Brit. J. Pharmacol. (1966), **26**, 345–350.

THERAPEUTIC ACTION OF METHIXENE HYDROCHLORIDE ON PARKINSONIAN TREMOR AND A DESCRIPTION OF A NEW TREMOR-RECORDING TRANSDUCER

BY

S. CLARKE (*Senior Technician*) AND G. A. HAY (*Senior Lecturer*)

From the Department of Medical Physics, University of Leeds

AND

C. J. VAS* (*Senior Research Registrar*)

From the Department of Neurology, The General Infirmary at Leeds

(*Received August* 24, 1965)

No safe drug has yet been found to suppress Parkinsonian tremor. Consequently, the search for an effective therapeutic agent in this condition continues.

Intravenous methixene, a thiaxanthen derivative (Tremonil; Wander), was said to suppress extrapyramidal tremor (Gozzano & Millefiorini, 1962) following an uncontrolled therapeutic study of this drug using electromyographic methods for assessment of tremor. The purpose of this paper is to report the results of a double-blind controlled therapeutic trial of intravenous methixene for suppression of tremor in Parkinsonian patients and to describe a new type of transducer, the L.G.I. (Leeds General Infirmary) transducer used for measuring the amplitude of tremor.

Apparatus for recording tremor

The purpose of the apparatus is to provide an objective measure of tremor. Previous authors, for example Wachs & Boshes (1961) and Marshall & Walsh (1956), have suggested the recording of accelerations and of unidirectional components of tremor: however significant these may be in special studies of "physiological tremor" it was felt that they did not adequately represent the compound Parkinsonian tremor. Accordingly, it was thought desirable instead to measure the total resultant amplitude of displacement of the limb or part of the limb, regardless of the direction of oscillation.

A basic requirement of any measuring apparatus is that the disturbance it causes in the measured function should be minimal. Transducers imposing large constraints on the limb, such as piezo-crystal devices, were therefore rejected; instead it was thought that the type of device commonly known as an accelerometer, which is attached to the limb and moves freely with it, but which by no means necessarily measures acceleration,

* Correspondence and requests for reprints to Dr C. J. Vas.

would be most satisfactory. No such transducer, with an omnidirectional response to displacement in a single plane, was known: it was therefore necessary to develop one.

Fig. 1 is a sketch of the prototype transducer; the following description pertains to the transducer in the position shown in the diagram. A cylindrical magnet (M) with a "seismic mass" (SM) of lead (to increase the inertia of the magnet) is held in a needle-bearing (NB) by three light coil springs (S). The system is thus free to oscillate about the point (NB), so that the lower end of the magnet can move in any direction in the horizontal plane. The natural frequency is determined by the moment of inertia of the moving system controlled by the stiffness of the springs. The end of the magnet lies within 1.5 mm of a soft iron pole-piece around which a coil of many turns of fine copper wire is wound. The coil is connected by a screened cable and suitable connectors to the input of a conventional electroencephalograph.

