EFFECT OF LOCAL ANAESTHETICS ON BARBITURATE SLEEPING TIME

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Received April 15, 1959

The effect of certain local anaesthetics on barbiturate sleep in the mouse and the guinea pig is described. One of a series of new local anaesthetics 1-(1-methyl-2-phenylcarbamoylethyl)pyrrolidine (WS 10) prolongs barbiturate sleep in the guinea pig 2·3 times at the optimal dose without obvious side effects; other closely related members of the same series diminish barbiturate sleep.

A wide variety of substances affect the actions of barbiturates, modifying both their dormitive and their anti-epileptic properties[1,2]. Various mechanisms have been suggested in explanation of these actions. For example, Lamson[3,4] demonstrated that certain intermediates of glucose metabolism potentiate the anaesthetic action of barbiturates such as hexobarbitone, barbitone, quinalbarbitone and thiopentone. Frommel[5–7] gave evidence that meprobamate potentiates the sedative action of phenobarbitone and other barbiturates. The intermediates of glucose metabolism, however, show no effect on the anaesthesia produced by ethanol or ether.

The potentiating action of the intermediates of glucose metabolism in the brain on barbiturates can be blocked by acetylcholine[8–11].

The present communication concerns the effect of certain local anaesthetics on the anaesthetic action of barbiturates, particularly phenobarbitone and pentobarbitone.

Experimental Methods

Guinea pigs, 400 to 1000 g., and preferably 500 to 600 g., were used. Animals under about 400 g., or over 1000 g. tended to give erratic results. Constant room temperature and relative humidity were found to be desirable for reproducible results. Temperatures of 21–24·5° and a relative humidity of 60–75 per cent were found to be optimal.

The same animals were re-used for sleep experiments after a minimum rest period of 5 days. Generally the intraperitoneal route was used, the barbiturate being injected first as a 1 per cent solution of the sodium salt in water, followed immediately by a 1 per cent solution of the hydrochloride of the local anaesthetic in water. In some experiments the local anaesthetic and the barbiturate was given by mouth. Essentially the same result was obtained irrespective of the route of administration.

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Each animal was placed in a separate cardboard box and the times noted at which the animal no longer resisted the dorsal position and then the time at which it reverted spontaneously to the ventral position.

The dose of barbiturate was kept constant, and that of local anaesthetic varied. The local anaesthetics used were the following: procaine, lignocaine, piperocaine, cinchocaine, WS 2, 4, 10, 13, 15, 17, 19, 20, 22, 23, 24, 25, 51, 53, 54, 56, 88 and 295, the formulae of which are given in Table V.

RESULTS

In the absence of barbiturates WS 10, 1-(1-methyl-2-phenylcarbamoyl-ethyl)pyrrolidine, showed a regular and lignocaine an irregular dormitive effect in the guinea pig at doses between 30–60 mg./kg. (i.p.), see Table I. These two substances together with WS 23 and 295 were among the most potent of those which prolonged barbiturate sleeping times.

TABLE I

SLEEP INDUCED BY LOCAL ANAESTHETICS ALONE IN THE GUINEA PIG

	Dose of local anaesthetic i.p. in mg./kg.	Number	Sleeping time in minutes mean
WS 10	15	6	0
	30	6	0
	45	6	32
	60	6	0
	90	6	0 (3 animals convulsed)
Procaine	30	6	0
	60	6	0
	90	6	0
Lignocaine	30	6	0
	45	6	5
	60	4	12
	90	3	0 (convulsions)

Table II shows the prolonging effect of WS 10 at various doses on the dormitive action of pentobarbitone compared with known local anaesthetics.

The prolonging effect of WS 10 is seen at low doses, whereas higher doses of lignocaine and procaine are needed. The barbiturate sleep-prolonging effect has no direct relation to the local anaesthetic action of these drugs, since lignocaine is, for example, a stronger local anaesthetic, weight for weight, than WS 10 while procaine is about the same. Piperocaine shows practically no sleep-prolonging effect of barbiturates, even at toxic doses. Similarly, cinchocaine showed poor sleep-prolonging action in spite of its high local anaesthetic activity.

For WS 10 a maximum potentiation of 2·3 times was observed at 75 mg./kg. (i.p.). At higher doses spasmogenic and excitatory effects became marked, resulting in progressively reduced sleeping time as the dose was increased. Finally, true sleep observations became unreliable owing to the typical convulsions produced by toxic doses of local anaesthetics. With cinchocaine the high toxicity masked true sleep at low doses, so that the results are given here with reserve.

