Brit. J. Pharmacol. (1958), 13, 213.

A COMPARISON OF SOME PHARMACOLOGICAL PROPERTIES OF DIOSCORINE AND DIOSCINE

BY

J. L. BROADBENT* AND H. SCHNIEDEN

From the Department of Pharmacology, University College, Ibadan, Nigeria

(RECEIVED NOVEMBER 27, 1957)

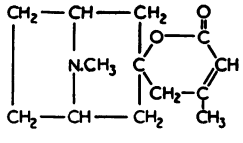
The alkaloids, dioscorine and dioscine, both obtained from yams, have been compared in respect of their convulsant activity, toxicity, analeptic action, local anaesthetic activity, adrenaline potentiating action, antidiuretic effect, and anti-acetylcholine activity. The alkaloids have similar properties, but in most respects dioscorine was the more potent. Aqueous solutions of dioscine are unstable.

The alkaloid dioscorine ($C_{13}H_{19}O_2N$) has been isolated from the tubers of *Dioscorea hirsuta* by Boorsma (1894) and the tubers of *Dioscorea hispida* by Levya and Guttierrez (1937). Dioscine ($C_{13}H_{21}O_2N$) is the name suggested for an alkaloid recently obtained from the tubers of *Dioscorea dumetorum* by Bevan, Broadbent, and Hirst (1956). In tropical lands tubers from varieties of these species are eaten. They are referred to locally as "yams." The alkaloids are of toxicological interest since poisoning characterized by convulsions may result from eating alkaloid-bearing varieties of yam.

In this paper the pharmacological properties of the two alkaloids, dioscorine and dioscine, are compared and contrasted.

MATERIALS AND METHODS

Dioscorine was supplied by Dr. A. R. Pinder, of the Department of Chemistry, University College, Cardiff, and dioscine by Professor C. W. L. Bevan, of the Department of Chemistry, University College, Ibadan, Nigeria. The chemistry of dioscine has been briefly described by Bevan *et al.* (1956), and that of dioscorine by Pinder (1952, 1953, and 1956), who proposes the following structure (Pinder, personal communication).



It has recently been reported by Bevan and Hirst (1958) that dioscine is probably an isomer of dihydrodioscorine.

The alkaloids, which were pale yellow liquids with an aromatic smell, were stored in stoppered tubes in a desiccator. Aqueous solutions of dioscorine were noticeably more opalescent than dioscine solutions of the same concentration. As dioscine is unstable in aqueous solution, freshly prepared solutions were used in the experiments except when otherwise stated.

Estimations of the intraperitoneal LD50 were made on groups of 20 white mice weighing from 18 to 26 g., the toxicity of the two alkaloids being determined simultaneously.

In studying the effects of the alkaloids on the blood pressure of the heparinized cat, the anaesthetic used was pentobarbitone sodium.

Isolated guinea-pig ileum preparations were suspended in aerated Tyrode solutions at 32°. Drugs were added directly to the bath. Local anaesthesia following intradermal injection was tested in guinea-pigs following the method of Bülbring and Wajda (1945). Antidiuretic actions were measured following the intravenous injection of the drugs into unanaesthetized hydrated male rats (weight 200 g. approximately) after the method of Ginsburg and Heller (1953). Analeptic effects were studied by measuring changes in the respiratory rate of rats anaesthetized with 60 mg./kg. of pentobarbitone sodium.

RESULTS

Convulsions.—In rats and mice both drugs caused convulsions. These were at first clonic but became tonic and death usually occurred in extensor spasm. The convulsions closely resembled those produced by picrotoxin. The LD50 value in mice was 60 mg./kg. for dioscorine and

* Present address : Department of Pharmacology, University of Leeds.

