Production of Hypoprothrombinemia by Moxalactam and 1-Methyl-5-Thiotetrazole in Rats

JAMES J. LIPSKY,1 JOHN C. LEWIS,2 AND WILLIAM J. NOVICK, JR.2

Division of Clinical Pharmacology, Department of Medicine and Department of Pharmacology and Experimental Therapeutics, The Johns Hopkins University School of Medicine, Baltimore, Maryland, 21205,1 and Hoechst-Roussel Pharmaceuticals Inc., Somerville, New Jersey 088762

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To determine whether the hypoprothrombinemia associated with antibiotics containing a 1-methyl-5-thiotetrazole (MTT) group is a result of the presence of the MTT group, rats were maintained on a vitamin K-deficient diet for 10 days and then received either intravenous moxalactam or cefotaxime or oral MTT for two additional days. MTT and moxalactam, which contains the MTT group, prolonged prothrombin time. Cefotaxime, which lacks the MTT group, had no effect.

The ability of cefotaxime, a drug which does not contain the MTT group, to produce hypoprothrombinemia was examined and compared with that of moxalactam. Cefotaxime was not able to produce a prolongation of the prothrombin time, but under the same conditions, moxalactam again increased the prothrombin time over fivefold (Table 2). Three animals in the moxalactam group died (two of hemorrhage) before the third prothrombin time determination.

The results of these experiments indicate that MTT and moxalactam containing MTT in its structure are capable of producing hypoprothrombinemia in vivo. Cefotaxime, which does not possess an MTT group, did not produce hypoprothrombinemia. Previous studies by others of rats on normal diets given doses of moxalactam up to 2.7 g/kg did not reveal any evidence of hypoprothrombinemia (12). The vitamin K-deficient diet used in our studies was chosen because a lack of vitamin K intake may be a contributing or necessary factor for humans to become hypoprothrombinemic while on MTT-containing antibiotics. Our use of rats on vitamin K-deficient diets may resemble the clinical situation, in which it appears that lack of oral intake of food, and thus possible decreased intake of vitamin K, may be a predisposing condition for hypoprothrombinemia to occur. Healthy humans on normal diets have been given 12 g of moxalactam per day for 7 days without producing changes in the pro-

![Image of Structures of Cefotaxime and Moxalactam](http://aac.asm.org/)

FIG. 1. Structures of cefotaxime and moxalactam. The 1-methyl-5-thiotetrazole group in moxalactam is highlighted.
thrombin time (1). These human studies and the studies in rats on normal diets may be analogous in that normal levels of vitamin K were present in both cases.

The large antibiotic dose used in our studies, 3 g/kg, was chosen because it is similar to the upper limit of the doses used to test these drugs in normal animals. Future studies will determine the minimum doses of both moxalactam and MTT necessary to produce hypoprothrombinemia.

MTT was administered orally because the gastrointestinal tract may be where MTT is liberated from the parent antibiotic. Evidence for the release of MTT from the parent antibiotic in humans is the finding of free MTT in the plasma of subjects who have received moxalactam (2). MTT has also been detected in the urine of subjects who have received cefmetazole, an antibiotic with an MTT side group (10). It has been hypothesized that the intact MTT-containing antibiotic is secreted into the bile and is then degraded in the intestine to release the MTT group. MTT is located in beta-lactam antibiotics in a "leaving group" position secondary to the lactam bond cleavage (3). This cleavage may be due to nucleophilic attack by bacterial enzymes or the chemical environment. After its release from the parent antibiotic, MTT could then be absorbed with subsequent inhibition of the carboxylase system in the liver. Since only a fraction of the parent antibiotic is secreted in the bile, and since MTT is only about one-fifth of the molecular weight of the intact antibiotic, the oral dose of MTT needed to produce hypoprothrombinemia may be less than that used in our studies.

In conclusion, we have shown that MTT and an antibiotic with the MTT side group, moxalactam, produced hypoprothrombinemia in rats on a vitamin K-deficient diet. Cefotaxime, which does not contain an MTT group, did not produce hypoprothrombinemia. These results support the hypothesis that hypoprothrombinemia is a consequence of the presence of MTT in the parent antibiotic. This is consistent with in vitro findings that MTT inhibits the vitamin K-dependent step in the synthesis of clotting factors.

LITERATURE CITED


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### TABLE 1. Effect of MTT and moxalactam on prothrombin time

<table>
<thead>
<tr>
<th>Day</th>
<th>Oral control (n = 5)</th>
<th>MTT (n = 10)</th>
<th>i.v. control (n = 5)</th>
<th>Moxalactam (n = 10)</th>
</tr>
</thead>
<tbody>
<tr>
<td>11</td>
<td>20 ± 7</td>
<td>18 ± 4</td>
<td>18 ± 1</td>
<td>19 ± 5</td>
</tr>
<tr>
<td>12</td>
<td>26 ± 10</td>
<td>33 ± 29</td>
<td>18 ± 4</td>
<td>34 ± 28</td>
</tr>
<tr>
<td>13</td>
<td>32 ± 18</td>
<td>97 ± 64a</td>
<td>18 ± 4</td>
<td>85 ± 53a</td>
</tr>
</tbody>
</table>

* Statistically significantly different from control (P < 0.05).

### TABLE 2. Effect of cefotaxime and moxalactam on prothrombin time

<table>
<thead>
<tr>
<th>Day</th>
<th>Control (n = 10)</th>
<th>Cefotaxime (n = 10)</th>
<th>Moxalactam (n = 10)</th>
</tr>
</thead>
<tbody>
<tr>
<td>11</td>
<td>21 ± 5</td>
<td>18 ± 3</td>
<td>19 ± 5</td>
</tr>
<tr>
<td>12</td>
<td>21 ± 8</td>
<td>21 ± 6</td>
<td>41 ± 23a</td>
</tr>
<tr>
<td>13</td>
<td>23 ± 8</td>
<td>25 ± 10</td>
<td>113 ± 82b</td>
</tr>
</tbody>
</table>

* Statistically significantly different from control (P < 0.05).

* Statistically significantly different from control (P < 0.01).