Effect of Quinidine on Digoxin Bioavailability

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Summary. To evaluate the possible effect of quinidine on digoxin bioavailability, the steady state digoxin kinetics was examined with and without concomitant quinidine therapy, in 7 cardiac patients after simultaneous administration of oral digoxin and intravenous [3H]-digoxin. In the presence of quinidine, the absorption rate constant of digoxin (ka) increased from 2.72 ± 1.04 to 3.53 ± 1.34 h⁻¹ (p < 0.05), whereas lag time and peak time decreased from 0.16 ± 0.10 to 0.05 ± 0.04 h (p < 0.05) and from 0.92 ± 0.27 to 0.69 ± 0.19 h (p < 0.02), respectively. Predose plasma digoxin increased from 0.41 ± 0.25 to 0.70 ± 0.31 ng/ml (p < 0.02), while peak plasma digoxin increased from 0.93 ± 0.34 to 1.63 ± 0.46 ng/ml (p < 0.02). The systemic availability of digoxin increased from 68.48 ± 13.35 to 79.09 ± 14.89% (p < 0.05) in the presence of quinidine. Quinidine had no effect on the biotransformation pattern of digoxin, as assessed by thin layer chromatography. Quinidine increases the rate and extent of digoxin absorption, and this interaction contributes significantly to the elevation in plasma digoxin during both its distribution and elimination phases.

Key words: quinidine, digoxin; interaction, kinetics, absorption, elimination

Pharmacokinetic studies of the digoxin-quinidine interaction have predominantly focussed on changes in the distribution and elimination kinetics of digoxin (Hager et al. 1979; Steiness et al. 1980; Schenck-Gustafsson and Dahlquist 1981). In preliminary studies, the combined oral intake of digoxin and quinidine was found to be associated with a pronounced elevation of the peak plasma digoxin level as compared to control values. The present investigation was performed to evaluate whether alteration in digoxin bioavailability was contributory to this action.

Material and Methods

Subjects

The investigation involved 7 cardiac patients, 1 female and 6 males, aged 58–70 years, who had given their informed consent to participation in the study. The patients suffered from paroxysmal atrial fibrillation or premature ventricular beats due to ischaemic or valvular disease, and all had been receiving combined digoxin-quinidine therapy for at least 6 months without adjustment in dosage. Digoxin was administered at 24-h intervals and the same brand of drug was used throughout the investigation. Administration of other drugs, which included furosemide, potassium chloride and warfarin, was not changed during the study. Haemodynamic conditions, as determined by regular clinical examination, were stable in all patients throughout the study, and no significant change in body weight was observed. Plasma sodium, potassium and creatinine concentrations were within normal limits. There was no evidence of malabsorption or other gastrointestinal disorders, except in 1 subject, who complained of watery stools four-six times daily during quinidine therapy. The symptoms disappeared after quinidine withdrawal.

Protocol

Following repeated measurements of plasma digoxin and quinidine, which ensured patient compliance and confirmed the presence of the steady state, each
Table 1. Recovery and thin layer chromatographic fractionation of urinary tritium activity excreted from 0 to 48 h in the absence and presence of quinidine (x ± 1 SD)

<table>
<thead>
<tr>
<th></th>
<th>Chloroform-ethanol extractable activity</th>
<th>Digoxin</th>
<th>Metabolitesa</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>% of total activity</td>
<td>% of activity in extract</td>
<td></td>
</tr>
<tr>
<td>Control</td>
<td>94.2 ± 3.5</td>
<td>91.2 ± 4.2</td>
<td>6.0 ± 2.1</td>
</tr>
<tr>
<td>Quinidine</td>
<td>95.0 ± 3.2</td>
<td>89.5 ± 3.0</td>
<td>6.9 ± 2.4</td>
</tr>
</tbody>
</table>

a Digoxigenin-bis-digitoxoside, digoxigenin-mono-digitoxoside, digoxigenin and dihydrodigoxigenin

patient simultaneously received an oral dose of digoxin and a single intravenous dose (150–250 μCi) of [3H]-digoxin (specific activity ~18 Ci/mmol). The investigation was performed after a 12-h fast and food was not allowed for 4 h after drug administration. Blood samples for measurement of tritium activity and plasma digoxin concentration were obtained at scheduled time intervals during the 24-h dosing interval; plasma tritium activity was measured for a further 144 h. Total urine collections were obtained at 12-h intervals for seven days.

