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The Effects of Alkyl substitution in Drugs—II. The Action of some Substituted β-Dimethylaminoethyl benzhydryl Ethers against the Tremor induced by 1,4-Di-*N*-pyrrolidino-2-butyne

M. C. DE JONGE, H. M. TERSTEEGE, A. F. HARMS, A. B. H. FUNCKE and W. TH. NAUTA, *Research Department of the N.V. Koninklijke Pharmaceutische Fabrieken v/h Brocades-Stheeman and Pharmacia, Amsterdam, The Netherlands*

Introduction

In the first article of this series[1] we reported on the antihistaminic, antiacetylcholinic, myotropic-spasmolytic and local anaesthetic activity of a number of alkyl substituted β-dimethylaminoethyl benzhydryl ethers (see also Harms[2, 3]). As one of these compounds, β-dimethylaminoethyl 2-methylbenzhydryl ether HCl (orphenadrine*), was found to be active against Parkinsonism (Bijlsma *et al.*[4, 5]) we decided to compare its activity in this respect with that of a number of closely related compounds and at the same time with that of some other well-known anti-Parkinson drugs.

The test method, which offered itself as one of the most reliable, was the inhibition of the tremors induced by 1,4-di-*N*-pyrrolidino-2-butyne (Tremorine). In test animals this compound, discovered by Everett *et al.*[6-10] in 1956, elicits a complex of symptoms, which in mice consists of prolonged tremor, salivation, diarrhoea, miosis and hypothermia, while muscular weakness and a certain degree of rigidity are also observed. Lenke[11] and Chen[12] furthermore mention narcosis-potentiating and analgetic effects, which may partly be attributed to the hypothermia.

Anti-Parkinson drugs, in particular, antagonize the entire complex of symptoms, while parasympatholytics such as

* Mephenamin ®, Disipal ®

methantheline bromide* only suppress the peripheral symptoms without any effect on the tremor. Tremorine probably acts on the brain stem, because the tremor also occurs in decerebrate and decerebellate animals.

Shortly before completing this investigation, we read the article by Frommel,[13] who during an investigation into the pharmacology of a number of anti-Parkinson drugs, also studied the anti-Tremorine action.

Methods

The protective action of a compound can be demonstrated in various ways, namely by administering the compound under investigation (S) and the Tremorine (T) to the test animal by various routes. We applied two methods.

Method 1. S is injected subcutaneously, while immediately afterwards 25 mg/kg of T is administered intravenously. The ED50 is that dose which in 50 per cent of the mice prevents the occurrence of tremors for 90 min. The percentage of protected mice is plotted against the log dose on probability paper and the ED50 is determined graphically.

Method 2. S is injected intraperitoneally and 15 min later 20 mg/kg of T is administered subcutaneously. The time of observation is 120 min. This method is similar to the one used by Everett (*loc. cit.*).

According to the method followed by Frommel,[13] S is administered orally and T (20 mg/kg) subcutaneously, the disappearance of the initially-occurring tremor being regarded as an indication of the action.

Results

The results of our investigation are listed in Table I.

For comparison, the values found by Frommel have been listed with our own values obtained by methods 1 and 2. The data obtained by method 2 have been tabulated in mg/kg as well as in μmoles/kg, because this affords a better insight into the relative activity. For those compounds which do not display a protective effect before toxic symptoms appear, this toxic dose is recorded, while the antiacetylcholine action of the amino ethers determined by Harms[1,3] on the isolated guinea pig intestine is also indicated.

* Banthine ®

The peripheral (visceral) symptoms caused by Tremorine are excellently antagonized by diphenhydramine and orphenadrine[1, 2] as well as by trihexyphenidyl,* scopolamine, atropine, diethazine,† ethopropazine,‡ benzotropine methane sulphonate§ and caramiphen‖.

The other compounds tested bring about a reduction in these symptoms, but the available data do not allow a classification into relative effectiveness.

Discussion

Since Frommel does not state whether his oral doses refer to a 50 per cent or a 100 per cent protection, it is sufficient to observe that his values in general correspond with those found by us.

As a comparison between the values obtained by methods 1 and 2 does not show any significant differences, a discussion of the data obtained by method 2 and expressed in μmoles/kg will be made.

