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Clinical Pharmacology of Drugs Used in the Treatment of Patients with Peptic Ulcer

Gyula Mozsik and Imre Szabó

2.1. Primary (genuine) and secondary (associated with stress, sepsis, stroke, pulmonary and liver diseases, burn, trauma) Peptic Ulcer Diseases (PUD)

The criteria of diagnosis and treatment of peptic ulcer disease (PUD) have been changed significantly in the past 40–50 years. At the beginning of this period, peptic ulcer disease was only diagnosed by X-ray examination. Currently, gastrofiberoscopy has also become a common practice in medical diagnosis.

Clinically, the PUD was divided into two groups: “primary” and “secondary”. The diseases in the “secondary group” associated with a chronic liver, lung, brain damage or burn; however, no obvious reasons for the PUD could be provided as the etiological factor and these forms of the diseases were named as “genuine diseases.”

The presence of two main factors was emphasized in the development of gastroduodenal ulceration: the hyperacidity and hypoxemic damage of gastroduodenal mucosa.

There was a significant contradiction between these mentioned factors, namely the gastric hyperacidity associated with the increased gastric mucosal blood flow (GMBF) and ulcer development, and it was practically impossible to understand the development of gastroduodenal mucosal damage based on the increased gastroduodenal mucosal blood flow (Bowen and Fairchild, 1984).

2.2. Medical treatment with anticholinergic agents in patients with gastric and duodenal ulcers

Our scientific attention focused on the medical treatment of patients with peptic ulcer diseases from 1960 onwards.
Our original aim was to create a complete scientific methodology for the evaluation of efficiencies of different drugs (previously, parasympatholytic agents, antacids) in the field of gastroenterology. We have to emphasize that during 1960–1970, no clinical pharmacology existed.

We wanted to introduce into the conventional human clinical pharmacological approaches using that we were established in our group at Debrecen, Hungary, in the field of gastroenterology (in the period of 1962–1970).

Our interest focused on changes of gastric secretory responses in patients with duodenal ulcer (DU) during chronic atropine treatment. In the earlier days, only atropine and scopolamine were used for treating DU patients in whom we studied the presence of DU using X-ray examination (fiberoptic endoscopy did not exist earlier).

We studied (at present) the changes of gastric acid secretory responses in patients with duodenal ulcer before and after a classical medical treatment. We measured the gastric basal acid output (BAO) and secretory responses to superluminal (but submaximal) dose of histamine.

We were surprised to find that the patients with DU were cured by a chronic (2–4 weeks) treatment with atropine. However, the gastric secretory responses in patients were not decreased (Mózsik et al., 1965c; Mózsik and Jávor, 1966 a, b; Mózsik et al., 2011) (see Table 1).

<table>
<thead>
<tr>
<th>Examined Parameters</th>
<th>Before</th>
<th>After</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>A</td>
<td>B</td>
</tr>
<tr>
<td>Volume of gastric juice (mL/h)</td>
<td>180±32</td>
<td>175±37</td>
</tr>
<tr>
<td>H⁺ output (mEq/h)</td>
<td>0.97±0.02</td>
<td>1.49±0.2</td>
</tr>
</tbody>
</table>

Table 1. Gastric secretory responses before and after (3 × 0.3 mg orally given for 2–4 weeks) a chronic atropine treatment without and with histamine (A and B, respectively) (0.5 mg subcutaneously injected). The results were expressed as means ± SEM in ten patients. P-values between the identical parameters before and after chronic atropine treatments are not significant. [Mózsik et al., 1965c; 1966b (with kind permission).]

These results showed that duodenal protection could be obtained by independent effects on acid secretion: a phenomenon that defied the earlier well-established view, “no acid, no ulcer” originally pioneered by Lester Dragstedt in 1943 (Gustafson and Welling, 2010).

Following these observations, the acute inhibitory effect of atropine was tested on the gastric acid secretion before and after a chronic atropine treatment. Here, we observed that the extent of acute inhibitory effect of atropine on patients’ acid secretion decreased significantly after a chronic treatment (Mózsik et al., 1965c; Mózsik and Jávor 1966b; Mózsik et al., 2011).
<table>
<thead>
<tr>
<th>Examined Parameters</th>
<th>Before</th>
<th>After</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>A</td>
<td>B</td>
</tr>
<tr>
<td>Volume of gastric juice (mL/h)</td>
<td>125±10</td>
<td>137±10</td>
</tr>
<tr>
<td>$\text{H}^+$ output (mEq/h)</td>
<td>0.25±0.08</td>
<td>0.4±0.1</td>
</tr>
</tbody>
</table>

Table 2. Changes in the gastric secretory responses before and after (3×0.3 mg orally given for 2–weeks) a chronic atropine treatment without and with histamine (A and B, respectively) (0.5 mg subcutaneously injected) administration in eight patients. The results were expressed as means ± SEM. $P$-values between the identical parameters before and after a chronic atropine treatment: $P < 0.05$. [Mózsik et al., 1965c; 1966b (with kind permission).]

