Effects of Lactulose and Neomycin on Urea Metabolism in Cirrhotic Subjects

FREDRICK L. WEBER, JR., KATHLEEN M. FRESARD, and BARBARA R. LALLY
Veterans Administration Medical Center and Department of Medicine, University of Kentucky Medical School, Lexington, Kentucky

In our previous studies of cirrhotic subjects lactulose caused a 25% decrease in the urea production rate associated with a decrease in urinary urea excretion and an increase in stool nitrogen. The decrease in the rate of urea production was an indirect measure of reduction in gut ammonia production. The present study was designed to determine if the poorly absorbed antibiotic neomycin had an additive effect in reducing ammonia production when administered in combination with lactulose. Six stable cirrhotic subjects received isonitrogenous diets during separate lactulose and lactulose + neomycin treatment periods. The addition of neomycin to a lactulose regimen caused a 17% reduction in the urea production rate that was quantitatively accounted for by a 70% reduction in the urea degradation rate. The intestinal urea clearance rate demonstrated a parallel reduction, indicating an inhibition of bacterial ureolysis. There was no evidence that neomycin altered the effects of lactulose since urinary urea excretion did not rise, fecal nitrogen remained high, and stools remained acidic. These results demonstrate that neomycin inhibited bacterial ureolysis when administered with lactulose while lactulose itself was metabolized and its individual effect on nitrogen metabolism persisted. Lactulose and neomycin, when administered together, had an additive effect in reducing gut ammonia production in cirrhotic subjects.

Both lactulose and neomycin are therapeutic agents with proven efficacy in the treatment of portal-systemic encephalopathy. With each drug clinical benefit had been linked to a reduction in arterial blood ammonia (1-3). However, it has been uncertain whether these drugs may be used together to produce additive effects in reducing the blood ammonia concentration. In most individuals the synthetic disaccharide lactulose is metabolized by intestinal flora, a process that can be monitored by the production of acid stools. Clinical efficacy and reduction in blood ammonia have been linked to bacterial metabolism of lactulose (2). In contrast, the poorly absorbed antibiotic neomycin has been thought to act by reducing ureolytic and putrefactive activity of the enteric microflora (4). Since neomycin kills bacteria while lactulose depends on intact bacterial metabolism for its beneficial effects, it might be considered inappropriate to use these drugs in combination. However, since the two drugs may interact with different bacterial populations, they could have additive effects in reducing intestinal ammonia production.

Previous studies have analyzed changes in the urea production rate to quantify changes in intestinal ammonia production. Lactulose has been shown to cause a mean reduction of 25% in the urea production rate associated with a reduction in urinary urea excretion and an increase in fecal nitrogen (5,6). On the other hand, antibiotics including neomycin have been shown to reduce the urea production rate by inhibiting urea degradation and hence, preventing the recycling of urea and ammonia nitrogen (7-9). In this study we have assessed the effects of combination therapy with lactulose and neomycin on gut ammonia production by measuring changes...
in urea production and degradation rates as well as intestinal urea clearance.

**Methods**

**Patients**

Six stable patients with biopsy-proven cirrhosis caused by alcohol were studied. Their ages ranged from 52 to 65 yr and their weights from 69 to 87 kg (mean, 76 kg). None of these patients had ascites, edema, encephalopathy, or gastrointestinal bleeding. They took no drugs during the study other than neomycin and lactulose. All patients denied alcohol ingestion for at least 6 mo before study; this was confirmed by family members. Conventional liver tests were either normal or mildly abnormal and remained stable throughout the study period. Initial values included serum glutamic oxaloacetic acid transaminase, 36 ± 6 IU/L (mean ± 1 SD; normal, 10–40); alkaline phosphatase, 98 ± 38 IU/L (normal, 30–110); total bilirubin, 1.3 ± 1.3 mg/dl (normal, 0.2–1.0); albumin 4.0 ± 0.5 g/dl (normal, 3.5–5.0). Only 1 patient had a prothrombin time 2 s longer than control. Serum creatinine and creatinine clearance were 1.1 ± 0.2 mg/dl and 84 ± 13 ml/min/1.73 M2, respectively, and did not change throughout the study period. Serum electrolytes were also normal and did not change.

All subjects gave written informed consent to participate in the study. The protocol was approved by the Human Investigations and Studies Committee of the University of Kentucky on January 22, 1979.

