Brief Report

Autoantibodies against a kidney—liver protein associated with quinolone-induced acute interstitial nephritis or hepatitis

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Abstract. In the present study we report on four cases of acute interstitial nephritis (AIN) and two cases of hepatitis induced by quinolone. We show by immunoblotting analysis that all sera from these patients contained autoantibodies that recognize a 65-kDa protein expressed in normal human kidney and liver microsomes. Only 6% of sera from healthy individuals who did not ingest quinolone recognized the same protein.

These findings suggest that the presence of autoantibodies could be used as a sensitive marker and that a modification of microsomal proteins by quinolone itself or by a metabolite could generated an autoimmune response.

Key words: quinolone; acute interstitial nephritis; hepatitis; autoantibodies; P-450

Introduction

Acute interstitial nephritis (AIN) is an uncommon but serious adverse effect of many drugs [1]. Quinolones, antimicrobial agents, have been reported to cause AIN [2] and hepatitis [3]. Here, we report on four cases of AIN and two cases of hepatitis induced by quinolone in which autoantibodies against a microsomal kidney and liver protein were found (Table 1).

Subjects and methods

Subjects

After initiation of antibiotic therapy all four patients with AIN developed acute renal failure, which disappeared after quinolone withdrawal. Three patients received only quinolone (ciprofloxacin, norfloxacin), while the fourth received cyclosporin in addition to ciprofloxacin. In all patients, quinolone was prescribed for an infectious disease.

Immunoblot analysis

Fifty micrograms of human liver and 100 μg of kidney microsomal proteins were subjected to SDS-and then transferred electrophoretically to nitrocellulose sheets as previously described [7]. The staining was performed with a 1:200 diluted serum.

Table 1. Presence of autoantibodies in human sera

<table>
<thead>
<tr>
<th>Subjects</th>
<th>Positive sera</th>
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<tbody>
<tr>
<td></td>
<td>Liver microsomes (%)</td>
</tr>
<tr>
<td>Quinolone-induced AIN (n = 14)</td>
<td>100</td>
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<tr>
<td>Quinolone-induced hepatitis (n = 2)</td>
<td>100</td>
</tr>
<tr>
<td>Quinolone treatment without AIN/hepatitis (n = 15)</td>
<td>13</td>
</tr>
<tr>
<td>Other drug-associated AIN or hepatitis (n = 20)</td>
<td>15</td>
</tr>
<tr>
<td>Other kidney diseases (n = 13)</td>
<td>8</td>
</tr>
<tr>
<td>Normal volunteer (n = 16)</td>
<td>6</td>
</tr>
</tbody>
</table>

In two patients, AIN was confirmed by renal biopsy. Two other patients treated with quinolones either for a pulmonary infection (ofloxacin) or for the nephrotic syndrome (pofloxacin) [4], developed cytolytic and cholestatic hepatitis, which also resolved after cessation of therapy. One patient also received clavulanic acid and amoxicillin. The imputability of quinolone was quite strong. As controls, we used 15 quinolone-treated patients without AIN or hepatitis, 20 patients with AIN or hepatitis induced by other drugs, 13 patients under haemodialysis with glomerulonephritis, and finally 16 normal volunteers who never ingested quinolone (Table 1).

Human kidney and liver microsomes

Human liver and kidney samples were obtained from donors for transplantation. Microsomes were prepared as previously described [5,6].

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Results and discussion

Blood was withdrawn from all subjects, and autoantibodies against human liver and kidney microsomal proteins were sought by immunoblotting analysis, as described by Bourdi et al. [8]. As shown in Figure 1, all sera from patients with quinolone-associated AIN or hepatitis recognized a 65-kDa protein in kidney and liver microsomes. These autoantibodies were very uncommon in patients with other kidney diseases (8%, Table 1). The percentage of autoantibody-positive sera was slightly higher in the two other control groups. It could not be ruled out that the latter subjects had never been treated with quinolone. By contrast, among healthy volunteers who were checked specifically for the absence of quinolone intake, only 6% had autoantibodies.

These autoantibodies therefore were relatively specific and could be used as a sensitive marker for quinolone-induced AIN and hepatitis. These results also strengthened the hypothesis that quinolone-induced AIN and hepatitis are of immune origin. Hepatitis following exposure to dihydralazine [8], anti-convulsants [9] or tienilic acid [10] were also found associated with the presence of autoantibodies that recognized liver and/or kidney microsomes (anti-LM or anti-LKM antibodies). It has been shown that these antibodies were directed against the enzyme involved in the metabolism of the causative drug [11]. Indeed, anti-LKM2 and anti-LM antibodies recognized the cytochrome P-450 involved in drug metabolism, mainly P-450 2C9 for tienilic acid [12] and P-450 1A2 for dihydralazine [13]. To our knowledge, autoantibodies against a renal autoantigen have not been previously detected in drug-induced AIN. In addition to potential interest of our findings for diagnosis, they suggest a common pathogenic mechanism for drug-induced AIN and hepatitis. This observation should be extended to a larger number of patients. It will also be of major importance in identifying the autoantigen and its potential role in quinolone metabolism.

Acknowledgements. This work was supported by grants Bio 2 CT 920316 and a fellowship from the Institut National de la Santé et de la Recherche Médicale.

References


Received for publication: 12.2.97
Accepted in revised form: 11.4.97

![Fig. 1.](image-url) Human liver microsomes (50 µg) were subjected to 7.5% SDS–PAGE. Immunodetection of proteins transferred to nitrocellulose was performed by using serum diluted 1:200 from a patient with AIN induced by a drug different from quinolone (lane 1) and a patient with quinolone-induced AIN (lane 2).