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COMPARISON OF EFFECTS OF VALYL^3-OXYTOCIN AND SYNTOCINON ON THE CARDIO-VASCULAR SYSTEM OF MAN

BY

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Valyl^3-oxytocin has similar circulatory effects in man to those of Syntocinon (synthetic oxytocin). On intravenous administration, it caused a rise in limb blood flow and in pulse rate and a fall in blood pressure. It had a direct vasodilator effect on limb blood vessels. Valyl^3-oxytocin was 1.5 to 2 times more potent than Syntocinon in terms of its circulatory effect in man. The circulatory effects of valyl^3-oxytocin were less readily antagonized by vasopressin than are those of Syntocinon.

It has been shown recently by Kitchin, Lloyd, and Pickford (1959) that both Pitocin and synthetic oxytocin (Syntocinon), administered intravenously, cause an increase in limb blood flow, accompanied by a fall in blood pressure and a rise in pulse rate and cardiac output. The vasodilatation in the limbs appears to be due to a direct action of the hormone on blood vessels.

Valyl^3-oxytocin is one of a series of structural analogues of oxytocin recently described by Boissonnas, Guttmann, Jacquemond, Waller, Konzett, and Berde (1956). Its chemical composition is

Cys-Tyr-Val-Glu(NH_2)-Asp(NH_2)-Cys-Pro-Leu-Gly(NH_2)

It differs from synthetic oxytocin only in the substitution of a valyl group for the isoleucyl group. When given in terms of doses assayed by the pharmacopoeial methods for oxytocin, valyl^3-oxytocin was found to be several times more active than Syntocinon in its effect on the human uterus (Smyth, 1958). The object of the present experiments was to compare its cardiovascular actions in man with those of Syntocinon and to determine whether the two substances were qualitatively similar in their effects and, if so, their relative potency.

METHODS

Observations were made on 10 healthy subjects ranging from 20 to 61 years of age. They were lightly clad and lay on a couch in a room at 18 to 20°. During the experiments, a slow intravenous infusion of saline was maintained (1.5 ml./min.) into the infusion system from a constant-speed motor-driven syringe, and the test substances were administered through the same system either as a single injection or as a constant infusion. The time of administration of the substances was unknown to the subject.

Both the preparations used, Syntocinon and valyl^3-oxytocin, were supplied by Sandoz Ltd.

The standardization of valyl^3-oxytocin was carried out by the method of the British Pharmacopoeia (1958), that is the effect on the blood pressure of the chicken and on the isolated rat uterus, in comparison with International Standard Pituitary (Posterior Lobe) Powder. In the present series of experiments when comparing the effects of oxytocin and of the analogue, the injections were given in pairs, using the same dose of each substance. The order was varied in different subjects in order to try to compensate for the tendency to a diminishing response with repeated administration. Intra-arterial injections were also given in nine subjects through the indwelling intra-brachial needle used for blood pressure measurements.

Hand and forearm blood flow was recorded by venous occlusion plethysmography, the water in the plethysmographs being kept at 32 to 34°. Flows were recorded at half-minute intervals, and more frequently following injections. *Blood pressure* was recorded in nine cases by indwelling intra-brachial arterial needle connected to a Minirack electromanometer (Southern Instruments) and photographically-recording Elmquist galvanometer. *Pulse rate* changes were read from plethysmograph or blood pressure tracings.

