TRIALS WITH CARBOCAINE

A New Local Anaesthetic Drug

BY

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CHEMISTRY

A new series of local anaesthetics have been synthesized. They all have the general formula

\[
\begin{align*}
\text{CH}_2 & \quad \text{CH}_2 \\
\text{CH}_3 & \quad \text{NH} - R_2 \\
\text{N} & \quad \text{R}_1
\end{align*}
\]

where \( R_1 \) represents an aliphatic hydrocarbon radical and \( R_2 \) an aromatic hydrocarbon group.

The interest was directed to the hydrated pyridine carboxylic acids, as hitherto these amino acids have hardly been studied as elements of synthesis in compounds of this type.

The formation of an amide between the hydrophilic amino acid and the lipoidic aromatic radical was chosen because of the good general stability of the amide linkage.

The hydrogen attached to the nitrogen of the piperidine ring was substituted with a hydrocarbon chain of varying length, and a great number of different aromatic radicals were used as the aromatic part (\( R_2 \)).

The present series of amino acid amides have, among others, included compounds with pipecolic, nipecotic and isonipecotic acid as the acid part. It was found that an increased effect was obtained the nearer the carboxylic group was situated to the nitrogen of the heterocyclic nucleus. In the place of pipecolic acid proline can be used.

These cyclic amino acids have two stereoisomers in the \( \alpha \) as well as in the \( \beta \) positions. So far no evidence has been found as to any pharmacological difference between the stereoisomers.

Comparatively extensive pharmacological and clinical studies were done with \( d\)-1-N-methyl-pipecolic acid 2-6-dimethylanilide or Carbocaine. It has the following structural formula:

\[
\begin{align*}
\text{CH}_3 & \quad \text{CH}_2 \\
\text{CH}_2 & \quad \text{NH} \quad \text{CH} - \text{C} - \text{NH} - \text{R}_2 \\
\text{CH}_3 & \quad \text{N}
\end{align*}
\]

The base has a molecular weight of 246 and a melting point of 151 °C. The molecular weight of the hydrochloride is 285.5 and its melting point 261 °C.

The base is poorly soluble and the hydrochloride easily soluble in water and very resistant to both alkaline and acid hydrolysis.
PHARMACOLOGY

The lethal dose 50 (LD50) of Carbocaine when injected intravenously in mice was found to be 40.0±4.0 mg/kg body weight.

The same investigation with lignocaine and procaine gave 33.3±2.3 mg/kg and 54.2±5.7 mg/kg respectively.

Unanaesthetized dogs were injected intravenously with increasing doses of local anaesthetics. A dose which on 50 per cent of the dogs caused a reaction characterized by drowsiness, dullness, loss of balance, and vomiting was called "subtoxic dose 50". These figures were for Carbocaine 7.2±0.6, lignocaine 2.5±0.5 and for procaine 3.7±0.5 mg/kg body weight.

No toxic reactions were observed with rabbits injected daily (subcutaneously) for 30 days with 10 mg of Carbocaine.

Rabbit ears were injected with 1 ml of Carbocaine solutions of increasing strength; 1.2 and 4 per cent solutions did not give any tissue reaction. An 8 per cent solution caused in some cases a slight darkening of the weal. Bleeding and haemolysis appeared with solutions of 16 and 32 per cent strength. However, no necrosis or inflammation ensued.

By means of heat rays focused on mice tails a pain reaction was caused. After subcutaneous injection of 0.2 ml of a 1 per cent solution of local anaesthetics at the tail base, the time for the absence of the pain reaction was measured. This was 45.6±1.5 min for Carbocaine, 31.5±3.4 min for lignocaine, and 21.6±2.1 for procaine.

Intravenous injections of 2 mg/kg body weight of Carbocaine in anaesthetized rabbits did not cause a fall in blood pressure or change in respiration.

CLINICAL TRIALS

For about a year Carbocaine has been used clinically. Previously lignocaine has been the drug favoured in this institution for local anaesthesia. For that reason it was natural to use lignocaine as the control drug for the trials with Carbocaine.

Weal Tests.

On the forearms on two groups of medical students intracutaneous weals were raised with 0.3 ml of six test solutions containing 2, 1 or 0.5 per cent Carbocaine or lignocaine. In one group adrenaline 1/100,000 was added to the solutions. Not until the whole investigation was completed did the investigator obtain any information of the content of the test solutions. In practically all the weals complete anaesthesia was obtained immediately. The duration was tested by applying an induction current, which clearly exceeded the pain threshold for an unanaesthetized area nearby.

Tables I and II show the result of the weal tests. In the tests without adrenaline, Carbocaine had a longer duration. In tests with adrenaline, lignocaine had a slightly longer duration in two of the three concentrations.

Anaesthesia.

Carbocaine was used for anaesthesia in 652 cases (see table III). Satisfactory results were obtained in infiltration anaesthesia with 0.5 and 0.25 per cent solution with or without adrenaline. The results did not differ from those
TRIALS WITH CARBOCAINE

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Table I

Weal tests without adrenaline.
The duration of 0.3 ml intracutaneously.

