LETTER TO THE EDITOR

ANTICONVULSANT AND ANALGESIC ACTIVITY OF 1, 2, 4-THIADIAZOLES - *A PRELIMINARY REPORT*

Sir,

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Acetazolamide has been used clinically in certain convulsive disorders. However, its utility is limited due to several factors. A variety of similar five membered heterocyclic compounds have been synthesised and screened for anti-convulsant activity. Recently, Stilling *et al.* (1) reported on potent anticonvulsant properties of substituted 1, 3, 4-thiadiazoles in rats and mice against electrically and chemically induced seizures. This prompted us to synthesize a few 1, 2, 4-thiadiazoles (which are isomeric with 1, 3, 4-thiadiazoles) and test their anticonvulsant and analgesic activity, alongwith their safety indices.

A total of 10 analogues were prepared according to method described by Indu Kumari *et al.* (2). They were soluble in alcohol, propylene glycol and chloroform. Albino rats (CF) of either sex (100-200 g) were used in all work. All drugs were given as solutions in propylene glycol (10 *mg/ml* 0.5 *ml*, ip). Diphenyl hydantoin sodium (Sigma, ip) and phenobarbitone sodium (IDPL, ip) were used as standards for work on anticonvulsant activity. They were given in aqueous solution (ip). Control groups received either propylene glycol or normal saline (as the case may be). Morphine sulphate was the standard in analgesiometry (control animals received only normal saline). There were ten or eight animals per group.

Seizures were induced by DC (See 3; 150 mA, for 0.2 sec) delivered through a pair of corneal electrodes, using a Techno-convulsiometer. The presence or absence of hind limb extensor was taken as the end point, showing protection or a lack of it. Drugs were administered (ip) to groups of animals 24 hr after initial screening for convulsion,

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TABLE I : Anticonvulsant (Electro shock) and analgesic activity of 1, 2, 4-thiadiazoles (Fig. 1).

Compound No.	*Treatment R*	*Partition coeff. 27°C; pH 7.9*	*Anticonvulsant activity (% protection) (n=10)* [a]	*Analgesic activity Latent period of tail flick response (sec) Mean ± SEM (n=10)* [a]	
				Cont.	*Treated*
Saline	—	—	0		
I	H	8.09	80**	5.30±0.74	15.00±2.50
II	*p*-Cl	6.14	60*	5.94±4.939	7.18±1.024
III	*m*-Cl	4.32	40	6.37±0.734	11.13±1.085**
IV	*o*-CH_3	4.13	75**	4.90±0.81	13.40±1.448
V	*p*-CH_3	6.14	40	5.48±0.746	9.53+1.56
VI	*m*-CH_3	1.03	60*	4.88±0.419	12.08±2.73*
VII	*o*-OCH_3	1.43	25	6.15±0.758	13.47±0.843***
VIII	*p*-OCH_3	3.16	50	5.73±0.686	15.80±5.32
IX	*m*-OCH_3	3.76	50	5.70±0.726	19.97±2.86
X	*p*-OC_2H_5	8.07	60*	7.42±0.29	16.72±2.18
	Diphenyl hydantoin Sod.		60*		
	Phenobarbitone Sod.		100***		
	Morphine Sulphate			6.06±0.667	19.24±1.66

All drugs were given (ip) in dose of 2 *mg/kg*; see text for details.

* P<0.05 | a, n=number of animals; (n=8) for IV, VII, VIII and IX.
** P<0.01 | Control : Saline (0.5 *ml*);
*** P<0.001 | Chi-square test for anticonvulsant and 't' test for analgesic activity.

and their effect determined after 1 hr in MES test. Convulsions were also induced chemically. Strychnine hydrochloride (IDPL, 4 *mg/kg*, sc) was administered in all groups 45 min after 'drug' administration, and the animals observed for another 45 min for convulsions. Pentylene tetrazole (100 *mg/kg*, sc) and picrotoxin (14.5 *mg/kg*, sc) were also used as chemiconvulsants in some experiments. The results were analysed by Chi-square test.

To Measure analgesia tail flick method (4) was used. The tail was subjected to a radiant heat (6 mA) at three different positions and mean time taken for the withdrawl of tail was noted. Animals showing the flick time in range of 3 to 10 sec only were selected. All treatments (2 *mg/kg* or morphine, 10 *mg/kg*, ip) were administered to groups of animals. After 1 hr tail flick time was determined again. The results were analysed by Student's 't' test. The ED_{50} and LD_{50} were calculated by making use of the probit transformation (5).

All the compounds exhibited anti-MES activity. The parent unsubstituted compound (2 *mg/kg*) was found to have 80% protection with safety index of 40.4 (ED_{50}=0.89 *mg/kg* and LD_{50}=36 *mg/kg*). Substitution in the benzene ring reduced the anticonvulsant effect of (I). The ortho methyl substituted drug (ED_{50}=0.2 *mg/kg*, LD_{50}=24 *mg/kg*, with safety index 120) and meta methyl substituted drug (ED_{50}=0.4 *mg/kg* and LD_{50}=24 *mg/kg*, safety Index 60) were found to have 75% and 60% protection respectively, while para substituted (V) drug gave 40% protection. Unsubstituted 1, 2, 4-thiadiazole and para and ortho-substituted compounds (R=Cl, CH_3, OC_2H_5) gave 50% protection against strychnine induced seizures. However, no protection against pentylene tetrazole and picrotoxin was observed at doses used. The results indicated a probable site of action on spinal cord.

Most of the compounds of the series were analgesic. Compound VII R=o-OCH_3) shows very highly significant analgesic value ($P<0.001$). The parachloro derivative (compound II) was the only compound not to give analgesic activity. Table I shows the potency rating in comparison with a dose of morphine (10 *mg/kg*). Since some of the drugs tested exhibit a wide safety margin, they need a further, more extensive study as anticonvulsant and analgesic drugs. The most active compound (I) has the highest partition coefficient.

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