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CLINICAL COMPARISON OF ERGOTOXINE AND ERGOTAMINE

A REPORT TO THE THERAPEUTIC TRIALS COMMITTEE OF
THE MEDICAL RESEARCH COUNCIL*

BY

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The subject of ergot, the method of its preparation and the nature of its active principles, has been the source of more discussion during recent years than probably any other matter in pharmacology. Even now, twenty-six years after the discovery of the active alkaloid ergotoxine, and fourteen years after the isolation of the closely related alkaloid ergotamine, there remains an uncertainty not only with regard to the clinical action of these alkaloids, but also with regard to the part played by other constituents present in the crude ergot, or formed during its manufacture into medicinal preparations. The matter is one which interests pharmacologists and clinicians alike, for the urgent and sometimes desperate emergencies of

obstetric practice demand the use of therapeutic agents whose mode of action is understood, and whose reliability is thoroughly proved.

CHOICE OF METHOD

Since ergot is now no longer used before delivery of the foetus it is difficult to get objective evidence of its action: clinical observations such as the timing of the duration of the red lochia¹ or the measuring of the rate of involution of the uterus² have been shown to be unreliable. A more direct method is called for, such as a recording of the actual uterine contractions. In 1927 Bourne and Burn² published the results of an investigation of the action of oxytocic drugs administered during labour. By means of a bag passed between the foetal membranes and the uterine wall and connected with tubing to a manometer, they were able to make tracings of the variations of intrauterine pressure; the tracings thus obtained showed very clearly the effect of drugs on the uterine activity. The work dealt chiefly with the action of pituitary extract and its dosage, but included three experiments with ergotamine.

The usefulness of this method of investigating the uterine action is limited by certain serious disadvantages. It is sometimes difficult to introduce a bag above the foetal head, and this usually requires an anaesthetic. The patient is frequently very restless during labour, which makes for obvious difficulties, and causes false and erratic recordings. Again, the duration of the experiment is limited by the termination of labour. Lastly, many oxytocic drugs are used, not during labour, but in the puerperium. This is the case with the ergot group, and it is therefore of more interest to record their action at this time than it is during parturition. For these reasons I resolved to modify the method and to try the effect of introducing a bag into the uterus in the late puerperium. As in the previous experiments the bag was connected with tubing to a mercury manometer, and this in turn was fitted with a float by means of which variations of intra-uterine pressure were recorded on a slowly moving drum. Before use, the bag and tubing (previously sterilized by boiling) were filled with water to a pressure equivalent to 2.5 cm. of mercury and introduced into the uterus with full antiseptic precautions. The early trials were encouraging, and showed that this apparatus could record the normal contractions of the uterus which take place every ten to twenty minutes, and that the physiological variations such as occur with the act of suckling could also be clearly shown. The seventh day of the puerperium proved to be the most satisfactory, although the sixth and eighth days are almost as good.

At the request of the Therapeutic Trials Committee of the Medical Research Council an investigation was made of the clinical effects of ergotoxine ethanesulphonate; in the experiments to be recorded this alkaloid was contrasted with ergotamine tartrate (femergen or gynergen).

HISTORICAL CONSIDERATIONS

The history of these alkaloids is of interest, for they have been the source of much dispute amongst pharmacologists. A very fair statement of the position is given in a letter by Sir H. H. Dale³ to the *Lancet*. The history is briefly this. In 1906 Carr and Barger isolated an active alkaloid, ergotoxine, the pharmacological effects of which were fully studied by them and by other British workers, notably by Dale. Unfortunately, appeals to clinicians to test the action of this pure substance met with little response, and to this day no adequate clinical trial has been reported. In the meantime, in 1918, Professor A. Stoll, working in the Sandoz laboratories, isolated a new alkaloid—ergotamine—which was found to be very active. This substance was eagerly tried out by German and Swiss clinicians, and ample evidence was soon accumulated to prove its worth: under the

* The ergotoxine ethanesulphonate used in these tests was submitted to the Therapeutic Trials Committee by Messrs. Burroughs Wellcome and Co.

trade names of femergin and gynergen, ergotamine has now come into wide use in this country and in America. In 1923 the following statement appeared in the *British Pharmaceutical Codex*: "Ergotoxine has been used clinically for its action on the uterus, but it is disappointing, and gynaecologists are now generally agreed that it is not the active constituent they want." Because of this statement, and because of the scanty reports on ergotoxine, the opinion was formed by many that ergotamine was the active constituent of ergot, and that the other alkaloids were useless or at least less desirable ingredients. Previous to this the combined work of Dale and Spiro⁴ had shown that from the pharmacological point of view the actions of the two drugs were indistinguishable. A later investigation by Burn and Ellis⁵ also proved that within the margin of experimental error the one alkaloid was as active as the other. Nevertheless, in 1930, Stoll⁶ wrote: "I cannot agree with S. Smith and G. M. Timmis⁷ concerning their conclusions drawn from the pharmacological identity of ergotoxine and ergotamine regarding the clinical virtues of the two alkaloids. The clinical comparison cannot be executed but by clinical investigation. Practice has proved in numerous cases the occasionally big differences between pharmacological and clinical experience, especially in actions on the nervous system."

