Comparative Evaluation of the Pharmacokinetics of N-Methylthiotetrazole following Administration of Cefoperazone, Cefotetan, and Cefmetazole

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The comparative pharmacokinetics and in vivo production of N-methylthiotetrazole (NMTT) were evaluated following administration of cefoperazone, cefotetan, and cefmetazole. In a randomized-crossover manner, 11 healthy male volunteers received single 2-g intravenous doses of each agent and serial blood and urine samples were collected. Concentrations of NMTT and the parent compound in plasma, urine, and the reconstituted antibiotic solution were determined by high-pressure liquid chromatography. The amounts of NMTT administered were 6.06 ± 0.46, 14.4 ± 0.87, and 17.4 ± 1.06 mg for cefoperazone, cefotetan, and cefmetazole, respectively (P < 0.05). The mean NMTT plasma concentration-time profiles following administration of each cephalosporin were markedly different. Six hours after dosing, NMTT concentrations in plasma following cefoperazone administration were higher than those following administration of cefotetan and cefmetazole. Urinary recoveries of NMTT averaged 137.0 ± 37.1, 38.3 ± 6.98, and 25.2 ± 5.95 mg following administration of cefoperazone, cefotetan, and cefmetazole, respectively (P < 0.01). The apparent amount of NMTT produced in vivo, calculated by subtracting the amount of NMTT administered from the amount of NMTT excreted in urine, was significantly lower following cefmetazole administration than after administration of cefoperazone and cefotetan (P < 0.01). The discrepancy between in vitro NMTT production (cefmetazole > cefotetan > cefoperazone) and the amount of NMTT formed in vivo and excreted unchanged (cefoperazone > cefotetan > cefmetazole) suggests that in vivo production of NMTT is dependent on the disposition of the parent cephalosporin. These results further suggest that cephalosporins which undergo extensive biliary excretion, such as cefoperazone, are associated with the greatest amount of in vivo NMTT release, whereas cephalosporins which are primarily renally excreted, such as cefmetazole, are associated with the lowest in vivo production of NMTT.

Cefmetazole is a cephalosporin with a broad spectrum of antimicrobial activity. The structure of cefmetazole is similar to those of moxalactam, cefoperazone, cefotetan, and cefamandole in that all of these agents contain an N-methylthiotetrazole (NMTT) side chain. This side chain has been reported to dissociate from its parent molecule and has been implicated in the development of disulfiram-like reactions and changes in prothrombin time (1, 7, 9, 11, 12).

It has been postulated that the NMTT side chain which is cleaved from the cephalosporin is responsible for inhibition of vitamin K metabolism and subsequent development of antibiotic-associated hypoprothrombinemia (7, 8, 11, 12, 15). Two theories are offered to account for the mechanism of NMTT inhibition of vitamin K metabolism (7, 8, 15, 17). By using an in vitro system, Lipsky demonstrated that NMTT irreversibly inhibits vitamin K-dependent carboxylase activity in a dose-dependent manner (7, 8). However, the concentration of NMTT required to produce in vitro inhibition of gamma carboxylation is rarely obtained in patients (18). Other investigators have hypothesized that NMTT or a metabolite of NMTT inhibits vitamin K 2,3-epoxide reductase in a manner similar to that of the coumarin oral anticoagulants (2, 4, 14). This hypothesis is based on studies which have demonstrated accumulation in vitamin K 2,3-epoxide following administration of an NMTT-containing antibiotic to hospitalized patients (2, 14). On the basis of data obtained with oral anticoagulants, one would predict that NMTT inhibition of vitamin K epoxide reductase would also be dependent on the amount (dose) of NMTT available as an inhibitor (16). Although the latter hypothesis is currently favored, both mechanisms could coexist (11). Regardless of the mechanism, the dose of NMTT is potentially a critical factor.

