LOCAL ANAESTHETIC ACTIVITY OF SOME NEW SUBSTITUTED ACYLAMIDES II

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Summary: Six new substituted acylamides, chemically related to lignocaine were studied for local anaesthetic activity and toxicity in mice, frogs and guinea pigs. Only one of these compounds, *w*-pyrrolidino 2, 3, 5, 6 tetramethyl acetanilide was found to possess potency comparable to lignocaine with a slightly higher therapeutic index. Study of the S.A.R. of this group indicated that by removal of two methyl groups at position 3 and 5 in the above compound, a local anaesthetic with greater potency than lignocaine may be obtained. Further exploration of the potentialities of a compound having pyrrolidine group as a part of basic side chain is indicated.

Key words: lignocaine derivatives local anaesthesia

INTRODUCTION

Grewal and Singh, (4) stated that clinical experience with lignocaine has been so encouraging that one is tempted to believe that some where among the vast number of compounds having the chemical configuration,

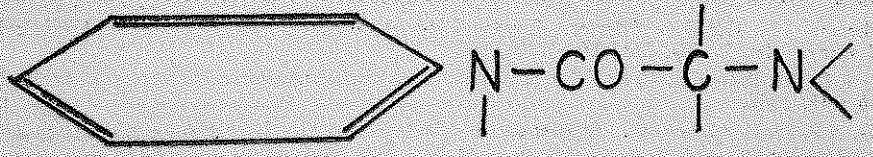

Fig. 1

an ideal local anaesthetic might be discovered. In the above communication the authors described the local anaesthetic activity of dialkyl amino, morpholino and piperidino derivatives of acetanilide with one ethyl group in the benzene ring in Ortho/meta/or para position. None of the compounds tested, however, approached the potency of lignocaine. In the present work local anaesthetic activity and acute toxicity of a new series of compounds chemically related to lignocaine, has been studied in comparison with lignocaine.

MATERIAL AND METHODS

In all, six compounds were selected. These were synthesized by S. Sukhdev Singh, M. Pharm., Department of Pharmacology, Medical College, Patiala. Their chemical and physical characters are detailed in Table I and the chemical structure is described in Fig. 2.

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The hydrochloride salts of these compounds were used. The solutions were made in physiological saline. Lignocaine hydrochloride was used as reference standard.