**Protocol**

Patients were studied under metabolic ward conditions. Diets were composed of 1 g protein/kg body wt and sufficient calories to maintain body weight. Weighed food items were taken from constant sources for each patient. Patients ate under observation and generally consumed their entire diet. Any uneaten food was reweighed. Two patients were studied during control, lactulose, and neomycin–lactulose periods while the other 4 patients were studied during lactulose and neomycin–lactulose periods only. During control periods patients received no drugs. Lactulose syrup (67% wt/vol) was initially given in an oral dose of 20 g/h until the first loose bowel movement and then in individualized doses (30–80 g/day) to produce 2–4 bowel movements per day. Neomycin in a dose of 4 g/day was subsequently added to the lactulose regimen. The order of treatment periods was not randomized because it was uncertain how long it might have taken for the colonic flora to have become reestablished if neomycin had been given during the first period. Individual study periods lasted from 8 to 10 days. The first 3 days were necessary for equilibration on a drug regimen and the remaining days for collection of stool (1–3 day collections), urine (24-h collections), and blood (daily). After 3 days patients reached a steady state in regard to blood urea concentration and urinary urea excretion. Urea production and degradation rates were determined on day 5, 6, or 7 of each study period according to the method of Walser and Bodenlos (7). After an overnight fast, patients were injected intravenously with approximately 5 μCi of sterile pyrogen-free [14C]urea at 8:30 A.M. They then continued to ingest their protocol diet. Urine and blood collections for determination of [14C]urea were carried out as previously described (5).

[14C]urea was determined in plasma and urine as total [14C] on a Packard Tri-Carb scintillation counter (Packard Instrument Co., Inc., Downers Grove, Ill.) using an external standard to correct for quenching. In urine and plasma samples taken from this type of study we and others have found no difference between the counts determined in total [14C] and counts determined in [14C] released by urease treatment (6,10). Total nitrogen was determined in neomycin tablets, selected diets, and stool and urine samples as previously described (5). Stool dry weight was determined on lyophilized specimens. Other chemical determinations were carried out on Technicon SMA-6 and SMA-12 instruments (Technicon Instruments Corp., Tarrytown, N.Y.).

**Data Analysis**

The principles and calculations employed in determining urea production and degradation rates have been previously described (5,7). The urea synthetic rate was determined by analysis of the logarithmic decline in plasma [14C]urea specific activity after injection of a known amount of [14C]urea. Urea synthesized in the body has two primary fates: excretion in the urine or degradation in the gut. Urinary urea was measured directly. This value has been termed the urea appearance rate when changes in the total body urea pool were added (11). However, in these patients there were no changes in the urea pool during individual study periods; hence, urea appearance was equal to urinary urea excretion. The urea degradation rate was determined as the difference between the urea production rate and the urea appearance rate. The extrarenal or intestinal clearance rate of urea was determined by dividing the urea degradation rate by the plasma urea concentration.

Data in the text and tables have been presented as the mean ± standard error of the mean. Statistical significance was determined by paired t-tests (12).

**Results**

**Urea Synthesis and Degradation**

In the 2 patients who were studied during a control period, lactulose caused a fall in the urea production rate, urea appearance rate, and urea pool as has been consistently seen in previous studies (5,6). When neomycin was added to lactulose in the current study there was a further reduction in the urea production rate that was entirely accounted for by 70% mean reduction in urea degradation (Table 1). Individual patients demonstrated a strong correlation between reductions in urea production and urea degradation (Figure 1). Neither the urea appear-
Table 1. Effects on Urea Metabolism after Neomycin Was Added to Lactulose

<table>
<thead>
<tr>
<th></th>
<th>Lactulose</th>
<th>Lactulose + neomycin</th>
<th>Change</th>
</tr>
</thead>
<tbody>
<tr>
<td>Urea production (mg N)^a</td>
<td>119 ± 10</td>
<td>102 ± 8</td>
<td>-17 ± 4^b</td>
</tr>
<tr>
<td>Urea appearance (mg N)^a</td>
<td>92 ± 8</td>
<td>94 ± 8</td>
<td>+2 ± 1</td>
</tr>
<tr>
<td>Urea degradation (mg N)^a</td>
<td>27 ± 4</td>
<td>9 ± 2</td>
<td>-18 ± 4^b</td>
</tr>
<tr>
<td>Plasma urea (mg N/dL)</td>
<td>14 ± 2</td>
<td>14 ± 3</td>
<td>—</td>
</tr>
<tr>
<td>Urea pool (mg N/kg)</td>
<td>78 ± 11</td>
<td>74 ± 13</td>
<td>-2 ± 3</td>
</tr>
<tr>
<td>Renal urea clearance (ml)^p</td>
<td>665 ± 65</td>
<td>695 ± 74</td>
<td>+30 ± 28</td>
</tr>
<tr>
<td>Intestinal urea clearance (ml)^p</td>
<td>182 ± 32</td>
<td>58 ± 15</td>
<td>-123 ± 24^c</td>
</tr>
</tbody>
</table>