Investigators have demonstrated that the amount of NMTT administered with each dose of a cephalosporin is dependent on the agent, the pH of the solution, and contact time in the intravenous bottle before administration (19, 20). For example, Wise and Dent demonstrated that in vitro hydrolysis to the free NMTT side chain was greater with moxalactam following 6 h of reconstitution at pH 2.0 than with moxalactam reconstituted for 1 h in more basic solutions. Moxalactam was less stable in vitro than other NMTT-containing antibiotics, such as cefamandole, cefoperazone, and cefotetan (20). We demonstrated that the amounts of NMTT cleaved from the cephalosporins in vivo are different among the various NMTT-containing antibiotics (19). On the basis of the proposed mechanisms of inhibition, one may hypothesize that differences in NMTT production among the

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cephalosporins may be associated with differences in the relative risk for hypoprothrombinemia.

Information regarding both the relative incidence of hypoprothrombinemia and the amount of NMTT liberated from cefmetazole is lacking. Therefore, on the basis of the differences in NMTT formation previously identified in our laboratory (19), we undertook a study to evaluate NMTT disposition following cefmetazole administration. Specifically, we compared the pharmacokinetics of NMTT and the parent cephalosporin in healthy male volunteers following single intravenous doses of cefoperazone, cefotetan, and cefmetazole. To assess potential differences in apparent in vivo production of NMTT, we determined the amount of NMTT administered with each cephalosporin dose and measured NMTT concentrations in both the plasma and urine of healthy volunteers.

MATERIALS AND METHODS

Subjects. Thirteen male volunteers were enrolled in a randomized-crossover trial, and eleven subsequently completed all three treatment phases. The study was approved by the Human Research Committee at Millard Fillmore Hospital, and written informed consent was obtained from each subject before enrollment in the study. The subjects were 20 to 35 years old. The mean total body weight of the 11 subjects who completed the study was 78.1 (+9.55) kg; all were within 10% of the ideal body weight. Before study initiation, all volunteers were judged to be in good health on the basis of medical history, physical examination, electrocardiogram, and clinical laboratory tests. The subjects had no known history of hypersensitivity to penicillins or cephalosporins. Subjects with a history of drug or alcohol abuse were excluded from participation in the study.

Drug administration. During each of the three treatment phases, the subjects were confined to the clinical research unit at the Clinical Pharmacokinetics Laboratory, Millard Fillmore Hospital, Buffalo, N.Y. In a randomized-crossover manner, each subject received 2-g doses of cefoperazone sodium (lot no. 81805 and 71006; Roerig), cefotetan disodium (lot no. 4386F and 4071F; Stuart), and cefmetazole sodium (lot no. 24602 and 24603; Upjohn), which were administered intravenously over 30 min with an Abbott Lifecare pump. Three grams of each agent was reconstituted with 5% glucose. Two-gram doses of the antibiotics were administered to the volunteers, and the remainder of the solution was immediately frozen for analytical determination of NMTT and cefalosporin concentrations.

Specimen collection. Blood samples for determination of NMTT and cefalosporin concentrations were collected in heparinized VACUTAINER tubes before and at 0.25, 0.50, 0.75, 1.0, 2.0, 3.0, 4.0, 6.0, 8.0, 12.0, 18.0, 24.0, 36.0, and 48.0 h following initiation of the antibiotic infusion. To minimize in vitro production of NMTT, blood samples were immediately placed on ice and centrifuged at 2,000 rpm for 12 min at 4°C in a Beckman refrigerated centrifuge. The plasma was harvested and immediately flash-frozen by using a methanol-dry ice bath. Samples were stored at −70°C until analysis.

Urine was collected before (baseline) and at 0- to 2-, 2- to 4-, 4- to 8-, 8- to 12-, 12- to 24-, 24- to 36-, 36- to 48-, 48- to 60-, and 60- to 72-h intervals. During each collection interval, urine was stored at 4°C. At the end of each collection interval, the total urine volume and pH were measured. Subsequently, 20-ml samples were placed in polypropylene containers and frozen at −70°C until assayed for NMTT and cephalosporin concentrations.

