ESTERS OF DIALKYLAMINO METHANOLS AS LOCAL ANESTHETICS.*

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In a former paper (1) the preparation of a group of sixteen esters and soluble salts of eight of them, having a structure analogous to that of procaine, was described. Several of these esters were examined as to local anesthetic value. Two methods were used in this examination: (1) the time required to paralyze a motor-nerve-fibre and (2) the time required to anesthetize the cornea of a rabbit.

EXPERIMENTAL PART.

PARALYSIS OF MOTOR-NERVE-FIBRE.

The technique described by Sollmann (2) for determining the time required for paralysis of a motor-nerve-fibre was used.

Muscle-nerve preparations were obtained from frogs. They were made to include the lower end of leg from knee down and the entire sciatic nerve from the knee to the spinal cord with a bit of bone attached.

The muscle-nerve preparation was laid in 0.73 per cent NaCl in tap water until ready for use. In making the tests, the entire nerve was immersed in the anesthetic solution while the muscle was kept in the 0.73 per cent NaCl solution. The excitability of the nerve was tested with the platinum electrodes of an inductorium, activated by a current of about 3 volts. The stimulation was, of course, considerably above the threshold.

The stimulus was applied at the distal end of the nerve; that is, within one centimeter of the spinal origin. Generally, when the block was completed at this point, response could be obtained by moving the electrodes half down the nerve; but this was disregarded.

Experiments were made at room temperature (between 20° C. and 30° C.). The compounds soluble in water were dissolved in 0.73 per cent NaCl solution while those insoluble in water were dissolved in olive oil. The concentrations of the compounds were in geometric ratio ($^1/_2$, 1, 2, 4, 8 per cent).

All the hydrochlorides were dissolved in 0.73 per cent NaCl solution. Three of these salts showed some hydrolysis in solution, namely, di-*n*-butylaminomethyl-*p*-aminobenzoate HCl, diisoamylaminomethyl-*m*-aminobenzoate HCl and di-isoamylaminomethyl-*p*-aminobenzoate HCl, but gave good physiological tests. All the cinnamates and benzoates had to be dissolved in olive oil, since they are not soluble in water and their soluble salts have not been prepared.

The following table gives the results obtained:

TABLE I.—TIME OF PARALYSIS OF SCIATIC NERVE IN MINUTES.

Compound. (Dissolved in 0.73% NaCl Solution.)	Percentage of Compound. 8.	4.	2.	1.	$^1/_2$.
Procaine HCl	...	5–10	10–20	40–50	50–60
Diethylaminomethyl-*m*-aminobenzoate HCl	...	20–30	30–40	78–80	90–100
Di-*n*-propylaminomethyl-*m*-aminobenzoate HCl	...	10–20	20–30	20–30	30–40

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Compound. (Dissolved in 0.73% NaCl Solution.)	Percentage of Compound. 8.	4.	2.	1.	1/2.
Di-*n*-butylaminomethyl-*m*-aminobenzoate HCl	...	– 5	5–10	20–25	25–30
Di-iso-amylaminomethyl-*m*-aminobenzoate HCl	...	– 5	– 5	15–20	20–25
Diethylaminomethyl-*p*-aminobenzoate HCl	...	10–20	40–50	60–70	Uncertain
Di-*n*-propylaminomethyl-*p*-aminobenzoate HCl	...	5–10	10–20	20–30	30–40
Di-*n*-butylaminomethyl-*p*-aminobenzoate HCl	...	– 5	– 5	10–15	20–30
Di-iso-amylaminomethyl-*p*-aminobenzoate HCl	...	5– 7	10–15	20–25	30–35
NaCl 0.73 per cent solution 1	...	...	...	110–	...
(Dissolved in Olive Oil.)					
Diethylaminomethyl cinnamate	20–30	None	...	....	...
Di-*n*-propylaminomethyl cinnamate	None	...	...	....	...
Di-*n*-butylaminomethyl cinnamate	None	...	...	....	...
Di-iso-amylaminomethyl cinnamate	None	...	...	...	...
Diethylaminomethyl benzoate	– 5	10–15	20–25	35–40	...
Di-*n*-propylaminomethyl benzoate	20–25	25–30	None	....	...
Di-*n*-butylaminomethyl benzoate	None	...	...	....	...
Di-iso-amylaminomethyl benzoate	None	...	...	....	...
Olive Oil 1	...	...	50–60	....	...

