DENTAL TRIAL OF CARBOCAINE

A New Local Anaesthetic

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A recent report from Scandinavia (Dhunér et al., 1956) describes a clinical trial of Carbocaine in which 652 cases were injected with results which the authors describe as raising "expectations that Carbocaine may prove to be of great value as a local anaesthetic drug." It was found that, when no adrenaline was used, anaesthesia lasted longer with Carbocaine than with lignocaine (Xylocaine), for 1/2, 1 and 2 per cent solutions. Using adrenaline, anaesthesia lasted longer with lignocaine. However, none of the above cases was for dental operation. This paper describes a trial of the drug in dental cases and gives the results obtained.

It is considered that a search for new local anaesthetics is necessary because, although lignocaine is a great improvement on earlier local anaesthetics, clinical experience shows that it does not provide consistently successful anaesthesia. Sherman, Fiasconaro and Chilton (1954) obtained complete elimination of pain in 84 per cent of cases with lignocaine 2 per cent plus epinephrine 1:50,000, and in 88 per cent of cases with lignocaine 2 per cent plus epinephrine 1:100,000.

It must be remembered that although Björn (1947) and Huldt (1947) obtained 100 per cent success with lignocaine, they worked only on upper lateral incisors and tested anaesthesia by Björn's (1946) electrical method, not by surgery.

Chemistry of Carbocaine

Carbocaine is d, 1-N-methyl-pipecolic acid 2, 6-dimethylanilide and has the structural formula (Ekenstam and Egner):

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

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

Preliminary Trial

Two per cent Carbocaine without adrenaline was first tried in 65 dental cases for both regional and infiltration anaesthesia in order to obtain some idea of the following factors:

1. Dosage. This must be sufficient to give reasonable success, but 100 per cent success must not be obtained, as a smaller concentration or volume might still produce 100 per cent success.

2. The time between injection and anaesthesia.

3. The frequency of anaesthesia.

4. The duration of anaesthesia.

5. The depth of anaesthesia.

6. Any adverse effects, e.g. prolonged numbness of the soft tissues.

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The results of the preliminary trial were similar to those to be given for the blind testing trial which followed and, therefore, need not be detailed.

**MAIN TRIAL**

**Blind Testing.**

The need for blind testing in the study of drugs is well established. The drugs, which were 2 per cent Carbocaine and 2 per cent lignocaine, each without adrenaline, were prepared in 21 bottles containing 0.1 per cent chlorocresol and labelled with a code number. The key to this code was not revealed to the operator until the end of the trial.

**Operator.**

All the injections were done by one operator, thus eliminating variations of technique, etc.

**Patients.**

These were both male and female, from 11 years of age upwards, who were undergoing a course of treatment in the department of operative dentistry of this university. These patients are usually both intelligent and co-operative and are preferable to "casual" patients in this respect. In all cases anaesthesia of permanent teeth was investigated.

**Dosage.**

2.3 ml (35 minims) were given for regional anaesthesia; 1.7 ml (25 minims) were given for infiltration anaesthesia.

**Method of Determining Onset of Anaesthesia.**

The operation was started, and only when the patient experienced pain was the injection given. This was considered important, because it eliminated two sources of error:

1. Anaesthesia might occur whilst the bur was still in enamel. The dentine would then be insensitive when reached, but the exact time of anaesthesia would not be known.

2. The tooth, for physiological or pathological reasons, might be insensitive even without an injection. If the injection had been given first such a case would have been wrongly classified as a successful anaesthesia. It is interesting to note that 11 such cases occurred during this trial. They were, of course, excluded.

An injection was given rapidly in 5–10 seconds and the time was noted to the nearest quarter-minute. A revolving bur was applied to the dentine at short intervals and the time at which complete anaesthesia occurred was noted to the nearest quarter-minute. In many cases partial anaesthesia was experienced before this time, but only the time of onset of complete anaesthesia was recorded.

It should be noted that anaesthesia to probing and excavating was sometimes present when there was not anaesthesia to the bur.

**Termination of Anaesthesia.**

Cavity preparation was continued and the time was noted at which pain was again experienced. This gave the exact duration of anaesthesia. A period of partial anaesthesia often followed and this was sometimes adequate to permit continuation of the operation.

Each operation was done by a student. This was a real advantage because students work much more slowly than do those who are qualified. It was, therefore, often possible to determine the exact termination of anaesthesia. Nevertheless, in many cases the operation on dentine was concluded whilst anaesthesia was still present. This time was noted and gave the minimum period of anaesthesia.

