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Comparative Pressor Effects of Parahydroxyphenylisopropylamine (Paredrine) and Parahydroxyphenylisopropylmethylamine (Paredrinol).

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The introduction of new sympathomimetic amines is of interest to the pharmacologist and the clinician. Two recently developed substances of this group which have been described under the names 'paredrine' and 'paredrinol' are of especial interest in that as compared with epinephrine, they are stable, having an action which is prolonged and effective on oral administration. Parahydroxyphenylisopropylamine (Paredrine) has been investigated in this country but the reports have been few in number. Parahydroxyphenylisopropylmethylamine (Paredrinol) which is the N methyl derivative of paredrine (Fig. 1) has received a great deal of attention in the German literature under the trade name "Veritol."[1] Special advantages over other sympathomimetic substances have been ascribed to this compound, and the drug has been recommended as a superior agent in the treatment of shock. In this country, Stead and Kunkel[2] studied extensively the mechanism of the pressor action of paredrinol and concluded that this resulted from one or both of the following mechanisms: (1) a direct vaso-constrictor effect on minute blood vessels, and (2) a primary increase in venous tone causing an increased venous return to the heart and a secondary rise in arterial pressure. Kunkel, Stead and Weiss[3] concluded that paredrinol is a useful drug in the treatment of collapse caused by the pooling of blood in a dilated venous system.

Although there are studies on the pressor effect of paredrine, there are no comparative studies of the two related compounds. Alles

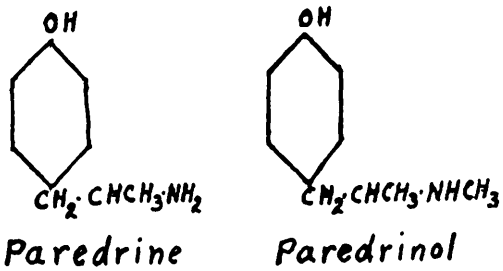

FIG. 1.
Chemical Structure of Paredrine and Paredrinol.

and Prinzmetal[4] have shown that paredrine has a more intense pressor action than phenylisopropylamine. Abbott and Henry[5] concluded that paredrine is about twice as effective as ephedrine in raising blood pressure. Altschule and Iglauer[6] found that paredrine was a more effective pressor substance than benzedrine and concluded that the drug may be useful in the treatment of certain types of

1 Rein, H., *Arch. f. exp. Path. u. Pharmakol.*, 1937, **187**, 429; Rein, H., *Klin. Wchnschr.*, 1937, **16**, 700; Rein, H., *Arch. f. exp. Path. u. Pharmakol.*, 1937, **187**, 617; Lindner, W., *Arch. f. exp. Path. u. Pharmakol.*, 1937, **187**, 444; Schneider, D., *Klin. Wchnschr.*, 1937, **16**, 736; Robbers, H., *Munchen. med. Wchnschr.*, 1937, **84**, 819; Grosse-Brockhoff, F., and Kaldenberg, F., *Klin. Wchnschr.*, 1937, **16**, 948; Schneider, H., and Kipp, H., *Klin. Wchnschr.*, 1937, **16**, 1672; Schondorf, T., *Munchen. med. Wchnschr.*, 1938, **85**, 333; Klostermeyer, W., and Jonsson, B., *Klin. Wchnschr.*, 1937, **16**, 1724; Meyer, F., and Spiegelhoff, W., *Klin. Wchnschr.*, 1937, **16**, 1342; Grosse-Brockhoff, F., and Kaldenberg, F., *Arch. f. exp. Path. u. Pharmakol.*, 1938, **188**, 383.

2 Stead, E. A., Jr., and Kunkel, P., *J. Clin. Invest.*, 1939, **18**, 439.

3 Kunkel, P., Stead, E. A., Jr., and Weiss, S., *J. Clin. Invest.*, 1939, **18**, 679.

4 Alles, G. A., and Prinzmetal, M., *J. Pharm. and Exp. Therap.*, 1933, **48**, 161.

5 Abbott, W. O., and Henry, C. M., *Am. J. Med. Sc.*, 1937, **193**, 661.

6 Altschule, M. D., and Iglauer, A., *J. Clin. Invest.*, 1939, **18**, 476.

TABLE I.
Comparison of the Maximum Pressor Responses (in mm of Hg) Following the Subcutaneous Administration of Paredrine and Paredrinol in Doses of 20 mg and Doses of 40 and 80 mg by Mouth.

	Subcutaneous 20 mg		Oral 40 mg		Oral 80 mg	
	Systolic	Diastolic	Systolic	Diastolic	Systolic	Diastolic
Paredrine	37	14	54	14	82	33
Paredrinol	8	0	40	14	28	18
Paredrine	34	10	60	16	48	10
Paredrinol	8	0	32	6	40	12
Paredrine	58	32	14	6	28	18
Paredrinol	32	4	6	0	11	2
Paredrine	30	10	25	16	78	28
Paredrinol	5	2	16	17	30	18

shock. Nathanson[7] demonstrated that paredrine was very effective in the prevention of the cardiac standstill which may be induced in man by pressure on the carotid sinus. In several instances, studying the comparative effects of paredrine and paredrinol by this method it was found that paredrine was definitely more active. It seemed desirable, therefore, to study the comparative pressor actions of these compounds.

