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THE PHARMACOLOGICAL ACTION OF FOUR CORYDALIS ALKALOIDS

K. K. CHEN, ROBERT C. ANDERSON, AND T. Q. CHOU

(From the Lilly Research Laboratories, Indianapolis, Indiana, U.S.A. and the Insitute of Materia Medica, the National Academy of Peiping and the Sino-French University, Shanghai)

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In previous communications, one of us [Chou, 1928; 1929; 1933; 1934] reported the separation of 13 crystalline alkaloids from the Chinese drug Yen-hu-so, or botanically, *Corydalis ambigua*. On account of the scanty knowledge about their chemical constitution and for the sake of convenience, these alkaloids have been provisionally called corydalis A, B, C, D, E, F, G, H, I, J, K, L, and M. Included in Chou's first paper [1928] are brief accounts of the pharmacological action of corydalis B and C by Chu and Pak, respectively. It was found by Chu that corydalis B had a narcotic and local anesthetic effect, and by Pak that corydalis C was a convulsant substance. As shown by Wang [Chou, 1933], both corydalis I and J cause initial depression followed by convulsions in animals. The most interesting feature of corydalis B and K is their bulbocapnine-like action, that is, the production of catalepsy, which was discovered by Wang and Lu [1933]. The present physiological study has been made with corydalis B, J, L and M on those phases not covered by our predecessors. Hydrochlorides were prepared from the four above mentioned alkaloids. Corydalis B hydrochloride is soluble in water to the extent of 0.5 per cent, but the other salts readily go into solution of a concentration convenient for injection purposes, such as 1 per cent. In view of the fact that these alkaloids are not entirely stable, fresh solutions were always prepared on the day of experimentation.

Catalepsy. Mice injected intravenously with corydalis B.HCl or L.HCl, in the dosage of 50 or more mg per kg, usually assumed a lethargic state within 1 to 3 minutes, lay on their side, and made no attempt to right themselves. They could be aroused, however, to correct their posture by mechanical stimuli. When hung on the edge of a glass by their front feet, they would remain there without any protest for 1 to 2 minutes. Recovery took place in 11 to 42 minutes after medication. Neither corydalis J nor corydalis M had the same cataleptic effect.

One cat received by the femoral vein a dose of corydalis L.HCl (50 mg per kg). It showed acceleration of respiration, stupor, weakness of limbs, and closure of eyes. It became entirely normal in a little less than 3 hours. Another cat was injected with a larger dose of corydalis L.HCl by the same route. Four minutes after the injection the animal had convulsive movements, and in 9 minutes it was successfully hung on the back of a chair, each time for 45 to 60 seconds. The nictating membrane was powerfully contracted. The cat was lethargic and stayed motionless wherever she was put. Complete recovery occurred 3 2/3 hours after the injection. Similar results in cats were obtained by Wang and Lu with corydalis B [1933].

In a small monkey, a dose of corydalis B.HCl, 10 mg per kg, injected by the saphenous vein produced hanging response [see Richter and Paterson, 1931] 6 minutes after injection. The action reached its peak in 27 minutes, and lasted for 45 minutes. Another monkey, female, weighing 4.156 kg, received a dose of 20 mg per kg by the same route. The hanging response appeared 4 minutes after injection, and lasted each time from 4 to 30 seconds. The animal was so stuporous that it was not necessary to tie its legs as advised by Richter and Paterson [1931]. The maximal effect with this dose was attained 30 minutes after injection. The entire duration of action was 80 minutes. Somewhat similar results were obtained with corydalis L.HCl. A monkey, female, weighing 3.357 kg, was given a dose of 30 mg per kg by vein. Immediately after injection, tonic convulsions and erection of hair occurred. The animal gradually became relaxed, and made epileptic movements. There was foaming at the mouth and the hands at times assumed a praying position. Ten minutes after injection, it started to move

around in the cage. It was not until 80 minutes after injection that catalepsy definitely developed. Each hanging response lasted from 4 to 46 seconds. The peak of action was reached 10 minutes after the onset of catalepsy. The monkey completely recovered at the end of approximately 3 hours after the medication.

Toxicity. On account of a limited supply of material, toxicity was determined only in mice by injection into a tail vein. The minimal lethal doses of corydalis B.HCl, J.HCl, L.HCl and M.HCl, as shown in table 1, were found to be 103, 42, 150 and 41 mg per kg respectively. With corydalis J and M, rapid respiration, jumping, and clonic convulsions preceded death.

TABLE 1.