Sample analysis. (i) NMTT analysis. Concentrations of NMTT in plasma and urine samples and antibiotic intravenous solutions were determined by high-pressure liquid chromatography (HPLC) by using the following modifications of a previously published procedure (19). 2-Thiobarbituric acid was eliminated as the internal standard. The mobile phase consisted of a mixture of acetonitrile–0.1 M sodium phosphate buffer containing 0.005 M tetrabutylammonium hydroxide with a final pH of 7.35. A 15:85 (acetonitrile-buffer) mixture at a flow rate of 1.0 ml/min was used for the plasma assay, and a 13:87 mixture at a flow rate of 1.3 ml/min was used for the urine assay. Plasma samples (0.1 ml) were prepared by using SAX and C18 solid-phase extraction columns (J. T. Baker), while urine samples (0.1 ml with 900 μl of water) were prepared only over C18 solid-phase extraction columns. The limits of quantitation were 0.05 and 1.25 μg/ml in plasma and urine, respectively. Recoveries of NMTT from plasma and urine were 80.8 and 69.8%, respectively. The average interday variabilities of NMTT plasma standards and seeded controls were 2.7 and 5.0%, respectively, with maximum variabilities of 4.1 and 6.2%, respectively. The average interday variabilities of NMTT urine standards and seeded controls were 4.5 and 4.9%, respectively, with maximum variabilities of 6.6 and 5.4%, respectively.

(ii) Cefoperazone analysis. Concentrations of cefoperazone in plasma and urine samples and antibiotic intravenous solutions were determined by using a previously published HPLC procedure (19). The limits of quantitation were 0.50 and 5.0 μg/ml in plasma and urine, respectively. The average interday variabilities of cefoperazone plasma standards and seeded controls were 1.8 and 8.6%, respectively, with maximum variabilities of 2.9 and 15.3%, respectively. The average interday variabilities of cefoperazone urine standards and seeded controls were 1.2 and 1.7%, respectively, with maximum variabilities of 2.8 and 2.5%, respectively.

(iii) Cefotetan analysis. Cefotetan concentrations in plasma and urine samples and antibiotic intravenous solutions were determined by HPLC by using a Waters 6000A HPLC pump, a Spectrophysics SP8780 autosampler, a Kratos 757 UV detector, and a Spectrophysics SP4270 integrator. Plasma samples (0.5 ml) were treated with 0.1 ml of 0.025 M phosphate buffer (pH 7.0), 0.1 ml of the internal standard (cephaloridine at 500 μg/ml), and 0.2 ml of acetonitrile-perchloric acid (4:1) to precipitate plasma proteins. After cooling, centrifugation, and 1:1 dilution with cold 0.1 M phosphate buffer, 50 μl of the sample was chromatographed on a Phenomenex column packed with C18 μBondapak resin (3.9 by 150 mm) preceded by a 0.45-μm-pore-size prefIlter. The mobile phase consisted of acetonitrile–0.1 M monosodium phosphate–85% phosphoric acid (10:90:0.3) and was pumped at a flow rate of 1.5 ml/min. Peak height determinations were made at 280 nm. The plasma standards ranged from 1.0 to 200 μg/ml. The overall recoveries of cefotetan and cephapazone by this procedure were 67.2 and 76.1%, respectively. The limit of quantitation was 1.0 μg/ml for plasma. The average interday variabilities of plasma standards and seeded controls were 2.0 and 3.7%, respectively, with maximum variabilities of 4.4 and 7.0%, respectively. Concentrations of cefotetan in urine were determined by a method similar to that of the plasma assay, with the following modifications. Urine samples (50 μl) were treated with 900 μl of water and 50 μl of the internal standard (norfloxacin at 190 μg/ml). After vortexing, 50 μl of the sample was chromatographed with a mobile phase consisting of acetonitrile–0.1 M monosodium phosphate–85% phosphoric acid
were made at 280 nm. The urine cefotetan standards ranged from 10.5 to 3,160 \( \mu g/ml \). The overall recoveries of cefotetan and norfloxacin with this procedure were 108.6 and 99.3\%, respectively. The limit of quantitation was 10.5 \( \mu g/ml \) for urine. The average interday variabilities of urine standards and seeded controls were 1.9 and 4.5\%, respectively, with maximum variabilities of 3.8 and 5.4\%, respectively.