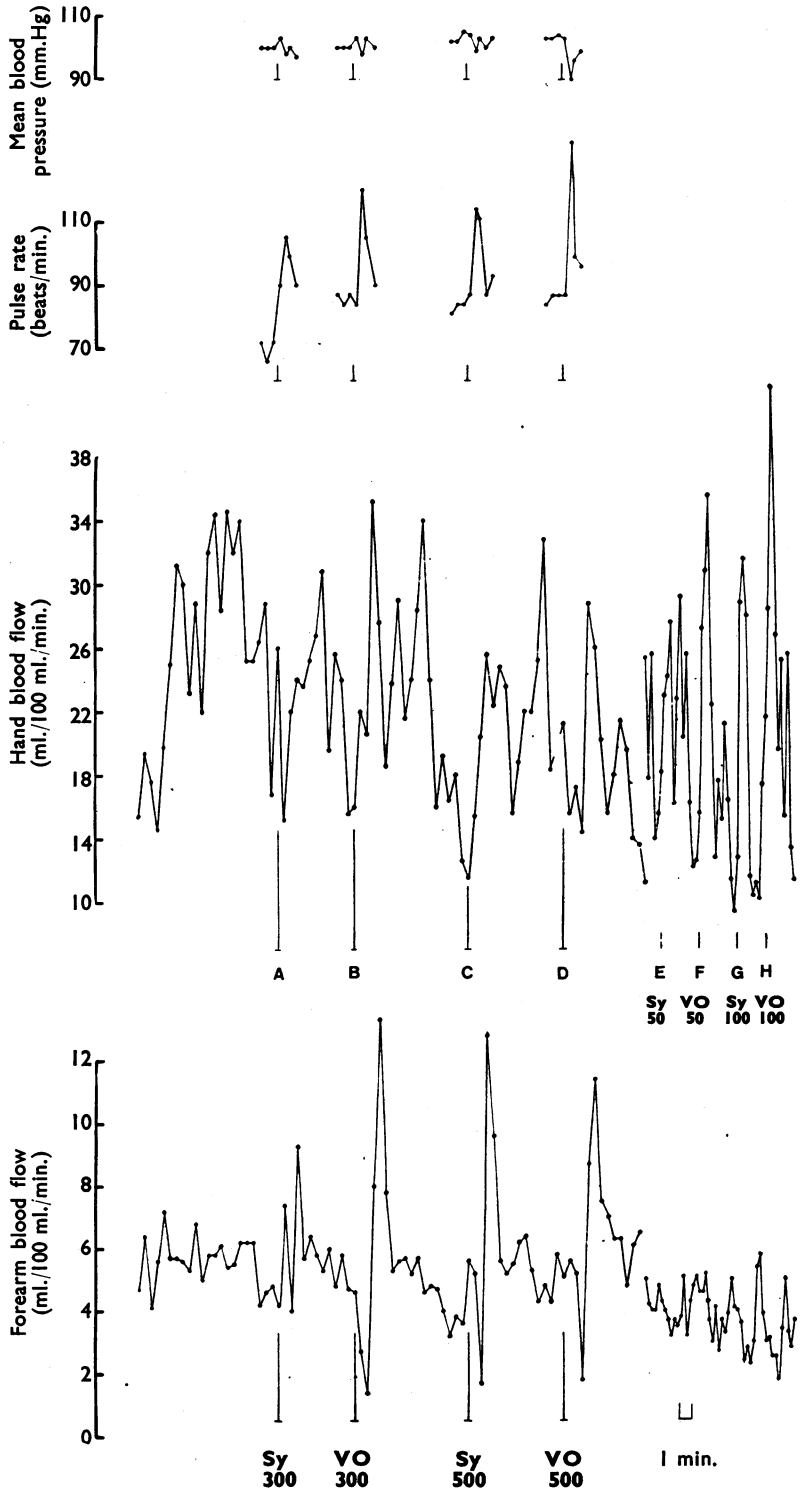

FIG. 1.—The effect in one subject of single injections of valyl³-oxytocin (VO) and Syntocinon (Sy). The records from above downwards are of mean blood pressure in mm. Hg; pulse rate in beats/min.; blood flow through hand and forearm in ml./100 ml. of tissue volume/min. Intravenous injections given at **A, B, C** and **D** and intra-brachial artery injections at **E, F, G** and **H**. The numerals under **VO** and **Sy** indicate the dose in mU.

RESULTS

Fig. 1 shows the response of one subject to single intravenous injections of valyl³-oxytocin and Syntocinon. It can be seen that the effects of the two polypeptides were qualitatively similar, and this held true in all subjects; both substances caused a rise in blood flow in the hand and forearm, a rise in pulse rate, and a small drop in blood pressure. The duration of the effects of the two substances was short and similar. The threshold doses were about 200 mU. for a single intravenous injection. On intra-arterial injection, both drugs caused a vasodilatation in the hand and forearm, sometimes with as little as 20 mU. (see Figs. 1, 2, and 3). With continuous intravenous infusions of 1 U./min., the pattern of response was again similar in the two drugs (Fig. 2), the vasodilator and hypotensive effect of valyl³-oxytocin usually being greater than that of Syntocinon.