NATURE OF INVESTIGATION

Such a clinical investigation as recommended by Professor Stoll I have endeavoured to carry out on a series of puerperal patients by the method already described. The drugs used were ergotoxine ethanesulphonate (supplied by Burroughs Wellcome and Co.) and ergotamine tartrate (issued under the name of femergin by the Sandoz Company). A different patient was used for each test, because the long duration of the action of these drugs prevents the recording of two experiments on one patient. For this reason a slight difficulty arises. No two patients give quite the same type of recording; one uterus may be almost inert, while another may be fairly active; most uteri show moderate contractions every ten to twenty minutes, but a few show frequent small contractions. These objections, however, are of little practical importance, because the contractions engendered by the drugs in question are widely different in their character, frequency, and duration from those of the spontaneous variety. To reduce this error still further it was customary to take a normal recording for from half an hour to two hours before administering the drug.

DETAILS AND RESULTS

Twenty-five cases were given either ergotoxine or ergotamine in doses as follows:

Ergotoxine.—Intravenous:

0.25 mg. (3 cases)

Intramuscular:

0.25 mg. (2 cases)

0.5 mg. (1 case)

1.0 mg. (2 cases)

By mouth:

1.0 mg. (1 case)

2.0 mg. (2 cases)

2.5 mg. (1 case)

2.5 mg. (with histamine and tyramine)
1 case.

Ergotamine.—Intravenous:

0.25 mg. (2 cases)

0.5 mg. (2 cases)

Intramuscular:

0.25 mg. (1 case)

0.5 mg. (2 cases)

1.0 mg. (2 cases)

By mouth:

1.5 mg. (1 case)

2.0 mg. (1 case)

3.0 mg. (1 case)

These doses refer to the weight of the salt. In the case of ergotoxine ethanesulphonate the base accounts for 83.6 per cent. of this weight; in the case of ergotamine tartrate it accounts for 84.5 per cent. of the weight.

It may be said at once that both alkaloids were found to be very active in stimulating uterine contractions. A typical chart for each drug is shown in the accompanying illustrations.

FIG. 1.—Ergotoxine 0.25 mg. by intravenous injection.

FIG. 2.—Ergotamine 0.25 mg. by intravenous injection.

FIG. 3.—Ergotoxine 0.5 mg. by intramuscular injection.

FIG. 4.—Ergotamine 0.5 mg. by intramuscular injection.

The Nature of the Contractions.—This was the same for both drugs. In the larger doses (0.5 to 1 mg.) the contractions were almost always alike. They came at intervals of about one minute, and there was a characteristic heaping up of smaller waves on top of the larger ones. In the smaller doses (0.25 mg.), the contractions, although definitely stimulated in frequency and magnitude, showed some variation in character in different cases. It was found, however, that every variety of contraction with the one drug could be matched by a similar result obtained with the other drug.

Rise in Base Line.—This may be regarded as a measure of the tonicity of the uterus. It may mean that the whole uterus has gone into a long-sustained contraction, or that waves of contraction pass through the muscle substance so frequently that they overlap and cause the organ as a whole to compress its cavity. The tracings obtained with both ergotoxine and ergotamine showed that when these drugs were given in a dose of 0.5 mg. or over, the base line was usually raised during the time that the alkaloid was producing its greatest effect. The amount of the rise was not as a rule of very marked degree.

The Time of Onset.—This varied with the method of administration, but was always slow by comparison with other drugs such as pituitrin. By intravenous injection, four to ten minutes elapsed before an effect was seen; by intramuscular injection fifteen to forty-five minutes were required; while by mouth the effect was erratic, and not seen for thirty-five minutes to one hour or longer.

Duration.—The nature of the experimental method made it impossible to determine the duration of the effect of the alkaloid. It was certainly in excess of three hours.

Side Effects.—It was not part of this investigation to record effects such as changes in blood pressure, pulse rate, etc. These may be studied more profitably and easily in circumstances other than the lying-in wards of a maternity hospital, where patients are apprehensive and easily upset by any unusual investigation. No serious symptoms were noted after the administration of either drug, although three patients complained of a feeling of depression and weight in the head, and one patient of nausea and headache; the effects were of short duration. The doses received by these patients were 0.25 mg. ergotamine (intravenous), 0.5 mg. ergotamine (intramuscular), 1.5 mg. ergotamine (by mouth), and 0.5 mg. ergotoxine (intramuscular).