(iv) Cefmetazole analysis. Cefmetazole samples were analyzed by HPLC by using a Hitachi 653A-11 HPLC pump, a Waters 710B autosampler, a Schoeffel SF-770 Spectroflow UV detector, and a Hewlett-Packard 3390A integrator with methods similar to those of Bothwell and coworkers (3). Plasma samples (0.3 ml) were treated with 0.6 ml of 1.0% trichloroacetic acid in methanol containing sodium barbital (500 \( \mu g/ml \)) as the internal standard to precipitate plasma proteins. After cooling, centrifugation, and 1:1 dilution with cold 0.1 M citrate buffer, 100 \( \mu l \) of the supernatant was chromatographed on a DuPont Zorba octadecyl-silane column (4.6 by 250 mm) preceded by an RP-18 Brownlee guard column (3.2 by 15 mm) with a mobile phase consisting of 13% acetonitrile in 0.01 M (pH 5.4) citrate buffer at a flow rate of 1.7 ml/min. Peak height determinations were made at 254 nm. The overall recoveries of cefmetazole and sodium barbital by this procedure were 99.4 and 99.3\%, respectively. The limit of quantitation was 0.5 \( \mu g/ml \) in plasma. The average interday variabilities of plasma standards and seeded controls were 1.6 and 2.7\%, respectively, with maximum variabilities of 5.7 and 4.4\%, respectively. Concentrations of cefmetazole in urine were determined by a similar method, with the following modifications. The equipment included a Waters 6000A HPLC pump, a Waters 712 autosampler equipped with a Waters WISP cooling unit, a Kratos 757 UV detector, and a Hewlett-Packard 3388A integrator. Urine samples (0.1 ml) were diluted with 400 \( \mu l \) of water and 500 \( \mu l \) of 0.5% trichloroacetic acid in methanol containing sodium barbital (6,000 \( \mu g/ml \)) as the internal standard. After cooling, centrifugation, and 1:1 dilution with cold 0.1 M (pH 5.4) citrate buffer, 50 \( \mu l \) of the sample was chromatographed by using a mobile phase consisting of 12% acetonitrile in 0.01 M (pH 5.4) citrate buffer. The overall recoveries of cefmetazole and sodium barbital by this procedure were 101.3 and 104.4\%, respectively. The limit of quantitation was 10.0 \( \mu g/ml \) in urine. The average interday variabilities of urine standards and seeded controls were 1.7 and 3.3\%, respectively, with maximum variabilities of 2.8 and 3.6\%, respectively.

Pharmacokinetic analysis. Cephalosporin and NMTT pharmacokinetic parameters were determined by noncompartmental analysis (6). The apparent elimination rate for each of the cephalosporins was determined from the terminal slope of the log-linear phase of the plasma concentration-versus-time curve. The areas under the plasma concentration-time curve from 0 h to the last measurable concentration at time \( t_{\text{max}} \) for NMTT and each of the cephalosporins were determined by the linear trapezoidal rule. The area under the curve for each of the cephalosporins was extrapolated to infinity (\( \text{AUC}_{\infty} \)). The total body clearance (\( \text{CL}_p \)) of each of the cephalosporins was calculated by dividing the cephalosporin dose by the \( \text{AUC}_{\infty} \) for the cephalosporin in plasma.

The actual doses of cephalosporin and NMTT administered to each subject were determined as the basis of the concentrations determined in the residual antibiotic intravenous solution multiplied by the volumes of medication delivered to the subject.

Urinary excretion of each of the cephalosporins and NMTT was determined by multiplying concentrations in urine by the corresponding urine volumes. Cumulative urinary recoveries of NMTT and the cephalosporins were calculated by summing the amounts recovered during each of the collection intervals. Renal clearance (\( \text{CL}_r \)) of each of the cephalosporins was calculated by dividing the total amount of cephalosporin excreted in the urine by the respective \( \text{AUC}_{\infty} \) for plasma. The \( \text{CL}_r \) of NMTT was estimated by dividing the amount of NMTT collected in the urine over 48 h by the \( \text{AUC}_{\infty} \).

