SOME OBSERVATIONS ON THE PHARMACOLOGY OF 10-METHOXYDESERPIDINE

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10-Methoxydeserpidine caused a slow sustained fall in the arterial blood pressure of the anaesthetised cat when doses of 2 to 4 mg./kg. were given, an effect seen only when the initial blood pressure was high. Unlike reserpine and deserpidine, 10-methoxydeserpidine did not cause ptosis or loose stools in mice or rats when used at doses of from 10 to 80 mg./kg. and although pentobarbitone sleeping time was not increased, at higher doses of 40 to 80 mg./kg. there was reduction of motor activity, respiratory depression and some animals died. Unlike deserpidine the 10-methoxy derivative had no effect on the pressor responses to compression of the abdominal aorta or stimulation of the splanchnic nerve, but depressed the response to occlusion of the common carotid arteries. The LD50 of 10-methoxydeserpidine was found to be 82 $\pm$ 2·6 mg./kg. in mice. Methyl reserpate and reserpic acid showed reserpine-like activity in intact animals and isolated tissues only at very high doses.

EXTRACTS of *Rauwolfia serpentina* and the alkaloid reserpine are employed in the treatment of hypertension and mental illness. Reserpine and extracts which contain it may cause side effects, among the more important of which is mental depression. This has led to a search for compounds with reserpine-like antihypertensive properties, but which do not cause mental depression. Velluz[1], Velluz, Peterfalvi and Jequier[2], Gros, Peterfalvi and Jequier[3] and Peterfalvi and Jequier[4] have shown that 10-methoxydeserpidine meets this requirement. In addition it was less toxic than reserpine in mice and as actively hypotensive as reserpine in anaesthetised cats and rabbits. In the rat, made hypertensive with sodium chloride and desoxycorticosterone acetate it exerted a marked hypotensive action, and abolished the response to carotid artery occlusion[4]. In clinical trials[3,5] 10-methoxydeserpidine reduced both systolic and diastolic blood pressures in hypertensive patients.

Deserpidine itself has been studied by a number of workers who have reported its effects upon intact animals[6–13]. It has reserpine-like hypotensive and sedative activity[6–9,11,13] and in all other respects appears to have typical reserpine-like pharmacological properties, indicating that the removal of the 11-methoxy group causes no qualitatively important effects. We have compared the properties of deserpidine with those of 10-methoxydeserpidine on isolated tissues and organs and in intact anaesthetised animals and have also tested reserpic acid and methyl reserpate; compounds which lack the trimethoxybenzoic acid moiety of the reserpine molecule. Plummer and his associates[13] and Boin[14] point out that, in experimental animals, reserpic acid lacks the sedative and hypotensive effects of reserpine. Methyl reserpate has about one-third

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TABLE I

COMPARISON OF THE PHARMACOLOGICAL EFFECTS OF 10-METHOXYDESERPIDINE WITH DESERPIDINE, RESERPIC ACID HYDROCHLORIDE AND METHYL RESERPATE

