Br. J. Pharmac. (1969), 37, 468–475.

Tremor induced by tetrabenazine

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1. Acute administration of tetrabenazine produced tremor in cats, in doses which caused sedation but not hypothermia.

2. The pattern of movements resembled shivering rather than Parkinsonism, and warming the skin suppressed the tremor.

3. The tremor was not influenced by hyoscine.

4. Tremor produced by amylobarbitone was essentially similar to that induced by tetrabenazine.

There have been many attempts to establish an experimental model of Parkinson's syndrome. Certain drugs which cause Parkinsonism in man have been studied in attempts to produce a comparable syndrome in animals. Intravenous reserpine results in rigidity and occasional tremor in rats (Steg, 1964). Chlorpromazine does not have this effect, but it lowers the level of striatal dopamine in cats (Laverty & Sharman, 1965) and a similar biochemical change occurs in human Parkinsonism (Hornykiewicz, 1966). Administration of harmaline to monkeys with surgical lesions in the brainstem leads to a static " pill-rolling " tremor similar to that seen in human Parkinsonism (Poirier, Sourkes, Bouvier, Boucher & Carabin, 1966).

The present studies were undertaken to investigate the possible value of tetrabenazine in the quest for a pharmacological model of Parkinsonism. This drug produces Parkinson's syndrome in from 2 to 85% of human subjects according to dosage (Lingjaerde, 1963). It has an action similar to reserpine in lowering brain monoamines, but it possesses certain experimental advantages in that it acts more rapidly, for a shorter duration, with less effect on peripheral nerve endings (Quinn, Shore & Brodie, 1959).

Methods

Cats were trained to rest suspended in a sling with their paws just off the experimental table. Limb movement was recorded with a piezo-electric crystal (gramophone cartridge) strapped to one hind paw, electromyograms from subcutaneous needle electrodes, and respiration from a pressure transducer connected to a sphygmomanometer cuff beneath the thorax. All recordings were displayed graphically (Ediswan pen recorder) or monitored on a cathode ray oscilloscope after suitable DC (limb movement and respiration) or AC (electromyogram) amplification. Quantitative evaluation of limb movement and electromyographic activity

was obtained by integrating the recorded voltages to give a digital output which was displayed on electromagnetic counters (Laurence & Webster, 1958). Body temperature was recorded with a rectal thermometer. The skin was warmed with a 250 W infrared lamp at a distance of 60 cm and two 75 W lamps at a distance of 30 cm. Cooling was accomplished with a domestic fan. Room temperature varied from 21° to 22° C.

Tetrabenazine methanesulphonate (25 mg/ml.; Nitoman, Roche) and hyoscine hydrobromide (10 mg/ml.) were given in aqueous solution. Drugs were injected intraperitoneally, after allowing the animal to become acclimatized to the sling for about 5 min.

Results

Tetrabenazine

Tetrabenazine was injected in doses of 5, 10, 15 and 20 mg/kg. Tremor and sedation were sometimes seen at lower dose levels, and they invariably occurred at 20 mg/kg. There was no rigidity. Sedation developed 5–10 min after injection, and was followed by tremor within 30 min. Both sedation and tremor lasted about 2·5 hr. Activity recorded after this time was distorted by the return of spontaneous voluntary movements. Figure 1 illustrates a typical example of the integral of movement recorded from the left hind paw. Recordings were not made routinely before injection of tetrabenazine because the cats were usually too restless for reproducible observations. The tremor consisted of high frequency, flexion-extension movements (15–30 c/s) occurring in bursts of 0·25–1·5 sec duration. The bursts developed