The amount of NMTT produced in vivo and excreted unchanged in the urine was calculated by subtracting the infused dose of NMTT from the cumulative urinary recovery of NMTT. Estimation of the apparent amount of NMTT produced in vivo assumed that NMTT was eliminated only as unchanged drug in the urine. For comparison, NMTT parameters were adjusted for differences in the molecular weights of the cephalosporins and the millimolar ratio of NMTT to each of the parent cephalosporins was examined.

Statistical analysis. Pharmacokinetic parameters for NMTT were compared by using the General Linear Models procedure of the Statistical Analysis System (version 5; SAS Institute, Cary, N.C.) for a mixed-effects analysis of variance model with group, period, and treatment as fixed effects and subject within group as a random effect. Assumptions inherent in applying this analysis of variance procedure were evaluated by distributional analyses and Bartlett’s test for equality of variances. If these assumptions were invalid for a given parameter, the analysis of variance was repeated on ranked data. The Waller-Duncan K ratio \( t \)-test procedure was used for pairwise comparison of treatment means. Significance was defined as \( P < 0.05 \).

RESULTS

Following intravenous administration of each of the cephalosporins, the concentrations of the parent cephalosporins in plasma declined in a log-linear fashion. The doses administered were 2,008 \( \pm 45.4, 2,236 \pm 52.9, \) and 1,655 \( \pm 19.8 \) mg for cefoperazone, cefotetan, and cefmetazole, respectively. The milligram doses of the three cephalosporins administered were statistically significantly different (\( P < 0.05 \)). The pharmacokinetic parameters for each of the parent cephalosporins are listed in Table 1.

The amounts of NMTT administered with each dose of the three cephalosporins were statistically significantly different; the NMTT doses were 6.66 \( \pm 0.46, 14.39 \pm 0.87, \) and 17.38 \( \pm 1.06 \) mg for cefoperazone, cefotetan, and cefmetazole.
TABLE 2. Pharmacokinetic parameters of NMTT following cefoperazone, cefotetan, and cefmetazole administration

<table>
<thead>
<tr>
<th>Drug</th>
<th>(C_{\text{max}}) ((\mu)g/ml)</th>
<th>(T_{\text{max}}) (h)</th>
<th>(\text{AUC}_{0-48}) ((\mu)g L(\cdot)h/ml)</th>
<th>(\text{CL}_{\text{R}}) (ml/min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cefoperazone</td>
<td>0.93 ± 0.47</td>
<td>14 ± 8.3</td>
<td>18.3 ± 5.85</td>
<td>122 ± 22.4</td>
</tr>
<tr>
<td>Cefotetan</td>
<td>0.83 ± 0.09</td>
<td>0.55 ± 0.10</td>
<td>5.38 ± 1.24</td>
<td>115 ± 20.2</td>
</tr>
<tr>
<td>Cefmetazole</td>
<td>0.99 ± 0.17</td>
<td>0.50 ± 0.00</td>
<td>3.17 ± 0.51</td>
<td>135 ± 38.3</td>
</tr>
</tbody>
</table>

* \(C_{\text{max}}\): Maximum concentration of drug in plasma; \(T_{\text{max}}\): time to maximum concentration of drug in plasma. Values are means ± standard deviation.
* No statistically significant difference.
* Significant difference between cefoperazone and cefotetan.
* Significant difference between cefoperazone and cefmetazole.
* Significant difference between cefotetan and cefmetazole.

respectively. On a milligram-per-milligram basis, the dose of NMTT ranged from 0.3 to 1.1% of the cephalosporin dose.

