SCIENTIFIC SECTION, AMERICAN PHARMACEUTICAL ASSOCIATION

EMETOIDINE* (KRYPTONINE).

A STUDY OF ITS PHARMACOLOGY.

BY HOWARD S. BROWNE.

INTRODUCTION.

Historical: More than thirty years ago, John Uri Lloyd, in working with ipecac on a large scale, obtained a substance having alkaloidal qualities and which he at that time, for want of a better name, called "black tar." In 1915 he again became interested in this substance, and succeeded in isolating, from 125 pounds of ipecac, two grammes of a colloidal black scaly substance. From three subsequent lots of ipecac, 125 pounds each, he obtained, respectively, 112.4 grammes, 107 grammes, and 120 grammes.

At the suggestion of Dr. H. W. Wiley, he named this non-crystallizable, colloidal alkaloid, "Kryptonine," which comes from the Greek, meaning "the hidden thing." Since all things are hidden until they are discovered, and since subsequent investigation has demonstrated the similarity of the drug to emetine, it was suggested by Dr. Bernard Fantus that the name be changed to "Emetoidine."

The following description of its physical and chemical qualities is given by Lloyd:[1] It is a colloidal substance, orange-yellow when in fine state of subdivision, garnet-red in coarser particles and black in mass, scales, or bulk, thus agreeing in a very interesting manner with Ostwald's color law of colloidal substances.

Not only the base, but also compounds with acids, are colloidal. It is not deliquescent. It has a very bitter taste and colors saliva yellow. It is soluble in water, alcohol, chloroform, glycerin, dilute acids and dilute alkalies. It is insoluble in ether and benzol. Dilute solutions in water and alcohol are yellow to red, in accordance with concentration. With alkalies, the yellow solution turns red. Acids added to excess, turn the red, back to yellow.

Fehling's test: No reaction or a very faint one. Ferric chloride does not produce any obvious change in the solutions.

Alkaloidal tests: Heavy precipitate with Mayer's reagent, which leaves the supernatant liquid colorless. Picric acid, tannin and other alkaloidal reagents also produce precipitation.

Chloroform solution: Yellow to red, in accordance with proportions, alkalies turn this solution green. The addition of alcohol turns the green to red. If the solution be more concentrated, the green and red plays of color are more pronounced. On standing, the green of the chloroformic solution gradually fades, red resulting.

Formula: Dr. Sigmund Waldbott, $C_{29}H_{40}N_2O_9$.

A comparison of the above formula with that of emetine ($C_{15}H_{22}NO_2$) shows that emetine has approximately one-half the molecular weight of emetoidine.

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* Read before Scientific Section, A. Ph. A., Indianapolis meeting, 1917.

TOXICITY.

It appears that in the study of this new drug the toxicity is perhaps of prime importance. To this end, the effect upon low forms of life as well as the higher was tried.

Because of their availability and their ease of growth, the *Paramecium caudatum* was first used. The toxicity of emetoidine for these organisms is quite great, as will be seen from Table I:

TABLE I.

Dilution.	Result.
1 : 500	Motion stopped immediately
1 : 1,000	Motion stopped immediately
1 : 2,000	Motion stopped immediately
1 : 10,000	Motion stopped in 12 minutes
1 : 22,500	Motion still present at end of 24 hours
1 : 50,000	Motion still present at end of 24 hours

Comparison of the above results with those obtained by Wherry[4] shows that emetine is perhaps somewhat more toxic for paramecia, as he found it to kill the organisms in twenty-four hours in a dilution of 1 : 100,000.

(*b*) *Toxicity for Rabbits:* To determine the toxicity of Emetoidine for rabbits, two methods of administration were used; namely, by stomach and intravenously. The drug was introduced into the stomach by means of a stomach tube and washed down with water. For intravenous injection the marginal vein of the ear was selected. The accompanying table (II) shows the results. Since the intravenous method is the most reliable, more animals were used with this. The fatal dose appears to be approximately 4.5 mg. per kilo of body weight. I found, however, that the results vary, depending upon the rapidity of the injection. The drug, when slowly injected, is not so rapidly fatal as when quickly injected.

TABLE II.

Toxicity of Emetoidine for Rabbits.

