Alteration of Gentamicin and Cefazolin Kinetics with Control of the Hypothyroid State in Humans

PHILIPPE CHANSON,1 VÉRONIQUE JOLY,2 ALAIN CONTREPOIS,2 JEAN-JACQUES GARAUD,3 JACQUELINE BAUCHET,2 JACQUELINE MOHLER,2 NGUYEN PHONG CHAU,3 AND CLAUDE CARBON2

Service d’Endocrinologie, Hôpital Lariboisière,1 Institut National de la Santé et de la Recherche Médicale U13, Hôpital Claude Bernard,2 and Institut National de la Santé et de la Recherche Médicale U263, Université Paris VII,3 Paris, France

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We studied the effect of the control of the hypothyroid state in humans on the pharmacokinetic parameters of cefazolin and gentamicin after a single intravenous injection. These two antibiotics were chosen because of their different patterns of binding to serum albumin (0% for gentamicin and 82% for cefazolin). In hypothyroidism, the behavior of cefazolin only was altered, with a decrease in the total body clearance, possibly due to reduced urinary excretion, and a decrease in the volume of distribution without a significant alteration of cefazolin binding to serum protein.

The extravascular accumulation of albumin and fluid in primary myxedema was previously assessed by Parving et al. (10). This increased extravasation of albumin, fluid, and presumably all other plasma proteins could change the pharmacokinetic behavior of drugs. Furthermore, the binding of drugs to plasma proteins may be altered in thyroid disease. Feely et al. (8) reported that the degree of binding of propranolol (basic compound) increased in hypothyroid patients, whereas that of warfarin (acidic compound) decreased in hyperthyroid patients. Usually, drug administration does not take the thyroid state into account. The effect of hypothyroidism on the pharmacokinetic behavior of antibiotics has never been reported. The purpose of this study was to evaluate the pharmacokinetic parameters of cefazolin and gentamicin in humans before and after the control of the hypothyroid state. These two antibiotics are not metabolized in humans and are mainly cleared through urinary excretion. They differ in their degrees of binding to serum albumin, i.e., 0% for gentamicin and 82% for cefazolin (6, 9). This fact allowed us to study independently the roles of increased vascular permeability and of altered protein binding in the hypothyroid state.

Five women (mean age, 59 ± 19 years) participated in the study after giving informed consent. They were treated for thyroid cancers (two by radiotherapy and three by surgery). They were studied initially when they were rendered hypothyroid and then at least 3 months later when they became euthyroid through replacement hormone therapy. Euthyroidism was assessed by the normalization of serum thyrotropin, tri-iodothyronine, and thyroxine, with normal values being 0 to 7 mU/liter, 60 to 190 ng/dl, and 4.5 to 11 μg/dl, respectively. Before each step, serum samples were taken to measure creatinine, albumin, tri-iodothyronine, thyroxine, and thyrotropin. At each step, each subject received an intravenous bolus injection (over 3 min) of 2 mg of gentamicin and 15 mg of cefazolin per kg. An indwelling butterfly cannula was used to withdraw blood samples at 3, 5, 10, 15, 20, 30, 45, 60, and 120 min after the injection. Although a sampling period of 2 h only is inadequate to define the elimination character with any accuracy when the terminal half-life of the antimicrobial agent approaches 2 h, samples were not taken beyond 2 h for ethical reasons, this study being performed in cancer patients during dynamic tests for thyroid function. Blood specimens were centrifuged for the collection of plasma, which was stored at −20°C until analyzed. Serum tri-iodothyronine, thyroxine, and thyrotropin were measured by a radioimmunoassay. The albumin and creatinine concentrations were determined by routine automated laboratory methods. Gentamicin concentrations were measured by a radioenzymatic assay as previously described (1). Cefazolin concentrations were determined by high-pressure liquid chromatography (3); cefazolin was extracted from serum with acetone/trile (vol/vol), and after centrifugation, the supernatant was injected into the chromatographic column. Phosphate buffer samples from the binding study were injected without extraction. The chromatographic column was a µBondapak C18 column, and the mobile phase was a mixture of isopropanol and phosphate buffer (10−2 M) (pH 5.30). The detection limit was about 0.5 μg/ml in serum and 0.2 μg/ml in phosphate buffer. The binding of 100 μg of cefazolin per ml to serum proteins evaluated by equilibrium dialysis as described elsewhere (5) was studied in vitro on the sera taken from four of the five patients after cancer treatment (hypothyroid) and after normalization by replacement therapy (euthyroid).

For the pharmacokinetic analysis, only model-independent parameters were assessed, as described by Wagner (12). We determined the terminal half-life, the area under the curve, total body clearance, V₈ (extrapolated distribution volume), and V₉ (total distribution volume).

Statistical evaluation was performed by using the paired Student t test. Differences were considered significant when \( P < 0.05 \).

Euthyroidism was assessed on the basis of posthypothyroidism normalization of thyrotropin (42 ± 12 versus 0.6 ± 0.4 mU/liter), tri-iodothyronine (20.8 ± 14.5 versus 87 ± 18.4 ng/dl), and thyroxine (0.46 ± 0.5 versus 7.6 ± 2.6 μg/dl) through replacement hormone therapy. Passage from the hypothyroid state to the euthyroid state resulted in a body weight loss, but it was not significant (60 ± 4 versus 58 ± 4.