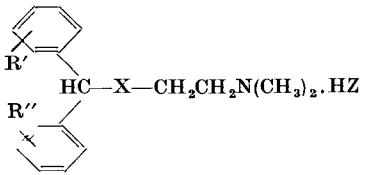
The first conclusion to be drawn is that introduction of one *ortho*-substituent [methyl (compd. 2), methoxyl (compd. 7), isopropyl (compd. 9), *tert*-butyl (compds. 12–13)] generally has a favourable effect, provided the group is not too great, e.g. contrast amyl (compds. 15, 16), *n*-propyl (compd. 8), *n*-butyl (compd. 10) and isobutyl (compd. 11). Substitution in both nuclei (compds. 5 and 6) or in the *meta* or *para* position in one nucleus (compds. 3 and 4) yields compounds which in non-toxic doses are inactive. Replacement of the oxygen of the ether bridge by a sulphur atom (compd. 17) intensifies the action of the 2-methyl derivative.

The compounds with a *tert*-butyl group in the *ortho* position (compds. 12–14) display a distinct difference in activity between the two optical isomers. The (+)-compound is inactive, which would suggest that the (−)-isomer would be twice as active as the racemic mixture; this was not the observed result.

Of all the compounds tested, scopolamine is the most active, followed by atropine, benzotropine methane sulphonate§ and trihexyphenidyl.* The observed activity of the compounds against the Tremorine tremor did not run parallel with the values found by Harms[1, 3] for the antiacetylcholine effect on the guinea

* Artane ® † Diparcol ® ‡ Parsidol ®
§ Cogentine ® ‖ Parpanit ®

Table I. Protective action of a number of substituted dimethylaminoethyl benzhydryl ethers and of some other compounds against the tremor induced in mice by Tremorine

Cmpd.	 R′ R″		X	HZ	Name	1* ED50 mg/kg	2* ED50 mg/kg	2* ED50 μmoles/kg	ED (Frommel[13]) mg/kg	Toxic dose mg/kg	Anti-acetyl-choline action (*in vitro*) Diphen-hydra-mine=1
1	H	H	O	HCl	Diphenhydramine HCl	23	15	52			1
2	2-CH_3	H	O	HCl	Orphenadrine HCl	19	12·5	41	25		2·1
3	3-CH_3	H	O	HCl		—	—	—		40	1·3
4	4-CH_3	H	O	HCl	Neobenodine®; Toladryl®	—	—	—		40	0·4
5	2-CH_3	2′-CH_3	O	HCl		—	—	—		40	1·3
6	2,6-diCH_3	2′,6′-diCH_3	O	HCl		—	—	—		25	1·8
7	2-OCH_3	H	O	maleic		28	8	20			—
8	2-*n*-C_3H_7	H	O	oxalic		—	—	—		40	4·9
9	2-iso-C_3H_7	H	O	HCl		32	12·5	38			6·5

10	2-*n*-C_4H_9	H	O	oxalic		—	—	—		25	5·5
11	2-iso-C_4H_9	H	O	oxalic		—	—	—		25	16·0
12	2-*tert*-C_4H_9	H (±)	O	HCl		16	8	23			33·0
13		H (−)	O	HCl		21	6·25	18			60·0
14		H (+)	O	HCl		—	—	—		200	0·5
15	2-*n*-C_5H_{11}	H	O	oxalic		—	—	—		35	1·7
16	2-*tert*-C_5H_{11}	H	O	oxalic		—	—	—		>20	18·0
17	2-CH_3	H	S	HCl		24	6·25	20			2·4

18	1-Cyclohexyl-1-phenyl-3-piperidino-propan-1-ol HCl	Trihexyphenidyl	12	4	12	5	
19	1-Phenylcyclopentyl-diethylamino-ethyl-1-carboxylate HCl	Caramiphen		12·5	38		
20	*N*-(2-Diethylaminoethyl) phenothiazine HCl	Diethazine		20	60	50	
21		Scopolamine HBr		0·5	1·3	5	
22		Atropine Sulphate		2·5	7·4	10	
23	Tropinyl benzhydrylether CH_3SO_3H	Benzotropine methane sulphonate		3	7·5		
24	*N*-(2-Diethylaminopropyl)phenothiazine HCl	Ethopropazine		20	57	20	

* In these columns a dash means that the substance offered no protection until toxic doses were reached.

pig intestine. Also Frommel[13] fails to demonstrate such a parallelism in his compounds.

Though it would seem now that all the anti-Parkinson drugs with the exception of Tigloidine (Trautner[14]) inhibit or suppress the Tremorine tremor, this action does not run parallel with the clinical effect. There is a doubt, therefore, as to whether all compounds showing activity in the Tremorine test might be expected to be clinically suitable. Further investigation both into the principle of the action of Tremorine and into that of its antagonists is necessary.

Summary. The action of some substituted β-dimethylaminoethyl benzhydryl ethers against the Tremorine tremor in mice has been investigated and the influence of variations in the substituents has been studied. For comparison some other compounds with known anti-Parkinson activity were included in the investigation.

The anti-Tremorine activity does not run parallel with the *in vitro* anti-acetylcholine activity.

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