SOME PHARMACOLOGICAL ACTIONS OF AN ALKALOID ISOLATED FROM BERBERIS LYCIUM

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Some pharmacological actions of the alkaloid described here have been studied. The alkaloid has a depressant action on the isolated rabbit heart and auricles. 5 mg and 10 mg/kg doses when administered intravenously in dogs produce an acute fall in blood pressure followed immediately by a gradual recovery to initial level. The fall in blood pressure is accompanied with cardiac depression.

Introduction

Berberis lycium (family Berberidaceae) is abundantly available around Murree hills and in Gallies. The aqueous root extract of the plant is used in the indigenous medicine for the treatment of hyperpyrexia, mild constipation, anorexia and haemorrhoids. The extract is also considered useful in peptic ulcers. Crude powdered roots taken with milk, are reported to relieve various painful conditions of joints.

The berberis are not easily distinguished from one another and considerable ambiguity still exists, especially as most of them are known by the same vernacular names and posses identical properties. The five varieties of *Berberis vulgaris* Linn, as given in the Flora of British India are now considered to be distinct species.[1,2] The isolation of umbellatine from *Berberis umbellata* and *B. lycium* was reported by Chatterjee. The roots of *Berberis lycium* were reexamined and a series of alkaloids separated. Results of pharmacological investigation of the colourless alkaloid provisionally named *berbenine* are being reported.

Experimental

Preparation of Solution

For pharmacological investigations alkaloidal solutions were prepared in dilute acetic acid with a pH of 6.5.

Drugs Used

Acetylcholine chloride 10 μg/ml, adrenaline 10 μg/ml, atropine sulphate 1 mg/ml, and acetic acid at 6.5 pH were used.

Isolated Rabbit Auricles

The auricles were suspended in an oxygenated Locke's solution kept at a temperature of 29°C. The volume of the bath was 50 ml. Contractions were recorded on a revolving smoked drum by a light straw directly attached to the auricles through a thread.

Isolated Rabbit Perfused Heart

Isolated hearts were perfused by Langendorff's technique using oxygenated Locke's solution at 37°C. Drugs (upto 0.5 ml) were injected into the cannula at the point of attachment of the aorta.

Intact Dog Heart

Effects on the heart were studied in dogs (anaesthetised with pentobarbitone sodium 33 mg/kg intraperitoneally) with intact circulation. The heart was well exposed by opening the chest and artificial respiration was given. The cardiac contractions were recorded through hooks attached either to the apex or the right auricle. Drugs were administered through the femoral vein.

Blood Pressure

Dogs (wt. 4-17.5 kg) anaesthetised with pentobarbitone sodium (33 mg/kg) intraperitoneally) were used. All the drugs were administered by injection into the femoral vein and the blood pressure was recorded from the common carotid artery through a mercury manometer.

In all the experiments 5% solution of sodium citrate, and heparine were used as anticoagulants. 5,000 units of heparine (in 1 ml solution) were injected into the bulb of the cannula inserted in the carotid artery prior to the removal of the clamp on the artery.

Results

Isolated Rabbit Auricles

A comparison of the effects of the alkaloidal solution was made with dilute acetic acid solution at 6.5 pH.

1.0 ml of the acetic acid solution was added to the bath, and was allowed to remain for 2 minutes. This did not produce any depressant effect. At the end of this interval the solution was washed out, and after the tissue reposed for 15 minutes 1.0 ml of 1 mg/ml solution of the alkaloid was instilled in the bath. This solution was also allowed to remain in contact with the tissue for two minutes and it was observed that the alkaloidal solution produces a well marked diminution in the amplitude of auricular contractions. For checking the sensitivity of the tissue, a response to 25 μg Ach was obtained at the beginning of the experiment (Fig. 1A.)