The NMTT pharmacokinetic parameters for each of the cephalosporins are shown in Table 2. The NMTT plasma concentration-versus-time profile following administration of each of the three cephalosporin is depicted in Fig. 1. The time to peak was extremely variable following cefoperazone administration and ranged from 0.5 to 24 h. In contrast, the times to peak following administration of cefotetan and cefmetazole were more consistent and averaged 0.55 and 0.50 h, respectively. The durations over which NMTT concentrations were detectable were dramatically different among the three cephalosporins. On average, NMTT concentrations were below the limit of detection 8, 24, and 36 h following administration of cefmetazole, cefotetan, and cefoperazone, respectively (Fig. 1). The average areas under the NMTT plasma concentration-versus-time curves from zero to the last measured concentration were significantly different among the three cephalosporins (cefoperazone > cefotetan > cefmetazole).

Table 3 shows the amount of NMTT recovered in the cumulative urine collection (0 to 72 h), the amount of NMTT administered, and the apparent amount of NMTT produced in vivo. The apparent amount of NMTT produced in vivo was calculated by subtracting the amount of NMTT administered from the amount of NMTT excreted in the urine and more precisely reflects the amount of NMTT produced in vivo and excreted unchanged in the urine. Apparent in vivo production and excretion of NMTT was significantly lower following cefmetazole and significantly higher following cefoperazone administration than with cefotetan. The urinary NMTT excretion profiles of the three agents were also markedly different (Fig. 2).

To correct for differences in the molecular weights and doses of the cephalosporins, the millimolar ratios of NMTT to the three parent cephalosporins were compared (Table 4). Statistically significant differences (\(P < 0.01\)) among the three agents were maintained with regard to the amounts of NMTT excreted, the NMTT doses, and the apparent amounts of NMTT produced in vivo. This millimolar transformation indicated that a 19-times-greater amount of NMTT was produced following cefoperazone administration than following cefmetazole administration.

**DISCUSSION**

The present study confirms many of the findings in our previous report (19). Apparently, NMTT is cleaved both in vitro and in vivo from parent cephalosporin molecules (19). In addition, the amount of NMTT cleaved from the cephalosporin is dependent on the agent (19).

When comparing in vitro productions of NMTT, we found that the amount of free NMTT available in the reconstituted vial was markedly lower in this study than in our previous investigation (19). On average, the amounts of NMTT administered with cefoperazone and cefotetan were 6.1 and 14.4 mg in the current study, compared with 15.2 and 22.1 mg in the previous study. The observed differences strongly suggest a lot-to-lot variation in the NMTT contents of the reconstituted vials and raise the potential of stability changes during storage of vials. In addition, the amount of NMTT administered with a cephalosporin dose is dependent on the pH of the reconstituted solution, the time between antibiotic preparation and administration, the agent, and the particular lot of the agent which is used (19, 20). It is important to assess the relative significance and clinical impact of these factors in future investigations.
TABLE 4. Molar ratios of NMTT to parent cephalosporins

<table>
<thead>
<tr>
<th>Drug</th>
<th>Molar ratio (mean ± SD)*</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>NMTT excreted</td>
</tr>
<tr>
<td>Cefoperazone</td>
<td>0.38 ± 0.017</td>
</tr>
<tr>
<td>Cefotetan</td>
<td>0.085 ± 0.017</td>
</tr>
<tr>
<td>Cefmetazole</td>
<td>0.062 ± 0.014</td>
</tr>
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</table>

* The differences between the values for cefoperazone and cefotetan, cefoperazone and cefmetazole, and cefotetan and cefmetazole are statistically significant.

Our previous and current investigations demonstrate that NMTT production in vivo is submaximal (19). If each molecule of NMTT was cleaved from its parent cephalosporin, the theoretical maximum productions of NMTT based on a 2.0-g dose would be 359.7, 403.5, 446.3, and 492.6 mg for cefoperazone, cefotetan, moxalactam, and cefmetazole, respectively. Thus, on a molecular basis, we would have predicted that cefmetazole would produce the greatest amount of NMTT in the current trial. This clearly was not the case and supports our previous contention that in vivo production of NMTT cannot be predicted on the basis of the in vitro stability of a cephalosporin (19). However, in vitro NMTT release was greatest with cefmetazole and least with cefoperazone. In vitro release was directly proportional to the amount of NMTT available to be cleaved from the parent compound. Thus, molecular structure indirectly influences in vitro formation of NMTT when time and pH remain constant, but these relationships must still be tested in vivo (19).

