

## Experimental Spinal Anaesthesia Produced by Members of a Homologous Series

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Recently, a series of potent local anaesthetics possessing high local anaesthetic activity and relatively low irritancy were studied in this laboratory.<sup>1</sup> This finding was of special interest because the compounds had ether groups but not ester or amide groups. A series of five homologous 3-bromo-4-(2-diethylaminoethoxy)-5-alkoxyanilines, tested by intradermal injection in guinea pigs,<sup>2</sup> showed an increase in activity, toxicity and irritancy with the increase in length of the alkoxy chain.

We thought that it would be of interest to evaluate the local anaesthetic activity of this series by intraspinal injection in rabbits in order to determine the relationship between the length of the alkoxy side chain on the one hand and spinal local anaesthetic activity and duration of action on the other. The results obtained are described in this paper.

### Method

The method of Bieter *et al.*,<sup>3, 4</sup> with minor modifications, was used in all the experiments. Some of the minor modifications have already been described.<sup>5, 6</sup> In another departure from the original technique, the rabbit sat on a table firmly held between the experimenter's left arm and left side, while the injection was being made with the right hand. The solutions were freshly made up in physiological salt solution, except in the case of a 4.0

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per cent solution of compound I which was made up in 0.45 per cent sodium chloride solution.

A total of 248 rabbits was used. Each drug was tested in concentrations graded at 0.3 log intervals on an average of 7 or 8 animals (range: 5 to 15 rabbits). The average duration of urethral anaesthesia<sup>5</sup> was plotted on semi-log paper against the concentration and the Threshold Anaesthetic Concentration<sub>5</sub> (TAC<sub>5</sub>) was estimated from the linear dose-effect curves obtained. The TAC<sub>5</sub> is the concentration expected to produce an average duration of anaesthesia (absence of the urethral reflex) of 5 min.

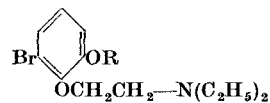
### Results and Discussion

Most of the results are summarized in Table I. Although the concentrations are listed as grams of the salt per cent, the Threshold Anaesthetic Concentration<sub>5</sub> (TAC<sub>5</sub>) and the procaine ratios have been calculated in terms of the bases, and on a molar basis. (These ratios were calculated by using a value for procaine previously reported.<sup>6</sup>)

All the concentrations tested were found to produce spinal anaesthesia in all the animals injected. With the exception of the hexoxy homologue, these compounds were relatively short-acting. The urethral reflex disappeared promptly after injection. The general pattern of anaesthesia was similar to that observed by Bieter *et al.*<sup>3, 4</sup> with procaine. Sensory anaesthesia reached the upper or lower thorax with the higher concentrations, and was less extensive with the smaller concentrations. By the time the urethral reflex reappeared, the animal still failed to respond to pinpricks on the hind legs and there was also some degree of hind leg motor impairment.

As with other local anaesthetics, there was an approximately linear relationship between the mean duration of anaesthesia and the log of the concentration (Fig. 1).

The 5-methoxy aniline homologue (compound I) was found to be approximately 6.8 times more active than procaine, in terms of the bases. The activity gradually increased with the length of the 3-alkoxy chain. The rate of increase was slight up to the 3-propoxy homologue. The two higher members of the series



R (salt)	Conc., %	No. of rabbits tested	Duration of spinal anaesthesia, absence of urethral reflex, min		Spinal anaesthetic activity			
			Mean	Slope of dose-duration curve	TAC <sub>5</sub> <sup>b</sup>	Procaine ratios		
						In terms of bases	Molar	Activity/irritancy ratio <sup>c</sup>
CH <sub>3</sub> (·HCl)	4·0	5	47·5					
	2·0	10	43·0					
	1·0	14	28·9					
	0·5	10	19·5	7·41	0·074	6·8	9·0	3·5
	0·25	10	18·0					
	0·125	10	9·7					
	0·062	6	4·1					
C <sub>2</sub> H <sub>5</sub> (·HCl)	2·0	6	45·0					
	1·0	8	34·0					
	0·5	8	33·7	7·66	0·053	9·4	13·0	2·9
	0·25	8	16·2					
	0·125	8	14·4					
<i>n</i> -C <sub>3</sub> H <sub>7</sub> (·2HCl)	0·062	8	6·7					
	1·0	14	56·8					
	0·5	15	32·8					
	0·25	12	23·7	10·8	0·048	10·4	15·0	2·4
	0·125	8	14·4					
<i>n</i> -C <sub>4</sub> H <sub>9</sub> (·2HCl)	0·062	12	13·3					
	0·5	10	57·5					
	0·25	8	48·5					
	0·125	8	35·6	11·3	0·015	33·0	51·0	3·7
	0·062	8	25·0					
<i>n</i> -C <sub>6</sub> H <sub>13</sub> (·HCl)	0·031	8	13·0					
	0·125	7	107·5					
	0·062	8	82·5	26·9	0·007	71·0	116·0	2·6
	0·031	9	55·8					
	0·016	9	26·0					

<sup>a</sup> In terms of salts.

<sup>b</sup> In terms of bases.