Preparation	10-Methoxydeserpidine	Deserpidine	Reserpic acid hydrochloride	Methyl reserpate
B.P. Anaesthetised cat. (See also refs. 4, 7 and 8)	2–6 mg./kg. No immediate effect. In cats with low initial blood pressure level no fall even up to 6 hr. after first dose of drug. 9 mg. caused slight fall after 3 hr. When initial blood pressure level high, slow sustained fall in blood pressure with 2–4 mg./kg.	2–4 mg./kg. Immediate, short-lived fall, gradual secondary fall (40–60 mm.) at maximum in 1–1½ hr. Bradycardia	2–4 mg./kg. Immediate, short-lived fall, slight secondary fall after 2 hr.	2–4 mg./kg. Little or no immediate or delayed fall unless initial blood pressure high when 4 mg. caused 20–30 mm. fall and 5–10 mg. 30–40 mm. fall, after 1–1½ hr.
	2–6 mg./kg. No antagonism but slight increase in pressor response to Ad. or NA. (2–5 μg./kg.)	1–2 mg./kg. Increase in pressor responses to Ad. or NA. (1–2 μg./kg.)	2–7 mg./kg. No effect on pressor responses to Ad. or NA. (1–4 μg./kg.)	5–7 mg./kg. Little or no modification of pressor responses to Ad. or NA. (1–2 μg./kg.)
	5 mg./kg. No modification of depressor responses to 5 μg./kg. Hm. or Ach.	1–2 mg./kg. No modification of depressor responses to 1–5 μg./kg. Hm. or Ach.	2–5 mg./kg. No modification of depressor responses to 1–5 μg./kg. Hm. or Ach.	2–5 mg./kg. No modification of depressor responses to 1–5 μg./kg. Hm. or Ach.
Vasopressor reflexes: (i) Bilateral occlusion of common carotid arteries. (See also refs. 4, 8)	2–4 mg./kg. No immediate or delayed effect when initial blood pressure low. Reversible depression when initial level high (>150 mm. Hg)	2 mg./kg. Delayed reduction in response (40 min.)	2–5 mg./kg. No effect	4–5 mg./kg. No effect
(ii) Compression of abdominal aorta	2–4 mg./kg. No immediate or delayed effect	1–2 mg./kg. Marked reversible inhibition of responses	2–5 mg./kg. No effect	4–5 mg./kg. No effect
(iii) Electrical stimulation of left greater splanchnic nerve	2–6 mg./kg. Slight increase in magnitude of response	1–2 mg./kg. Delayed inhibition of pressor response (40–60 min.). Recovery in 2–3 hr.	2–5 mg./kg. No effect	4–5 mg./kg. No effect
(iv) Electrical stimulation central end of cut vagus. (See also ref. 7)	2–6 mg./kg. Abolition of pressor response followed by reversal (Fig. 1)	1–2 mg./kg. Abolition and reversal of responses (delayed 20–40 min.). Recovery incomplete after 3 hr.	5 mg./kg. No effect	5 mg./kg. No effect
Nictitating membrane. (See also refs. 4, 7)	5 mg./kg. No effect	1–2 mg./kg. No effect	4–5 mg./kg. No effect	4–5 mg./kg. No effect

TABLE I—*continued*

Preparation	10-Methoxydeserpidine	Deserpidine	Reserpic acid hydrochloride	Methyl reserpate
Respiration (cat). See also refs. 4, 8)	2–5 mg./kg. *Slight respiratory depression in* most cases but in some marked depression of respiration (Fig. 2)	5 mg./kg. Slight respiratory depression	5 mg./kg. No effect	1–2 mg./kg. No effect
B.P. Anaesthetised rat	300 μg.–1 mg. Fall in blood pressure after about 20 min. Maximum in 1 hr. Slight enhancement of pressor *responses to Ad. or* NA. (1 μg.). No effect on depressor response to 5-HT (5 μg.)	100–200 μg. Immediate, sharp fall of small magnitude, prolonged secondary fall (40–50 mm. after 40–60 *min.*). Enhancement of pressor responses to Ad. and NA. (1–2 μg.) 100–200 μg. No effect on depressor response to 5 μg. 5-HT	1–2 mg. Immediate sharp fall. No secondary fall. Delayed (20–40 min.) enhancement of pressor responses to Ad. and NA. (1–2 μg.) 1–2 mg. As deserpidine	1–2 mg. Immediate sharp fall. No secondary fall. No effect or slight inhibition of responses to Ad. and NA. (1–2 μg.) 1–2 mg. As deserpidine
Cardiac muscle: (i) Rabbit heart	20–120 μg. *Decrease in rate, tone and ampli*tude and increase in outflow (Fig. 3)	40–100 μg. Decrease in rate, tone and amplitude (irreversible). Increase in outflow	125–500 μg. Slight fall in tone and increase in outflow	0·5–1·0 mg. No effect on tone or amplitude. Small increase in outflow 20–50 μg/ml. Perfused for 15 min. caused reversible depression in rate, tone and amplitude.
(ii) Guinea pig or rabbit auricles	18–30 μg. Slight reversible reduction in responses to NA. and Ad. (1–2 μg.) 18–60 μg./ml. No effect on response to Ach. (0·5 μg./ml.)	4–14 μg./ml. Reversible reduction in rate and amplitude 4–30 μg. ml. Slight reversible reduction in responses to NA. and Ad. (1–2 μg.). No influence on response to Ach. (0·1–0·5 μg./ml.)	200–500 μg./ml. No effect on responses to NA. and Ad. (1–2 μg.) 10–20 μg./ml. No effect on responses to Ach. (0·1–0·5 μg./ml.)	20–50 μg./ml. No effect on responses to NA. and Ad. (1–2 μg.) 8–20 μg./ml. No effect on responses to Ach. (0·1–0·5 μg./ml.)
Vascular smooth muscle: (i) Horse carotid arteries	20–200 μg./ml. Slight reversible inhibition of Ach. (0·01–0·1 μg./ml.) Ad. (0·1–0·2 μg./ml.) NA. (0·1–0·2 μg./ml.) and 5-HT (0·5 μg./ml.) - induced contractions	5–10 μg./ml. Marked, incompletely reversible inhibition of Ach.-induced contractions. (Ach. 0·01–0·04 μg./ml.). Reversible antagonism to Ad. or NA.-induced contractions. (Ad. or NA. 0·01–0·02 μg./ml.)	100–200 μg./ml. Reversible inhibition of Ach.-induced contractions (Ach. 0·01–0·04 μg./ml.). No effect on tone	100–200 μg./ml. Reversible inhibition of Ach.-induced contractions (Ach. 0·01–0·04 μg./ml.). No effect on tone

