LETTERS TO THE EDITOR

Anticonvulsant Activity of Procaine and its Five Congeners against Experimentally Induced Convulsions

SIR,—The concept of a single fundamental mechanism of excitation in nervous and cardiac tissue has been stressed by Harris and Kokernot (1950). On the basis of this hypothesis the anticonvulsant activity of procainamide was studied by Arora and Kapila (1959), but subsequent detailed studies revealed that procainamide had a low therapeutic index. Considering the effectiveness and toxicity of procainamide, it was thought that a study of the action of the parent substance (procaine) and some of its other congeners might prove them to be better anticonvulsant agents.

The anticonvulsant activity of procainamide hydrochloride, procaine hydrochloride and its four congeners with methyl substitution in the benzene ring was studied against maximal electro-shock and also leptazol-induced seizures (Arora, Sharma and Kapila, 1958) in adult albino rats and was compared with phenytoin sodium. The neurotoxicity (Swinyard, 1949) and acute toxicity were also tested and the ED50, TD50, LD50, (Litchfield and Wilcoxon, 1949), and the therapeutic indices and protective indices of the drugs were calculated.

These compounds were effective only against maximal electro-shock seizures. Procaine and its congeners were effective within 10 min. and the effect lasted for 2–3 hr., while the effect of phenytoin sodium lasted much longer. Toxicity studies revealed that procaine hydrochloride and its congeners caused clonic convulsions before death.

Procainamide hydrochloride had a low therapeutic index (2·8) compared with that of phenytoin sodium (9·4) (Table I).

Procaine hydrochloride was effective in low doses (ED50=5·56 mg./kg.) and had a therapeutic index of 36. However, neurotoxicity was observed at low doses and so the protective index was only 5. Procaine and its methyl substituted congeners had higher protective and therapeutic indices compared with phenytoin sodium (Table I).

TABLE I

ANTICONVULSANT ACTIVITY, TOXICITY, PROTECTIVE INDICES AND THERAPEUTIC INDICES OF PROCAINAMIDE, PROCAINE, PHENYTOIN AND PROCAINE CONGENERS IN RATS

Drugs	ED50 against maximal electric shock seizures* mg./kg.	TD50 mg./kg.	Protective index TD50/ED50	LD50 mg./kg.	Therapeutic index LD50/ED50
Procainamide hydrochloride	80·0 (62·98–101·6)	115·3 (96·49–137·78)	1·4	225	2·8
Procaine hydrochloride	5·56 (4·09–7·56)	28·18 (21·51–36·91)	5	200	36
2-Diethylaminoethyl-2,3-dimethylbenzoate hydrochloride	18·0 (10·28–31·50)	146·0 (127·0–168·0)	8·1	300	16·7
2-Diethylamino-2,3,5,6-tetramethylbenzoate hydrochloride	8·61 (5·69–13·02)	50·93 (34·66–74·86)	5·9	200	23·2
2-Diethlaminoethyl-2,5-dimethylbenzoate hydrochloride	9·34 (5·66–15·41)	142·0 (121·36–166·14)	15	350	37·4
2-Diethylaminoethyl-3,5-dimethylbenzoate hydrochloride	5·07 (2·53–10·14)	144·5 (120·92–172·67)	28·5	325	64·1
Phenytoin sodium	16·29 (10·84–24·46)	72·44 (65·26–80·40)	4·4	153	9·4

* Figures in parenthesis are the 95 per cent confidence limits.

Of the methyl substituted procaine congeners, 2-diethylaminoethyl-3 5-dimethylbenzoate hydrochloride was most effective having a therapeutic index of 64·1 and a protective index of 28·5.

2-Diethylaminoethyl-2,3-dimethylbenzoate hydrochloride and 2-diethylaminoethyl-2,3,5,6-tetramethylbenzoate hydrochloride had higher protective indices, but lower therapeutic indices compared with procaine hydrochloride.

Compared with procaine hydrochloride, 2-diethylaminoethyl-2,5-dimethylbenzoate hydrochloride has slightly higher therapeutic index (37·4), but a much higher protective index.

The present study reveals that methyl substitution at position 3 and 5 in the benzene ring of procaine yields a compound which has much higher protective and therapeutic indices compared with the parent substance procaine.

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Orally Effective Hypoglycaemic Agents from Plants

SIR,—Hypoglycaemic agents from *Allium cepa* Linn. (the domestic onion), *Ficus bengalensis* Linn. and *Eugenia jambolana* Lam. have already been reported by us (1961). The present communication describes two more orally effective hypoglycaemic principles extracted from *Allium sativum* Linn. (garlic) and from an Indian indigenous plant, *Ficus religiosa* Linn.

TABLE I

BIOLOGICAL ASSAY OF ORALLY EFFECTIVE HYPOGLYCAEMIC AGENTS FROM *Allium sativum* AND *F. religiosa.* COMPARED WITH TOLBUTAMIDE

Substance administered	Dose	Blood sugar response mg./100 ml. Initial average values for six rabbits	4 hr. pool average values for six rabbits	Mean reduction per cent	Mean hypoglycaemic potency as per cent of tolbutamide
Tolbutamide (Albert David and Co.)	0·5 g.	100	74·98	25 ± 2·1	100
Total ethyl ether (34–36°) extract from 50 g. dry garlic powder ..	0·5 g.	117·3	100·03	14·72 ± 3·5	58·88
Total water extract from 50 g. dry root bark powder of *F. religiosa*..	2·5 g.	117·9	95·52	18.97 ± 4·34	75·9

The hypoglycaemic effect of the different fractions of garlic extracts was reported by Laland and Havrivold (1933). *F. religiosa* Linn. is used throughout India as a natural remedy for diabetes mellitus as mentioned by Chopra (1933).