CLINICAL TRIAL OF SYNTHETIC OXYTOCIN

BY

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Du Vigneaud *et al.* (1953) and Tuppy (1953) independently showed that the oxytocic factor of the posterior lobe of the pituitary gland is a polypeptide with the following structure:

This substance was synthesized by different methods by du Vigneaud *et al.* (1954) and by Boissonnas *et al.* (1955). It was shown by du Vigneaud *et al.* (1954) and Konzett *et al.* (1956) to have physical, chemical, and biological properties identical with those of the naturally occurring oxytocin. Synthetic oxytocin has had only a limited trial in the human being (Douglas, Bonsnes, and du Vigneaud, 1955; Bösch and Käser, 1956) and is not so far generally available in this country. We were fortunate to have a supply put at our disposal by Dr. H. Holgate, of Sandoz Ltd., for use in obstetric practice, and this is a preliminary report on our experience with it.

Materials and Methods

The synthetic oxytocin used was "syntocinon" prepared by the method of Boissonnas and supplied in ampoules standardized biologically to 10 international units per ml. by comparison with the international standard preparation of natural oxytocin. The purified natural oxytocin ("pitocin") was used as a control.

Thirty-one patients near term or in labour were treated in the Liverpool Maternity and Mill Road Maternity Hospitals, and the indications for using oxytocin were as follows:

Inefficient uterine action:	
Hypotonic inertia during the first or second stage of labour	12
Failed induction of labour by artificial rupture of the membranes	6
Induction of labour:	
Oxytocin alone	5
Oxytocin as a preliminary to artificial rupture of the membranes	4
Oxytocin and artificial rupture of the membranes combined	4

The treatment was explained to the women themselves, and when one preparation was compared with another they were invariably interested in the recorded effects. The synthetic oxytocin was administered by continuous intravenous drip infusion of 5% dextrose solution containing 2.5 I.U., 5 I.U., or 10 I.U. per litre, the actual dose being controlled by the rate of the drip, which was regulated according to the uterine response. Uterine contractions were recorded by a Lorand tocograph and the blood pressure and foetal heart rates were measured at 20-minute intervals. Observations were restricted to the first and second stages of labour.

In 17 cases the action of the synthetic product was compared with that of the natural oxytocin by the alternate

administration of the two substances at equal strength and rate of drip for 20-minute periods. An interval of 20 minutes was allowed between the two treatments, and during this time 5% dextrose solution was used alone to rid the tubing between the Y-connexion and the intravenous needle of any traces of the previous preparation.

In 14 women the synthetic oxytocin was administered continuously, the maximum duration being nine hours.

Results

Oxytocic Effect

Syntocinon proved strongly oxytocic in all cases (Figs. 1, 2, and 3), and the type, amplitude, and frequency of the uterine contractions were indistinguishable from those induced by the same dose of pitocin (Fig. 4). The exact

FIG. 1.—Para 1, gravida 3, age 20. Inefficient uterine action of hypotonic type. Synthetic oxytocin started after 15 hours of labour.

FIG. 2.—Primigravida, age 22. Artificial rupture of the membranes at 36 weeks' gestation for hydrocephalus and spina bifida failed to induce labour. Synthetic oxytocin begun 23 hours later. Note the increase in uterine tone following temporary administration at an excessive rate.

FIG. 3.—Primigravida, age 22. Inefficient uterine action following spontaneous rupture of membranes. Synthetic oxytocin was begun after 10 hours of labour.

FIG. 4.—Para 1, age 35. Induction of labour for post-maturity by artificial rupture of the membranes combined with oxytocin. Note the similarity of action of synthetic and natural oxytocin.

quantitative relationship was not surprising, because the manufacturers standardize their synthetic preparation biologically against the natural product. Synthetic oxytocin was also similar to the natural substance in that it caused a rise in the basic tone of the uterine muscle when the dose was too high, but this disappeared when the rate of flow was corrected (Fig. 2). Moreover, like natural oxytocin, it also sometimes caused a refractory state in the uterine muscle when it was administered for long periods. The clinical results are set out in Table I.