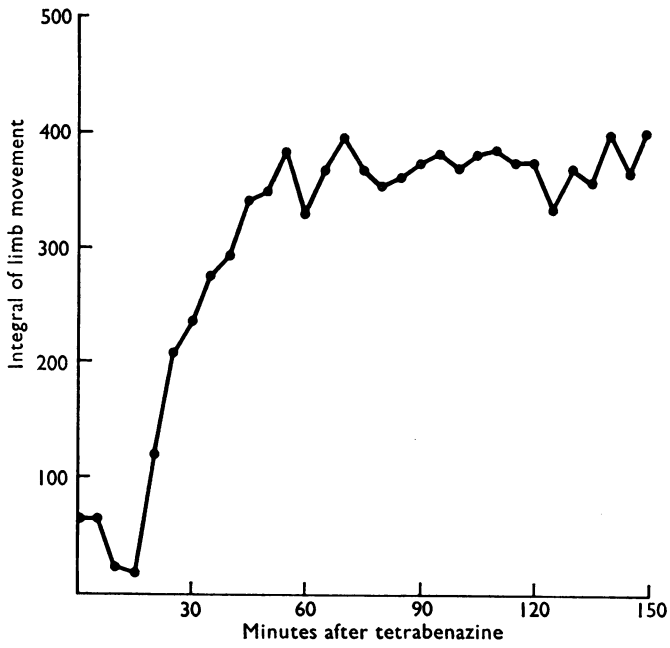

FIG. 1. Time course of integrated limb movement in a cat following intraperitoneal injection of tetrabenazine 20 mg/kg. The initial low level of spontaneous activity declined with sedation at 10–15 min, when tremor developed.

irregularly every 0·75–3·0 sec and sometimes became confluent. Movement was most prominent in the hind paws, but synchronous activity was commonly seen in all limbs and sometimes involved the trunk. The bursts of tremor were not related to respiratory movements. A typical pattern of activity is shown in Fig. 2.

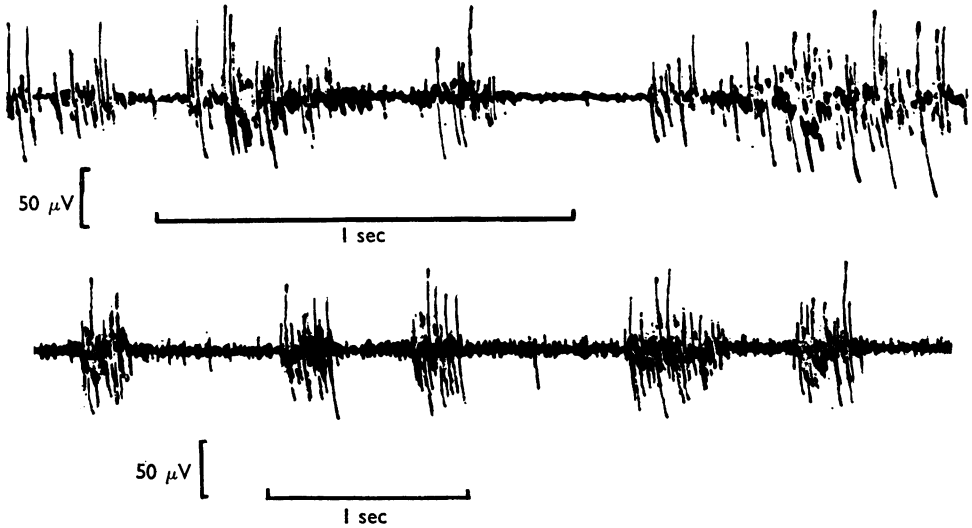

FIG. 2. Electromyograms recorded from cat's gastrocnemius muscle during tremor induced by tetrabenazine.