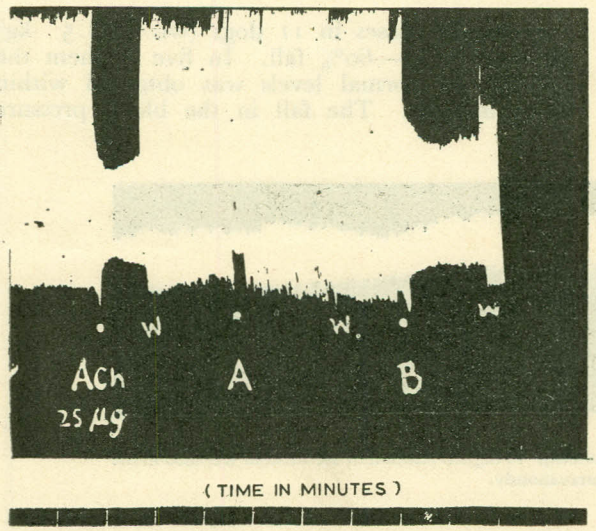

Fig. 1A.— Isolated Rabbit Auricles.
A. 1 ml acetic acid solution.
B. 1 ml solution of the alkaloid (1mg/ml).

The alkaloid can produce its depressant effect even in the presence of atropine. 100 μg atropine which effectively blocked the response to 25 μg. acetylcholine, could not antagonize the depressant action of 1 mg of the alkaloid. (Fig. 1B.)

ISOLATED RABBIT PERFUSED HEART

0.5 ml of 10 mg/ml solution of the alkaloid when injected into the tube produced a diminution in the rate and amplitude of cardiac contractions. This effect was obtained within about 10 seconds of the injection of the alkaloidal solution and reached to its maximum in 10 minutes. Recovery could not be obtained even in two hours. The injection of 0.5 ml of acetic acid solution before the administration of the alkaloidal solution produced no effect. Before observing the response

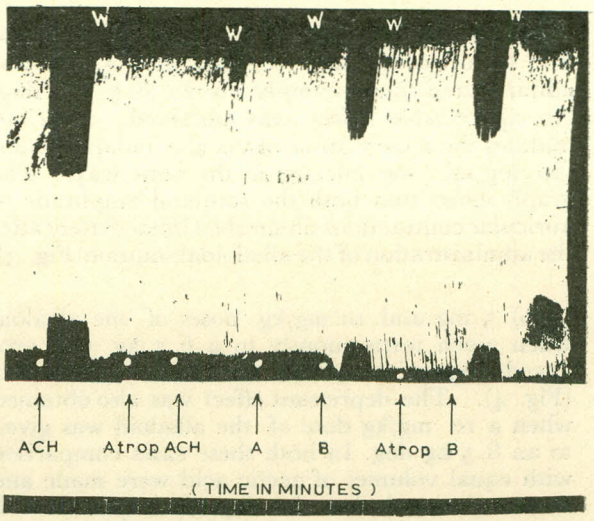

Fig. 1B.—Isolated Rabbit Auricles A. 1 ml acetic acid solution. B. 1 ml solution of the alkaloid (1 mg/ml) first given alone and then in the presence of 100μg. Atropine. All the solutions were allowed to remain in the bath for 1minute.

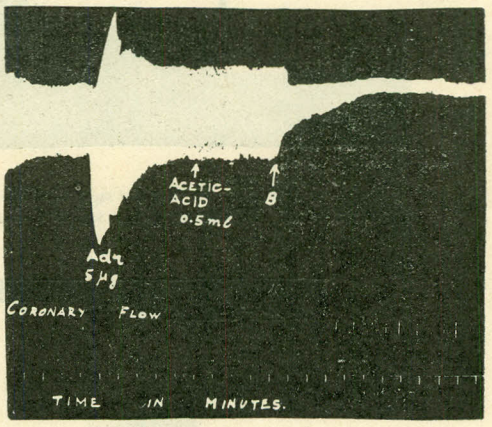

Fig. 2.—Isolated Rabbit Heart
10 mg/ml solution of the alkaloid was used in the experiment. At. "B" 0.5 ml of this solution was injected into the tube.

to acetic acid solution, 5 μg adrenaline was added to the perfusion fluid and its effects were recorded. (Fig. 2.)

The depressant effect on the myocardium is a prolonged one. In a series of experiments it was observed that the heart took 30-60 minutes to regain its original force of contraction after the administration of 0.2 and 0.5 mg of the alkaloid.

The myocardial depression is obtained even after the previous administration of atropine.