TABLE I.—*Clinical Results*

Indication	No of Cases	Vaginal Delivery	Caesarean Section	Induction of Labour Unsuccessful	Cervix Rendered Suitable for A.R.M.	Cervix Still Unsuitable for A.R.M.
Inefficient uterine action:						
Hypotonic inertia ..	12	12				
Failed induction by A.R.M. ..	6	5	1			
Induction of labour:						
Oxytocin alone ..	5	2		3		
Oxytocin as preliminary to A.R.M. ..	4				3	1
Oxytocin and A.R.M. combined ..	4	4				

Pressor Effects

The maximum increases in systolic and diastolic blood pressure recorded in the intervals between uterine contractions during the first and second stages of labour are shown in Table II, together with the variations observed during normal labour in 31 untreated patients who served as a control group. The considerable blood-pressure changes observed in the control series are consistent with those reported by Brown (1951).

TABLE II.—*Maximum Increase in Blood Pressure During First and Second Stages of Labour*

Maximum Changes in Blood Pressure	40–30 mm. Hg	30–20 mm. Hg	20–10 mm. Hg	10–0 mm. Hg	Nil or Fall
Syntocinon: intermittent administration (17 cases) { Systolic Diastolic			1	2 3	14 14
Pitocin: intermittent administration (17 cases) { Systolic Diastolic				4 5	13 12
Syntocinon: continuous administration (14 cases) { Systolic Diastolic	1	2 1	3 4	5 4	3 5
Control series (31 cases) { Systolic Diastolic	3 1	2 1	6 2	6 11	14 16

There was thus no appreciable difference in the rise in blood pressure following the intermittent administration of syntocinon and pitocin. The rise following continuous administration of syntocinon was similar to that observed during untreated labour, but a slight pressor effect cannot be excluded.

Among the women treated there were two with pre-eclampsia and two with essential hypertension, and none suffered any ill-effect that could be attributed to the treatment. In one case of pre-eclampsia the blood pressure rose from 140/90 to 160/110 following a 20-minute administration of synthetic oxytocin solution in the strength of 2.5 I.U. per litre at the rate of 16 drops a minute. The same patient showed an increase to 150/105 following the administration of the natural hormone in equal concentration for a similar period, and an increase to 190/130 after 5% dextrose solution was given. This suggested that the blood-pressure response was not directly related to the administration of either oxytocic substance.

Other Effects

None of the women developed untoward symptoms or signs, and in none was it necessary to interrupt treatment. At no time was foetal distress noticed during the administra-

tion of oxytocin, but the dose was always carefully regulated to avoid excessive uterine action which might have disturbed placental circulation. In this respect our experience of this new preparation as well as of the old suggests that the optimum concentration of solution for intravenous injection is 5 I.U. per litre. All except three babies were born alive and well. The other three were stillborn: two died *in utero* before treatment was begun, and the other died from hydrocephalus and spina bifida during labour.

Discussion

Induction of labour is often necessary in cases of pre-eclampsia and essential hypertension, and many have feared to use natural oxytocin as, despite purification, it still contains 4% (Konzett *et al.*, 1956) to 7% (Douglas, 1955) of vasopressin. One of the attractions of synthetic oxytocin to the clinician is that it is completely free from vasopressin. This does not necessarily mean that it might not have a pressor effect, and, indeed, the biological investigations of Gyermek and Fekete (1955) and Konzett *et al.* (1956) did show elevations of blood pressure. It is interesting to note, on the other hand, that Popenoe *et al.* (1952) and Lawler and du Vigneaud (1953) found highly purified samples of natural oxytocin to be free from pressor effects.

Du Vigneaud *et al.* (1953) and Popenoe and du Vigneaud (1954) identified the vasopressor factor of the posterior lobe of the pituitary gland as an octapeptide with a structure similar to that of oxytocin except that it contains phenylalanine instead of isoleucine, and arginine (in the cow) or lysine (in the pig) in place of leucine. These amino-acids are not used in the production of synthetic oxytocin, so the final product should be free from vasopressin. The close similarity between the structure of either type of vasopressin and oxytocin and the proved oxytocic activity of vasopressin (Blair-Bell *et al.*, 1933), even when highly purified (Popenoe *et al.*, 1952), suggests the possibility of some overlap in the pharmacological actions of vasopressin and oxytocin. It would therefore not be surprising if synthetic oxytocin showed some pressor effect.

Conclusions

The action of synthetic oxytocin upon the human uterus is indistinguishable from that of purified preparations of the natural substance.

The synthetic product appears to be free from undesirable side-effects. It probably possesses slight pressor activity, but this is not sufficient to contraindicate its use in therapeutic dosage.

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