Procedure. Fifteen subjects were studied from the hospital wards. These consisted chiefly of convalescent post-operative patients who were confined to bed. The paredrine was administered as the hydrobromide and the paredrinol as the sulphate.* The studies were made under basal conditions, and were all carried out in the morning with breakfast omitted. Repeated observations were made under the same conditions. After several control readings of the blood pressure the drug was administered, and subsequent blood pressure readings were made at 5, 15, 30, 45 and 60 min after the subcutaneous administration; and 15, 30, 60 and 90 min; and in 2 instances, 2 hr after the oral administration. After a subject had received one of the drugs, at least 24 hr elapsed before studies were repeated with the second compound. Fifteen subjects received both drugs subcutaneously in doses of 20 mg. Nine subjects had both compounds by mouth in doses of 40 mg and 4 of these also received 80 mg by mouth.

Table I shows the results in 4 subjects receiving 20 mg subcutaneously and 40 and 80 mg by mouth.

Figure 2 shows the blood pressure responses in 4 subjects after the subcutaneous administration of paredrine and paredrinol.

Results. In each instance a rise in arterial pressure was observed which varied greatly in different individuals. In every case, paredrine showed a much greater rise of pressure than paredrinol. On oral administration, the pressor effect was observed in 15 minutes in most instances, and the maximum effect occurred in 30 to 60 min. The duration of the pressor action with the 40 mg dose of paredrine was 60 to 90 min, and with 80 mg one and a half to 2 hr. In each instance Paredrine showed a considerably more prolonged effect than paredrinol. Following the subcutaneous injection, the onset of the effect was within 5 to 10 minutes; and the maximum effect was observed usually within 15 to 30 min. The blood pressure returned to normal in an hour in 13 of the 15 cases. The duration of the effect was again consistently shorter with the paredrinol.

Conclusions. Paredrine and paredrinol have a definite pressor effect in man when administered orally or subcutaneously. The systolic pressure is much more influenced than the diastolic pressure. Paredrine consistently

[7] Nathanson, M. H., *Ann. Int. Med.*, 1939, **12**, 1855.

* The Paredrine Hydrobromide was supplied by the Smith, Kline and French Laboratories of Philadelphia, and the Paredrinol Sulphate by Dr. Gordon Alles of Pasadena.

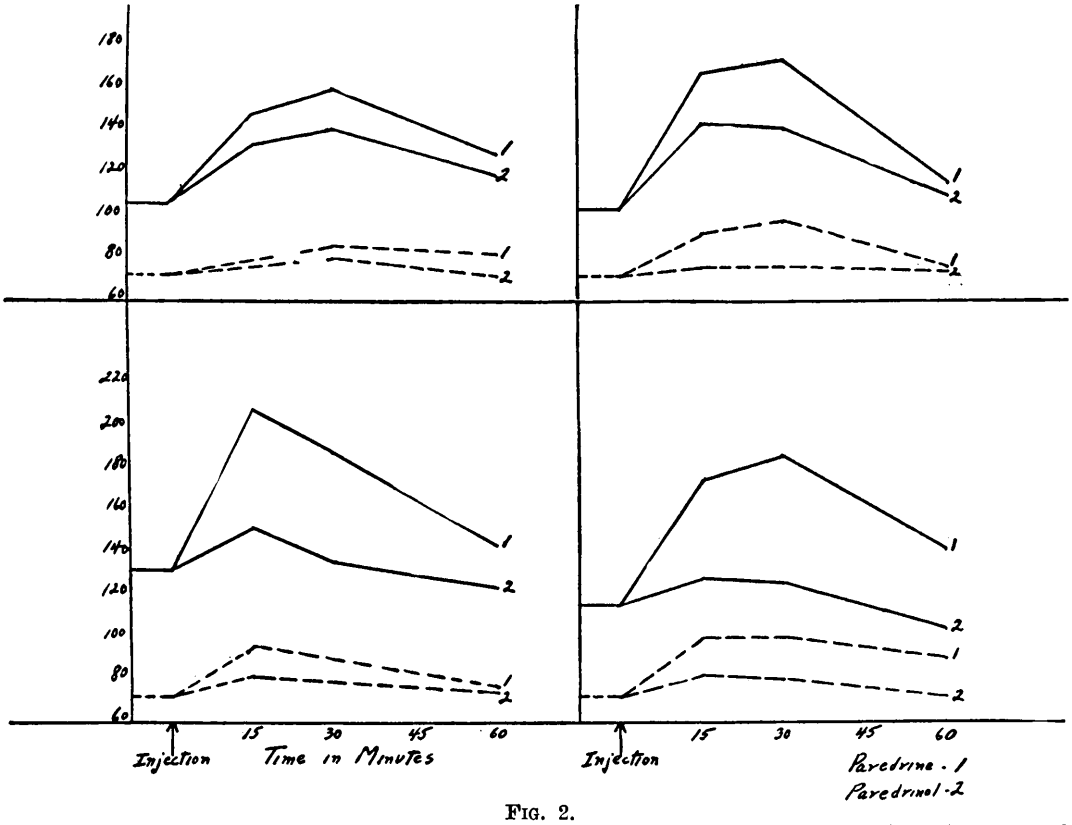

FIG. 2.

Typical course of blood pressure reaction following the subcutaneous administration of 20 mg of paredrine and 20 mg of paredrinol in 4 subjects. (1) Represents the response to paredrine and (2) the response to paredrinol. Solid lines indicate the systolic pressures and broken lines the diastolic pressures.

shows a much greater and more prolonged pressor action than paredrinol. There is a marked variation in response in different individuals to a given dose.

A comparison of the results of oral and subcutaneous administration in the same individual indicates in most instances a complete or practically complete absorption and utilization of these compounds when administered by mouth.