TABLE I—*continued*

Preparation	10-Methoxydeserpidine	Deserpidine	Reserpic acid hydrochloride	Methyl reserpate
(ii) Rat hindquarters	500 μg.–2 mg. No direct vasodilatation. No effect on Ad., NA. or 5-HT (0·5–1 μg.) vasoconstriction	50–300 μg. No direct vasodilatation. Marked reduction in constrictor responses to Ad. and NA. (1–2 μg.). No effect on responses to $BaCl_2$ (0·25–1 mg.) or 5-HT (1 μg.)	1–2 mg. No direct vasodilatation. Reversible reduction in constrictor responses to Ad. or NA. (1–2 μg.) and as deserpidine	0·5–1 mg. No direct vasodilatation. Slight reduction in constrictor responses to Ad. and NA. (1–2 μg.) and as deserpidine
Intestinal smooth muscle: (i) Guinea pig ileum	20–75 μg./ml. No direct action or slight relaxation. Inhibition of stimulant effects of Ach.(0·1–1·0 μg./ml.) Hm (0·01–0·1 μg./ml.) $BaCl_2$ (0·25–1 mg./ml.) and 5-HT (1·0–5·0 μg./ml.). Recovery delayed but complete	5–10 μg./ml. No direct action. Marked inhibition of stimulant effect of Ach. (0·01–0·1 μg./ml.) Hm (0·01–0·1 μg./ml.) $BaCl_2$ (0·25–1 mg./ml.) and 5-HT (1–5 μg./ml.). Recovery delayed but complete	50–100 μg./ml. No direct action. Marked inhibition of stimulant effects of Ach. (0·01–0·1 μg./ml.) Hm (0·01–0·1 μg./ml.) $BaCl_2$ (0·25–1 mg./ml.) and 5-HT (1–5 μg./ml.). With lower doses effects rapidly reversible, higher doses as deserpidine	150–500 μg./ml. As reserpic acid hydrochloride
(ii) Rabbit duodenum	20–75 μg./ml. Relaxation of gut with inhibition of peristalsis. Recovery 20 min.	5–10 μg./ml. Relaxation of gut with inhibition of peristalsis. Recovery 20–40 min. 10–20 μg./ml. Marked antagonism to Ach. (0·01 μg./ml.)-induced contractions. Recovery 1–1½ hr. Antagonism to Ad. (0·1 μg./ml.) - induced relaxation. Recovery 20 min.	50–100 μg./ml. Brief reversible relaxation, reduction of tone and inhibition of peristalsis 18–50 μg./ml. Reversible antagonism to Ach. (0·01 μg./ml.)-induced contractions. No effect on Ad. (0·1 μg./ml.)-induced relaxation of gut	100–200 μg./ml. Brief reversible relaxation, reduction of tone and inhibition of peristalsis. Reversible antagonism to Ach. (0·01 μg./ml.)-induced contractions.
Skeletal muscle. Frog rectus abdominis	50–100 μg./ml. Contraction of muscle (winter frogs). Irreversible antagonism to Ach. (1·0–3·0 μg./ml.)	5–10 μg./ml. No direct action. Slight irreversible inhibition of effects of 0·1–1·0 μg./ml. Ach.	50–100 μg./ml. No direct action. Slight reversible inhibition of effects of 0·1–1·0 μg./ml. Ach.	100–200 μg./ml. As reserpic acid hydrochloride