It would have been statistically more convenient to be able to determine the exact end of anaesthesia in every case. This could have been achieved by decreasing the dose, but such a step would have decreased the number of successful anaesthesias, which would not be giving the patients fair consideration.

**Termination of Soft Tissue Symptoms.**

These are usually described as "numbness", "tness", "coldness", etc. It is desirable to reduce the duration of these as much as possible. The time of termination was obtained by asking the patient to complete a stamped addressed postcard. The results are only approximate, for the accuracy depends on the patient’s interest, observation and energy.

**Successful Injection.**

An injection was regarded as successful if anaesthesia occurred within 10 minutes. This is an arbitrary time but it is regarded as generous because a dentist usually only allows 30 minutes or even less for his appointments. The injection
was also regarded as successful no matter how short the duration of anaesthesia. It is important to note this fact, because an operator would not normally regard an anaesthetic as successful if it failed to cover the entire period of the operation. However, this objection is overcome by presenting the results for the duration of anaesthesia as well as for the percentage of successful injections.

**Anaesthesia of Dentine when the Pulp is still Sensitive.**

In this investigation anaesthesia was determined for the dentine only. It was sometimes found that the dentine was anaesthetized when the pulp (accidentally exposed by a student operator) was not. This has also been noticed by Björn (1947).

**Regional Anaesthesias.**

These were divided into inferior dental nerve injections which were administered for the lower molars, and posterior superior dental nerve injections which were administered for the upper second and third molars.

**Infiltration Anaesthesias.**

These were used for all other teeth. However, the upper central incisor was excluded from the test because it usually needs an injection on each side of the midline and it is not permissible simply to add the two doses.

The upper first molar sometimes requires two injections, although, in this project, it was given only one infiltration injection. It is therefore considered in a group by itself.

**Hydrogen Ion Concentration.**

The pH of the Carbocaine solution was 6.5 whilst that of the lignocaine was 5.4. It is generally considered that the more acid the solution the longer will it take to dissociate in the tissues with release of the anaesthetic base. Theoretically, therefore, the Carbocaine in this trial had a slight advantage over the lignocaine as regards the time of onset of anaesthesia. Practically, however, this is probably not the case. Tainter, Thondson and Moose (1939) and Tainter (1941) showed that there is little or no advantage in rendering the solutions alkaline as regards onset, duration, dose and incomplete anaesthesia. According to Björn and Huldt (1947), "the efficiency of a neutral Xylocaine-adrenaline solution was found to be essentially the same as for that of an acid (pH = 5) Xylocaine-adrenaline solution." Later they stated that "the effect of both, therefore, can safely be compared to that of the acid (pH = 5) procaine solution." In 1953, Huldt found that "for Xylocaine + epinephrine, the hydrogen ion concentration (within the range pH 4–7) is of no practical importance to the efficiency." He considered that "had the experiments been performed with lower concentrations of Xylocaine (than 1 ml 2 per cent and 1 ml 1 per cent) it is possible that a difference might have shown up."

On the other hand, Brynholf (1947) found that "A 2 per cent procaine-adrenaline solution ... with pH 7.34 gave a shorter analgesia latency than the same solution with pH 4.85 and with pH 3.61. It also gave longer duration of the analgesia than the same solution with pH 3.61."

However, the differences in pH used by Brynholf were very much greater than those concerned in the present investigation. It was therefore considered that a valid comparison could be made between the two solutions concerned.

**RESULTS**

**Successful Anaesthesias.**

Table I details, under each anaesthetic, the number of successes as judged by the above criteria. It will be observed that of the 126 injections of lignocaine, 48.3 per cent resulted in anaesthesia, whereas of 87 injections of Carbocaine, 82.8 per cent were effective. This difference is significant as also is the difference in success rate between the two drugs for both infiltration and regional anaesthesias.

**Onset of Anaesthesia.**

Table II is an analysis of the times of onset of anaesthesia with the two drugs and it can be seen that there is no significant difference between the drugs in this respect. The numbers of cases are obviously smaller as only the successful injections could be assessed for time of onset.