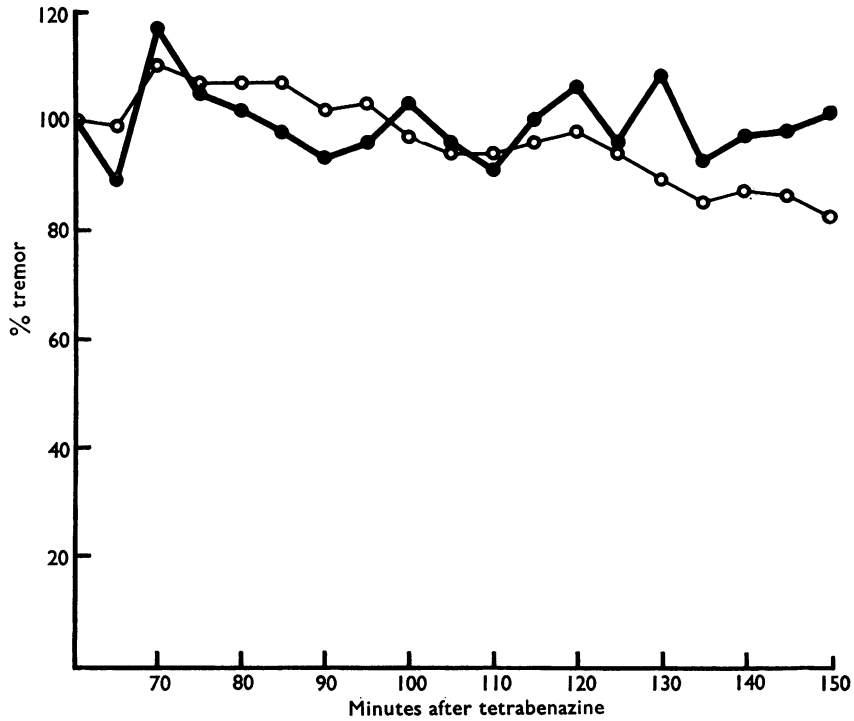

FIG. 3. Effect of hyoscine (2 mg/kg) on tetrabenazine tremor. Hyoscine (●) or saline (○) were injected intraperitoneally 60 and 120 min after tetrabenazine. Each graph is the mean result for five animals, and activity is represented as a percentage of the level present at 60 min.

Effect of hyoscine on tetrabenazine tremor

In view of the known therapeutic value of antimuscarinic drugs in Parkinsonism, hyoscine (2 mg/kg) was injected intraperitoneally 1 hr after tetrabenazine (20 mg/kg), when tremor was usually well developed. Control observations were also made with saline. None of these injections consistently influenced the time course of the tremor (Fig. 3).

Effect of suspension in a sling on rectal temperature

The tremor induced by tetrabenazine bore a resemblance to the motor activity of shivering, and it was noted that rectal temperature usually fell by 1·0°–1·5° C over the course of the first hour of an experiment. However, animals suspended in a sling at room temperature without administration of tetrabenazine also displayed a comparable fall in rectal temperature of 1·0°–1·5° C (Fig. 4) and in these circumstances tremor was not observed. It was considered possible that the presence of sedation in the tetrabenazine group might be related to the appearance of tremor, and so it was decided to observe the action of another hypnotic drug on cats suspended in a sling.

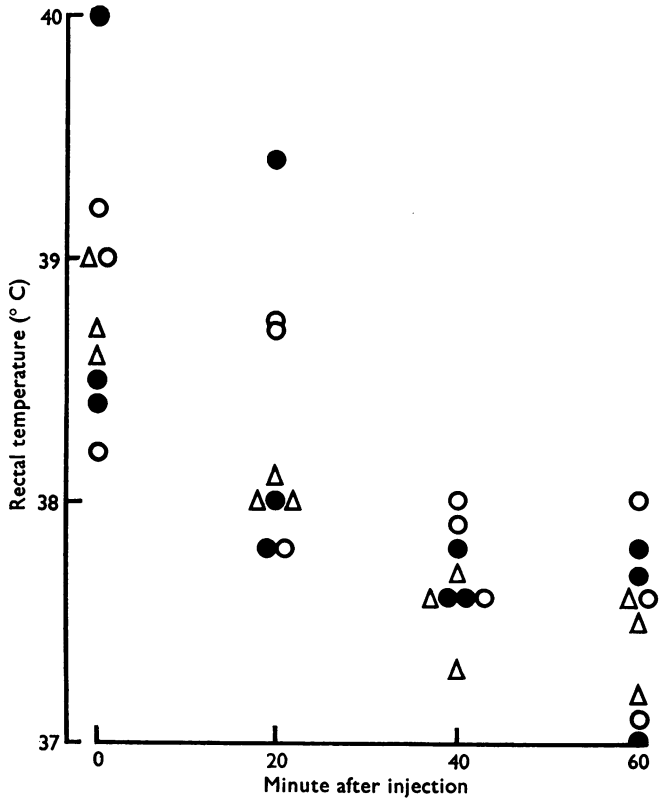

FIG. 4. Rectal temperature of cats suspended in a sling after tetrabenazine 20 mg/kg (●), amylobarbitone 25–35 mg/kg (△) or no drug (○).