TABLE II

PROLONGATION OF PENTOBARBITONE, 10 MG./KG. I.P., SLEEPING-TIME IN THE GUINEA PIG

Dose local anaesthetic i.p. mg./kg.	No. of animals	Mean $\bar{X}$ sleeping time min.	Prolongation per cent	Standard deviation min.
W.S. 10 2·5	15	85·0	10·4	12·0
" " 5·0	18	115·6	50·5	10·6
" " 10·0	23	117·4	52·0	16·8
" " 15·0	24	149·4	97·6	15·9
" " 30·0	18	153·4	104·7	14·2
" " 45·0	18	177·3	130·0	15·1
" " 60·0	18	207·9	170·0	17·5
" " 75·0	28	254·7	231·0	22·0
" " 90·0	21	228·0	194·2	20·1
Procaine 30·0	12	107·0	38·9	9·8
" 60·0	22	143·1	60·5	21·4
" 90·0	22	121·6	41·7	27·0
" 120·0	12	105·0	36·4	15·1
Piperocaine 10·0	10	81·3	5·5	8·2
" 20·0	6	81·5	5·9	13·9
" 40·0	6	89·5	16·2	14·6
Cinchocaine 5·0	18	79·2	2·9	9·8
" 10·0	18	124·0	60·9	17·9
" 20·0	18	127·8	65·8	14·9
" 40·0	12	112·5	46·0	23·4
Lignocaine 15.0	12	113·3	47·1	16·1
" 30·0	18	139·6	82·1	11·0
" 45·0	18	157·3	105·3	15·5
" 60·0	18	164·7	113·8	15·5
" 75·0	15	142·8	86·7	14·3
" 90·0	15	142·3	87·4	17·0
Control Pento-barbitone 10·00	56	77·05	0	5·5

Parallel results with barbiturates other than pentobarbitone are reported in Tables III and IV. It was not thought of immediate interest to work with large enough numbers of animals to allow a statistical treatment of the data. The results obtained with phenobarbitone and WS 10 both by mouth are given in Table III.

TABLE III

PROLONGATION OF PHENOBARBITONE SLEEPING-TIME 30 MG./KG. BY MOUTH IN THE GUINEA PIG

Dose WS 10 mg./kg.	No. of animals	Sleeping time in minutes mean	Prolongation per cent
10	4	80	57
35	8	105	105
0	4	51	0
50	4	290	222
0	4	90	0
75	4	174	123
0	4	78	0
100	4	90	76
0	4	51	0

Since the number of animals was small, each experiment was made with a simultaneous control. In some of the preliminary siting experiments the room temperature and the relative humidity were not controlled,

so that the control values for sleep with each potentiating agent vary. But the results show that the general pattern is similar to that seen with pentobarbitone under more rigidly controlled conditions. A maximum prolongation is reached at about 50 mg./kg. of WS 10. Here again, on increasing the dose, the spasmogenic effect of the local anaesthetic appears, thus reducing the sleeping time. Table IV shows similar effects with hexobarbitone and WS 10 in the mouse.

TABLE IV

PROLONGATION OF HEXOBARBITONE SLEEPING-TIME 75 MG./KG. I.P. IN THE MOUSE

Dose WS 10 in mg./kg.	No. of animals	Sleeping time in minutes mean	Prolongation per cent
10 s.c.	5	100	29
0	5	77	0
20 s.c.	5	149	109
0	5	71	0
100 by mouth	5	104	39
0	5	75	0

To test the generality of this potentiating effect preliminary siting tests were made with some selected members of the same chemical series as WS 10 with the results given in Table V.

The results bring out some interesting relations between structure and activity.

DISCUSSION OF STRUCTURE: ACTIVITY RELATIONS

Barbiturate sleeping-time prolongation appears often in this type of local anaesthetic but does not seem to be a direct function of the local anaesthetic activity of these substances[12,13]. WS 15 and WS 17 show about the same local anaesthetic activity but possess widely differing properties of barbiturate sleeping-time prolongation. Further, WS 13, 15 and 25 are all more powerful local anaesthetics than WS 10, yet are weaker in prolonging sleeping-time. Substitution in the benzene ring seems, in general, to increase the local anaesthetic activity but sometimes to lower the barbiturate effect.

In general, the presence of a carbamoyl group seems to favour sleep-prolongation, as shown by the high activity of WS 10, 23, 295 and lignocaine, and by the lower activity of the ester type of local anaesthetic like procaine and piperocaine. This must be qualified by remarking that the presence of a morpholino group in the side chain, as in WS 51, 53, 54, 56 seems to neutralise this activity of the carbamoyl group without at the same time lowering significantly the local anaesthetic activity.

It is commonly assumed for structure: activity relation purposes that, in local anaesthetics of the above type, the pyrrolidin-1-yl and piperidino groups are interchangeable without appreciably altering the pharmacology.