In a previous paper (Kitchin *et al.*, 1959) it was shown that the dilator effect of infusions of

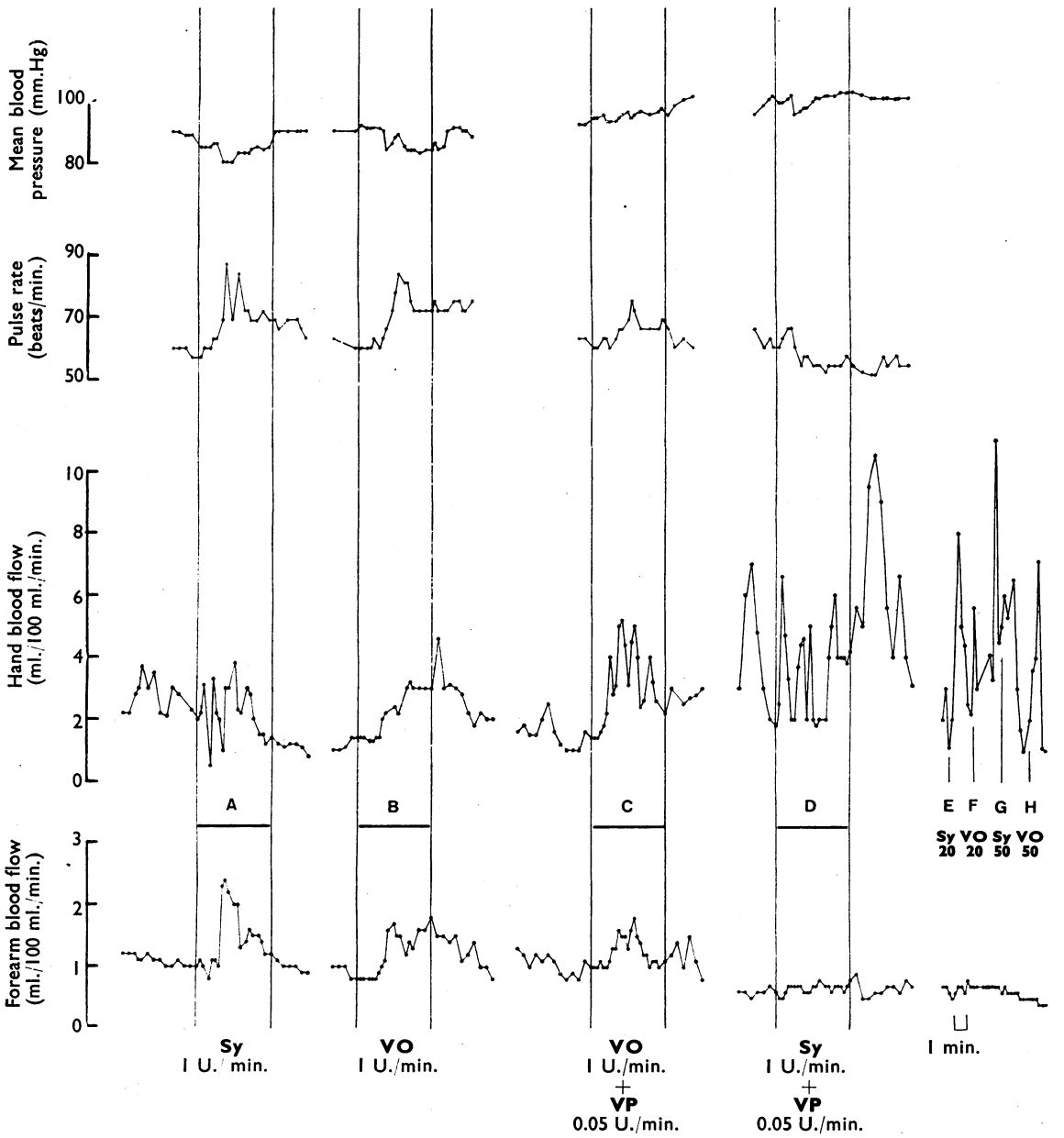

FIG. 2.—The effect in one subject of infusions of valyl³-oxytocin (VO) and Syntocinon (Sy). The records from above downwards are of mean blood pressure in mm. Hg; pulse rate in beats/min.; blood flow through hand and forearm in ml./100 ml. tissue volume/min. Infusions given between vertical lines marked 'A, B, C and D. Intra-brachial artery single injections given at E, F, G and H. The numerals under these capitals indicate the dose in mU. During periods C and D, vasopressin (VP) was added to the infusion fluid.