Quinidine was then withdrawn, while the administration of digoxin and other drugs was continued with the same dose and dose interval. Following a two-month wash-out period, the investigation was repeated with a similar mode of drug administration and identical sampling of blood and urine.

All plasma samples and aliquots of urine were kept at −21 °C until assayed.

Materials

[3H]-digoxin (specific activity ~18 Ci/mmol) dissolved in ethanol-benzene (9:1 v/v) was purchased from New England Nuclear Corporation, USA. The solvent was evaporated by a stream of nitrogen and the digoxin was redissolved in ethanol-water (10:1 v/v) for intravenous administration. Thin layer chromatography revealed a radiochemical purity of more than 97%. The final solution was sterile and lacked pyrogens.

Digoxigenin-bis-digitoxoside, digoxigenin-mono-digitoxoside, digoxigenin, dihydrodigoxin and dihydrodigoxigenin were gifts from the Boehringer-Mannheim Co., FRG. Liquid scintillation solution (Picofluor 30) was obtained from Packard Instrument Company, USA. Chloroform, ethanol, methanol, methylene chloride, acetic acid and ethyl acetate were obtained from Merck Co., FRG. All chemicals were of analytical grade.

Analytical Methods

Thin layer chromatographic separation of digoxin and its metabolites was performed using a modification of the method of Carvalhas and Figueira (1973). Urine specimens were extracted three times with 5 volumes of chloroform-ethanol (1:1 v/v). The combined extracts were evaporated to dryness, redissolved in chloroform-methanol (1:1 v/v) and applied to thin layer chromatographic plates (Merck Silica Gel Coated Plates). The chromatograms were developed twice in the same direction using ethyl acetate-chloroform-acetic acid (90:5:8 v/v) as solvent. Digoxin, digoxigenin-bis-digitoxoside, digoxigenin-mono-digitoxoside, digoxigenin, dihydrodigoxigenin and dihydrodigoxin were similarly eluted on parallel tracks and were visualized with ultraviolet light at 366 nm after drying and heating at 110 °C for 7 min. The spots corresponding to the reference substances and other parts of the chromatogram were scraped off separately and transferred to scintillation vials containing 5 ml Picofluor scintillation fluid and counted. Plasma samples were extracted 3 times with methylene chloride and eluted as described for urine specimens. The amount of digoxin and metabolites is expressed as a fraction of the activity of the extracts applied on the chromatograms. The total tritium activity in all plasma and urine samples was also analyzed. Tritium activity was measured in an Isocap 300 scintillation counter (Nuclear, Chicago) with appropriate correction for background activity and using the method of external standard channel ratio for quench correction. Counting errors of less than 1% and 4% for urine and plasma samples were achieved by adequate counting times.

Plasma and urinary concentrations of digoxin were determined in duplicate by radioimmunoassay using a commercial 125I-kit (Diagnostic Products Corporation, USA), as described elsewhere (Pedersen et al. 1981).

Data Analysis

After correction for plasma [3H]-digoxin activity, the plasma digoxin versus time data were individually analyzed using the computer program NONLIN (Metzler 1969). The data were fitted to pharmacokinetic functions composed of the smallest number of exponential terms necessary to describe the data adequately. The pharmacokinetic parameters of digoxin absorption were then determined from the fitted functions (Gibaldi and Perrier 1975). Plasma and urine activity versus time data were similarly analyzed.