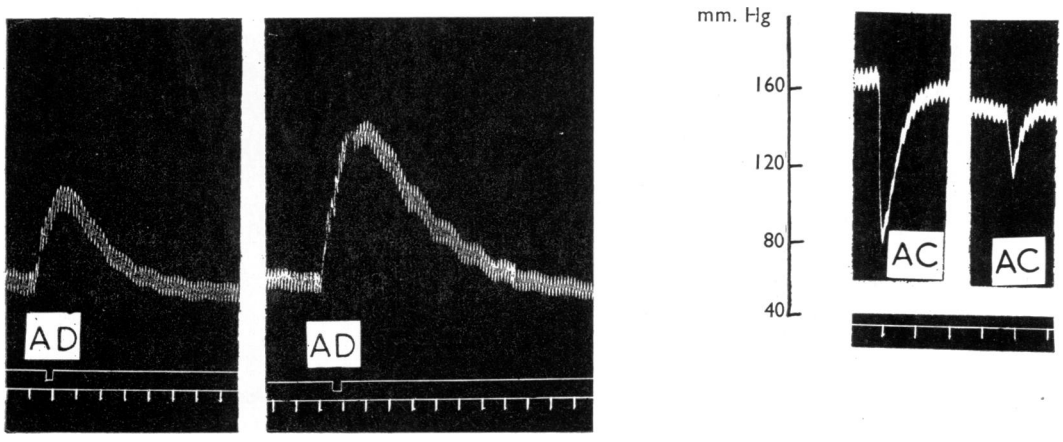


FIG. 1.—The effect of 10 μg. of adrenaline (AD) on the blood pressure of a 3 kg. spinal cat before and after 20 mg./kg. of dioscine given intravenously and the effect of 1 μg. of acetylcholine (AC) on the blood pressure of a 3.75 kg. cat before and after 15 mg./kg. of dioscine given intravenously are shown. Similar experiments have been performed thrice with dioscine and twice with dioscorine. In all experiments adrenaline actions were potentiated and acetylcholine effects were reduced. Time, 30 sec.

100 mg./kg. for dioscine. With dioscine the convulsions seemed to be at least partly spinal in origin, since spasms could be produced in spinal preparations. Dioscine convulsions in an anaesthetized cat were not attended by a measurable rise of rectal temperature or by hypoglycaemia.

Instability of Aqueous Solutions of Dioscine.—1% solutions of dioscine and dioscorine were injected intraperitoneally into mice at the estimated LD100 of 110 mg./kg. of dioscorine, and 160 mg./kg. of dioscine. Each solution killed 10/10 mice. The solutions were left overnight in a refrigerator, and tested on the following day when dioscorine killed 10/10 mice but dioscine killed only 4/10. After two days dioscorine killed 10/10 mice and dioscine 0/10 mice. When a week old, dioscorine solution killed 9/10 animals. It is thus apparent that aqueous solutions of dioscine rapidly lost convulsant properties. Anti-acetylcholine activity as measured on the isolated guinea-pig ileum was also less in old solutions of dioscine.

Analeptic Activity.—40 mg./kg. dioscorine and 60 mg./kg. dioscine, when administered intravenously, increased the respiratory rates of anaesthetized rats These doses were close to the convulsant dose.

Local Anaesthetic Effects.—A 5% solution of either dioscorine or dioscine when applied to the corneae of guinea-pigs did not prevent the corneal reflex, in fact some blepharospasm was noted. However, when injected intradermally into 12 guinea-pigs, both alkaloids had local anaesthetic activity, dioscorine in 0.5% solution and dioscine in 1% solution having approximately the same activity as 0.05% cocaine.

Effects on Cat Blood Pressure.—Neither substance produced significant changes in the cat blood pressure when injected intravenously in doses of 10 to 20 mg./kg., but the blood pressure responses to acetylcholine and adrenaline were altered. The fall in blood pressure produced by acetylcholine was reduced, and the rise in blood pressure caused by adrenaline was potentiated (Fig. 1). Mydriasis occurred during the intravenous injection of the alkaloids.