**Duration of Anaesthesia.**

The number of patients in which the duration of anaesthesia could be accurately measured was smaller still, as many left the operating room before recovery of sensation. However, it was possible to estimate the duration of anaesthesia in 74 patients
### Table I

**Effectiveness of Anaesthesia**

<table>
<thead>
<tr>
<th>Type of anaesthesia</th>
<th>Lignocaine</th>
<th>Carbocaine</th>
<th>Significance of difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. M. F. Average age</td>
<td>% Success</td>
<td>No. M. F. Average age</td>
<td>% Success</td>
</tr>
<tr>
<td>Infiltration of $6$</td>
<td>12 8 4 19.9 (12-38)</td>
<td>16.7</td>
<td>7 3 4 15.7 (12-20)</td>
</tr>
<tr>
<td>$\frac{2345}{12345}$</td>
<td>46 23 23 24.1 (12-51)</td>
<td>30.4</td>
<td>39 19 20 20.4 (12-49)</td>
</tr>
<tr>
<td>Regional: Inferior dental</td>
<td>45 19 26 20.3 (11-44)</td>
<td>70.1</td>
<td>32 15 17 21.3 (12-42)</td>
</tr>
<tr>
<td>Regional: Posterior superior dental</td>
<td>17 9 8 18.8 (11-31)</td>
<td>58.9</td>
<td>9 7 2 17.6 (12-29)</td>
</tr>
<tr>
<td>All cases</td>
<td>120 59 61 21.9 (11-51)</td>
<td>48.3</td>
<td>87 44 44 20.1 (12-49)</td>
</tr>
</tbody>
</table>

### Table II

**Time of Onset of Anaesthesia**

<table>
<thead>
<tr>
<th>Type of anaesthesia</th>
<th>Lignocaine</th>
<th>Carbocaine</th>
<th>Significance of difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. M. F. Average age</td>
<td>Time of onset (minutes)</td>
<td>No. M. F. Average age</td>
<td>Time of onset (minutes)</td>
</tr>
<tr>
<td>Infiltration of $6$</td>
<td>2 2 7 19 (12-38)</td>
<td>3.5</td>
<td>5 2 3 15.6 (12-18)</td>
</tr>
<tr>
<td>$\frac{2345}{12345}$</td>
<td>14 7 7 24.8 (13-51)</td>
<td>2.4 ± 0.36</td>
<td>30 15 15 22.3 (12-49)</td>
</tr>
<tr>
<td>Regional: Inferior dental</td>
<td>32 12 20 20.8 (11-44)</td>
<td>2.92 ± 0.29</td>
<td>28 13 15 21.5 (12-42)</td>
</tr>
<tr>
<td>Regional: Posterior superior dental</td>
<td>10 4 6 20.7 (12-30)</td>
<td>2.46 ± 0.39</td>
<td>9 2 7 17.6 (12-29)</td>
</tr>
<tr>
<td>All cases</td>
<td>58 25 33 20.7 (11-51)</td>
<td>2.73</td>
<td>72 32 40 20.8 (12-49)</td>
</tr>
</tbody>
</table>
### TABLE III

**Duration of Anaesthesia.**

<table>
<thead>
<tr>
<th>Type of anaesthesia*</th>
<th>Cases in which actual duration of anaesthesia was measured</th>
<th>All cases: including those in whom the duration of anaesthesia was greater than that of operation†</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Lignocaine</td>
<td>Carbocaine</td>
</tr>
<tr>
<td></td>
<td>No. of cases</td>
<td>Average duration (min)</td>
</tr>
<tr>
<td>Infiltration of (\frac{2345}{12345})</td>
<td>12</td>
<td>13.8 ± 2.9</td>
</tr>
<tr>
<td>Regional: Inferior dental</td>
<td>18</td>
<td>25.9 ± 1.5</td>
</tr>
<tr>
<td>Regional: Posterior superior dental</td>
<td>9</td>
<td>14.7 ± 2.7</td>
</tr>
<tr>
<td>Total</td>
<td>39</td>
<td>19.5 ± 1.6</td>
</tr>
</tbody>
</table>

* Infiltration of 6 not included, because of small number of cases.

†Duration of anaesthesia in cases not in lefthand column is taken as duration of operation (which was always less than actual anaesthesia).
and from the lefthand columns of table III it can be seen that the two drugs gave very similar results.

The series with each drug were comparable in respect of age and sex distribution, but for the sake of clarity these details are not shown.

If the remaining cases, in which only the minimum anaesthesia was determined, were also included, the results obtained (righthand columns of table III) confirm that the drugs give a similar length of time of anaesthesia.

Duration of Soft Tissue Symptoms.
The duration of soft tissue symptoms was determined in a very much smaller number of patients and again no difference between the two drugs was demonstrable (table IV).

