PLASMA CONCENTRATIONS OF LIGNOCaine AND ITS METABOLITES DURING FIBROPTIC BRONCHOSCOPY

D. A. JONES, A. McBURNEY, P. J. STANLEY, C. TOVEY AND J. W. WARD

SUMMARY

Lignocaine metabolites are known to have both antiarrhythmic and toxic effects. Large plasma concentrations of these metabolites have been reported following endotracheal instillation of lignocaine. We measured plasma lignocaine monoethylglycinexylidide (MEGX), and glycinexylidide (GX) concentrations for up to 4 h after fibroptic bronchoscopy. The total dose of lignocaine required to suppress coughing varied between 230 mg and 364 mg. Small therapeutic lignocaine concentrations occurred transiently in nine of 19 patients after the bronchoscopy examination had finished. Only one patient achieved a plasma lignocaine concentration in the range of minor toxicity. Metabolite peaks occurred later and were of much smaller magnitude. They were unlikely to contribute to prophylaxis of cardiac arrhythmia or to toxicity. It would seem to be safe to use topical lignocaine in doses greater than the currently recommended maximum (200 mg) in conscious patients during fibroptic bronchoscopy.

Although fiberoptic bronchoscopy is a relatively safe procedure, about one-third of the documented complications have been attributed to the use of the local anaesthetic agent (Credle, Smiddy and Elliott, 1974). Plasma concentrations of lignocaine have been reported during fibroptic bronchoscopy (Patterson et al., 1975; Clausen et al., 1976), but the major metabolites monoethylglycinexylidide (MEGX) and glycinexylidide (GX) have received scant attention.

Both the antiarrhythmic activity and the toxicity of MEGX and GX are well recognized in animals, and these metabolites have been implicated in producing adverse effects in man in the presence of therapeutic concentrations of lignocaine (Strong et al., 1975). Smith (1976) reported that tracheal instillation of lignocaine resulted in plasma GX concentrations considerably greater than simultaneous lignocaine concentrations.

In this study we measured plasma concentrations of lignocaine, MEGX, and GX during routine fibroptic bronchoscopy.

PATIENTS AND METHODS

The first two patients booked for consecutive bronchoscopy lists over 3 months were invited to take part in the study. Nineteen gave informed consent and were examined bronchoscopically by one of two physicians (D.A.J., P.J.S.). Atropine 0.6 mg and papaveretum 7.5–15 mg according to body weight were given i.m. 30 min before the procedure. An “Atomist” hand nebulizer was used to deliver no more than six sprays of 4% lignocaine solution to each nostril and a similar number to the oropharynx. The nebulizer was weighed before and after use. A flexible bronchoscope (Olympus BF-B3) lubricated with a smear of 2% lignocaine gel was introduced via the nose and two injections of 4% lignocaine solution 1 ml were administered onto the vocal cords. Further 2-ml aliquots of 2% lignocaine solution were delivered to the proximal bronchial tree as required to suppress coughing, which was achieved within 10–15 min from the start of the procedure. Blood was withdrawn at intervals from an indwelling needle in a forearm vein.

Heparinized plasma was separated immediately and frozen at -20°C. Lignocaine concentrations were measured within 4 days, and MEGX and GX within 48 h, using the gas-liquid chromatographic technique of Adjepon-Yamoah and Prescott (1974). The method was modified as follows: lignocaine was extracted and assayed separately using 1 ml of plasma; the internal standard was phенacetin 100 μl litre of 40 μg ml⁻¹ solution for lignocaine, 10 μl litre for MEGX and GX; derivatization was at room temperature for 5 min using trifluoroacetic anhydride 10 μl litre. Gas chromatography conditions were: injector/detector temperature 250°C; oven temperature 210°C for lignocaine, 220°C for MEGX and

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The maximum dose of lignocaine was 364 mg in patient 19. The maximum plasma lignocaine concentration was 3.34 µg ml⁻¹ in patient 10. This is within the therapeutic range recommended for suppression of arrhythmia (1.5–7.5 µg per ml of plasma (Aps et al., 1976)) and in total nine of the patients achieved concentrations within this range at times varying from 30 to 90 min from the start of nasal spraying. The mean peak plasma lignocaine concentration was 1.54 ± 0.15 µg ml⁻¹ (± SEM) and occurred between 30 and 90 min. Neither total lignocaine dose nor dose per kilogram body weight correlated well with the peak plasma concentrations of lignocaine (r = 0.2 and r = 0.1 respectively). In 13 patients it was possible to estimate the half-life of elimination (T½) of lignocaine; this varied considerably between the patients with a mean of 159 ± 25 (SEM) min.

