 0.5 cc.	++	+++
16.2 mgm. in 0.5 cc.	++	+++
16.2 mgm. in 0.5 cc.	++	+++
16.2 mgm. in 0.25 cc.	+++	++
16.2 mgm. in 0.25 cc.	++	+++
		Cephaeline isopropyl ether phosphate
16.2 mgm. in 0.5 cc.	++	+
16.2 mgm. in 0.5 cc.	+	+
16.2 mgm. in 0.5 cc.	++	++
32.4 mgm. in 0.5 cc.	++	++ (died after 1 day)
		Cephaeline butyl ether phosphate
32.4 mgm. in 0.5 cc.	++	++
32.4 mgm. in 0.5 cc.	+++	++
16.2 mgm. in 0.5 cc.	+	+++
16.2 mgm. in 0.5 cc.	++	++
		Cephaeline iso-butyl ether phosphate
32.4 mgm. in 0.5 cc.	+++	++
16.2 mgm. in 0.5 cc.	+++	++
		Cephaeline tertiary butyl ether phosphate
32.4 mgm. in 0.5 cc.	++	+
16.2 mgm. in 0.5 cc.	+	++
		Cephaeline iso-amyl ether phosphate
32.4 mgm. in 0.5 cc.	++	+++
16.2 mgm. in 0.5 cc.	++	+++
16 2 mgm. in 0.5 cc.	+++	++++
16.2 mgm. in 0.5 cc.	++	+++
		Cephaeline allyl ether phosphate
16.2 mgm. in 0.5 cc.	+++	+++
16.2 mgm. in 0.25 cc.	+++	++
16.2 mgm. in 0.5 cc.	++	+++
16.2 mgm. in 0.5 cc.	++	++

Slight inflammation (+), severe inflammation (++), very severe inflammation (+++), necrosis (++++).

As may be seen the various derivatives were not tested against each other in the same rabbit, but each was tested against emetine phosphate, so that these results only in a general way indicate the relative irritating effect of the alkaloids tested. Suffice it to say that the cephaeline iso-amyl ether phosphate, which was least irritating in the conjunctiva tests, was the most irritating when given intramuscularly. Cephaeline and all of its derivatives tested by this method were quite irritating when given in the above dilutions and none of them possessed any decided advantage over emetine in this respect.

We have personally injected doses of $\frac{1}{2}$ grain cephaeline iso-amyl ether hydrochloride in 1 cc. in four patients and have had reports of four other cases in which this drug was used. In all cases severe pain and local inflammation was caused. We have made from three to six injections of $\frac{1}{2}$ grain cephaeline propyl ether hydrochloride or phosphate at daily intervals in twelve patients and have reports from similar injections in several others and in none of them was there more than slight local soreness at the point of injection. In three of these patients emetine hydrochloride was also injected for comparison and no difference could be noted in its local action and that of cephaeline propyl ether hydrochloride.

It may be that the apparently lessened irritating effect of these derivatives of cephaeline when tested on the rabbit's eye and their lowered toxicity when given subcutaneously to rats and guinea pigs is due to their being more difficultly absorbed from the tissues. Those compounds difficult of absorption would be washed out of the eye before seriously affecting the conjunctiva and when injected intramuscularly these compounds would be more irritating on account of their remaining longer in contact with the tissues. The further fact that their toxic dose bears an entirely different relation to emetine when given intravenously and when given subcutaneously would tend to confirm the above assumption.

In connection with the irritating action of the alkaloids of ipecac, we would like to record some incidental observations on the action of powdered ipecac root in producing "ipecac asthma."

In our laboratories there are seven men in whom typical bronchial asthmatic attacks occur whenever they come in contact with ipecac dust in the air. On days when ipecac is being ground in the drug mills these men, although they may be one or two buildings distant from the grinding room, will suffer from asthma. In some cases this attack is so severe as to temporarily incapacitate them. In some the attacks are mild and pass off after a short time in the open air. In others the attack may be mild at first and then become more severe at night after the patient has gone home and the effects may be noticed for as long as a week. Six of these cases have never had asthma at any other time or from any other cause. On the other hand certain individuals who are subject to asthma and who frequently come in contact with powdered ipecac are not affected by it. In four of the above cases adrenalin hydrochloride has been given hypodermatically and relieves the difficult breathing quite promptly. That this ipecac asthma is not due to the alkaloids is evident, for no one handling either cephaeline or emetine has ever made such complaint. Two of the men mentioned above are chemists and frequently come in contact with the alkaloids but are never affected by them. Powdered ipecac root, from which the alkaloids have been removed, is still capable of producing these asthmatic attacks in susceptible persons, so that this would seem to be another instance of vegetable protein sensitization.

CONCLUSIONS

These experiments have demonstrated that in cats the emetic dose of emetine hydrochloride is approximately twice that of cephaeline hydrochloride, and that the higher homologues of this series decrease in emetic power very much in the same ratio as they do in toxicity, as reported in a previous paper (1). Furthermore, it has been shown that the hydrochloride, hydrobromide and hydroiodide of emetine vary only slightly in their emetic power, but that the hydroiodide of cephaeline iso-amyl ether, due to its relative insolubility, is about one-half as emetic as the hydrobromide or hydrochloride of cephaeline iso-amyl ether and only one-sixth as emetic as emetine hydrochloride.

When tested on the conjunctiva of rabbits, emetine and cephaeline are the most irritant of this series and cephaeline iso-amyl ether is least irritating.

When injected intramuscularly in rabbits cephaeline iso-amyl ether is the most irritant while the difference between the other less irritant members of the series is not marked.

Cephaeline propyl ether phosphate gives no more than a slight local reaction when injected hypodermatically into persons, while cephaeline iso-amyl ether salts cause severe pain, soreness and local inflammation.

REFERENCE

(1) Walters and Koch: Journ. Pharm. and Exp. Ther., 1917, x, 73.