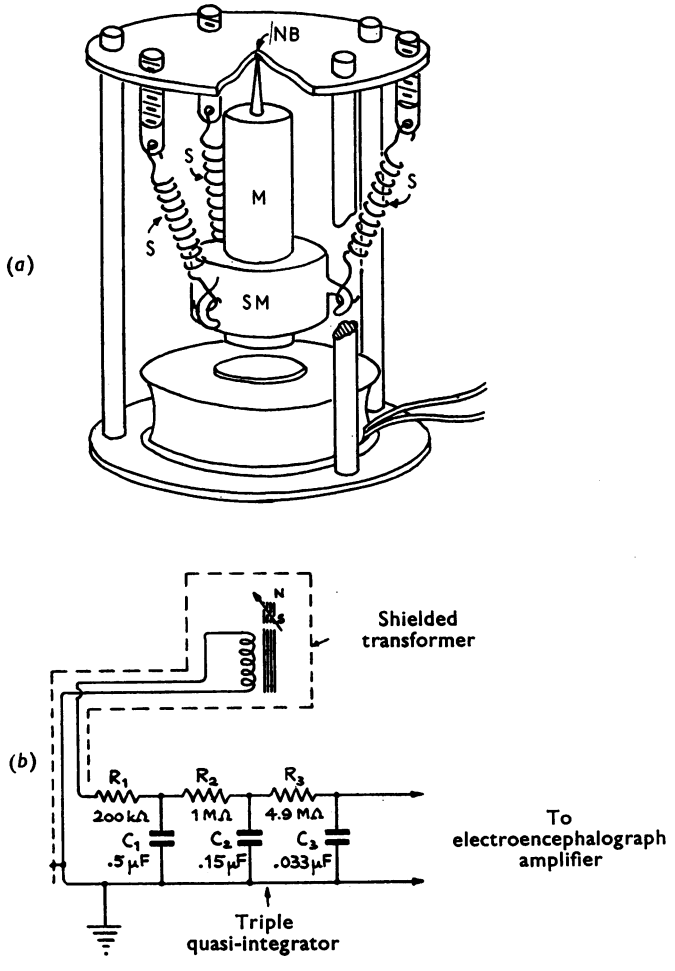

Fig. 1. (*a*) Perspective view of transducer showing principal parts; details such as screw threads, etc., are for clarity omitted. See text for description. (*b*) Electrical connexions of the transducer and its correcting circuit.

If an oscillatory displacement d is imparted to the whole transducer, an oscillatory displacement x between the magnet and the coil will result. If the system is so designed that its natural frequency lies above the range of tremor frequencies, x will be a measure of the *acceleration* of the tremor. By placing the natural frequency below the tremor frequency range, x may in principle be made proportional to the *displacement*; however, this condition is not practicable because of the need for large masses and weak springs, with resultant instability of the rest position of the system. The natural frequency of the prototype is about 23 cycles/sec. Movement of the magnet relative to the coil induces an electromotive force in the coil whose magnitude is proportional to the *velocity* of the movement. Hence over the relevant tremor frequency-range, taken as 4.2 to 8.6 cycles/sec (Wachs & Boshes, 1961), the transducer output is proportional to the *rate of change* of acceleration of the transducer.

To produce an output voltage proportional to displacement, the coil output is processed by an electrical circuit which over the frequency range required effectively performs three processes of mathematical integration. The circuit, a triple quasi-integrator of time-constant 0.15 sec, together with all relevant electrical details, is shown in Fig. 1, *b*.

Fig. 2,*a* shows the overall sensitivity of the transducer for a constant vertical input displacement of 10 mm, the axis of the transducer now being horizontal. It will be

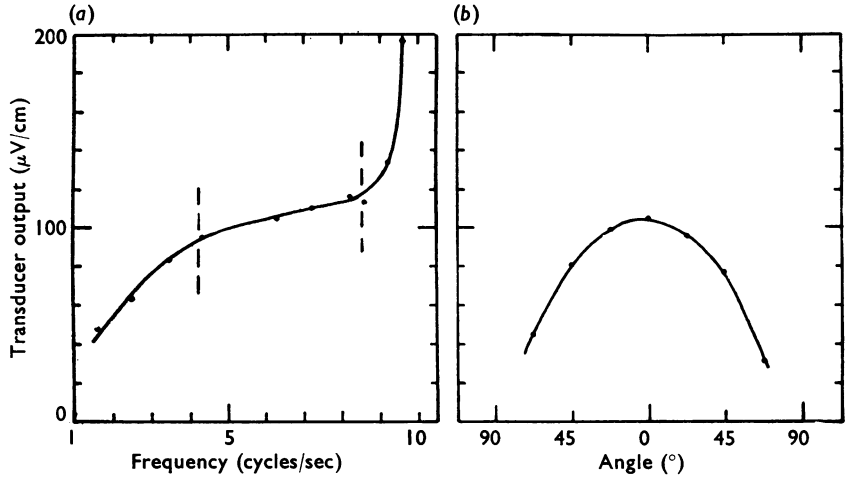

Fig. 2. Electrical output of transducer and its correcting circuit in microvolts peak-to-peak per centimetre for change of (*a*) frequency and (*b*) angle.

