

PROCEEDINGS OF THE BRITISH PHARMACOLOGICAL SOCIETY

3RD-5TH JANUARY, 1973

SCHOOL OF PHARMACY, UNIVERSITY OF LONDON

COMMUNICATIONS

In communications with more than one author, an asterisk (*) denotes the one who presented the work.

Effect of dimethothiazine on tonic vibration reflex in man

F. E. H. CRAWLEY, P. KENNEDY and M. SWASH* (introduced by D. R. MAXWELL)

Department of Neurology, The London Hospital, El and Pharmacological Research Laboratories, May & Baker Ltd., Dagenham, Essex

Dimethothiazine is a compound which abolishes intercollicular decerebrate rigidity (Keary & Maxwell, 1967) and which depresses the activity of static and dynamic fusimotor neurones, probably at a supraspinal level (Maxwell & Rhodes, 1970). Dimethothiazine has proved of some value in the relief of spasticity in man (Matthews, Rushworth & Wakefield, 1972).

Objective measurement of fusimotor activity in man is difficult, but is essential for a proper evaluation of the mode of action of a centrally acting anti-spastic drug (see Phillips, Richens & Shand, 1970). As an index of motoneurone activity in man, we have used the tonic vibration reflex (TVR), a reflex increase in muscle tension which occurs in response to vibration applied to the belly of a muscle or its tendon (Marsden, Meadows & Hodgson, 1969), and which is known to depend on selective stimulation of the muscle spindle primary endings (Bianconi & van der Meulen, 1963).

Twelve single blind experiments were carried out in four healthy male volunteers. Measurements were made of the tension which developed in response to vibration (100 Hz) applied to the Achilles tendon for one min at various intervals up to 8 h after the oral administration of single doses of 50 or 200 mg dimethothiazine mesylate, or a placebo.

Plasma levels of dimethothiazine together with desmethyldimethothiazine were determined spectrofluorimetrically at intervals during the experiments in three of the subjects.

Dimethothiazine reduced the TVR, the reduction being greater following the 200 mg than the 50 mg dose. Drowsiness was reported following the 200 mg but not the 50 mg dose. There was no clear-cut relationship between the plasma levels of dimethothiazine and reduction in the TVR; the maximal reduction in the TVR sometimes preceded the maximal blood level (Fig. 1). Desmethyldimethothiazine was identified as an important plasma metabolite; this has one-third the potency of dimethothiazine in reducing experimental decerebrate rigidity (Sumpter, personal communication).

The data are consistent with the view that dimethothiazine reduces fusimotor activity in man.

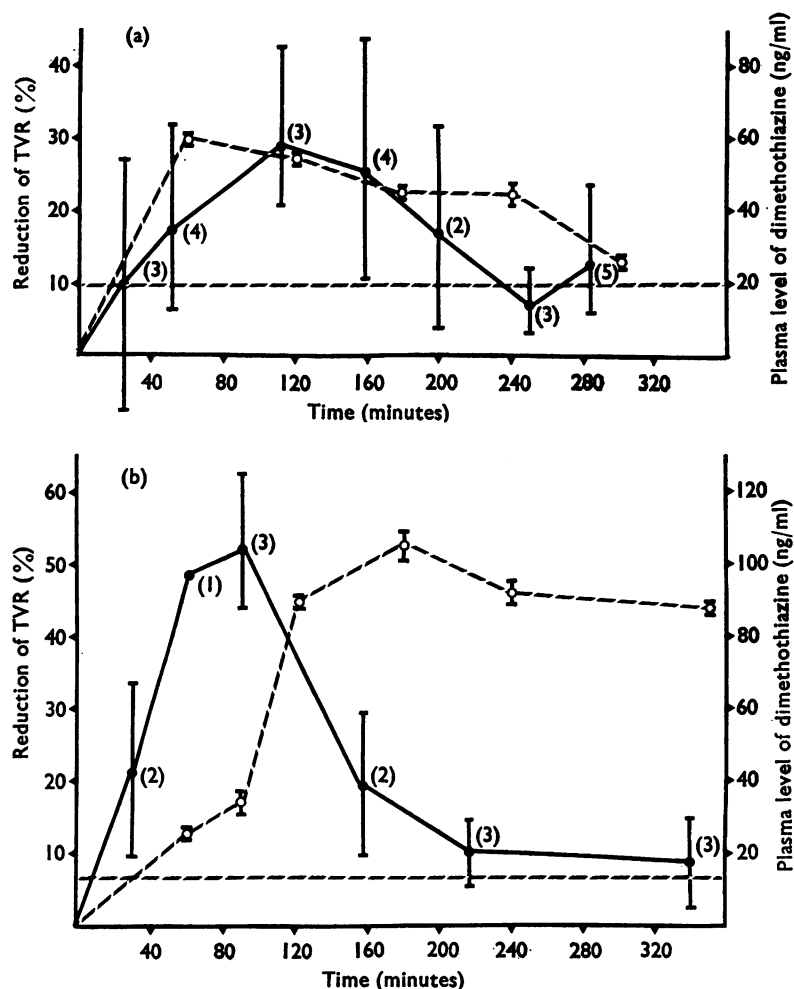


FIG. 1. Plasma level of dimethothiazine together with desmethyldimethothiazine (○----○) and reduction of TVR (●—●) following a single oral dose of (a) 50 mg and (b) 200 mg dimethothiazine mesylate in a healthy male volunteer (75 kg). Figures for the TVR are means of the number of measurements indicated in brackets. Values for plasma levels are the means of two determinations. Vertical lines indicate the range of individual values, and the horizontal lines (-----) the standard error of the control value of the TVR.

REFERENCES

- BIANCONI, R. & VAN DER MEULEN, J. P. (1963). The response to vibration of the end-organs of mammalian muscle spindles. *J. Neurophysiol.* **26**, 177-190.
- KEARY, E. M. & MAXWELL, D. R. (1967). A comparison of the effects of chlorpromazine and some related phenothiazines in reducing the rigidity of the decerebrate cat and in some other central actions. *Br. J. Pharmac. Chemother.*, **30**, 400-416.
- MARSDEN, C. D., MEADOWS, J. C. & HODGSON, H. J. F. (1969). Observations on the reflex response to muscle vibration in man and its voluntary control. *Brain*, **92**, 829-846.
- MATTHEWS, W. B., RUSHWORTH, G. & WAKEFIELD, G. S. (1972). Dimethothiazine in spasticity. A further attempt at pharmacological control. *Acta Neurol. Scand.* In press.
- MAXWELL, D. R. & RHODES, K. F. (1970). The effects of dimethothiazine on muscle spindle activity in the decerebrate cat. *Br. J. Pharmac.* **39**, 520-532.
- PHILLIPS, S. J., RICHENS, A. & SHAND, D. G. (1970). A method for studying spinal pharmacology in man. *Br. J. Pharmac.* **40**, 577-578P.