INTACT HEART

(a) Before injecting the alkaloidal solution, 8.5 ml of acetic acid solution at 6.5 pH was administered intravenously to an 8.5 kg dog. No appreciable effect was obtained. After 10 minutes the same volume of the alkaloidal solution (10 mg/ml) was injected in the same way. The graph shows that both the rate and amplitude of auricular contractions diminished immediately after the administration of the alkaloidal solution (Fig. 3).

(b) 5 mg and 10 mg/kg doses of the alkaloid when given intravenously to a 6.5 kg dog produced depression of the ventricular movements (Fig. 4). The depressant effect was also obtained when a 10 mg/kg dose of the alkaloid was given to an 8.5 kg dog. In both these cases comparison with equal volumes of acetic acid were made and it was observed that the depression produced is due to the alkaloidal content of the solution.

BLOOD PRESSURE

Blood pressure starts falling immediately after the i.v. administration of the alkaloid. The maximum fall is produced within 30-60 seconds followed by a gradual recovery to the initial level. Comparisons with equal volumes of acetic acid at 6.5 pH show that the hypotensive effect is exclusively due to the alkaloidal content of the solution and not due to the presence of acetic acid.

In an 8 kg dog a 5 mg/kg dose produced a fall from 155 to 90 mm Hg. In an other dog the same dose produced a fall from 175 mm Hg to 75 mm Hg.

10 mg/kg doses in 11 dogs (wt. 4-17.5 kg) produced a 50—60% fall. In five of them the recovery to normal levels was obtained within 60-90 minutes. The fall in the blood pressure

Fig 3.—Intact heart (Record of right auricular contractions). 10 mg/ml solution of the alkaloid was used in the experiment. At "B" 8.5 ml of this solution was given intravenously.

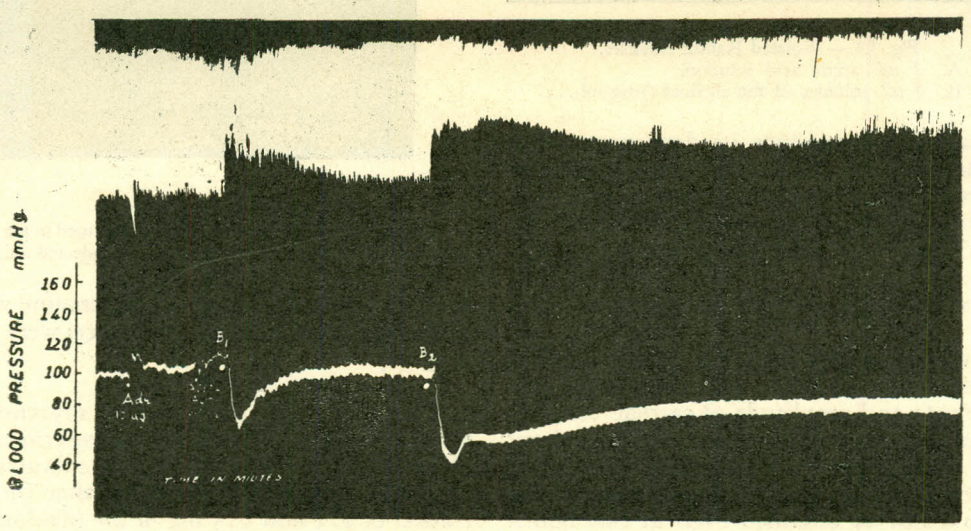

Fig. 4.—Intact heart. Above, record of ventricular contractions. Below, blood pressure in mmHg. B1. 5 mg/kg dose of the alkaloids given intravenously. B2. 10 mg/kg dose of the alkaoid given intravenously.

depends on the initial level (Table 1) and the gradual recovery starts immediately after the maximum fall is obtained. (Fig. 5).

TABLE 1.—BLOOD PRESSURE OF ANAESTHETISED DOGS BEFORE AND AFTER THE ADMINISTRATION OF 10 mg/kg DOSES OF THE ALKALOID.