Amylobarbitone

Intraperitoneal injection of amylobarbitone (25–35 mg/kg) failed to exert any hypothermic action. Rectal temperature fell to the same extent as when an animal was suspended in a sling without drugs (Fig. 4). These doses of amylobarbitone produced sedation, and tremor developed which conformed to the general pattern already described after administration of tetrabenazine.

Tetrabenazine tremor with cutaneous warming or cooling

It appeared that tetrabenazine and amylobarbitone might be lowering the threshold of the shivering response. In order to investigate this possibility, cutaneous temperature was increased by exposure to infrared radiation or decreased by cooling with a fan. The effect of such manœuvres was consistent. Heat applied to the skin reduced and frequently abolished the tremor induced by tetrabenazine, though animals often developed tachypnoea. Changes in tremor occurred within 5–10 min, before any alteration in rectal temperature. Tremor returned 5–10 min after turning

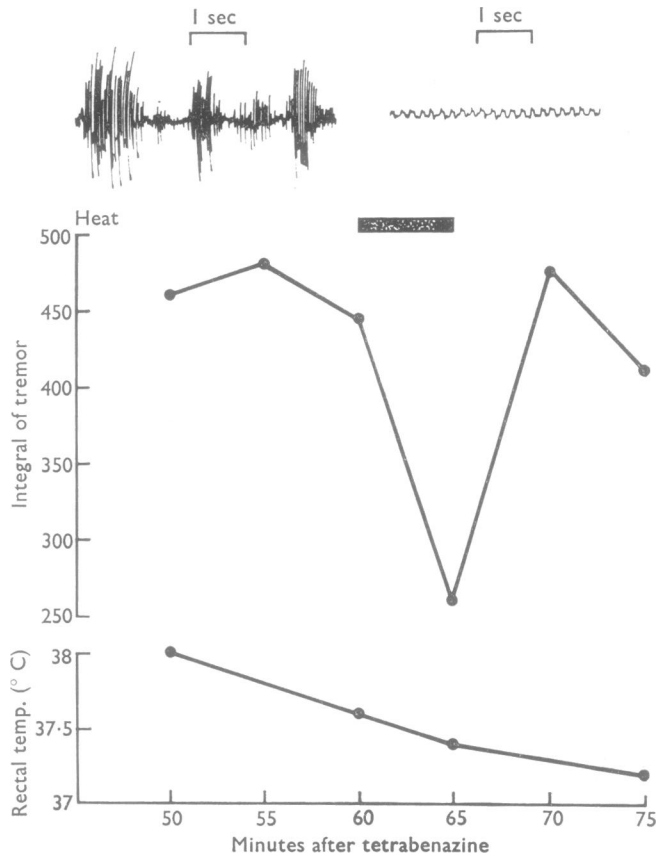

FIG. 5. Effect of localized cutaneous warming on tetrabenazine tremor. Integrated movement and rectal temperature are shown. Heat from infrared lamps was applied from 60 to 65 min and produced a marked reduction in tremor which was replaced by panting. Appropriate pen oscillograms of limb movement taken before and during warming are shown above the graphs of integrated activity.

off the infrared lamp. This response is illustrated in Fig. 5. Correspondingly, cooling the skin with a fan produced an exacerbation of tremor, often without any alteration in rectal temperature. Similar observations were made on tremor induced by amylobarbitone.

Discussion

The salient problem in evaluating experimental models of Parkinsonism is the interpretation of the significance of tremor, which is often the most noticeable clinical feature. The characteristics of Parkinsonian tremor are that it occurs when the limb is at rest, commonly involves a complex movement such as " pill-rolling " and has a frequency between 3 and 8 c/s, which is relatively stable though the amplitude is very variable. Parkinsonian tremor usually occurs intermittently, for periods lasting anything from 1 to 30 min. Comment on the influence of environmental temperature does not appear in clinical descriptions, which might be taken to imply that temperature changes do not exert any striking effect.

