Influence of Food on Bioavailability of Amdinocillin Pivoxil

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Amdinocillin pivoxil (formerly known as pivmecillinam and also referred to as pivaminocillin) is the pivaloyloxy-methyl ester of amdinocillin, a drug which is active against gram-negative bacteria and which acts synergistically with other β-lactam antibiotics (1, 2, 6, 9-11; R. Cleland, W. DeLorenzo, G. Beskid, E. Titsworth, J. Christenson, and E. Grunberg, Program Abstr. 19th Intersci. Conf. Antimicrob. Agents Chemother., abstr. no. 199, 1979). Amdinocillin in the parenteral forms is indicated for the treatment of urinary tract infections caused by susceptible strains of Escherichia coli, Klebsiella spp., and Enterobacter spp. and is commercially available as Coactin. Amdinocillin pivoxil itself has no antibacterial activity; however, after oral administration as the hydrochloride salt, it is rapidly and nearly completely hydrolyzed during absorption from the gastrointestinal tract, thereby liberating the microbiologically active amdinocillin (8).

Food has been shown to reduce or delay the absorption of several penicillins (12, 13). Earlier studies have shown that although the absorption rate of amdinocillin pivoxil was reduced by food, the extent of bioavailability was not (7). According to a recent report (4), food significantly increased both the absorption rate and the extent of availability of amdinocillin from amdinocillin pivoxil. In view of these conflicting data, this well-controlled study was designed to reexamine the effect of food on the rate and extent of amdinocillin pivoxil absorption.

Eighteen healthy volunteers (12 men and 6 women not of childbearing potential) aged 19 to 55 years (mean, 26 years) and weighing 48.6 to 84.5 kg (mean, 70.9 kg) were enrolled in the study. Written informed consent was obtained from each volunteer after study approval by the Institutional Review Board at Hazleton Laboratories America, Inc., Madison, Wis. The study was a four-way randomized crossover design with a 1-week washout period separating drug treatments. After an overnight fast, subjects received two 200-mg tablets of amdinocillin pivoxil (equivalent to 274 mg of amdinocillin) with 120 ml of water 1 h before, with, and 1 h after a standard breakfast as well as under fasting conditions (control). The standard breakfast consisted of six ounces of orange juice, two large eggs, one slice of toast with margarine, and eight ounces of skim milk. The meal was completely consumed within 20 min of being served. Food intake, except for the specified standard breakfast, was not permitted for 4 h after drug administration.

Heparinized plasma and urine samples were collected at appropriate intervals for 12 h. The samples were immediately frozen in an acetone-dry ice mixture and were stored at −70°C. Plasma and urine samples were assayed for amdinocillin by a modification of the high-performance liquid chromatography method of Lee and Brooks (5). Modifications included a doubling of all volumes in the assay extraction method and a guard column (4 by 150 mm) placed before the injector. The interassay precision was 8.3% over a 0.5 to 25 μg/ml concentration range in plasma and 3.4% over a 0.025 to 5.0 mg/ml concentration range in urine.

Maximum concentration in plasma (Cmax) and the time of its occurrence (Tmax) were read directly from the plasma concentration-time data. Area under the plasma concentration-time curve (AUC) from time zero to infinity was calculated by conventional trapezoidal summation and extrapolation methods. The elimination rate constant (β) was estimated from the terminal log-linear portion of the concentration-time profiles by linear regression analysis. The terminal elimination half-life was calculated as ln2/β. Renal clearance (CLr) was estimated by dividing the amount of amdinocillin in the urine over a given time interval by the corresponding AUC over that interval. The fraction of the amdinocillin pivoxil dose excreted in the urine (fE) in 12 h was determined by dividing the cumulative amount of amdinocillin excreted in the urine by the amdinocillin dose.

FIG. 1. Mean amdinocillin concentrations in plasma after an oral dose of two 200-mg tablets of amdinocillin pivoxil administered during a complete fast (×), 1 h before a standard breakfast (O), with a standard breakfast (Δ), and 1 h after a standard breakfast (□).
For statistical evaluation, an analysis of variance of the logarithms with a model from Hedayat and Afarinejad (3) was performed accounting for the effects of subjects, treatments, time periods, and possible carry over from the preceding treatment.

The pharmacokinetic profile of amdinocillin after amdinocillin pivoxil administration 1 h before a standard breakfast was essentially the same as that observed for the control treatment (Fig. 1; Table 1). Compared with the control treatment, Cmax was decreased slightly and other parameters were unchanged. The lack of food effect in this treatment is understandable since most of the drug is absorbed by the time of food ingestion and is, therefore, unavailable for a potential food-drug interaction.

The concurrent ingestion of amdinocillin pivoxil with a standard breakfast increased the Cmax and AUC, but had no effect on Tmax, β, CLR, and fα. Ingestion of amdinocillin pivoxil 1 h after a standard breakfast increased the Cmax, Tmax, AUC, and β and had no effect on CLR and fα. These findings indicate that the extent of absorption was increased by about 20% when the drug was given with or 1 h after a standard breakfast. This finding is consistent with the data reported by Hey et al. (4).