<table>
<thead>
<tr>
<th>Type of anaesthesia</th>
<th>Lignocaine</th>
<th>Carbocaine</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. of cases</td>
<td>Average duration (min)</td>
</tr>
<tr>
<td>Infiltration of...</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>17</td>
<td>105</td>
</tr>
</tbody>
</table>

DISCUSSION
The results show that, as regards the percentage of successful anaesthesias, carbocaine (82.8 per cent) was decidedly superior to lignocaine (48.3 per cent). This low percentage with lignocaine may be compared with the results of Huldt (1953). He used Björn's (1946) method and obtained the results given in table V. Because of the different methods and dosage it is not possible to compare closely his results with those obtained in the present investigation, but it is interesting to see that they are somewhat similar.

In view of the greater effectiveness of Carbocaine it might be combined with smaller concentrations of adrenaline and might possibly prove more effective as an anaesthetic than lignocaine. This was not done in this trial, as interest was directed to the relative effectiveness of the two drugs alone.

It should be borne in mind, however, that the work of Ekenstam et al. (1956) on caudal anaesthesia suggests that the duration of anaesthesia with Carbocaine is not as proportionately prolonged by the addition of adrenaline as it is with lignocaine.

<table>
<thead>
<tr>
<th>Dose of Adrenaline</th>
<th>No. of subjects</th>
<th>Incidence of anaesthesia</th>
</tr>
</thead>
<tbody>
<tr>
<td>2 ml 1%</td>
<td>25</td>
<td>16%</td>
</tr>
<tr>
<td>2 ml 2%</td>
<td>25</td>
<td>60%</td>
</tr>
<tr>
<td>1 ml 2%</td>
<td>20</td>
<td>60%</td>
</tr>
<tr>
<td>1 ml 4%</td>
<td>12</td>
<td>75%</td>
</tr>
</tbody>
</table>

SUMMARY AND CONCLUSIONS
A new local anaesthetic, Carbocaine, has been compared with lignocaine, using the blind testing method. Adrenaline was not added.

It was found that, under the conditions described, Carbocaine gave 82.8 per cent and lignocaine 48.3 per cent of successful anaesthesias.

There was no significant difference as regards onset, duration or soft tissue symptoms.

It is suggested that further research on this anaesthetic might well prove valuable.

ACKNOWLEDGMENTS
We must express our gratitude to Dr. J. W. Dundee, for his very considerable help in the statistical aspects of the trial; to the students and patients in the Liverpool Dental Hospital; and Mr. Alstead, the Dispenser of the Liverpool Royal Infirmary, for making up the blind solutions.
REFERENCES


CORRESPONDENCE

CITRATE INTOXICATION FOLLOWING RAPID MASSIVE BLOOD TRANSFUSION

Sir,—Dr. Argent does well to draw attention to the complicated subject of citrate intoxication in the March issue of the Journal. Investigators and clinicians in America have been interested in this subject during the last few years (Bunker et al., 1955; Smith, 1956; Hubbard et al., 1956; Bunker, 1957).

The fall in the level of ionized calcium with consequent upset in the calcium/potassium ratio is responsible for the cardiac depression seen in citrate intoxication. In this condition the picture would, ordinarily, be that of gradually diminishing contractions ending in asystole. Ventricular fibrillation, as in the case described by Dr. Argent, is unusual.

The article does not mention the controversy over the possible effects of low ionized calcium levels on the bleeding time. Although calcium is often given in the hope of decreasing haemorrhage, most authorities (Bunker et al., 1956; Goodman and Gilman, 1955) doubt if calcium deficiency is ever responsible for prolonged bleeding time.

Citrate intoxication is particularly likely to occur when there is liver disease or interference with hepatic circulation. It should be remembered that if the body is unable to ionize or metabolize the citrate it is unlikely to be able to ionize adequately or metabolize the gluconate. Calcium chloride, a rapidly dissociated source of ionized calcium (Goodman and Gilman, 1955), is the drug of choice in acute calcium deficiency.

Calcium replacement is not without its risks and should be performed cautiously. It is particularly dangerous in digitalized patients, as the digitalis effect may be potentiated (Gold and Edwards, 1927). It is difficult to gauge the exact amount of calcium required when citrate intoxication is diagnosed or suspected. A dose of 2 to 3 ml of 10 per cent calcium chloride given slowly, intravenously, repeated at intervals of a few minutes until the blood pressure and, when the heart is visible, the cardiac contractions are improved, has given a satisfactory response on several occasions. Calcium therapy should certainly be considered when massive transfusion is likely, especially in the presence of liver disease.

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REFERENCES