Dosage.—It may safely be said that in the case of both ergotoxine and ergotamine the optimum dosage for intramuscular injection is 0.5 mg. Doubling this dosage produced but slight increase of action: on the other hand, 0.25 mg. did not produce the full effect of the drug. Oral administration of ergotoxine and ergotamine, even in doses of 2 mg., did not yield consistent results. The contractions produced were much smaller and more erratic than those seen after the drugs had been given by injection. In several instances the contractions ceased after about an hour, to appear again about an hour later. Doses of 2.5 mg. produced a more definite result. Burn⁸ has made the observation that in the cat only about one-third of a dose of ergotoxine is absorbed from the alimentary canal after forty-eight hours. My results suggest that only a very small fraction of a dose is absorbed by the human subject during the two or three hours following oral administration.

These observations appear to justify a definite statement that ergotamine and ergotoxine are indistinguishable from each other in their clinical actions. If further experiments

should show that there is any difference in activity, that difference must be of such a small order that it is of no practical importance.

CONCLUSIONS

1. A method is described by which the response of the human puerperal uterus to oxytocic drugs may be directly recorded.

2. Both ergotoxine and ergotamine bring about strong contractions in the puerperal uterus when they are administered by injection.

3. Ergotoxine and ergotamine are indistinguishable from each other in their action on the puerperal uterus.

4. The effect comes on slowly, and takes fifteen to forty-five minutes to appear after intramuscular injection.

5. The most suitable dosage for intramuscular injection is 0.5 mg.

6. Oral administration gives slow and erratic results, even after comparatively large doses of the drug.

It is a pleasure to express thanks to Sir H. H. Dale for useful advice and encouragement in this work.

Note.—A further communication by the same author dealing with the action of ergot preparations on the puerperal uterus, with special reference to the activity of the liquid extracts, will be published in a subsequent issue of the *Journal*.

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THE MENACE OF OBESITY *

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The experience of life assurance companies is that weight, especially in relation to age, is an important factor in longevity, and the old tag *corpora sicca durant* has had statistical confirmation. The medical profession has been slow to apply these actuarial lessons to practice, and medical precept has lamentably lagged behind the dictates of fashion. Our advice has too frequently been sought for aesthetic rather than for hygienic reasons. An examination of some of the ascertained facts may be of interest. Should the national overweight continue to grow unchecked, the mortality from the degenerative, non-bacterial diseases will diminish the average expectation of life. This has been increased during the last century by the control of infectious diseases and by the reduction in infant mortality, but the scourge of degenerative disease remains to be tackled.

CAUSES OF OBESITY

The Controlling Mechanism.—The body weight after childhood represents the balance of two factors—the quantity of food ingested on the one hand, and the expenditure of energy in maintaining body heat and in glandular and muscular activity on the other. Some controlling mechanism must exist, and Grafe and Grunthal¹ have, as the result of experiment, suggested its localization in the hypothalamic region: this may explain the gross obesity in such diseases as chronic epidemic

encephalitis and hypothalamic tumours. The controlling mechanism is so perfect that the adult weight tends to remain constant in spite of an ever-varying food intake and energy output. Silver and Bauer² regard obesity as due to an upset in this mechanism, but they stress the importance of the hereditary factor.

The Endocrine Glands.—The part played by these glands in obesity is most controversial. The basal metabolic rate is usually within normal limits. Bauer² found clinically recognizable disorders of the endocrine glands in 2.6 per cent. of 276 cases, whilst Dunlop and Murray Lyon³ state that 62.8 per cent. of 493 cases gave "histories suggesting the possibility of glandular disturbance being a factor"; little evidence of such disturbance was found on physical examination. The endocrine factor, if it exists, must be a slight error operating over a long period.

Hyperinsulinaemia.—Nissl, En Shui, and Gordon,⁴ in a study of 500 obese people, found a normal intake of fat and protein but an immoderate consumption of carbohydrate; they suggest that this excessive carbohydrate causes pancreatic stimulation with hyperinsulinaemia, which in its turn provokes a craving for carbohydrate to check the uncomfortable symptoms of hypoglycaemia during brief fasts. There would appear to be much evidence and some theoretical considerations against this view.

CLASSIFICATION OF OBESITY

To review all the theories of the causes of obesity is without the scope of this paper, but the following classification suggests itself.

1. **Exogenous Group.**—This is a small but important group, due to gross and persistent immoderation in the intake of food and alcohol.

* A paper given before the Nuneaton and Tamworth Division of the British Medical Association, December 12th, 1931.