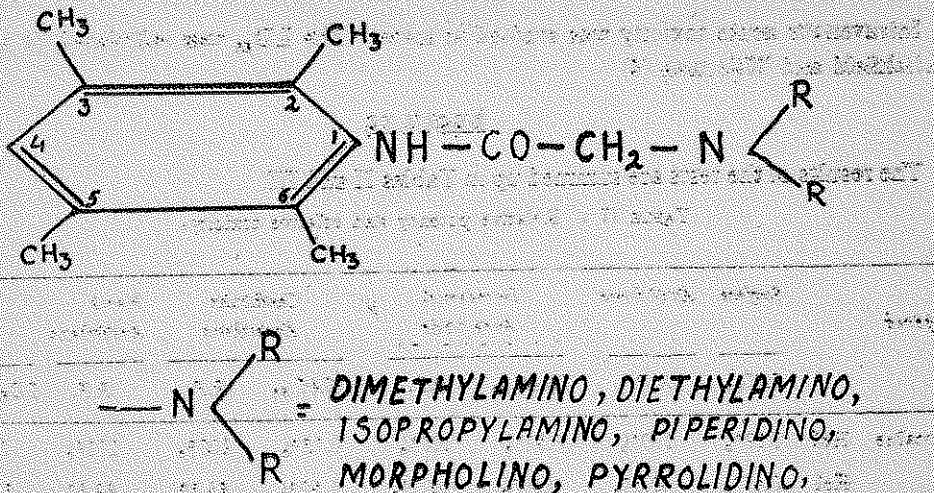

Fig. 2

TABLE I

Compound Number	*Chemical name*	*Physical characters*
C_I	*w* – Dimethylamino-2,3,5,6-tetramethyl acetanilide	m.p. 231-32°C, light cream coloured flakes, soluble in water and normal saline.
C_{II}	*w* - diethylamino-2,3,5,6-tetramethyl acetanilide	m.p. 164-66°C, white flakes, readily soluble in water and normal saline.
C_{III}	*w* - isopropylamino-2,3,5,6-tetramethyl acetanilide	m.p. 225-26°C, white powder, moderately soluble in water and normal saline.
C_{IV}	*w* - piperidino-2,3,5,6-tetramethyl acetanilide	m.p. 214-15°C, light yellow crystalline, soluble in water and normal saline.
C_V	*w* - morpholino-2,3,5,6-tetramethyl acetanilide	m.p. 227-29°C, white powder, soluble in water and normal saline.
C_{VI}	*w* - pyrrolidino-2,3,5,6-tetramethyl acetanilide	m.p. 227-29°C, white powder, soluble in water and normal saline.

Local anaesthetic activity of these compounds was studied by the following methods; (i) surface anaesthetic action on guinea pig cornea (3), (ii) intradermal anaesthetic action on the back of guinea-pigs (2), (iii) conduction anaesthesia on the tail of mice (1) and (iv) plexus anaesthesia in frogs (2). The details of these techniques have been described in an earlier paper by Grewal and Singh (4). A modification was made in conduction anaesthesia by the tail-pinch method; pinch cock was used in place of an artery clip to apply the stimulus because it was found

that the former gives a more uniform stimulus. The results were plotted and calculations were made as discussed by Grewal and Singh (4).

Intravenous acute toxicity was studied in mice. The LD_{50} was calculated by the method of Litchfield and Wilcoxon (6).

RESULTS

The results of the tests are summed up in Tables II and III.

TABLE II : Relative potency and relative toxicity.

Compound		*Surface Anaesthesia*		*Intradermal Anaesthesia*		*Conduction Anaesthesia*		*Plexus Anaesthesia*	*Acute Toxicity*	
		SAC_{50}	*R.P*	$IDAC_{50}$	*R.P.*	CAC_{50}	*R.P.*	*R.P.*	LD_{50} *mg/kg*	*R.T.*
Lignocaine	Hcl	0.19%	100%	0.21%	100%	0.75%	100%	100%	34	100%
C_I	Hcl	0.47%	40.5%	0.50%	42.0%	1.20%	62.5%	69.6%	62	54.8%
C_{II}	Hcl	0.40%	47.5%	0.32%	65.6%	1.35%	55.6%	84.6%	31	109.7%
C_{III}	Hcl	0.41%	46.3%	0.46%	45.7%	1.30%	57.7%	64.9%	45	75.6%
C_{IV}	Hcl	0.37%	51.4%	0.44%	47.7%	2.75%	27.8%	60.8%	40	85.0%
C_V	Hcl	0.88%	21.6%	3.70%	5.7%	4.00%	18.7%	31.0%	143	23.9%
C_{VI}	Hcl	0.21%	90.5%	0.22%	95.5%	0.72%	104.2%	105.7%	33	103.0%

R.P = Relative Potency
S.A.C. = Surface Anaesthetic Concentration
IDAC = Intradermal Anaesthetic Concentration
R.T. = Relative Toxicity
CAC = Conduction Anaesthetic Concentration

TABLE III : Relative rating

Compound	*Salt employed*	*Relative Rating = R.P. / R.T. Surface Anaesthesia*	*Intradermal Anaesthesia*	*Conduction Anaesthesia*	*Plexus Anaesthesia*
Lignocaine	Hcl	1	1	1	1
C_I	Hcl	0.74	0.77	1.14	1.27
C_{II}	Hcl	0.43	0.60	0.50	0.77
C_{III}	Hcl	0.61	0.60	0.76	0.86
C_{IV}	Hcl	0.60	0.56	0.33	0.71
C_V	Hcl	0.90	0.24	0.78	1.30
C_{VI}	Hcl	0.88	0.93	1.01	1.03