After all drug treatments, concentrations of amdinocillin in urine were relatively high and remained significantly above the MICs for most urinary tract pathogens up to 6 h after drug administration (Table 2).

Drug-related adverse experiences were encountered in five subjects. Three subjects reported headache of mild severity; one subject complained of stomach cramp; and one subject experienced a brief spell of dizziness, nausea, and momentary loss of vision. The dizziness, nausea, and loss of vision occurred 30 min after administration of test drug at the time of the third venipuncture. This was probably a vasovagal reaction to the needle stick. These experiences were transient in nature and did not require medical intervention. Not a single subject dropped out from the study because of adverse experiences. Overall, the drug was well tolerated by subjects.

Amdinocillin pivoxil is recommended for administration on a three times daily regimen. At some point during drug therapy, the patient may need to take the drug at mealtime. Since the bioavailability is not pronouncedly affected by food, patients may conveniently take the drug with or without food.

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LITERATURE CITED

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**TABLE 1. Pharmacokinetic parameters of amdinocillin after oral administration of amdinocillin pivoxil**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>A</th>
<th>B</th>
<th>C</th>
<th>D</th>
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<tr>
<td>Cmax (µg/ml)</td>
<td>3.6 ± 0.9 (2.2–5.8)</td>
<td>3.2 ± 0.6* (2.2–4.1)</td>
<td>4.3 ± 0.5* (3.4–5.4)</td>
<td>4.1 ± 0.9* (2.7–5.6)</td>
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<td>Tmax (h)</td>
<td>1.2 ± 0.4 (0.75–2.0)</td>
<td>1.4 ± 0.6 (0.75–3.5)</td>
<td>1.3 ± 0.5 (0.75–2.5)</td>
<td>1.7 ± 0.5* (1.0–2.5)</td>
</tr>
<tr>
<td>AUC (µg · h/ml)</td>
<td>8.1 ± 2.0 (5.4–12.1)</td>
<td>7.7 ± 1.8 (5.1–10.7)</td>
<td>10.0 ± 1.8* (6.8–13.4)</td>
<td>9.7 ± 1.8* (7.5–13.6)</td>
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<tr>
<td>β (h⁻¹)</td>
<td>0.71 ± 0.16 (0.39–0.96)</td>
<td>0.66 ± 0.19 (0.34–0.99)</td>
<td>0.73 ± 0.13 (0.52–0.92)</td>
<td>0.79 ± 0.12* (0.65–1.14)</td>
</tr>
<tr>
<td>t₁/₂ (h)b</td>
<td>1.0 (0.7–1.6)</td>
<td>1.0 (0.7–2.1)</td>
<td>0.9 (0.8–1.3)</td>
<td>0.9 (0.6–1.1)</td>
</tr>
<tr>
<td>CLR (liters/h)</td>
<td>9.6 ± 3.4 (4.7–15.5)</td>
<td>10.2 ± 5.2 (3.4–26.1)</td>
<td>9.5 ± 3.0 (4.1–14.6)</td>
<td>9.7 ± 4.0 (3.9–21.7)</td>
</tr>
<tr>
<td>fα (%)</td>
<td>27 ± 8.5 (11–46)</td>
<td>27 ± 12 (13–53)</td>
<td>33 ± 6.8 (17–43)</td>
<td>34 ± 12 (15–61)</td>
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</table>

* Treatments: A, fasting (control); B, drug 1 h before a standard breakfast; C, drug with a standard breakfast; D, drug 1 h after a standard breakfast.

**TABLE 2. Concentrations of amdinocillin in urine after a 400-mg oral dose of amdinocillin pivoxil**

<table>
<thead>
<tr>
<th>Urine collection interval (h)</th>
<th>Conc of amdinocillin (µg/ml) with treatmentc:</th>
<th>A</th>
<th>B</th>
<th>C</th>
<th>D</th>
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<td>2–4</td>
<td>272 ± 311 (31–1,389)</td>
<td>169 ± 132 (37–482)</td>
<td>202 ± 158 (54–759)</td>
<td>284 ± 227 (52–1,033)</td>
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<tr>
<td>4–6</td>
<td>80 ± 93 (NM–333)</td>
<td>66 ± 59 (NM–197)</td>
<td>86 ± 63 (NM–215)</td>
<td>108 ± 80 (23–348)</td>
<td></td>
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<tr>
<td>6–8</td>
<td>19 ± 28 (NM–85)</td>
<td>11 ± 22 (NM–83)</td>
<td>9 ± 16 (NM–52)</td>
<td>14 ± 22 (NM–67)</td>
<td></td>
</tr>
</tbody>
</table>

* Treatments: A, fasting (control); B, drug 1 h before a standard breakfast; C, drug with a standard breakfast; D, drug 1 h after a standard breakfast. Values shown are mean ± standard deviation, with the range in parentheses.

**a** Nonmeasurable (NM) concentrations included as 0 µg/ml in calculation of the mean.