Plasma MEGX concentrations, measured in 11 patients, were much smaller than the lignocaine values, the maximum measured being 0.39 µg ml⁻¹. With one exception (patient 13, in whom the measured peaks occurred at the same time), MEGX peaks were later than lignocaine, and occurred between 60 and 210 min. The mean plasma peak MEGX was 0.25 ± 0.03 µg ml⁻¹ (± SEM).

Plasma GX concentrations were even smaller than

### RESULTS

Table I shows the total dose of lignocaine given, the maximum measured plasma lignocaine and MEGX concentrations, and the times when these were achieved in the 19 patients.

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age (yr)</th>
<th>Weight (kg)</th>
<th>Diagnosis</th>
<th>Liver function tests</th>
<th>Total dose lignocaine (mg)</th>
<th>Peak lignocaine concn (µg ml⁻¹)</th>
<th>Time to peak lignocaine concn (min)</th>
<th>Peak MEGX concn (µg ml⁻¹)</th>
<th>Time to peak MEGX concn (min)</th>
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<td>—</td>
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<td>270</td>
<td>1.35</td>
<td>55</td>
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<td>—</td>
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<td>30</td>
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<td>30</td>
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<tr>
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<td>1.19</td>
<td>90</td>
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<td>352</td>
<td>1.48</td>
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<td>70</td>
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<tr>
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<td>normal</td>
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<td>30</td>
<td>0.230</td>
<td>120</td>
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<td>1.46</td>
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<td>0.129</td>
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those of MEGX, and were undetectable or present in only trace amounts (that is up to 0.05 \( \mu \text{g ml}^{-1} \)) up to 4 h in six of the 11 patients in whom measurement was attempted. The plasma concentration v. time profiles for lignocaine, MEGX and GX are shown in figure 1.

Lignocaine \( T_\text{p} \) correlated well with time to peak plasma MEGX \( (r = 0.8) \). Thus, patients with short lignocaine half-lives showed early MEGX peaks. In two such patients (14 and 15) early peaks allowed \( T_\text{p} \) for MEGX to be estimated at 134 and 129 min respectively, and in patient 15, \( T_\text{p} \) for GX was 389 min. These values are in accord with previously published data (Adjepon-Yamoah and Prescott, 1973; Strong, Parker and Atkinson, 1973; Strong et al., 1975).

DISCUSSION

The recommended maximum dose of lignocaine for infiltration anaesthesia is 200 mg (Pharmaceutical Codex, 1979). Similarly, the manufacturers recommend the use of no more than 200 mg during fiberoptic bronchoscopy (Data Sheet Compendium, 1980–81), although a study of the literature lends no supportive evidence for this upper limit. As is the common practice in most centres, the patients in our study were given sufficient lignocaine to suppress coughing without any fixed upper limit in mind, and all required more than 200 mg for adequate anaesthesia. There were no complaints of adverse effects, and the greatest concentration of lignocaine was 3.34 \( \mu \text{g ml}^{-1} \) in a patient known to have impaired liver function (table I, patient 10). Objective adverse effects such as muscular irritability, convulsions and coma may occur at venous blood concentrations of 6–10 \( \mu \text{g ml}^{-1} \), and subjective central nervous system effects such as drowsiness and dizziness at concentrations of 3–5 \( \mu \text{g ml}^{-1} \) (Gianelly et al., 1967, Benowitz, 1974).

It is known that not all the lignocaine given during bronchoscopy reaches the systemic circulation. In addition to losses from initial coughing (Scott et al., 1976), or aspiration via the bronchoscope (Bartlett et al., 1976), some is swallowed and oral lignocaine has a bioavailability of only about 35% because of "first pass" hepatic metabolism (Boyes et al., 1971). In man, the main urinary metabolite is 4 hydroxy 2,6 dimethyl-aniline, but the compounds found in the blood known to be associated with pharmacological effects are MEGX and GX (Keenaghan and Boyes, 1972; Tucker, 1975). In rodents, MEGX is as toxic to the central nervous system as lignocaine (Smith and Duce, 1971) though GX is less so (Blumer, Strong and Atkinson, 1973), being devoid of convulsant activity and, in man, producing only minimal impairment of mental function at plasma concentrations up to 4 \( \mu \text{g ml}^{-1} \) (Strong et al., 1975).