One obvious similarity between Parkinsonian tremor and tetrabenazine tremor is that both occur at rest. The fact that tetrabenazine tremor consists of simple flexion-extension rather than the more elaborate movements of Parkinsonism might be attributable to the anatomical limitation of movements possible at distal joints of the cat's limbs. Similarly the disparity in the frequency of tremor might be consequent upon species difference. There are, however, certain points against an analogy between the tremor of Parkinsonism and that induced by tetrabenazine, namely that the latter occurs in a brief burst lasting 0·25–1·0 sec, synchronous in all limbs, and it is abolished by raising the skin temperature. In both these respects it resembles more closely the tremor induced by amylobarbitone, a drug which has never been claimed to cause Parkinsonism, though it is recognized that barbiturates often produce shivering in man.

Evidence concerning the physiology of shivering is consistent with the view that tetrabenazine can cause shivering at doses which do not produce hypothermia. Shivering is controlled by at least two mechanisms. One important factor is the temperature of the blood perfusing the central nervous system, particularly the caudal hypothalamus (Hemingway, 1963), but also other regions of the brain, and even the spinal cord (Klussman, 1964). The second controlling influence is input from cutaneous thermoreceptors, and this may be a more powerful stimulus than changes in central temperature. It has been suggested (Hensel, 1952) that the central nervous system modifies the sensitivity of the response to cutaneous thermoreceptors. The observations reported here lend some support to this view, as two drugs which act predominantly on the central nervous system, tetrabenazine and amylobarbitone, have been shown to facilitate a shivering response which can be abolished by warming the skin locally, without raising rectal temperature.

The mechanism of facilitation is not known, although there may be some correlation with sedation. Tetrabenazine and amylobarbitone both produce marked sedation and the anaesthetic drug halothane also induces shivering (Nikki and Tammisto, 1968). These actions depend to a considerable extent on dose because shivering does not occur in deep anaesthesia.

Further support for regarding tetrabenazine tremor as shivering rather than

Parkinsonism comes from the observation that muscarinic blocking agents such as hyoscine, which possess antiparkinsonian properties, influence neither physiological shivering (Hemingway, 1963) nor tetrabenazine tremor.

The effect of reserpine on brain monoamines is similar to that of tetrabenazine, but its action on shivering is not clear. Administration of reserpine has been claimed to induce (Hoffman, 1958) or suppress (Stuart, George, Freeman, Hemingway & Price, 1961) shivering.

It is somewhat surprising that rectal temperature did not increase with tetrabenazine tremor, but the interaction between mechanisms of heat loss and heat production are complex (Hemingway, 1963). The failure of rectal temperature to rise after cutaneous warming may have been consequent on disappearance of tremor with its calorigenic action.

The clinical features of tetrabenazine tremor are similar to the tremor induced by tremorine, but there are important differences. Tremorine tremor is suppressed by atropine or hyoscine (Everett, 1956; Spencer, 1965) and it is not influenced by warming rats or mice in ovens at 36°–38° C (Blockus & Everett, 1959; Cox & Potkonjak, 1967). Furthermore, tremorine tremor is usually accompanied by excitement, in contrast to the sedation associated with tetrabenazine tremor. Reasons have already been given for rejecting any analogy between tetrabenazine tremor and Parkinsonism, but there are other arguments against regarding tremorine tremor as an acceptable alternative (Curzon, 1967; Brumlik & Means, 1969). Thus the problem of obtaining a simple pharmacological model of Parkinsonism remains, in spite of the high incidence of this syndrome as a consequence of drug therapy in man.

We thank Mr. J. Jones for much valued assistance during this work and Mr. V. K. Asta for preparing the figures. Tetrabenazine (Nitoman) was generously supplied by Roche Products Limited. D. B. Calne is a Wellcome Fellow in Clinical Pharmacology.

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(*Received May* 27, 1969)