^a Results are expressed per 24 hours per kilogram. ^b p < 0.01. ^c p < 0.005. N = nitrogen.

ance rate nor the urea pool changed, indicating that the effects of lactulose were not reversed, and that urea metabolism was not changing solely as a function of time in these subjects. The intestinal clearance of urea fell by 68% in parallel with the fall in the urea degradation rate (Table 1). The fall in intestinal urea clearance was explained by a reduction in the urea degradation rate and the absence of a change in plasma urea concentration.

Stool Analysis

In the 2 patients studied during a control period, stool pH showed a characteristic fall, associated with lactulose administration, when they were begun on the drug (Figure 2). In the other 4 patients who were initially begun on lactulose, fecal pH was also low. The administration of neomycin along with lactulose had no effect on fecal pH suggesting that there was ongoing bacterial metabolism of lactulose.

In spite of giving individualized oral doses of lactulose to produce 2–4 bowel movements per day, total stool weight was higher during the administration of both lactulose and neomycin (604 ± 66 g/day) than when lactulose was given alone (402 ± 37 g/day). In 3 patients it was necessary to lower the dose of lactulose after beginning neomycin therapy. In all 6 patients the dose of lactulose was 63 ± 5 g/day when given alone and 55 ± 5 g/day when given with neomycin. Fecal solids, which averaged 55 ± 4 g/day during lactulose administration, also increased significantly after the addition of neomycin to 74 ± 8 g/day (p < 0.05). However, when the weight of neomycin (4 g/day) was subtracted from fecal solid weight, there was no longer a significant increase in fecal solids. Similarly, the increase in fecal nitrogen excretion caused by neomycin was not significant when the amount of nitrogen contained in neomycin (0.38 g/day) was subtracted (Table 2).

Total Nitrogen Intake and Nitrogen Balance

There was enough variability in dietary nitrogen intake that the small amount of nitrogen contained in neomycin caused no significant increase in total nitrogen intake (Table 2). Urinary nitrogen excretion was unchanged when neomycin was added to lactulose, and there was no change in net nitrogen balance in spite of a small increase in fecal nitrogen excretion.

Discussion

In previously studied patients and 2 patients from the current study lactulose caused a consistent fall in the urea production rate, urea appearance rate,
Table 2. Effects on Nitrogen Metabolism of Lactulose and Lactulose + Neomycin

<table>
<thead>
<tr>
<th></th>
<th>Lactulose</th>
<th>Neomycin</th>
<th>Change</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nitrogen intake</td>
<td>158 ± 2</td>
<td>161 ± 1*</td>
<td>+4 ± 3</td>
</tr>
<tr>
<td>Urinary excretion</td>
<td>109 ± 10</td>
<td>108 ± 8</td>
<td>-1 ± 4</td>
</tr>
<tr>
<td>Fecal excretion</td>
<td>33 ± 3</td>
<td>38 ± 2*</td>
<td>+5 ± 1.5b</td>
</tr>
<tr>
<td>Balance</td>
<td>+15 ± 9</td>
<td>+16 ± 7</td>
<td>+1 ± 5</td>
</tr>
</tbody>
</table>

* Includes nitrogen contained in neomycin. Results are expressed in milligrams of nitrogen per 24 hours per kilogram.

b p < 0.05.

and urea pool (Figure 3). However, lactulose alone has not had any consistent effect on intestinal urea clearance. The results obtained from the 6 cirrhotic patients included in this study demonstrated that when neomycin was added to lactulose therapy there was a fall in gut ammonia production as assessed by a reduction in the urea production rate. This reduction in urea production was entirely accounted for by an inhibition of bacterial ureolysis as determined by reductions in both the urea degradation rate and the intestinal clearance of urea. Furthermore, there was no evidence that the effects of lactulose in reducing gut ammonia production were reversed by the administration of neomycin.

