Gas chromatographic and mass spectrometric analysis of articaine in urine

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Articaine hydrochloride (3-n-propylamino-α-propionylamino-2-carboxymethoxy-4-methylthiophene hydrochloride) is a new local anesthetic indicated for infiltration and nerve-block anesthesia in clinical dentistry. Its efficacy was shown to be similar to that of prilocaine, which has been used for some years [1].

According to the manufacturer's literature [2], the drug is extensively metabolized into two metabolites, and only these compounds were found in the urine. In a recent study, where a patient received 600 mg of articaine by epidural administration, both the parent compound and the 2-carboxy metabolite were found in the urine [3], although the metabolite was the predominant species. The analysis was carried out by high-performance liquid chromatography (HPLC) of diluted urine without extraction.

This report confirms the presence of unchanged articaine in the urine in two metabolic studies using the drug for infiltration and nerve block in dental work. The analysis was performed by gas chromatography (GC), while the identity of the drug was confirmed by mass spectrometry (MS).
EXPERIMENTAL

Chemicals
All solvents and chemicals used were of the best commercial grade. Diethyl ether, used as the extraction solvent, was distilled before use. Articaine was a gift from Hoechst Canada (Montreal, Canada).

Extraction
A 0.5-ml volume of 5 M potassium hydroxide and 3 g of sodium chloride were added to 5 ml of urine. A 2-ml volume of diethyl ether with 10 \( \mu g/ml \) diphenylamine was used to extract the drug. Diphenylamine was used as an internal standard. After centrifugation, the organic layer was transferred to a centrifuge tube, to which 1 ml of toluene was added. The mixture was then dried under a stream of nitrogen at 40°C to a volume of about 100 \( \mu l \). A 2-\( \mu l \) aliquot was injected into the gas chromatograph for quantitation or into the GC–MS system for identification.

Gas chromatography
A Hewlett-Packard HP 5980 gas chromatograph equipped with a nitrogen-specific detector was used. The column was a DB-1 polymethylsiloxane fused-silica capillary column, 15 m \( \times \) 0.25 mm I.D., 0.25 \( \mu m \) film thickness, from J & W Scientific (Folsom, CA, U.S.A.). The temperature program was as follows: the initial temperature was 80°C, raised to 100°C at a rate of 20°C/min, then raised to 200°C at a rate of 10°C/min, finally to 300°C at a rate of 20°C/min, and held at that temperature for 5 min. The carrier gas was helium. The technique of splitless injection was used. Under these conditions, the retention times of articaine and diphenylamine were 11.6 and 6.7 min, respectively.

Mass spectrometry
A Hewlett-Packard HP 5988 GC–MS system with a quadrupole mass filter was used to obtain the mass spectrum of the anesthetic. A 30-m DB-1 column was used, and the temperature program was identical to that in the GC analysis. The retention times of articaine and diphenylamine were 13.9 and 9.4 min, respectively.

Metabolic studies
A healthy male patient undergoing dental work received articaine injections on two different occasions. Urine samples were collected and stored in a refrigerator (4°C) until analyzed.

Case 1 One cartridge of Ultracaine D-S forte (68 mg articaine hydrochloride) was injected for buccal infiltration, and two cartridges of the same (136 mg) were used for mandibular block. The total dosage was 204 mg of articaine hydrochloride. At the same time 144 mg of prilocaine hydrochloride were also injected.
Case 2 Two cartridges of Ultracaine D-S forte (136 mg of articaine hydrochloride) were used for mandibular block

RESULTS AND DISCUSSION

The present method using GC with nitrogen-specific detection proves to be very sensitive towards the quantitation of articaine in urine. The extraction is simple and straightforward. The calibration, using peak-area ratios, is linear up to 10 µg/ml ($r = 0.9986$) with calibration points at 0, 0.05, 1.0, 2.0, 3.0, 5.0 and 10.0 µg/ml. The detection limit is lower than 0.01 µg/ml, as is demonstrated in Fig. 1, which shows a chromatogram of an urine sample with an articaine level of 0.01 µg/ml.

The previously reported study on the metabolism of articaine [3] showed the presence of articaine in the urine based on HPLC analysis. We now have MS results to demonstrate that, indeed, articaine is also excreted unchanged (Fig 2). The ion with $m/z$ 284 is the molecular ion, $m/z$ 86 is the (CH$_3$NHC$_3$H$_7$)$^+$ ion; $m/z$ 139 is derived from the molecular ion minus the CH$_3$NHC$_3$H$_7$ group from the side chain and the carbomethoxy group from position 2 of the ring; and $m/z$ 171 comes from the molecular ion minus the COCH$_3$NHC$_3$H$_7$ group and a proton transfer.

Results of the excretion studies are listed in Table I. Articaine can be detected as late as 9 h post-dose, however, at 12 h post-dose it can no longer be detected.

In sports the use of local anesthetics is allowed subject to certain restrictions. According to the rules of the Medical Commission of the International Olym-

Fig 1 Gas chromatogram of articaine extracted from a 9-h post-dose urine sample. Retention time is in minutes.
Fig 2 Mass spectrum of articaine extracted from an urine sample after articaine hydrochloride administration

TABLE I

<table>
<thead>
<tr>
<th>Time post-dose (h)</th>
<th>Concentration (µg/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Case 1 (dose = 204 mg)</td>
</tr>
<tr>
<td>20</td>
<td>1.07</td>
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<tr>
<td>25</td>
<td>-</td>
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<td>40</td>
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<tr>
<td>50</td>
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<td>0.02</td>
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<tr>
<td>90</td>
<td>-</td>
</tr>
<tr>
<td>120</td>
<td>Nil</td>
</tr>
</tbody>
</table>

pic Committee, only local or intra-articular injections may be administered. However, the injections should be medically justified and be reported immediately. The technique described here is a sensitive method for monitoring the misuse of articaine.

REFERENCES

1 D Donaldson, L James-Perdok, B J Craig, G D Derkson and A S Richardson, J Can Dental Assoc, 53 (1987) 38-42
2 C M E Krogh (Editor), Compendium of Pharmaceuticals and Specialties, Canadian Pharmaceutical Association, Ottawa, 23rd cd, 1988, pp 969-970