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ANTICONVULSANT AND CONVULSANT EFFECTS OF CHEMICALLY RELATED THIOSEMICARBAZIDE, THIOUREA AND UREA DERIVATIVES

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ABSTRACT

NISHIE, KEICA, MARLYS WEARY AND ARTHUR BERGER: Anticonvulsant and convulsant effects of chemically related thiosemicarbazide, thiourea and urea derivatives. J. Pharmac. exp. Ther. **153:** 387-395, 1966. Eleven thiourea derivatives and their corresponding urea and thiosemicarbazide (TSC) analogues were tested for anticonvulsant properties. Compounds which had *o*-chlorobenzyl or *o*-methylbenzyl substitutions on one of the nitrogens had the greatest anticonvulsant potency. The TSC derivatives may be divided into three groups, according to the relationship of activity and structure, as follows: 1) convulsant, with alkyl or allyl substitutions; 2) anticonvulsant against maximal electroshock seizures, with substituted phenyl or benzyl groups; and 3) both anticonvulsant and convulsant, with simple or substituted phenyl or benzyl groups. None of the TSC derivatives was anticonvulsant against Metrazol, and all tended to exacerbate this clonic seizure pattern. The convulsions produced by TSC derivatives could be abolished or prevented by pyridoxal HCl. All TSC derivatives with antimaximal electroshock seizure activity, including those which also induced delayed seizures, caused a reduction in spontaneous motor activity.

The ability of thiosemicarbazide (TSC) and other hydrazides to induce convulsions is well known and has been documented in numerous publications and reviews (Pfeiffer *et al.*, 1956; Jenney and Pfeiffer, 1958; Parks *et al.*, 1952; Dieke, 1949; Reilly *et al.*, 1953; Williams and Bain, 1961; Tower, 1960). Recently we reported that a series of newly synthesized TSC derivatives can be classified according to three distinct central nervous system actions (Nishie and Weary, 1964). Certain of these thiosemicarbazides showed convulsant properties only; others were effective agents against electroshock seizures; still others protected against electroshock initially and later produced convulsions. In view of these findings, chemically related thiourea, urea and thiosemicarbazide derivatives were synthesized and tested for possible convulsant and anticonvulsant activity.

METHODS. The anticonvulsant activity of some TSC, thiourea and urea derivatives was measured by determining their ability to prevent the tonic extensor component of maximal electroshock seizures (MES) and clonic convulsions induced by Metrazol (Met) injected subcutaneously (Swinyard *et al.*, 1952).

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CF no. 1 mice, weighing 18 to 25 g, were used in all experiments. The majority of compounds tested were insoluble in water and were therefore administered as suspensions in 10% gum acacia and physiologic saline. Pyridoxal hydrochloride was dissolved in saline and administered subcutaneously. The doses required to protect 50% of the mice against MES (MES ED50 ± S. E.) or Metrazol (Met ED50 ± S. E.) and to produce convulsion in 50% of the animals (CD50 ± S. E.) were determined in three groups of 10 mice each; the mice were given graded doses of the test compound. The ED50 and CD50 were computed by the log probit method of Miller and Tainter (1944). For those TSC derivatives with both anticonvulsant and convulsant activities, the dose necessary to protect 90% of the mice from the MES (MES ED90) was compared with the dose which induced convulsions in 90% of mice (CD90). The dosage of pyridoxal hydrochloride required to protect 90% of the animals (PD90) from the CD90 of TSC derivatives was determined. The ED90, CD90 and PD90 were estimated from the corresponding best fitting regression line from the log dose-probit response plot.

Four groups of mice containing 20, 20, 40 and 60 animals were treated intraperitoneally with 80 mg/kg (MES ED90) of 4-phenyl-3-TSC, a compound with both anti-MES and convulsant