Sr. No	Dog's wt. in kg	Before the injection	After the injection
1.	10	235	75
2.	9	200	55
3.	17·5	195	85
4.	10	170	65
5.	8	170	60
6.	18	165	75
7.	7	155	75
8.	8	145	60
9.	10	145	55
10.	6	135	40
11.	4	115	60

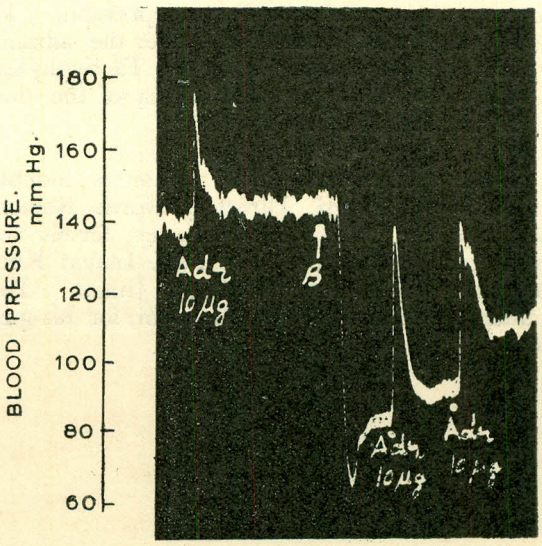

Fig. 6.—Dog's blood pressure. Hypertensive responses to 10 µg adrenaline before and after the intravenous administration of the alkaloid. Adr. Adrenaline; B 10 mg/kg dose of the alkaloid given intravenously.

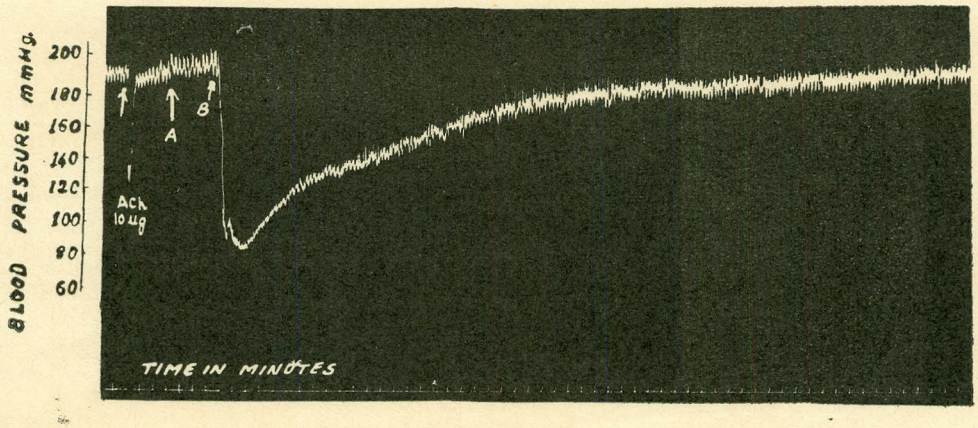

Fig. 5.—Dog's blood pressure response to 10 mg/kg dose of the alkaloid given intravenously.

Dog'swt., 17.5 kg.
Ach : Acetylcholine.
A : 17.5 ml acetic acid at 6.5 pH
B : 17.5 ml of 10 mg/ml solution of the alkaloid given intravenously.

In a 17.5 kg dog a 10 mg/kg dose produced a fall from 195 mm Hg to 85 mm Hg. After recovery to the initial state another dose of 10 mg/kg was injected which this time produced a fall to 115 mm Hg.

The hypertensive responses to adrenaline are not diminished when it is administered after a fall has been produced by 10 mg/kg doses of the alkaloid (Fig. 6).

Conclusions

The findings are summarised as follows:

(1) 5 mg and 10 mg/kg doses of the alkaloid when injected intravenously produce a sharp fall in the blood pressure. (2) The alkaloid has a depressant action on the isolated rabbit auricles and heart. This action is not opposed by atropine. (3) The fall in the blood pressure is

accompanied with cardiac depression. The depression begins immediately after the administration of the alkaloid. (**4**) Tachyphylaxis develops to the hypotensive effect of the doses given intravenously in succession.

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References

1. R.N. Chopra, *Indigenous Drugs of India* (1958).
2. R.N. Chopra, *Poisonous Plants of India* (1940).
3. R. Deininger, Pakistan J. Sci. Ind. Res. April-July (1959).
4. J.H. Burn. *Practical Pharmacology* (Blackwell Scientific Publication, Oxford, 1952).
5. K.S. Jamwal. J. Sci. Ind. Res., (New Delhi) **20,** 21-2 (1961).