A comparison between the sleep-prolonging effect shown by WS 2 and 4, for example, demonstrates this generalisation may be unsound, since WS

TABLE V

30 MG./KG. PHENOBARBITONE BY MOUTH IN THE GUINEA PIG

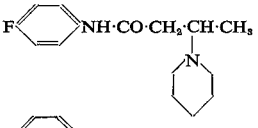
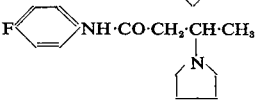
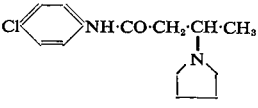
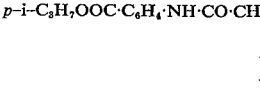
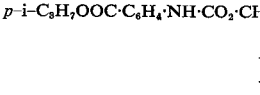
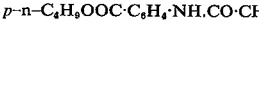
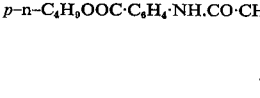
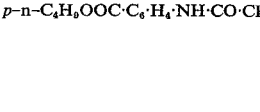
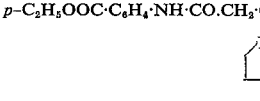
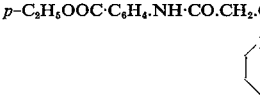
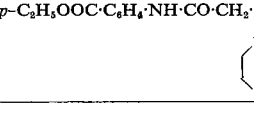
Number of anaesthetic	Formula	Number of guinea pigs	Dose of anaesthetic orally mg./kg.	Sleep prolongation per cent
WS 2		4 4 4	10 35 100	36 160 – 20
WS 4		4 4 4	10 35 100	– 39 – 5 – 20
WS 13 ..		4 4 4	10 35 100	53 35 – 60
WS 24 ..		4 4 4	10 35 100	– 40 – 33 – 100
WS 25 ..		4 4 4	10 35 100	– 31 20 47
WS 22 ..		4 4 4	10 35 100	– 32 – 19 – 100
WS 23 ..		4 4 4	10 35 75	79 124 40
WS 56 ..		4 4 4	10 35 100	– 33 – 36 – 100
WS 15 ..		4 4 4	10 35 100	144 20 – 59
WS 17 ..		4 4 4	10 35 100	– 67 – 64 – 100
WS 54 ..		4 4 4	10 35 100	– 79 – 47 – 41

TABLE V—*continued*

Number of anaesthetic	Formula	Number of guinea pigs	Dose of anaesthetic orally mg./kg.	Sleep prolongation per cent
WS 19 ..	*p*-$CH_3OOC{\cdot}C_6H_4{\cdot}NH{\cdot}CO{\cdot}CH_2.CH{\cdot}CH_3$ (N)	4	10	− 84
		4	35	− 87
		4	100	− 84
WS 20 ..	*p*-$CH_3OOC{\cdot}C_6H_4{\cdot}NH{\cdot}CO{\cdot}CH_2.CH{\cdot}CH_3$ (N)	4	10	41
		4	35	95
		4	100	− 99
WS 53 ..	*p*-$CH_3OOC{\cdot}C_6H_4{\cdot}NH.CO{\cdot}CH_2{\cdot}CH{\cdot}CH_3$ (N, O)	4	10	− 13
		4	35	− 27
		4	100	− 48
10 MG./KG. I.P. PENTOBARBITONE IN THE GUINEA PIG				
WS 10 ..	$C_6H_5.NH.CO.CH_2.CH.CH_3$ (N)	23	10	52
		18	45	130
		28	75	231
		21	90	194
WS 88 ..	$C_6H_5.NH.CO.CH_2.CH.CH_3$ (N)	5	10	− 15
		5	35	51
		5	50	7
		5	90	− 28
WS 295 ..	$C_6H_5.NH.CO.CH_2.CH.CH_3$ ($N(C_2H_5)_2$)	7	10	84
		7	25	146
		7	50	149
		5	90	− 44
WS 51 ..	$C_6H_5.NH.CO.CH_2.CH.CH_3$ (N, O)	7	30	− 4
		7	60	− 4
		5	90	51

4 shows a sleep-diminishing effect, while WS 2 gives a positive action. Both substances are about equal in their local anaesthetic activity. Yet the only chemical difference between the two types of compound lies in the pyrrolidin-1-yl and piperidino groups.

WS 24 and 25 show the same type of effect but in reversed order, the compound containing the piperidino group (WS 24) showing, in this case no prolonging action, whereas the pyrrolidin-1-yl compound (WS 25) shows moderate activity. Similar effects are seen in the compounds WS 22 and 23, WS 15 and 17.

Thus, the pharmacological action of even such similar groups as the piperidino and pyrrolidin-1-yl groups situated in identical basic structures is still unpredictable, as judged by our methods. It is possible that the study of the pharmacological properties of the (+)- and (−)-isomers of

these substances might throw further light on these relationships which are shown in Table V.

These experiments were begun in the Institut de Thérapeutique Expérimentale, Ecole de Médecine, Geneva, Switzerland (Directeur, Professeur Edouard Frommel) and completed during a visiting professorship held by one of us (A.E.W.S.) during the academic year 1957–58 at the University of Illinois Professional Colleges, Chicago 12, U.S.A., to whom thanks are due for laboratory facilities and a research grant.

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