* Corresponding author.
TABLE 1. Pharmacokinetic parameters of the antibiotics in the hypothyroid and euthyroid statesa

<table>
<thead>
<tr>
<th>Drug and state</th>
<th>β (h⁻¹)</th>
<th>t₁/₂ph (h)</th>
<th>AUC (µg · h/ml)</th>
<th>CLtd (ml/min)</th>
<th>Vτ (ml/kg)</th>
<th>Vβ (ml/kg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cefazolin</td>
<td></td>
<td></td>
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<td></td>
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<tr>
<td>Hypothyroid</td>
<td>0.46 ± 0.15</td>
<td>1.65 ± 0.49</td>
<td>332.2 ± 90</td>
<td>47.6 ± 13</td>
<td>107.6 ± 23</td>
<td>107.8 ± 23</td>
</tr>
<tr>
<td>Euthyroid</td>
<td>0.49 ± 0.10</td>
<td>1.45 ± 0.28</td>
<td>227.3 ± 42b</td>
<td>68.0 ± 13b</td>
<td>139.3 ± 16b</td>
<td>139 ± 19b</td>
</tr>
<tr>
<td>Gentamicin</td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Hypothyroid</td>
<td>0.35 ± 0.08</td>
<td>2.07 ± 0.53</td>
<td>27 ± 2.8</td>
<td>74.9 ± 7.8</td>
<td>218.6 ± 32.0</td>
<td>219.3 ± 35.1</td>
</tr>
<tr>
<td>Euthyroid</td>
<td>0.43 ± 0.15</td>
<td>1.83 ± 0.79</td>
<td>22.5 ± 5.9</td>
<td>93.1 ± 21</td>
<td>224.7 ± 50.7</td>
<td>229.2 ± 48.6</td>
</tr>
</tbody>
</table>

a Each value represents the mean ± standard deviation obtained from the same five subjects examined first in the hypothyroid and later in the euthyroid state. β, Elimination phase; t₁/₂ph, terminal half-life; AUC, area under the curve; CLtd, total body clearance.

b Significantly different (P < 0.05) from the value obtained in the euthyroid state.

kg); serum albumin remained stable (47 ± 3 versus 46 ± 2 g/liter), and serum creatinine decreased significantly (86 ± 5.5 versus 70 ± 12 µmol/liter, P < 0.05). The results of the pharmacokinetic studies (Table 1) show the effects of the normalization of the thyroid state. Total body clearance increased for both antibiotics in euthyroidism, but the difference was only significant for cefazolin. Other pharmacokinetic parameters for gentamicin were not influenced by the thyroid state. The serum area under the curve for cefazolin decreased, but Vβ and Vτ increased significantly when the patients became euthyroid. Cefazolin binding to serum proteins in vitro was 80 ± 7.6% in hypothyroidism and 79.5 ± 2.9% in euthyroidism, values similar to those previously reported (9).

Studies of patients with myxedema have revealed an accumulation of mucopolysaccharides in the skin and other organs (2). This is not the only mechanism of edema, since the existence of plasmalike effusions in serous cavities has been proven (11). An important factor in myxedema is the increased extravasation of plasma proteins with the lack of a compensatory increase in lymph flow and protein return rate, as demonstrated by Parving et al. (10). These authors reported the existence in the hypothyroid state of a low plasma volume, an increased transcapillary rate of albumin, and a remarkable increase in the extravascular mass of albumin. The significantly higher values of creatinine that we observed in our patients in the hypothyroid state could be the consequence of decreased renal blood flow subsequent to plasma volume reduction. We did not observe a higher value for the plasma albumin concentration in hypothyroidism, as described by Parving et al. (10). This difference could be due to the different etiology of hypothyroidism in our study (cancer) and to the short delay between the induction of hypothyroidism and the first step in our investigation. Gentamicin and cefazolin are mainly cleared by urinary excretion, and this may explain why the normalization of the thyroid state increased their elimination rate, since the glomerular filtration rate increased significantly during passage from the hypothyroid state to the euthyroid state.

The volume of drug distribution that we observed in the hypothyroid state was not what could be expected in view of the extravascular fluid and albumin modifications described previously. The Vβ and Vτ of gentamicin, an unbound compound, remained unchanged in the hypothyroid state after a single injection. This result could be due either to the absence of a significant increase in the extravascular fluid space in our patients or to inverse variations of the pharmacokinetic parameters, e.g., extravascular space volume and total body clearance.

The decreased glomerular filtration rate in hypothyroidism may account for the reduction in the terminal half-life and the increase in the serum area under the curve for cefazolin. The Vβ and Vτ of cefazolin decreased significantly in hypothyroidism. The reasons for these decreases are not clear. Since cefazolin and gentamicin differ in their capacities to bind to serum protein, we expected a modification of cefazolin protein binding during hypothyroidism: an increased binding to serum albumin would tend to decrease the apparent volume of distribution in hypothyroid patients (7). Altered protein binding has been reported in thyroid disease (8). However, such a difference did not appear in our in vitro study of cefazolin protein binding. This result could be due to a lack of sensitivity of the method, in part through drug binding to the dialysis membrane. However, our binding data do not support our hypothesis, and the alterations of Vτ and Vβ remain unexplained. These modifications in the volume of distribution of cefazolin were observed after a single injection, and we cannot extrapolate such results to long-term treatments. As was demonstrated with a tissue-cage model in rabbits (4), extravascular diffusion of antibiotics highly bound to proteins is delayed, and the equilibration rate is obtained after more than one injection.

In conclusion, our results, unexpected in view of previously reported extravascular space modifications, show that the pharmacokinetic behavior of drugs can be altered in hypothyroidism. No significant effect was observed on gentamicin pharmacokinetics. Thus, modifications of gentamicin dosing are apparently not warranted. The Vβ and Vτ of cefazolin decreased, but this result does not prove the necessity of changing cefazolin dosing in hypothyroidism. However, further investigations after long-term treatment should be performed before deducing that these results have no therapeutic consequences.

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