THE LOCAL ANAESTHETIC PROPERTIES OF ESTERS OF *N*-SUBSTITUTED α-AMINOPHENYLACETIC ACIDS

BY M. SHAPERO AND K. B. EDWARDS

From Ward, Blenkinsop & Co. Ltd., Research Laboratories, Wembley, Middlesex

Received November 6, 1961

The local anaesthetic properties of a series of esters of *N*-substituted α-aminophenylacetic acids are described. Compounds with an ethyl ester group showed little activity, but replacing this group by an isopentyl group produced local anaesthetic action. The cyclohexyl and 3,5,5-trimethylcyclohexyl esters induced a prolonged surface and infiltration anaesthesia; this was more pronounced in those compounds in which the central amino-group was tertiary. The relationship between structure and activity is discussed.

EDWARDS, Goldberg and Wragg (1960) have described the preparation and spasmolytic properties of esters of *N*-substituted α-aminophenylacetic acids; the local anaesthetic properties are now reported.

EXPERIMENTAL

Surface Anaesthesia in Guinea-pigs

0·1 ml. of a 2 per cent solution of each compound was instilled into the conjunctival sac and the eye-lid held closed for 30 sec. The duration of anaesthesia was evaluated by applying pressure with a fine camel hair brush to the cornea at regular intervals until the return of the corneal reflex.

Infiltration Anaesthesia in Mice

This was determined in 18 to 20 g. male albino mice by the method of Bianchi (1956). A bull-dog artery clip with its blades covered with thin rubber tubing was applied to the base of the tail; if the animal made repeated attempts to remove the clip within 30 sec. they were then used for the test.

Each compound was dissolved in saline and 0·1 ml. of a 2 per cent solution was injected subcutaneously about 1 cm. from the root of the tail; 15 min. later the clip was applied to the tail of each mouse in turn. If the animal made no attempt to remove the clip anaesthesia was present and the test was then repeated at 15 min. intervals until the return of the reflex.

RESULTS

Only results for those compounds that produced local anaesthesia in more than 50 per cent of the animals are given in Table I; activities are expressed as the mean duration and the range.

The compounds have been classified according to the nature of the ester group which is either ethyl, isopentyl, cyclohexyl or 3,5,5-trimethylcyclohexyl.

Ethyl series. Only two of the four compounds examined had local anaesthetic activity. Compound 3012 had no surface anaesthetic

properties, but subcutaneous injection into the tails of mice produced anaesthesia lasting for 30 min. in 2 out of 5 of the animals. Compound 3015 produced brief surface anaesthesia in 3 out of 5 mice and infiltration anaesthesia, similar to that found with compound 3012, in 2 out of 5 mice.

Isopentyl series. The three compounds examined induced topical anaesthesia when tested in guinea-pigs. Maximum activity within this group was exhibited by compound 3000, the surface anaesthetic effect of which had a mean duration of 40 min. This was approximately 3 to 4 times the duration for compounds 3001 and 3002.

Less than 50 per cent of the mice injected with compounds 3001 and 3002 developed local anaesthesia. The injection of compound 3000 was followed by prolonged local anaesthesia in 9 out of 10 mice.

Cyclohexyl series. The members of this series produced surface anaesthesia of about the same potency as the isopentyl series. The longest duration of anaesthesia was given by compound 3006 and that with the minimum activity was compound 3005. Compounds 3003 and 3004 showed intermediate activity.

TABLE I

LOCAL ANAESTHETIC ACTIVITY OF ESTERS OF *N*-SUBSTITUTED α-AMINOPHENYLACETIC ACIDS (DIHYDROGEN OXALATES)

