A CRITERION FOR OXYTOCIC ACTIVITY

Studies with Tochergamine

By W. J. Garrett and M. P. Embrey

From the Nuffield Department of Obstetrics and Gynaecology, University of Oxford

Received January 2, 1958

NN-Diethyl-*N'*-(2-tetralyl)-glycinamide, a substance of high oxytocic activity in the isolated uterus preparation, has been tested on the intact human puerperal uterus and been found to be without demonstrable activity, in doses of 1–20 mg. parentally. The absolute necessity for testing oxytocic activity by an objective method on the intact human uterus is stressed.

Species difference in drug response may be the source of surprise or disappointment when a new compound fresh from the laboratory is given its first clinical trial. Some 30 years ago, for example, it was thought that ergotoxine and ergotamine were the essential substances in crude ergot[1]. Yet, despite their potency in the laboratory, the effect of these alkaloids on the uterus in everyday clinical practice fell far short of expectations. Ergotoxine and ergotamine were much slower in action than the crude Extractum Ergotae Liquidum, B.P.[2,3]

With the discovery of ergometrine[3,4] rather the reverse obtained. In the intact human uterus ergometrine was found to be the most rapid and powerful oxytocic of all[5], although its effect in the laboratory proved disappointing. The standard preparations of isolated guinea pig and rat uterus are not reliable and give many negative results[6]. From such uncertain evidence a compound may be thought to be oxytocic which, in fact, is not. Or, worse still, a compound inactive in the laboratory may have sharp oxytocic properties in practice[7,8]. A more stringent test than those used hitherto is therefore obligatory. There should be some definite criterion for oxytocic activity which must be satisfied before a new compound is used in clinical practice for its oxytocic properties. The need for such a test has recently been re-emphasised for us by our experience with the new synthetic ergot-like derivative, Tochergamine*.

Tochergamine, *NN*-diethyl-*N'*-(2-tetralyl)-glycinamide or 621 I.S., has been preprepared as the tartrate[9] and studied by Bovet-Nitti[6]. She has found that this compound exhibits oxytocic activity equal in potency to that of ergometrine when tested on the isolated guinea pig and rabbit uterus and that, like ergometrine, intraperitoneal injections of the drug induce abortion in pregnant guinea pigs. Toxicity tests have shown that Tochergamine has one great advantage in that it is 36 times less toxic than ergometrine.

Independent clinical trials by Bertini[10] in Turin and Rodriguez-Bravo[11] in Rome have suggested that Tochergamine, in parenteral doses of 2 to 6 mg., promotes easy and quick retraction of the uterine musculature after

* Trade name of Farmitalia, Milan.

delivery and that it can reduce the incidence of post-partum haemorrhage. These subjective clinical observations await confirmation by an objective method.

METHOD

Spontaneous human uterine motility was recorded in the first three days after delivery by the external tocograph described by one of us[12]. The method is convenient in that it entails placing only a small receptor unit

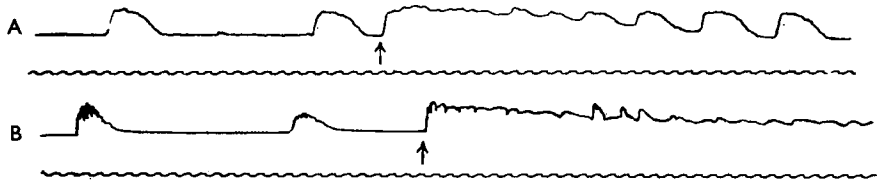

FIG. 1. Typical oxytocic response to pitocin and ergometrine (human puerperal uteri). A, at arrow, 1 unit pitocin i.v. B, at arrow, 0·25 mg. ergometrine i.v. Lower trace, time in minutes.

on the lower abdomen overlying the puerperal uterus, the contractions of which are relayed to a recording unit at the bedside. It is in effect a useful alternative to Moir's classical internal method[13] and one which is more acceptable to the patient.

After a suitable control period of recording, the drug to be studied is given to the patient and the uterine response observed graphically.