<table>
<thead>
<tr>
<th></th>
<th>Carbocaine</th>
<th>Duration</th>
<th>Standard dev.</th>
<th>Lignocaine</th>
<th>Duration</th>
<th>Standard dev.</th>
</tr>
</thead>
<tbody>
<tr>
<td>2%</td>
<td>48.9 min</td>
<td>s=21.9 min</td>
<td>42.5 min</td>
<td>s=23.3 min</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1%</td>
<td>49.7 min</td>
<td>s=24.0 min</td>
<td>33.8 min</td>
<td>s=18.2 min</td>
<td></td>
<td></td>
</tr>
<tr>
<td>½%</td>
<td>32.7 min</td>
<td>s=19.8 min</td>
<td>23.9 min</td>
<td>s=8.7 min</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

25 weals within each concentration.

Table II

Weal tests with adrenaline.
The duration of 0.3 ml intracutaneously.

<table>
<thead>
<tr>
<th></th>
<th>Carbocaine</th>
<th>Duration</th>
<th>Standard dev.</th>
<th>Lignocaine</th>
<th>Duration</th>
<th>Standard dev.</th>
</tr>
</thead>
<tbody>
<tr>
<td>2%</td>
<td>317 min</td>
<td>s=70 min</td>
<td>332 min</td>
<td>s=67 min</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1%</td>
<td>298 min</td>
<td>s=57 min</td>
<td>322 min</td>
<td>s=84 min</td>
<td></td>
<td></td>
</tr>
<tr>
<td>½%</td>
<td>289 min</td>
<td>s=47 min</td>
<td>283 min</td>
<td>s=61 min</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

24 weals within each concentration.

Table III

List of cases anaesthetized with Carbocaine

Small infiltrations ... ... ... ... 211
Larger infiltrations ... ... ... ... 117
Thyroids ... ... ... ... ... ... ... 41
Hernias ... ... ... ... ... ... ... 40
Epidural blocks ... ... ... ... ... ... 157
Caudal blocks ... ... ... ... ... ... 135
Nerve blocks ... ... ... ... ... ... 167
Brachial plexus blocks ... ... ... ... 100
Total 652

DISCUSSION

The clinical tests with Carbocaine confirm that this drug has very good anaesthetic properties. In infiltration anaesthesia both Carbocaine and lignocaine showed excellent and similar results. It is, however, impossible in these types of anaesthesia to make any proper evaluation of the two drugs. This was possible, however, in certain types of block anaesthesia and caudal and brachial plexus blocks (tables IV and V) were chosen for this investigation. In this rather small number of cases the time of onset and anaesthetic failures must be considered the same with the two drugs. In a few cases a fall in blood pressure occurred; in none of them was it severe. Other than that, nausea and vomiting were the only complications. With the two drugs no statistical difference in the number of complications can be observed.

For brachial plexus blocks 20 ml of a 2 per cent solution was used, lignocaine with adrenaline 1/80,000 and Carbocaine with adrenaline 1/100,000. For caudal blocks 20 ml of a 1 per cent solution without adrenaline was used.

obtained with lignocaine. Caudal and brachial plexus blocks, which in this hospital are used frequently, were selected for a detailed study. All cases done during the time of investigation both with Carbocaine and lignocaine are reported.
TABLE IV
Brachial plexus blocks.

<table>
<thead>
<tr>
<th></th>
<th>Carbocaine</th>
<th>Lignocaine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of cases</td>
<td>100</td>
<td>193</td>
</tr>
<tr>
<td>Incomplete anaesthesia</td>
<td>9 9%</td>
<td>18 9.3%</td>
</tr>
<tr>
<td>Anaesthesia worn off</td>
<td>5 5%</td>
<td>3 1.6%</td>
</tr>
<tr>
<td>Fall in blood pressure</td>
<td>13 6.7%</td>
<td>13 6.7%</td>
</tr>
<tr>
<td>Nausea</td>
<td>4 2.1%</td>
<td>4 2.1%</td>
</tr>
<tr>
<td>Time of onset</td>
<td>14.4 min (48 cases)</td>
<td>14.6 min (44 cases)</td>
</tr>
<tr>
<td>Duration</td>
<td>258 min (38 cases)</td>
<td>238 min (42 cases)</td>
</tr>
</tbody>
</table>

TABLE V
Caudal blocks.

<table>
<thead>
<tr>
<th></th>
<th>Carbocaine</th>
<th>Lignocaine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of cases</td>
<td>135</td>
<td>284</td>
</tr>
<tr>
<td>Incomplete anaesthesia</td>
<td>7 5.2%</td>
<td>26 9.2%</td>
</tr>
<tr>
<td>Anaesthesia worn off</td>
<td>2 1.5%</td>
<td>17 6.0%</td>
</tr>
<tr>
<td>Fall in blood pressure</td>
<td>7 5.2%</td>
<td>23 8.1%</td>
</tr>
<tr>
<td>Nausea + vomiting</td>
<td>4 4.2%</td>
<td>4 4.2%</td>
</tr>
<tr>
<td>Time of onset</td>
<td>19.0 min (78 cases)</td>
<td>19.0 min (69 cases)</td>
</tr>
<tr>
<td>Duration</td>
<td>173 min (29 cases)</td>
<td>126 min (28 cases)</td>
</tr>
</tbody>
</table>

This difference was statistically significant, and the same tendency was observed in brachial plexus blocks.

In this rather small number of cases Carbocaine has shown excellent anaesthetic properties. In comparing this drug with lignocaine the impression favours Carbocaine.

SUMMARY

A new series of local anaesthetics based on hydrated pyridine carboxylic acid amides, is described. One of these compounds rac. N-methyl-pipelic acid 2-6-xylidide (Carbocaine) was investigated pharmacologically, and submitted to clinical trial. The results raise expectations that Carbocaine may prove to be of great value as a local anaesthetic drug.

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