$C_6H_5CH.(COOR').NR''.CH_2CH_2R.$

Cmpd.	R″	R′	R	Surface anaesthesia in guinea-pigs: Mean anaesthetic time in min. and range			Infiltration anaesthesia in mice: Mean anaesthetic time in min. and range		
3012	H	ethyl	piperidino	(0/5)	0		(2/5)	0	
3013	H	,,	pyrrolidin-l-yl	(0/5)	0		(0/5)	0	
3014	H	,,	diethylamino	(0/5)	0		(1/5)	0	
3015	Me	,,	,,	(3/5)	7	(0–15)	(2/5)	0	
3001	H	isopentyl	piperidino	(7/10)	13	(0–30)	(2/5)	0	
3002	H	,,	pyrrolidin-l-yl	(6/10)	9	(0–20)	(4/10)	0	
3000	Me	,,	diethylamino	(15/15)	40	(30–45)	(9/10)	64	(0–105)
3003	H	cyclohexyl	piperidino	(8/10)	10	(0–30)	(3/5)	45	(0–60)
3004	H	,,	pyrrolidino-l-yl	(6/10)	13	(0–35)	(3/10)	0	
3005	H	,,	diethylamino	(3/10)	0		(8/10)	98	(0–195)
3006	Me	,,	,,	(15/16)	23	(0–45)	(10/10)	300	(120–430)
3007	H	3,5,5-trimethyl-cyclohexyl	piperidino	(20/20)	74	(60–95)	(1/5)	0	
3065	Me	,,	,,	(16/16)	83	(30–100)	(9/10)	82*	
3008	H	,,	pyrrolidino-l-yl	(6/10)	36	(0–40)	(10/15)	74	(0–150)
3009	H	,,	diethylamino	(3/5)	22	(0–40)	(7/10)	66	(0–120)
3064	Me	,,	,,	(16/16)	62	(40–100)	(10/10)	99**	

( ) No. of animals showing anaesthesia/no. tested.
* 6/10 still showing local anaesthetic activity.
** 7/10 still showing local anaesthetic activity.

The outstanding compound after the subcutaneous injection into mice was 3006. Examination of Table I shows that this compound induced a prolonged local anaesthesia. After injection recovery from the effect of this drug was slow and it was not until 430 min. that the response to pain was normal in all the animals. The injection of compound 3005 was followed by a less powerful effect and its duration was one-third of that

found with 3006; however, 195 min. after injection the reaction to pain in all the mice was found to be normal.

3,5,5-*Trimethylcyclohexyl series.* The instillation of the members of this series into the eye of the guinea-pig produced a prolonged anaesthesia. Table I shows that the mean duration of anaesthesia was approximately two to four times longer than for the corresponding cyclohexyl series.

The three outstanding surface anaesthetics in this series were compounds 3007, 3064 and 3065: the mean duration of anaesthesia ranged from 60 to 83 min.

With the exception of compound 3007, all were able to induce anaesthesia after the subcutaneous injection into the tails of mice. The mean duration of anaesthesia was similar for compounds 3008 and 3009. The injection of compounds 3064 and 3065 was followed by prolonged local anaesthesia and at the end of 105 min. it was found that 60 to 70 per cent of the mice still failed to respond to the pain stimulus. If the experiment had continued until all the mice had recovered, the mean duration of anaesthesia for these two compounds would have exceeded the values given in the Table.

Local Tissue Reactions

Local reactions after the instillation into the eye of the guinea-pig and infiltration into the mouse tail was not seen with compounds 3001, 3002, 3003 and 3004, 3012, 3013, 3014 and 3015. All the other compounds at 2 per cent concentration produced a slight discharge and irritation in the eye, and oedema and inflammation at the site of the injection; these were more severe with compounds 3009, 3064 and 3065.

Discussion

Analysis of the experimental data reveals that maximum local anaesthetic activity was related to the nature of the esterifying group and to the conversion of the secondary amino-group to a tertiary group.

The influence of the ester group on local anaesthetic activity is clearly illustrated in Table I. Compounds which were ethyl esters had poor anaesthetic activity compared with those in which isopentanol was the esterifying substance. Replacement of the isopentyl group by either a cyclohexyl or 3,5,5-trimethylcyclohexyl group produces long acting topical and infiltration anaesthesia in guinea-pigs and mice. In general, members of the 3,5,5-trimethylcyclohexyl series were capable of producing anaesthesia of longer duration than that given by a cyclohexyl group in this position.

Throughout the series it was found that conversion of the secondary α-amino-group into a tertiary group was followed by increased activity. This was well illustrated by comparing the behaviour of compound 3005 with 3006 and compound 3007 with 3065. Those compounds in which the α-amino-group was tertiary (3006 and 3065) were found to induce a more prolonged action than those in which this group (3005 and 3007) remained secondary.

From the evidence available it was not possible to establish the part played by the terminal nitrogenous group in influencing local anaesthetic activity.

Acknowledgement. The authors wish to thank Mr. B. Basil for some of the tests.

REFERENCES

Edwards, K. B., Goldberg, A. A. G. and Wragg, A. H. (1960). *J. Pharm. Pharmacol.*, **12**, 179–186.

Bianchi, C. (1956). *Brit. J. Pharmacol.*, **11**, 104–106.