Toxicity of four corydalis alkaloids by intravenous injection in mice

Drug	Strength of solution	Dose	Number of mice died/Number of mice used	Minimal lethal dose
	per cent	*mg/kg*		*mg/kg*
Corydalis B.HCl	0.5	100	0/3	103
		101	1/3	
		102	2/5	
		103	4/5	
Corydalis J.HCl	0.2	40	1/4	42
		41	0/5	
		42	5/5	
Corydalis L.HCl	1.0	140	0/1	150
		145	2/5	
		150	3/5	
Corydalis M.HCl	0.1	40	0/5	41
		41	3/5	

Circulation. Although the action of corydalis B and L differs from corydalis J and M upon the central nervous system, the four alkaloids have a close resemblance of effects upon other organs. Thus, in 22

frog hearts, perfused via inferior vena cava, they all caused a decrease in heart rate and amplitude of contraction, ventricular premature beats, A-V block, and arrhythmia. A concentration of 1:5,000 of each substance in the form of a hydrochloride gradually arrested the heart at diastole. Before final standstill, periods of bradycardia alternating with stoppage were frequently observed. If the solutions were more dilute than 1:10,000, the hearts usually continued to beat for a long time, only the rate and the amplitude slowly diminished. Ventricular extrasystoles occasionally occurred.

In 7 etherized cats, corydalis B.HCl, J.HCl, L.HCl and M.HCl, in a dosage of 10 to 30 mg (total), uniformly lowered the carotid blood pressure by intravenous injection. An amount of 40 mg of corydalis J.HCl killed a cat (anesthetized) weighing 2.57 kg. During the fall of blood pressure there was evidence of interesting electrocardiographic changes. This phase is subjected to further study and the results will be presented at a later date.

Smooth muscle organs. All four alkaloids stimulated isolated rabbits' small intestines in dilute concentrations, but inhibited the same in solutions of 1:20,000 to 1:10,000, after which barium chloride became ineffective. The action, therefore, is probably on the smooth muscle directly. A total of 14 strips of intestines were employed. The dilutions in which stimulation had been noted were 1:50,000 with corydalis B.HCl, 1:100,000 with corydalis J.HCl. 1:33,333 to 1:25,000 with corydalis L.HCl, and 1:250,000 with corydalis M.HCl.

In 7 strips of isolated guinea pigs' uteri, contraction uniformly occurred following the application of the four substances. The most effective concentrations for corydalis B.HCl and L.HCl varied from 1:500,000 to 1:50,000, and those for corydalis J.HCl and M.HCl were 1:5,000,000 to 1:500,000.

SUMMARY

1. Sublethal doses of the alkaloids corydalis B and L, intravenously injected, produce catalepsy in mice and monkeys as measured by the hanging response and the general posture. Similar effects have been noted with corydalis L in cats. The alkaloids corydalis J and M cause pure convulsions in lethal or near lethal doses in mice.

2. The minimal lethal doses of corydalis B, J, L, and M in the form of hydrochlorides have been determined to be 103, 42, 150 and 41 mg per kg, respectively, in mice by intravenous injection.

3. The four alkaloids have a similar depressant action upon the frog's heart as shown by a decrease in heart rate and amplitude of contraction, ventricular premature beats, A-V block, arrhythmia, and finally standstill. In etherized cats, all four substances lower arterial blood pressure.

4. The four alkaloids stimulate isolated rabbits' small intestines in dilute concentrations, but depress the same in relatively stronger solutions. They all cause contractions of the isolated guinea pig's uterus.

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LITERATURE

Chou, T. Q. (1927-28) Proc. Soc. exp. Biol., N.Y., **25**, 544.

Chou, T. Q. (1928) Chinese J. Physiol., **2**, 203.

Chou, T. Q. (1929) Amer. J. Physiol., **90**, 314.

Chou, T. Q. (1929) Chinese J. Physiol. **3**, 69 and 301.

Chou, T. Q. (1933) Ibid, **7**, 35.

Chou, T. Q. (1934) Ibid, **8**, 155.

Richter, C. P. and Paterson, A. S. (1931) J. Pharmacol., Baltimore, **43**, 677.

Wang, G. H. and Lu, T. W. (1933) Chinese J. Physiol., **7**, 13.

四種延胡索質鹼之葯理作用

陳克恢　安德生　趙承嘏

禮來研究所，印第安奶波禮司，美國，及北平研究院與中法大學葯物研究所，上海

靜脈注射致死量下之延胡索乙與丑，能使鼷鼠與猴生强直性昏厥，由吊懸反應與普通姿勢而側定。延胡索丑亦能使猫生同樣現象。延胡索癸與寅之致死量或近致死量，能使鼷鼠生純粹之驚厥。

延胡索乙，癸，丑與寅氫鹵化物的最低致死量，用鼷鼠行靜脈注射而側定，以每體重一公斤計算，爲103,42,150及41公絲。

此四種膺鹼對於蛙心有同樣之抑制作用，如心搏率減少，心縮廣闊度減低，心室過早衝動，心房與心室遮斷，心律不齊，以致停止。於醚麻醉之猫中，此四種膺鹼，皆能使血壓下降。

此四種膺鹼之淡溶液能興奮兎之離體小腸，其濃溶液則能抑制之。對於荷蘭猪之離體子宮，牠們皆能使之收縮。