The number to the left of the dash denotes the minutes when no paralysis noted, while the number to the right of the dash indicates the minutes required to paralyze the nerve.

ANESTHESIA OF RABBIT'S CORNEA.

Those of the compounds which formed water-soluble salts were examined as to anesthetic value by application to the cornea of a rabbit. The technique followed was that described by Sollmann (3). The salts were dissolved in 0.73 per cent NaCl solution. They were made in concentrations in geometric ratio (1/2, 1, 2, 4 per cent).

The lashes were clipped from the eyelids of the rabbits. The winking reflex was confirmed by touching the cornea with a pointed lead pencil. The lower eyelid was pinched into a pocket, into which was inserted an eyedropper filled with the anesthetic solution. The conjunctival sac was thus kept flooded for one minute, when the dropper was withdrawn and the rabbit released. In ten minutes the winking reflex was tested by touching the cornea, near the center, with the lead pencil. If this did not produce winking, the pencil was drawn across the cornea several times with moderate pressure. Great care must be taken to avoid touching the eyelid or the hairs about the eye.

If winking occurred with the first light touch, the result was considered negative as to anesthesia. If the winking occurred, but only sluggishly and after repeated and fairly severe pressure, it was interpreted as partial anesthesia. Absence of winking constituted the sign of complete anesthesia.

If after the end of the first period, the anesthesia was absent or only partial, the conjunctival sac was again filled with the solution, but the rabbit was not held for a minute, being released at once.

The tests and applications were repeated every ten minutes until five applications had been made, unless complete anesthesia had been attained before. No applications were made after anesthesia was complete. The tests, however, were continued for fifty minutes or longer to observe the time of partial anesthesia and complete recovering.

The following table gives the results obtained:

TABLE II.—ANESTHESIA OF RABBIT'S CORNEA.

Compound. (Dissolved in 0.73% NaCl Solution.)	Percentage of Compound. 4. A.	B.	2. A.	B.	1. A.	B.	1/2. A.	B.
Procaine HCl	4	30	None		....		....	
Diethylaminomethyl-*m*-aminobenzoate HCl	5*	?	5*	?	None		None	
Di-*n*-propylaminomethyl-*m*-aminobenzoate HCl	3	20	4	20	5	?	5*	?
Di-*n*-butylaminomethyl-*m*-aminobenzoate HCl	2	40	4	15	5*	?	None	
Di-iso-amylaminomethyl-*m*-aminobenzoate HCl	1	60	1	60	None		....	
Diethylaminomethyl-*p*-aminobenzoate HCl	5	10	None		None		None	
Di-*n*-propylaminomethyl-*p*-aminobenzoate HCl	1	60	None		None		....	
Di-*n*-butylaminomethyl-*p*-aminobenzoate HCl	2	20	2	10	None		....	
Di-iso-amylaminomethyl-*p*-aminobenzoate HCl	2	30	4	?	5	?	5*	?

"A" signifies number of applications (at 10-minute intervals) required to produce complete anesthesia.

"B" signifies number of minutes elapsing between the last application and complete recovery of sensation.

"*" signifies that the cornea was evidently less sensitive but still reacted.

"None" signifies no apparent anesthesia.

"?" signifies uncertain.

CONCLUSIONS.

The results of the experimentation indicate that all the soluble salts, and a few of the bases of which no salts were isolated, have local anesthetic action. Five salts, namely, di-*n*-propylaminomethyl-*p*-amino benzoate HCl, di-*n*-butylaminomethyl-*m*-aminobenzoate HCl, di-*n*-butylaminomethyl-*p*-aminobenzoate HCl, diisoamylaminomethyl-*m*-aminobenzoate HCl and diisoamylaminomethyl-*p*-aminobenzoate HCl were equal or better than procaine HCl when tested by paralysis of the sciatic nerve of a frog. Diisoamylaminomethyl-*m*-aminobenzoate HCl, di-*n*-butylaminomethyl-*p*-aminobenzoate HCl and diisoamylaminomethyl-*p*-aminobenzoate HCl were all about twice as effective as procaine HCl while diethylaminomethyl-*m*-aminobenzoate HCl, di-*n*-propylaminomethyl-*m*-aminobenzoate HCl and diethylamino-*p*-aminobenzoate HCl also caused paralysis but the effect was slightly weaker. In practically every case the anesthesia increased as the dialkyl group attached to the nitrogen became greater in molecular weight. Most of the *p*-aminobenzoate compounds were slightly more effective than the corresponding *m*-aminobenzoates. Diisoamylaminomethyl-*p*-aminobenzoate HCl decreased slightly in paralyzing effect over the corresponding di-*n*-butylamino compound, probably because its solution was hydrolyzed considerably. In general, the compounds of higher molecular weight were more subject to hydrolysis. This was especially true of the di-*n*-butyl and diisoamyl compounds.