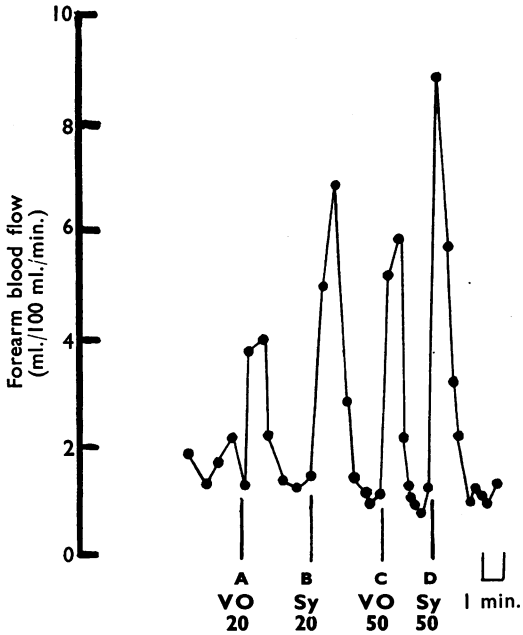

FIG. 3.—The effect in one subject of intra-arterial injections of valyl[3]-oxytocin (VO) and Syntocinon (Sy). The record is of the blood flow through the forearm in ml./100 ml. tissue volume/min. Intra-brachial artery injections given at A, B, C and D. The numerals under these capitals indicate the dose in mU.

Syntocinon was abolished by adding to the infusion fluid 1/20 the number of units of vasopressin. These experiments were repeated and a comparison made of the effect of infusions of Syntocinon and valyl[3]-oxytocin, to both of which 50 mU./min. of vasopressin had been added. The dilator effect of Syntocinon was largely abolished, while that of valyl[3]-oxytocin was reduced to a much lesser extent (Fig. 2). This difference was noted in both the subjects in whom this test was performed, and confirms the previous impression that valyl[3]-oxytocin is a stronger vasodilator and hypotensive agent than Syntocinon.

Quantitatively, the responses to valyl[3]-oxytocin were in most cases greater than those of Syntocinon given in the same doses. Table I shows as percentages the average amount by which the response to valyl[3]-oxytocin exceeded that of Syntocinon when intravenous injection and infusion as well as intra-arterial injection was used. It will be seen that, when given by intravenous injection and infusion, valyl[3]-oxytocin had a considerably greater effect on pulse rate, hand and forearm blood flow than had Syntocinon; its blood pressure lowering effect was also somewhat greater. Given by the intra-arterial route, valyl[3]-oxytocin also increased hand blood flow more than Syntocinon, but, on the forearm blood flow, Syntocinon appeared to be the more potent vasodilator (Fig. 3 and Table I). Only two pairs of observations were made, but they may be significant in view of the consistent results obtained in the hand.

TABLE I

PERCENTAGE BY WHICH THE RESPONSE TO VALYL[3]-OXYTOCIN DIFFERED FROM THE RESPONSE TO THE SAME DOSE OF SYNTOCINON

The numerals in brackets give the number of pairs of observations on which the comparison was made.

	Blood Flow		Blood Pressure	Pulse Rate
	Hand	Forearm		
Intravenous injection	+68 (16)	+65 (14)	+12 (13)	+86 (13)
Continuous infusion	+120 (4)	+57 (4)	+23 (4)	+38 (4)
Intra-arterial injection	+38 (11)	−23 (4)	0	0

DISCUSSION

The synthetic oxytocin, Syntocinon, has been found to have the same activity as natural oxytocin when tested by a variety of methods of assay, including the isolated rat uterus, the chicken blood pressure, milk ejection pressure in rabbits, cat uterus *in situ*, blood pressure and antidiuretic effects (Berde, Doeppner, and Konzett, 1957). Synthetic analogues of oxytocin, phenylalanyl[3]-oxytocin, leucyl[3]-oxytocin, glutaminyl[3]-oxytocin, and valyl[3]-oxytocin differ, however, in some respects in their relative potencies (Berde *et al.*, 1957). In particular, it has been shown that valyl[3]-oxytocin, standardized by the rat uterus and chicken blood pressure methods, has about four times the oxytocic effect of Syntocinon on the human uterus (Smyth, 1958).

The present experiments indicate that valyl[3]-oxytocin, again standardized using the rat uterus and chicken blood pressure, also has a greater effect than Syntocinon on the cardiovascular system in man, being about 1.5 to 2 times as active a vasodilator.

These observations, apart from a possible therapeutic bearing, illustrate the fact that specific actions of these cyclic octapeptides are independent of each other and depend on particular amino-acid groupings within the molecule.

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