RESULTS

The known oxytocics, pitocin and ergometrine, induced obvious uterine spasm in less than one minute by intravenous injection. This effect lasted a variable time (Fig. 1).

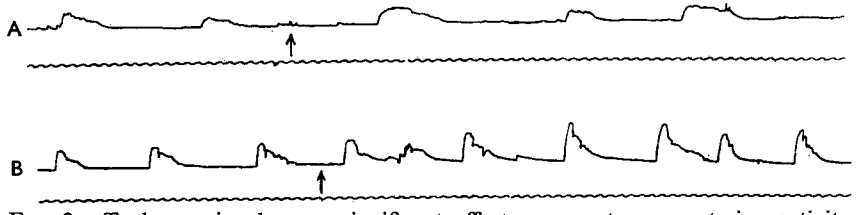

FIG. 2. Tochergamine has no significant effect on spontaneous uterine activity (human puerperal uteri). A, at arrow, 4 mg. drug i.v. B, at arrow, 20 mg. drug i.v. Lower trace, time in minutes.

Tochergamine was given similarly by intravenous injection to six volunteer patients in doses of 1 to 20 mg. The recommended dose is 2 to 6 mg. In none of these was an oxytocic response recorded, either immediate or delayed (Fig. 2, Table I), and no side effects were elicited.

DISCUSSION AND CONCLUSIONS

While Tochergamine has been found by others to act as a powerful oxytocic agent in laboratory animals, our experiments do not show it to

have a demonstrably useful effect on the human uterus in doses of 1 to 20 mg. The lesson is obvious, namely, that no substance can be considered suitable for clinical use as an oxytocic until it has been tested by an objective recording method on the intact human uterus, the only acceptable criterion.

TABLE I

THE EFFECT OF INTRAVENOUS DOSES OF TOCHERGAMINE, 1–20 MG., ON THE HUMAN PUERPERAL UTERUS

Patient	Day of Puerperium	Dose of Tochergamine mg. I.V.	Uterine response
1	3rd	1	No response in 28 minutes
2	3rd	4	No response in 80 minutes
3	2nd	4	No response in 10 minutes
4	3rd	10	No response in 41 minutes
5	1st	20	No response in 60 minutes
6	2nd	20	No significant response in 57 minutes

In the reports of Bertini and Rodriguez-Bravo, one may surmise that extraneous factors such as the stimulus of the observer's hand pressed on the fundus uteri initiated a uterine contraction which has been erroneously interpreted as a direct oxytocic effect of the drug. Favourable clinical impressions of an oxytocic agent may not always be borne out by tocographic experiment. Such objective methods remain the only safe way of determing oxytocic activity.

Acknowledgements. We are greatly indebted to Dr. Daniel Bovet of Rome for his suggestion that we should carry out this trial of Tochergamine and for making supplies of the drug available to us.

REFERENCES

1. Clark, *Trans. Edin. obstet. Soc.*, 1927, **86**, 109.
2. Moir, *Brit. med. J.*, 1932, **1**, 1022.
3. Moir, *ibid.*, 1932, **1**, 1119.
4. Dudley and Moir, *ibid.*, 1935, **1**, 520.
5. Moir, *ibid.*, 1936, **2**, 799.
6. Bovet-Nitti, *Rend. Istit. sup. Sanità*, 1952, **15**, 953.
7. Embrey and Garrett, *J. Obstet. Gynaec. Brit. Emp.*, 1955, **62**, 150.
8. Garrett and Embrey, *ibid.*, 1955, **62**, 523.
9. Marini-Bettolo, Frediani and Chiavarelli, *Rend. Istit. sup. Sanità*, 1952, **15**, 850.
10. Bertini, *ibid.*, 1952, **15**, 1033.
11. Rodriguez Bravo, *ibid.*, 1952, **15**, 1008.
12. Embrey, *J. Obstet. Gynaec. Brit. Emp.*, 1955, **62**, 1.
13. Moir, *Trans. Edin. obstet. Soc.*, 1934, **92**, 93.