Weight.	Dose per Kg.	Method.	Results.
1905 Gm.	0.066	By stomach	Survived
900 Gm.	0.072	By stomach	Death 22 days later
1820 Gm.	0.100	By stomach	Death 10 days later
780 Gm.	0.120	By stomach	Death 10 days later
865 Gm.	0.150	By stomach	Death 3 days later
1150 Gm.	0.170	By stomach	Death 7 days later
	Intravenous Method.		
1400 Gm.	0.00090	Intravenous	Survived
1200 Gm.	0.00170	Intravenous	Survived
1130 Gm.	0.00177	Intravenous	Survived
825 Gm.	0.00180	Intravenous	Survived
1265 Gm.	0.00320	Intravenous	Survived
1346 Gm.	0.00370	Intravenous	Survived
1085 Gm.	0.0042	Intravenous	Death 5 days later
1161 Gm.	0.0047	Intravenous	Death in 5 minutes
1714 Gm.	0.0049	Intravenous	Death in 3 minutes
1380 Gm.	0.0050	Intravenous	Death immediate
1547 Gm.	0.0100	Intravenous	Death immediate
1600 Gm.	0.0200	Intravenous	Death immediate
1430 Gm.	0.0450	Intravenous	Death immediate

The preceding table shows that emetoidine is fatal on intravenous injection in doses of approximately 4.5 mg. per Kg. to rabbits.

TOXICITY OF EMETINE FOR RABBITS.

Since emetoidine is probably closely related to emetine, I felt that it would be interesting to compare the toxicity of the two. Kolmer and Smith[2] state the lethal intravenous dose of emetine for a rabbit to be 0.01 to 0.0129 Gm. per Kg. Vedder[3] states that 2.5 mg. per Kg. is the minimum fatal dose. The results I obtained on intravenous injection (see Table III), though the series is small, agree approximately with those of Vedder.

Comparing results of Tables II and III, it seems that emetoidine is somewhat less toxic than emetine.

TABLE III.

Weight.	Dose per Kg.	Method.	Results.
1586 Gm.	0.00473	Intravenous	Immediate death
1335 Gm.	0.00447	Intravenous	Immediate death
1452 Gm.	0.0037	Intravenous	Immediate death
1492 Gm.	0.00268	Intravenous	Death 4 days later
1687 Gm.	0.00167	Intravenous	Survived

ACTION ON CIRCULATION.

Emetoidine in lethal doses arrests the heart in diastole, the animals from practically all of the cases showing this effect at necropsy. The coagulability of the blood is decreased, and appears as a black, thick fluid. The paralysis of the heart occurs, secondarily to that of respiration, the heart beating feebly for a few seconds after respiration stops.

EFFECT ON BLOOD PRESSURE IN THE DOG.

A dog weighing 15.7 kilos was prepared in the usual manner for a blood pressure tracing. After recording a normal tracing, a dose of 0.00057 gramme per kilo was injected into the femoral vein and washed in with normal saline. In about 20 seconds a drop of 25 mm. of mercury was recorded, which lasted for about 15 seconds and gradually recovered, the blood pressure going not quite so high as before the injection (see Fig. 1).

After allowing considerable time for the effect of the above dose to wear off, a dose of 0.004 gramme per kilo was similarly injected. In about 30 seconds there occurred an almost perpendicular drop in the blood pressure of 25 mm. followed by a gradual fall to within 5 mm. of the base line at which time the heart ceased to beat.

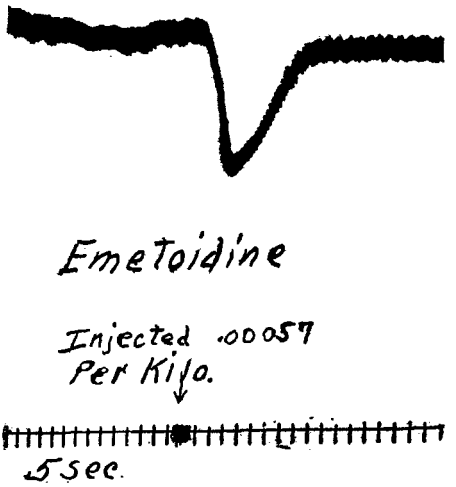

Fig. 1—Showing the Effect on Blood Pressure, Following the Intravenous Injection of 0.00057 Gm. per Kg. of Emetoidine into the Femoral Vein.

ACTION ON RESPIRATION.