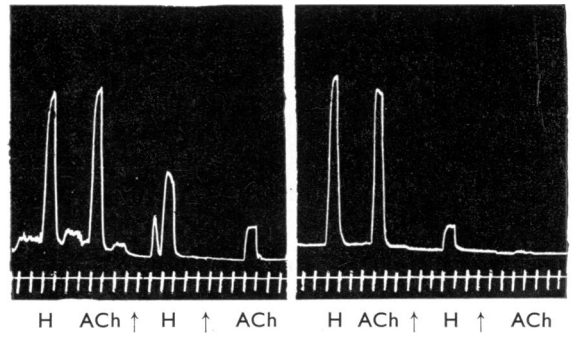


FIG. 2.—Isolated guinea-pig ileum preparation showing the effects of histamine (H) 0·5 μg. of base using the acid phosphate, and acetylcholine (ACh) 0·7 μg. The same ileum preparation was used for both tracings. The bath volume was 50 ml. The arrow in the first tracing indicates the addition to the bath of dioscine in a concentration of 10^{-5}, and in the second tracing the addition of dioscorine in the same concentration. Both alkaloids have anti-acetylcholine and antihistamine actions, but dioscorine is more potent. The experiment has been repeated several times with similar results. Time, 30 sec.

Effects on Isolated Guinea-pig Ileum.—When added to this preparation in concentrations of 10^{-5} a diminution of spontaneous movements was sometimes seen. The responses to acetylcholine and histamine were both reduced, the former more so than the latter, and dioscorine was more potent in these respects than dioscine (Fig. 2).

Dioscorine also showed slight anti-acetylcholine activity at a concentration of 10^{-6}, but dioscine was inactive at this concentration.

Isolated Rabbit Heart.—Dioscorine 2 mg. and dioscine 2 mg. had no effect on the isolated rabbit heart set up in the manner of Langendorff. But in these doses they diminished the responses of the heart to a subsequent injection of acetylcholine.

Antidiuretic Actions.—1 mg. of dioscorine had the activity of approximately 100 μU. of Pitressin, whereas 1 mg. of dioscine had the activity of approximately 20 μU. Pitressin.

Discussion

The pharmacology of dioscorine has been briefly described by Schutte (1897), Gorter (1911), and Levya and Guttierrez (1937). A more detailed account has been given by Green (1953). He described picrotoxin-like convulsions and analeptic effects and estimated that the LD50 for mice by intraperitoneal injection was 120 mg./kg., namely twice the value reported here. His observations that concentrations of 10^{-5} dioscorine did not affect the responses of isolated guinea-pig ileum to histamine and acetylcholine, and that doses of 20 mg./kg. of dioscorine did not alter the responses of the cat blood pressure to acetylcholine and adrenaline, differ from our findings.

Precise comparisons between the two alkaloids are hampered by the instability of dioscine in aqueous solutions. However, our experiments show that dioscorine and dioscine have actions that are qualitatively similar, but that dioscorine is the more toxic and has greater local anaesthetic activity, antidiuretic activity and depressant actions on the isolated guinea-pig ileum. Both resemble cocaine in causing potentiation of the pressor action of adrenaline on the cat blood pressure.

The most striking effect of the alkaloids, however, is the ability to cause convulsions, and this may be correlated with the convulsions that occur when alkaloid-bearing yams are eaten. The convulsions resemble those produced by picrotoxin and may be readily antagonized with pentobarbitone sodium (Broadbent and Reiff, 1956). Both alkaloids also resemble picrotoxin in possessing antidiuretic actions (Koiwa, 1939).

We consider that our results are consistent with the view that the two alkaloids are closely related chemically.

The authors are very grateful to Dr. A. R. Pinder and Professor C. W. L. Bevan for supplies of the alkaloids, and wish to acknowledge financial aid from the West African Drugs and Medicines Research Fund of the Nigerian Government.

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