Note: The following abbreviations are used in this Table. Ach. for acetylcholine chloride: Ad. for adrenaline bitartrate: NA. for noradrenaline bitartrate: 5-HT for 5-hydroxytryptamine creatinine sulphate: Hm for histamine acid phosphate: and $BaCl_2$ for barium chloride.

of the potency of reserpine, as shown by the mouse ptosis assay[15], but has no reserpine-like activity in the dog[14].

Experimental and Results

The methods used were similar to those reported previously[16]. The results are set out in Table I. In some instances we have repeated the experiments of others and where this has been done it is indicated in the table. Rat blood pressure was recorded by the method of Dekanski[17] using Condon's manometer[18]. Experiments on isolated spirals of horse carotid arteries were as described by Kirpekar and Lewis[19]. Ptosis in mice and rats was measured by the method of Rubin and Burke[15]. Effects upon barbiturate sleeping time were measured by

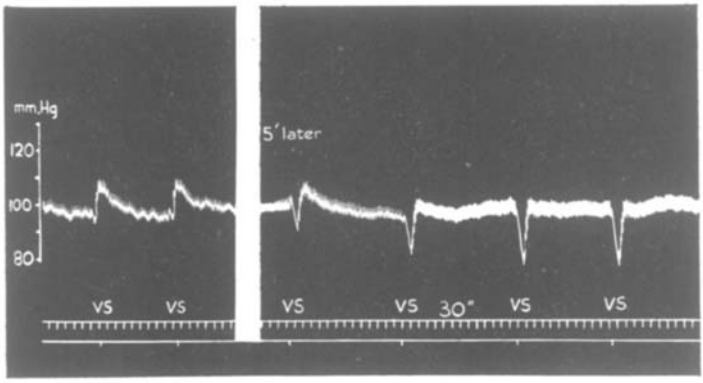

Fig. 1. Influence of 6 mg./kg. 10-methoxydeserpidine on the response to stimulation of the central end of the cut vagus of the cat. The drug was given 5 min. before the subsequent stimulus. Stimulation (VS) was with 10 sec. bursts of square wave impulses at 10 volts, 2 msec. duration and at a frequency of 1,000/min.

the method of Cronheim and his colleagues[20] but using 60 mg./kg. of sodium pentobarbitone. The intraperitoneal LD50 was estimated in groups of 20 mice, 15 to 16 g., by the method of Miller and Tainter[21].

Solutions of methyl reserpate, reserpic acid hydrochloride, deserpidine and 10-methoxydeserpidine were prepared by dissolving the solid in the minimal amount of glacial acetic acid and adjusting to volume with distilled water. The pH of the final solution was from 3·4 to 3·6. Control solutions prepared in the same way and at the same pH were used throughout for purposes of comparison.

Discussion

10-Methoxydeserpidine was found to cause a delayed fall in the arterial blood pressure of the anaesthetised cat when the initial blood pressure level was high. The effects of deserpidine on the arterial blood pressure were more marked and we have confirmed the observations of earlier workers[4,7,8]. 10-Methoxydeserpidine was less potent than deserpidine

in lowering the rat's arterial blood pressure but otherwise had similar effects. It caused bradycardia in the cat and both deserpidine and 10-methoxydeserpidine caused an increase in the pressor responses to adrenaline and noradrenaline. 10-Methoxydeserpidine reduced the pressor response to carotid artery compression, an effect shown by deserpidine. Unlike deserpidine the 10-methoxy compound did not inhibit the pressor response to compression of the abdominal aorta, had very little effect on the response to splanchnic nerve stimulation and did not