Emetoidine produces a profound de-

pression of the respiratory center, paralysis occurring almost immediately, following the lethal dose of the drug. A few short, convulsive movements occur and then respiratory action stops, the animal squats down and later falls on the side, dead.

EMETIC ACTION.

The emetic action of emetoidine was studied both by intra-muscular injections and by introduction of the drug into the stomach of dogs by means of the stomach tube. While as small an amount as 0.015 Gm. per kilo, when administered by the stomach tube, produces retching and vomiting in from 30 to 45 minutes, the intramuscular administration of 0.02 Gm. per kilo produces great prostration and death, but no emesis.

LOCAL ACTION UPON THE CONJUNCTIVA.

Instillation of solutions of various strengths into the conjunctival sac of rabbits shows that emetoidine is an irritant. Strong solutions produce pain and inflammation, while weaker solutions produce only hyperemia, which lasts for a short time.

FEEDING EXPERIMENTS.

(*a*) *Cat.*

A healthy cat weighing 3115 Gm. was fed once daily 0.008 Gm. of emetoidine with 100 Gm. of chopped meat. In addition 150 mils of sweet milk was given. Care was taken to see that the animal had just enough to eat, so that it ate all of the food each day. At the end of twenty-five days, the animal's weight had become reduced to 2840 grammes, a total loss of 275 grammes.

(*b*) *Rabbit.*

A rabbit weighing 842 Gm. was fed all the chopped carrots and oats it would eat each day. Powdered emetoidine, 0.02 Gm. per day, was mixed with the carrots. At the end of thirty days the animal weighed 852 grammes. At this time the emetoidine was discontinued and the same amount of food given daily. In fifteen days the animal gained 206 grammes, weighing at the end of the feeding period 1056 grammes.

No evidence of gastric disturbance, diarrhea or other intestinal manifestation was seen in either of the above cases. The loss of weight was not due to refusal or lack of food, hence must have been caused by some digestive or metabolic derangement. Which of the two was responsible for the result, I am at present unable to say.

SUMMARY.

1. Emetoidine seems to be somewhat less toxic for both paramecia and for rabbits than emetine.

2. It produces a similar fall in blood pressure when injected intravenously.

3. It depresses the central nervous system and respiration as does emetine.

4. It produces emesis by local irritant action rather than by direct stimulation of the vomiting center, which also agrees with the action of emetine.

5. The similarity of this drug in its action upon the circulation, the central nervous system, as an emetic, and in toxicity to emetine, has influenced me to recommend to Professor Lloyd that the name of this substance be changed from Kryptonine to Emetoidine, to which Professor Lloyd has agreed.

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(3) Vedder, Emetine in Dysentery, *J. A. M. A.*, Feb, 1914, p. 505.
(4) Wherry, *J. Infectious Diseases*, Vol. 10, No. 2.

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THE OCCURRENCE AND SIGNIFICANCE OF CREATININE IN URINE.*

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Much interest has been shown of late by physiological chemists, physiologists, and others in this body, creatinine, which is excreted with normal urine of the average adult male to the extent of about 14 Gm. per day; that is, about 0.08 percent in normal urine.

This interest is no doubt due in part to the discovery of fairly accurate methods for its isolation and determination. Its isolation in pure crystalline form has been followed by the determination of its molecular and constitutional formulae and by its synthesis, so that to-day we can call it the anhydride of creatine, which, in turn, depending upon how one looks upon it, is the ureide of sarcosine or methyl-glycocoll; or, methyl-guanidine-acetic acid.

By the direct union of methyl-glycocoll and cyanamide creatine is easily synthesized:

$$CH_3.NH.CH_2.COOH + NH_2CN \longrightarrow NH_2.C(NH).N(CH_3).CH_2.COOH.$$

The last product, creatine, is a colorless, crystalline substance which readily passes over to its anhydride creatinine. Aqueous solutions of creatine are neutral, but of creatinine are distinctly alkaline. Such alkaline solutions are unstable but the solution becomes stable upon acidifying.

Creatinine will reduce Fehling's solution, and will also reduce picric acid to picramic acid in alkaline solution. The picramic acid solution is distinctly reddish and upon this property of creatinine is based Folin's colorimetric method for its determination.

The process by which creatinine may be obtained in pure form is given in Hawk's "Physiological Chemistry," last edition.

It is probable that the creatinine of the urine is derived from the creatine of

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