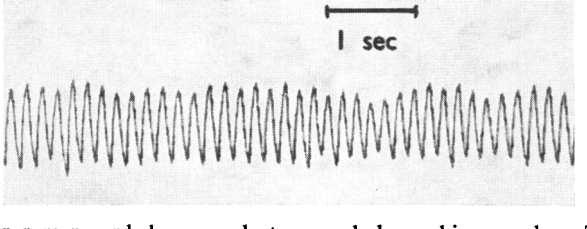

Fig. 3. Typical tremorgram recorded on an electroencephalographic recorder. The 1 sec calibration corresponds to 1.5 cm on the original.

seen that over the desired frequency range the sensitivity is about 100 μV/cm and is constant within $\pm 12\%$. At a given frequency the directional response is constant within $\pm 3\%$ for vertical movement, that is if the transducer is rotated throughout the range of 360°. For movements other than vertical in any one transducer position the sensitivity is somewhat reduced, as shown in Fig. 2, *b*. The maximum variation over an angle of $\pm 45°$ about the vertical, however, is $\pm 15\%$. Fig. 3 shows a typical record from one of the patients studied.

The prototype transducer is 3.5 cm in diameter, 4.75 cm long and weighs 54 g.

METHODS

Nine males and four females with persistent, marked Parkinsonian tremor volunteered for the double-blind controlled trial of methixene. All the patients continued taking either orphenadrine (Disipal) or benzhexol (Artane) during the experimental period.

The patients were admitted to a hospital ward, reassured and allowed to sit comfortably in bed with their arms and forearms resting on pillows but their hands unsupported. The Leeds General Infirmary (L.G.I.) transducer was strapped on to either the back or the front of the hand most affected by tremor. The tremor was recorded on an electroencephalographic recorder with the paper running at a rate of 1.5 cm/sec. The gain controls were adjusted from time to time during the experimental period to keep the amplitude of the tremor deflection within the range of movement of the recording pens. The graphic record of the tremor, henceforth referred to as a "tremorgram," was continuously recorded for a period of 90 min. At 30 min after the commencement of the tremorgram recording, 10 ml. of saline or 10 ml. of colourless methixene (10 mg) was injected intravenously on a double-blind and random basis, after which the tremorgram was recorded for a further period of 60 min. Four days later, each patient was readmitted to hospital and the double-blind experiment was repeated using methixene on this occasion if saline had previously been given, or *vice versa*.

The pulse rate and blood pressure were checked both at the beginning and at the end of the experimental periods. Any symptom mentioned by the patient was recorded.

Subjective impressions of the therapeutic action of drugs in Parkinsonism are notoriously inaccurate. Therefore, attention was focused on objective changes. The tremorgram records of the thirteen patients studied were analysed at the end of the trial. Ten-second periods at intervals of 4 min were selected; in each period the peak-to-peak amplitude of all tremor oscillations was measured. The mean amplitude of the tremor oscillations for these 10 sec periods was then calculated. From

TABLE 1

TREMORGRAM CHANGES AFTER INJECTION OF SALINE AND METHIXENE

Tremor activities are expressed as percentages of values before injection. $t=6{\cdot}93$; $P<0{\cdot}001$

Patient	Tremor activity (% of control) after injection	
	Saline	Methixene
W.H.	85	33
G.W.	73	42
F.H.	56	36
C.L.	112	55
J.P.	37	36
R.E.	89	0
N.C.	102	0
A.H.	78	0
J.F.	119	21
C.C.	53	0
E.K.	81	0
M.Mc.	57	17
C.A.	66	0
Mean	78	18

these mean values, a further mean amplitude of tremor was calculated for the two phases preceding and following the injection of either saline or methixene. The mean amplitude of tremor as seen in the tremorgram after the intravenous injection was calculated as a percentage of the mean amplitude of the tremor before the intravenous injection.