The changes in urea metabolism caused by neomycin were consistent with an interruption of the enterohepatic recycling of urea and ammonia. Hence, there was a reduction in the quantity of urea degraded to ammonia and, in turn, the quantity of urea resynthesized from ammonia. By inhibiting bacterial ureolysis, antibiotic therapy usually causes a reduction in the urea degradation rate and intestinal clearance of urea in both normal and uremic subjects. However, the urea pool and urinary urea excretion have not been found to change because the amount of circulating urea has not been altered (8,9). This relationship might not expect to hold if antibiotics significantly reversed deamination of dietary or endogenous amino acids, and, in patients with small intestinal bacterial overgrowth, broad spectrum antibiotics probably do reduce urinary urea excretion (9,13). In our study, the fall in the urea production caused by neomycin could be entirely accounted for by an inhibition of bacterial ureolysis. The increased catharsis caused by neomycin might have contributed to a reduction in ureolysis, but in a previous study, catharsis alone with magnesium sulfate had no effect on urea degradation (6).

The clinical effectiveness of lactulose and its effects on urea and nitrogen metabolism appear to depend on its capacity to be metabolized by the intestinal flora. Other cathartics have generally not been effective in treating portal-systemic encephalopathy, and in contrast to lactulose, the saline cathartic magnesium sulfate has no effect on urea metabolism except for a slight reduction in the urea pool (6). There was, however, no indication that neomycin inhibited bacterial metabolism of lactulose in our 6 patients. Fecal pH remained low after the introduction of neomycin indicating that there was ongoing production of organic acids from the catabolism of lactulose. In addition to stool acidification, a repeatedly observed effect of lactulose has been a reduction in urinary urea excretion associated with an increase in fecal nitrogen excretion (5,6).

We have considered these changes to be consistent with a reduced bacterial production of urea precursors such as ammonia from nitrogen-containing compounds in the colonic lumen. In the patients described in this study, a rise in urinary urea excretion or a fall in fecal nitrogen excretion might have indicated that neomycin had reversed the effects of lactulose. However, no such changes occurred after the addition of neomycin.

![Figure 3. Effects of lactulose on urea production, urea appearance, urea pool, and intestinal urea clearance in patients previously studied (●) (n = 12) (5,6) and in 2 patients from the current study (○). p-Values indicate significant changes by paired t-test. NS = no significant change, C = control period, L = lactulose period.](image-url)
The results of this study do not doubt relate to the heterogeneity of the intestinal microflora. Certain intestinal bacteria such as Bacteroides species can metabolize lactulose (14) but are generally resistant to neomycin. Other ureolytic bacteria are often sensitive to neomycin (15). Hence the additive effects of these two agents in reducing gut ammonia production probably occurred because the effect of each drug was mediated by different bacterial populations.

Several other observations have suggested that these two drugs might continue to act independently when used in combination. Conn found that neomycin caused fecal pH to become neutral in 3 of 11 patients who had acidic stools after lactulose (16). The other 8 patients had either a slight rise or fall in fecal pH indicating that neomycin did permit ongoing bacterial synthesis of organic acids from lactulose. Gilat et al. (17) found that neomycin caused no inhibition of lactulose metabolism by bacteria as assessed by breath hydrogen production. Furthermore, Murphy and Calloway (18) found that neomycin had no consistent effect on intestinal gas production after bean ingestion, demonstrating that neomycin permitted ongoing bacterial metabolism of another carbohydrate. Finally, Pirotte et al. (19) reported that a combination of neomycin and lactulose was more effective than either agent alone in reducing the blood ammonia concentration in 9 cirrhotic patients.

Because of the small number of patients included in our study, we cannot provide any assurance that experience with a larger population will not disclose a definite group of patients who fail to benefit from the combined use of lactulose and neomycin. Data obtained by Conn suggest that 27% of patients would have a favorable clinical effect if the drugs were used in combination (16). Presumably such patients would lack lactulose metabolizing bacteria that were resistant to neomycin. If neomycin were to be given to a patient receiving lactulose, it would be important to monitor stool pH and/or blood ammonia in addition to the patient’s clinical status to determine whether one was justified in continuing both drugs.

Further data may be needed to evaluate the clinical efficacy of a combined regimen of lactulose and neomycin in the treatment of portal-systemic encephalopathy. However, this study establishes a rationale for the combined use of these drugs.

References