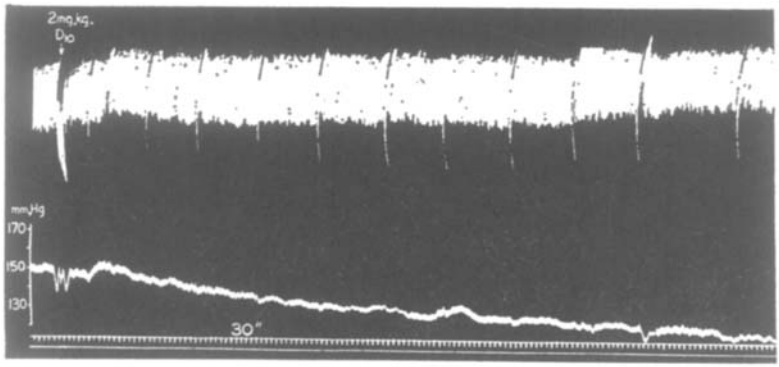

Fig. 2. Effect of 10-methoxydeserpidine (D_{10}) on respiration (upper record) and blood pressure (lower record) of the pentobarbitone-anaesthetised cat.

cause ptosis, diarrhoea or sedation in rats at doses of up to 20 mg./kg. In mice 40 to 80 mg./kg. of 10-methoxydeserpidine caused drowsiness and a reduction in motor activity but it was much less effective even at these dose levels than deserpidine or reserpine.

Sleeping time experiments indicated that at higher dose levels of 10-methoxydeserpidine there is a significant ($P = 0{\cdot}1$) increase in pentobarbitone sleeping time which may be related to respiratory depression and not therefore a typical reserpine-like effect.

The LD50 was found to be $82 \pm 2{\cdot}6$ mg./kg. in mice, a much lower figure than that obtained elsewhere[4]. Death was due to respiratory failure, the heart continuing to beat some time after respiration had ceased.

This change in pharmacological properties must presumably be attributed to properties conferred on the molecule by the change in position of the methoxy group from the 11- to the 10- position. More marked central activity is found in reserpine and in deserpidine. In the former there is a 10-methoxy group which is absent from the latter which may mean that the 10-methoxy group in 10-methoxydeserpidine either hinders the fit of the molecule on to the central receptor sites or perhaps prevents it from reaching them.

In the isolated perfused rat hindquarters 10-methoxydeserpidine did not inhibit vasoconstriction due to adrenaline, noradrenaline or 5-hydroxytryptamine. Otherwise its properties, as far as we have ascertained them (Table I), are similar to those of deserpidine.

Methyl reserpate and reserpic acid had little effect on the blood pressure of the cat and rat, even when doses about ten times greater than those of deserpidine or 10-methoxydeserpidine were used and, as pointed out by earlier workers, removal of the ester group caused almost complete

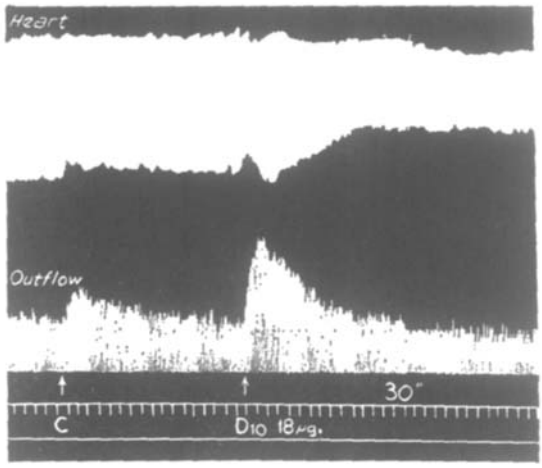

FIG. 3. Rabbit heart. Influence of 10-methoxydeserpidine on heart (upper record) and outflow from heart (lower record). At D_{10}, 18 µg. 10-methoxydeserpidine and at C control solution injected into the cannula.

loss of typical reserpine-like activity[13–15]. On isolated organs typical reserpine-like effects were shown but very large doses were needed. This seems to indicate that removal of the ester group causes a sharp fall in potency but does not completely eliminate all reserpine-like activity.

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