DISCUSSION

The compounds investigated fall into four groups chemically and these are enumerated below in the order of potency:

(1) Pyrrolidino substituted compound — C_{VI} — Most potent

(2) Alkylamino substituted compounds — C_I, C_{II} & C_{III} — Intermediate in potency

(3) Piperidino substituted compound — C_{IV} — Intermediate in potency

(4) Morpholino substituted compound — C_V — Least potent

Weidmann and Peterson (7) in their studies on the S.A.R. of local anaesthetics, found that alkyl substitution at benzene ring influences the local anaesthetic activity. Compounds with the ortho methyl substitution showed the highest activity. These findings were confirmed by Grewal and Singh (4). In their series, compound EA_7 and EA_8 resemble lignocaine chemically in all respects except that in the benzene ring, there is one ethyl group in place of two methyl groups and these compounds were found to be much less potent than lignocaine. In the present study also, chemical structure of compound C_{II} resembles lignocaine except that it has two additional methyl groups in position 3 and 5. This additional substitution in the benzene ring decreased the local anaesthetic activity.

The substitution at the amino nitrogen also influences the local anaesthetic activity (7); thus piperidino and diethyl amino substituted compounds were more active than their corresponding lower and higher alkylated homologues and morpholino derivatives were less potent. In the present series a new substitution with pyrrolidine ring was attempted at amino nitrogen and it led to an increase in potency. The compound C_{VI} was considerably more potent than dialkyl, piperidino and morpholino substituted compounds by all the tests performed. This compound was almost as potent as lignocaine by surface anaesthesia and intradermal anaesthesia tests and was slightly more potent than lignocaine by conduction anaesthesia and plexus anaesthesia tests. If we correlate these findings with the observations discussed in previous paragraph, it would appear that in compound C_{VI}, substitution of two additional methyl groups at position 3 and 5 of the benzene ring decreased the activity but with substitution by pyrrolidino group at the amino nitrogen, local anaesthetic activity was enhanced, so that the final compound had a potency equal to that of lignocaine. These two observations indicate that if a new compound is synthesized with a pyrrolidino substitution at tertiary nitrogen but with no methyl groups at position 3 and 5. (*w* - pyrrolidino 2 : 6 dimethyl acetanilide) it may be more potent than lignocaine. Koelzer and Wehr (5) have also reported that among the aminoacylamides two substituents in the benzene ring, in 2,6 position produced the maximal effect and that pyrrolidino derivatives showed maximal activity.

It was observed that in all these compounds, except C_{II} (R.T. 109%), the toxicity and potency were fairly parallel. Relative rating (Table III) is a useful index for comparing local anaesthetics because it takes into account both the relative potency and the relative toxicity. A

compound with a high potency, but with a disproportionately high toxicity is of no value for clinical application. Compound C_{VI} was slightly more potent by conduction and plexus anaesthesia tests and also had a relative rating of more than 1, so the compound appears to be useful for block anaesthesia. Compound C_I and C_V had a relative rating more than 1 by plexus anaesthesia and the former compound also by conduction anaesthesia; these were however, less potent than lignocaine. Remaining compounds were less potent and more toxic and thus appear to be of no therapeutic value as potential local anaesthetics. In conclusion it is suggested that compound with *w* - pyrrolidino substituion is a potentially useful compound and warrants further investigations.

ACKNOWLEDGEMENTS

Thanks are due to S. Sukhdev Singh, M. Pharm., Pharmacology Department, Medical College, Patiala for synthesizing and providing the compounds studied and to M/s Suhrid Geigy Trading Ltd., Bombay-19 for supply of the lignocaihe hydrochloride (Xylocaine hydrochloride) powder.

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