<sup>c</sup> The molar procaine irritancy ratios were obtained from Luduena and Hoppe.<sup>5</sup>

were considerably more active. In the case of the 3-hexoxy homologue, the injection of approximately 0.5 ml of a 0.016 per cent solution of the hydrochloride salt (80  $\mu$ g) produced anaesthesia of an average duration of 27 min.

As shown in Fig. 1, the slopes of the dose-effect curves increase gradually with the length of the 5-alkoxy chain. In the first members of the series, the difference in slopes is not very pronounced, but the difference is evident when the curves of the

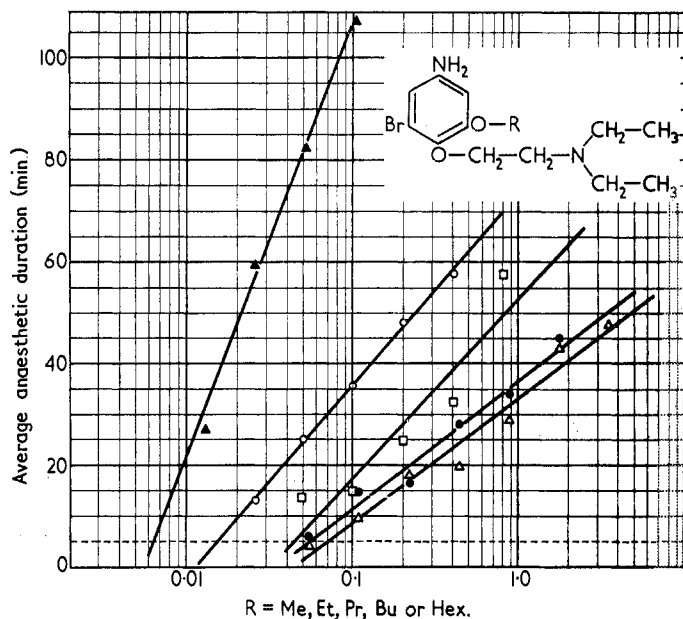


Fig. 1. Spinal anaesthesia in rabbits.

butoxy and the methoxy (or ethoxy) homologues are compared. The slope of the 5-hexoxy homologue is much higher. The slope represents in this case the increment in the average duration of anaesthesia obtained by doubling the drug concentration. It means that the higher homologues diffuse at a much lower rate out of their site of action. In other words, at equipotent concentrations several times higher than the corresponding  $TAC_5$ , the higher homologues produce anaesthesia of longer duration.

The slopes of the two lowest homologues are in the range of those of short-acting local anaesthetics like procaine, lidocaine and piperocaine;<sup>6</sup> but the former have higher activity/irritancy ratios.<sup>6, 1</sup> The slope of the dose-response curve of the hexoxy homologue (26·9, Table I) was somewhat lower than that obtained with tetracaine (32·6) in a previous investigation;<sup>6</sup> in other words, tetracaine is somewhat longer-acting than the hexoxy homologue.

This investigation has shown that, in the rabbit, the spinal anaesthetic/activity ratios (procaine = 1) of a series of five 3-bromo-4-(2-diethylaminoethoxy)-5-alkoxyanilines are, in general, higher than the procaine ratios obtained by intradermal injection in guinea pigs.<sup>1</sup> The duration of spinal anaesthesia produced by approximately equi-active concentrations increases with the number of carbons in the 5-alkoxy side chain, and it may be related to the increase in the oil/water partition coefficient of the unionized local anaesthetic base.

### Summary

*Summary.* The spinal anaesthetic activities of 3-bromo-4-(2-diethylaminoethoxy)-5-alkoxyaniline and the 5-ethoxy, propoxy and hexoxy homologues were determined in rabbits by the method of Bieter *et al.*<sup>3, 4</sup> The 5-methoxy homologue was approximately 6·8 times more active than procaine. Activity increased gradually with the length of the 5-alkoxy chain. The hexoxy homologue was 71 times more active than procaine. The lower homologues produced anaesthesia of short duration even in concentrations more than 30 times higher than the Threshold Anaesthetic Concentration<sub>5</sub> (TAC<sub>5</sub>). The duration of anaesthesia of equipotent concentrations, estimated from the slope of the dose-effect curves, increased with the length of the 5-alkoxy side chain.

*(Revised manuscript received 25 November, 1960)*

### References

- <sup>1</sup> Luduena, F. P., Hoppe, J. O., Page, D. F. and Clinton, R. O. This Journal, **3**, 545 (1961)
- <sup>2</sup> Bülbring, E. and Wajda, J. *J. Pharmacol.*, **85**, 78 (1945)

- <sup>3</sup> Bieter, R. N., Cunningham, R. W., Lenz, O. and McNearney, J. J. *J. Pharmacol.*, **57**, 221 (1936)
- <sup>4</sup> Bieter, R. N., McNearney, J. J., Cunningham, R. W. and Lenz, O. *J. Pharmacol.*, **57**, 264 (1936)
- <sup>5</sup> Luduena, F. P. and Hoppe, J. O. *J. Amer. pharm. Ass. Sci. Ed.*, **40**, 132 (1951)
- <sup>6</sup> Luduena, F. P. *Arch. int. Pharmacodyn.*, **109**, 143 (1957)