In all our patients, lignocaine concentrations were in excess of the concentrations of both MEGX and GX, an observation which is in marked contrast to two previous reports of high circulating metabolite concentrations following endotracheal lignocaine.
administration. Thus Cohn, Smith and Sievenpiper (1972) recorded plasma metabolite concentrations at least four times that of circulating lignocaine, and Smith (1976) reported serum GX peaks in excess of 6 μg ml\(^{-1}\) in the presence of lignocaine concentrations of less than 1 μg ml\(^{-1}\).

Nine of our patients achieved lignocaine concentrations in the lower range for suppression of arrhythmias, mostly at times well after completion of the examination. These concentrations were present only for a short period of time. Elguindi and others (1979) using doses much greater than in our series (580–1330 mg; mean 777 mg), reported that lignocaine decreased the frequency of major arrhythmias during fibreoptic bronchoscopy, but at the expense of producing dizziness in some patients. Under the conditions of our study, peak plasma concentration did not correlate with either the total dose of lignocaine given or the dose per kilogram body weight, so that it is not possible to predict which patients might be at risk of developing symptoms during or after the examination. It is of interest to compare this situation with lignocaine given by subcutaneous infiltration, when peak plasma concentration correlates reasonably well with the dose administered (r = 0.82), but not with the dose per kilogram body weight (Scott et al., 1972).

Peak concentrations of lignocaine occur after bronchoscopy in the majority, just as observation is becoming less intensive. Although we conclude that lignocaine in doses greater than 200 mg sufficient to suppress coughing is safe, our advice to patients and nursing staff now includes the possibility that minor subjective symptoms may occur for the first time after the procedure has finished. There would appear to be little danger of intoxication from metabolites.

REFERENCES


CONCENTRATIONS PLASMATIQUES DE LIGNOCAINA ET DE SES METABOLITES AU COURS DE LA FIBROSCOPIE BRONCHIQUE

RESUME
Les métabolites de la lignocaine sont connus à la fois pour leurs propriétés antiarythmiques et pour leurs effets toxiques. On a rapporté l’existence de fortes concentrations de ces métabolites après instillation endotrachéale de lignocaine. Nous avons mesuré les concentrations plasmatiques de lignocaine, de monoéthylglycinexilidide (MEGX) et de glycinexilidide (GX) au cours des quatre heures suivant une fibroscopie bronchique. La dose totale de lignocaine nécessaire à la suppression de la toux variant de 230 à 364 mg. Chez 9 patients sur 19, des concentrations thérapeutiques faibles de lignocaine ont été observées transitoirement après la fin de la fibroscopie. Il n’y a que chez un patient que les concentrations plasmatiques de lignocaine ont atteint la zone de toxicité mineure. Les pics de métabolites étaient plus tardifs et de bien moindre amplitude. Il y a peu chance qu’ils aient pu contribuer à la prophylaxie de troubles du rythme cardiaque ou à une quelconque toxicité. Il semblerait que Ton puisse en toute sécurité utiliser la lignocaine en application locale à des doses supérieures au maximum habituellement recommandé (200 mg) chez des sujets conscients au cours de fibroscopies bronchiques.

PLASMAKONZENTRATIONEN VON LIDOCAIN UND SEINER METABOLITE WAHREND DER FIBEROPTIK-BRONCHOSKOPIE

ZUSAMMENFASSUNG

CONCENTRACIONES DE LIGNOCAINA Y DE SUS METABOLITOS EN EL PLASMA DURANTE LA BRONCOSCOPIA CON FIBRA OPTICA

SUMARIO
Se sabe que los metabolites de lignocaina ejercen efectos tóxicos y antiarritmicos. Se ha notificado de la presencia de grandes concentraciones de estos metabolitos en el plasma a raiz de la instalacion endotraqueal de lignocaina. Medimos las concentraciones de lignocaina, monoetilglicenexilidida (MEGX) y glicenexilidida (GX) en el plasma por espacio de 4 horas después de la broncoscopia con fibra óptica. La dosis total de lignocaina necesaria para suprimir la tos varió entre 230 mg y 364 mg. En 9 de los 19 pacientes aparecieron pequeñas concentraciones de lignocaina terapéutica con carácter temporal después de haber terminado la broncoscopia. Sólo uno de los pacientes llegó a alcanzar una concentración de lignocaina en el plasma que caía dentro de la gama de la toxicidad menor. Las crestas correspondientes a los metabolitos tuvieron lugar con posterioridad y fueron de una magnitud mucho menor. No se considera probable que estos contribuyeran a la arritmia, profilaxis o la toxicidad. El uso de lignocaina topical parece ser seguro en dosis superiores al máximo actualmente recomendado (200 mg) en pacientes conscientes sometidos a broncoscopia con fibra óptica.