In our previous investigation, in vivo NMTT production was greater with cefoperazone than with cefotetan, while in vitro NMTT production was greater with moxalactam than with cefotetan and least with cefoperazone (19). The amounts of NMTT produced in vivo and in vitro in the current study differ from those of the previous study, partly because of longer urine collection times. However, the trends were maintained in that a greater amount of NMTT was produced in vivo with cefoperazone than with cefotetan. The results of this investigation indicate that cefmetazole produced the least amount of NMTT in vivo. Our results further support Lipsky’s hypothesis that the gastrointestinal tract is a primary site of cleavage for NMTT (7). Relative in vivo production of NMTT parallels biliary excretion patterns of the cephalosporins in that cefoperazone undergoes the highest degree of biliary excretion and was associated with the greatest release of NMTT in vivo. Additionally, the prolonged time to peak for NMTT in plasma following cefoperazone administration suggests that enterohepatic recycling influences the disposition of NMTT. In contrast, cefmetazole is primarily renally excreted and was associated with the lowest in vivo production of NMTT.

The mechanism by which NMTT is cleared from the body remains unknown. In vitro data suggest that NMTT which has been cleaved from the parent cephalosporin may be converted to an active byproduct via metabolism or undergo dimerization (8, 16, 17). This NMTT byproduct may subsequently inhibit vitamin K metabolism. Our determination of NMTT production reflects only the amount of NMTT produced in vivo and excreted unchanged. Theoretically, however, the amount of byproduct produced may directly relate to the amount of NMTT available. Thus, agents which produce minimal amounts of NMTT may correspondingly yield minimal amounts of the byproduct.

It has been hypothesized that differences in NMTT cleavage among the cephalosporins correspond to relative differences in their potential to cause antibiotic-associated hypoprothrombinemia (11, 13, 19). There is minimal information regarding the comparative incidences of hypoprothrombinemia among various antibiotics. However, it is well documented that patient risk factors are a major influence on the prevalence of coagulopathy (1, 5-9, 12). Malnourished patients who have marginal and/or depleted stores of vitamin K and receive an antibiotic containing the NMTT side chain are considered to be at greatest risk (1, 5, 9, 10, 12, 13).

Because of the complexity of patient populations and the varied clinical indications among the NMTT-containing antibiotics, there is a lack of comparative trials examining the relative incidence of hypoprothrombinemia caused by NMTT-containing cephalosporins. Grasela and coworkers evaluated the prevalence of hypoprothrombinemia associated with cefotetan versus that associated with non-NMTT-containing antibiotics (5). Overall, the incidence of hypoprothrombinemia was very low in the cefotetan treatment group (6.3%); in fact, it was highest in the patient population treated with an aminoglycoside plus an antianaerobic agent (8.2%). The incidence of hypoprothrombinemia observed with cefotetan was lower than that previously reported by Sattler et al. for cefoperazone (10) or by Baxter et al. for moxalactam (1). The low incidence of hypoprothrombinemia seen with cefotetan compared with that seen with cefoperazone and moxalactam probably reflects differences in the patient populations studied (1, 5, 10). Alternatively, it may be related to the lower amount of cleaved in vivo during cefotetan therapy than produced during cefoperazone therapy (19). If the latter hypothesis is true, then on the basis of our present study one would predict that cefmetazole would be associated with a lower incidence of hypoprothrombinemia than cefotetan. However, until conclusive comparative clinical trials evaluate the relative incidences of hypoprothrombinemia among NMTT-containing cephalosporins or the concentration-response relationship of NMTT in vivo is identified, the relative clinical importance of in vivo NMTT production (dose) will remain unclear.

LITERATURE CITED