RESULTS

The results are given in Table 1. Only one patient responded equally to the injections of saline and methixene, whereas in the remaining twelve patients the decrease in tremor amplitude was greater after the methixene. Furthermore, the drug abolished the tremor completely in six patients. The difference in amplitudes of tremor after the saline and methixene injections in the thirteen patients is statistically highly significant ($t=4.31$; $P<0.001$).

Parkinsonian features are easily accentuated by external stimuli. This accentuation was seen in all our patients at the time of injection both of saline and of methixene. Then the amplitude of tremor increased visibly, only to decrease again some time after the completion of the injection.

An analysis of the tremorgram after the methixene injections in the thirteen patients showed that, excluding the patient whose tremor responded equally to saline and methixene, the amplitude of the tremor began to decrease an average of about 5.5 min after the completion of the injection. In contrast, however, in the patient who responded equally to methixene and saline the decrease in tremor amplitude commenced 24 min after the methixene injection.

On the other hand, the tremor tended to wax and wane in eight patients (62%) throughout the observation period after the injection of saline. However, in five patients (38%) the tremor amplitude consistently decreased 10 min after the completion of the saline injections. No untoward effects of any sort were reported by the thirteen patients studied. The pulse and blood pressure did not change significantly after the injection of methixene.

DISCUSSION

The results of this controlled study show that methixene given intravenously is very effective in controlling Parkinsonian tremor and no immediate side-effects were detected. Controlled studies should be performed to assess the value of oral methixene in controlling Parkinsonian tremor, as no such studies have yet been reported. Oral methixene, however, is most unlikely to have any effect on tremor in patients who have not responded to intravenous methixene. Therefore, it might be worth trying the intravenous effect of such a drug before subjecting the patient to a lengthy oral trial.

The L.G.I. transducer has proved to be a useful instrument, despite its size, in this study of the therapeutic effects of intravenous methixene. Nevertheless, it is clearly desirable to design a smaller and lighter model, responding over a greater range of frequency and angle.

SUMMARY

1. A controlled double-blind therapeutic trial using intravenous methixene for suppression of Parkinsonian tremor has been performed and the results (comparison of methixene and saline) are highly significant statistically ($P<0.001$).

2. It is suggested that the oral preparation of methixene should be subjected to study in Parkinsonian tremor.

3. A new type of transducer which measures amplitude of Parkinsonian tremor has been described.

Our grateful thanks are due to Dr M. J. Parsonage, Consultant-in-charge of the E.E.G. Department, for his stimulus and interest in the production of the L.G.I. transducer, for permission to modify a portable electroencephalograph and to study patients under his care. We are grateful also to Dr Hugh Garland and to Mr W. R. Henderson for permission to study patients under their care. The therapeutic study of these patients would not have been possible but for the generous help of Sisters A. Atkinson and M. Thwaites and their nursing colleagues on the neurological wards. Dr B. Marsh, Medical Director of A. Wander Co., kindly supplied the intravenous preparation of methixene (Tremonil). Dr R. Maguire of the Department of Psychiatry, University of Leeds, helped us with the statistical analysis. Our thanks are due also to Miss C. L. Giles for secretarial help throughout this study. This project was undertaken during the tenure of a Research Fellowship awarded to Dr C. J. Vas by the Board of Governors of the United Leeds Hospital.

REFERENCES

GOZZANO, M. & MILLEFIORINI, M. (1962). Studio elletromiografico dell'azione del preparto Wander 60/SJ 1977 sul temore Parkinsoniano. *Il Lavoro Neuropsichiatrico*, vol. 31, fasc. II.

MARSHALL, J. & WALSH, E. G. (1956). Physiological tremor. *J. Neurol. Neurosurg. Psychiat.*, **19**, 260–267.

WACHS, H. & BOSHES, B. (1961). Tremor studies in normals and in Parkinsonism. *Arch. Neurol. (Chic.)*. **4**, 66–78.