Very few of the bases tested on the sciatic nerve of a frog gave results. Diethylaminomethyl cinnamate, diethylaminomethyl benzoate and di-*n*-propylaminomethyl benzoate caused paralysis but all were much weaker than procaine HCl. Diethylaminomethyl benzoate was about one-half as effective. Decreased solubilities of the bases probably accounted for the unsatisfactory results.

In general, the results obtained by paralyzing the sciatic nerve of a frog were duplicated when tested on the cornea of a rabbit. Di-*n*-propylaminomethyl-*m*-aminobenzoate HCl, di-*n*-butylamino-*m*-aminobenzoate HCl, and the corresponding *p*-aminobenzoate HCl's all appeared more effective than procaine HCl as a surface anesthetic. Only the diethylaminomethyl-*m*-aminobenzoate HCl and the

corresponding *p*-aminobenzoate HCl were less effective. In general, the anesthesia increased as the molecular weight of the dialkylamino group increased. Also the *p*-amino compounds were slightly more active than the *m*-amino compounds.

All of the compounds tested on the rabbit's cornea appeared to be more or less irritating as evidenced by the struggling of the rabbit when the first dose was applied and also, in some cases, by the inflammation of the lids. It appeared that the irritation increased considerably with the compounds which hydrolyzed the most, as the di-*n*-butyl and diisoamylamino-methyl-*p*-aminobenzoate HCl's. This irritation made it difficult in some cases to judge the time of recovery.

Summarizing the results of the pharmacological examination of the compounds, it was found that (1) dialkylaminomethanols esterified with *m*-aminobenzoic, *p*-aminobenzoic, benzoic and cinnamic acids have local anesthetic properties, (2) in general the anesthesia increased as the dialkyl groups attached to the nitrogen of the alcohol became greater in molecular weight, (3) the *p*-aminobenzoates were slightly more effective than the corresponding *m*-aminobenzoates, (4) benzoates and cinnamates could not be compared with the other compounds due to the inability of forming soluble salts, (5) five compounds were more effective or equal to procaine HCl when used to paralyze the sciatic nerve of a frog and the same five with one other appeared more effective or equal to procaine HCl when applied to the cornea of a rabbit, (6) the soluble salts hydrolyzed quite readily, which was especially true of the compounds of the higher molecular weight, (7) almost all of the compounds and especially those of the higher molecular weight were very irritating when applied to the cornea of a rabbit.

SUMMARY.

1. Sixteen compounds consisting of benzoyl, cinnamyl, *m*-aminobenzoyl and *p*-aminobenzoyl esters of a series of dialkylamino methanols, together with their salts, were compared with procaine HCl as to local anesthetic properties, (*a*) by paralysis of the sciatic nerve of a frog, and (*b*) by application to the cornea of a rabbit.

2. All the soluble salts prepared possessed considerably local anesthetic properties, several of them being more effective than procaine HCl. A few of the bases of which no salts were prepared showed some anesthetic properties.

3. The soluble salts, especially those of high molecular weight, were very irritating when applied to the cornea of a rabbit, which makes them objectionable for use as local anesthetics.

REFERENCES.

(1) Lynn and Lofgren, JOUR. A. PH. A., 21 (1932), 541.
(2) Sollmann, *Jour. Pharmacol.*, 10 (1917), 379.
(3) Sollmann, *Ibid.*, 11 (1918), 17.

The Chemist and Druggist states "**Pasta Zinci Oxidi Composita** introduces another variant of Lassar's Paste or what is known in the B. P. C. as **Pasta Zinci Composita**, as well as complicating things unnecessarily by what may become a persistent question as to what should be given for **Pasta Zinci Co.** The formula is included in most hospital pharmacopœias, the strength being usually the same as that of the B. P., but most of them contain in addition a small percentage of salicylic acid." The B. P. 1932 does not use the synonym—"Lassar's Paste."