EFFECT OF EXPERIMENTAL ACUTE RENAL FAILURE ON INTESTINAL BARRIERS TO DRUG ABSORPTION

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Intestinal absorption of poorly-absorbable sulfanilic acid was investigated in rats with acute renal failure by an in situ loop method. The acute renal failure was induced by an intramuscular injection of HgCl₂ or 50% glycerol, or by 5/6 nephrectomy. The mean blood urea nitrogen in the experimental group at the time of evaluation of intestinal absorption was significantly higher than in the control groups (normal or laparotomized). Absorption of sulfanilic acid by the small intestine was significantly increased in all renal failure groups examined, but it was unchanged in the laparotomy group. Reduction of barrier function in the intestinal mucosa during renal failure is indicated.

KEYWORDS——intestinal absorption; sulfanilic acid; acute renal failure; intestinal barrier function; rat

In patients with renal failure, the pharmacokinetic picture is often altered, not only by reduction of renal excretory function, but also by changes in the distribution and the metabolism.¹ Studies on the absorption of nutrients, such as glucose² and amino acids,³ ⁴ showed that even the absorption step is influenced during renal failure. Further, morphological or enzymical abnormalities in the intestine have occurred in chronic renal failure.⁵ However, there is little information available on the influence of impaired renal function on the gastrointestinal absorption of drugs. If drug absorption changes in the disease state, dosage adjustment may be required. We have, therefore, studied the effect of experimental acute renal failure on the barrier function of rat small intestine, by using poorly-absorbable sulfanilic acid as a model drug.

Acute renal failure was induced in male Wistar rats weighing 180-220 g by an intramuscular injection of nephrotoxic substances: HgCl₂ (5 mg/kg)⁶ or 50% glycerol (10 ml/kg).⁷ As a method that does not use nephrotoxic substances, 5/6 nephrectomy, i.e. the removal of the upper and lower poles of the left kidney with contralateral total nephrectomy, was also performed.⁸ Control animals were sham operated (laparotomized). Absorption experiments were performed at 24 h after glycerol injection or at 48 h after HgCl₂ injection or 5/6 nephrectomy. The absorption from whole small intestine was investigated by an in situ loop method.⁹ Five ml of sulfanilic acid solution (pH 6.5 isotonic sodium phosphate buffer solution at the concentration of 1 mM) was administered into the loop. After 1 h,
Table I. Blood Urea Nitrogen (BUN) and Intestinal Absorption of Sulfanilic Acid in Rats with Experimental Acute Renal Failure

<table>
<thead>
<tr>
<th>Group</th>
<th>BUN (mg/100ml)</th>
<th>% Absorbed in 1 h</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal(6)</td>
<td>18.0 ± 1.8</td>
<td>18.9 ± 1.5</td>
</tr>
<tr>
<td>HgCl₂-treated(7)</td>
<td>132.1 ± 21.7**</td>
<td>23.7 ± 0.8*</td>
</tr>
<tr>
<td>Glycerol-treated(4)</td>
<td>71.2 ± 18.0**</td>
<td>27.4 ± 1.3**</td>
</tr>
<tr>
<td>5/6 Nephrectomized(6)</td>
<td>32.4 ± 3.8*</td>
<td>29.9 ± 1.1**</td>
</tr>
<tr>
<td>Laparotomized(3)</td>
<td>18.1 ± 1.7</td>
<td>20.2 ± 0.4</td>
</tr>
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Results are expressed as the mean ± s.e. and number of rats in parentheses.
* p < 0.05, ** p < 0.01, compared with each control.

the amount of drug remaining in the luminal solution was determined spectrophotometrically. The absorption percentage was calculated from the difference between the administration dose and the remaining amount. Results are summarized in Table I.

After the treatments described above, blood urea nitrogen (BUN) was significantly increased. In the nephrectomy group, the increase of BUN was less than in the treated groups with HgCl₂ or glycerol. This may be caused by the difference in the way renal failure was induced and the short period after the operation (48 h). The morphological examination confirmed the abnormalities of the renal tissue, especially in the proximal tubule, in both the HgCl₂-treated and the glycerol-treated groups.

Small intestinal absorption of sulfanilic acid was significantly increased in all renal failure groups examined, but it was unchanged in the laparotomy group. Since the absorption of a drug with a low permeability is independent or nearly independent of intestinal blood flow, the increased absorption indicates an increase in membrane permeability, i.e., a reduction of barrier function of small intestinal mucosa during renal failure. Since results were similar in three experimental renal failure models, it appears quite likely that the increased absorption comes not from the direct effect of the nephrotoxic substances or other artificial factors, but from the renal failure states.

McDermott et al.11) reported that epithelial cell division was suppressed in renal failure. We also found morphological abnormalities of rat small intestinal mucosa during renal failure; sections stained with hematoxylin and eosin showed an expansion of lymphatic vessels resulting in hypertrophy of villi, and formation of stromal edema beneath the epithelial cell line. Furthermore, periodic acid Schiff-stained sections showed an increase of goblet cells filled with mucus. In the HgCl₂-treated group, mucus secretion was strikingly high, suggesting catarrh. These conditions may relate to the reduction of the intestinal barrier function.

Variation in the bioavailability results in high variation in the pharmacologic response to high potency drugs. Since drugs eliminated predominantly through the kidneys tend to be retained in the body during renal failure, the effect of variation in the absorption should multiply in these patients. Therefore,
patients with renal failure, careful drug dosage adjustment is required to obtain adequate therapeutic blood levels without increased toxicity, especially for high potency drugs with low bioavailability. Our experimental results suggest the reduction of intestinal barriers to drug absorption in renal failure. However, there was no significant correlation between the absorption of sulfanilic acid and BUN. It is an important subject for a future study to find an indicator of the extent of intestinal damage. Additional studies are in progress to examine the change in the intestinal function to absorb drugs with different absorbabilities including drugs transported by carrier-mediated mechanisms.

REFERENCES

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