Figure 1. Decreased inhibitory effect of atropine (1 mg sc.) before (A) and after (B) chronic atropine treatment in patients with peptic ulcer disease ($n=8$; means ± SEM). The results are expressed in percentage of their control. [Mózsik, Szabó, Czimmer: Curr. Pharm. Des. 17: 1556–1572, 2011 (with kind permission).]

2.3. Clinical Pharmacology of anticholinergic agents in patients with peptic ulcer disease (measurements of anticholinergic agents in the sera, urine in patients with duodenal ulcer)

It was hard to understand our previously demonstrated results obtained with application of atropine treatment in patients with duodenal ulcer because these results contradict the international experts’ opinions. We assumed that:

1. The atropine will not absorb from the gastrointestinal tract owing to some reasons (e.g., some pharmaceutical industrial problem(s) appeared during the drug pharmaceutical production);
2. Even if the atropine absorbs well, some other unknown pharmacological event (such as tolerance) will appear during a chronic (classical) atropine treatment.
To evaluate these questions, we have to establish the real basis of clinical pharmacology. Therefore, we have to provide a good and scientific possibility to bring about different answers for our questions.

In the first step, the concentration of anticholinergic agents was measured by sera and urine bioassay (using isolated guinea-pig ileum for biological titration of parasympatholytic drugs in Magnus vessel) of patients. The absorption, metabolism and urinary excretion of parasympatholytics were studied after chronically applied parasympatholytic treatments (Győrffy et al., 1964; Jávor et al., 1965; 1967; Mozsik, 1969a; Mozsik et al., 1965 a, b; 1967d; Mozsik and Jávor, 1966 a, b, c; 1968a).

The atropine absorbed well from the gastrointestinal tract (during 4–5 hours), and it was proved by titration of atropine in the sera and urine of patients. These observations were carried out in the same patients when the same doses of atropine were given orally or subcutaneously injected. It was clear that the absorbed quantities of atropine were the same (given in the same doses), indicating that the oral/parenteral ration of atropine absorption is equal to 1.0. Furthermore, when we carried out these observations, we found the same results (with respect to the absorption and excretion of atropine) in the treated patients.

Since we had classical clinical pharmacological methods (e.g., detection of small doses of atropine in the serum and urine of treated patients), we were able to exclude any changes of absorption in gastrointestinal tract, metabolism and urinary excretion of atropine as a consequence of the effects of chronic atropine treatment (Mózsik et al., 1966 a, b, c; 1968; 1969 a, b, c, d, e, f; Mózsik, 1969a).

Later, we observed the development of tolerance along with the development of “pharmacological denervation supersensitivity” (e.g., the efficiencies of drugs used in the treatment of patients decreased significantly). These phenomena exist together (Mózsik et al., 1967a; Mózsik and Jávor, 1968 a, b) in the background of unchanged gastric acid secretion during a chronic atropine treatment in DU patients. It was also interesting to note the development of tolerance to atropine and the disappearance of pharmacological denervation phenomena in 6–10 days after cessation of atropine treatment (Mózsik et al., 1965b; Mózsik and Jávor, 1968b; 1969; Mózsik, 1969a). The development of tolerance to atropine does not represent a specific phenomenon related to atropine (during a chronic atropine treatment) because the development of tolerance was found with other parasympatholytics, which were not used in the medical treatment (Mózsik and Jávor, 1969).

The results of the clinical pharmacological studies proved the following main points:

1. No change was obtained in the gastric acid secretion during a chronic anticholinergic treatment;
2. The gastroduodenal ulceration healed during this time period;
3. The results of the clinical pharmacology could not provide an obvious explanation of how the gastroduodenal ulceration was healed without any changes in gastric secretory responses (Mózsik et al., 1965b; 1967a; Mózsik and Jávor, 1966b; 1968 a, b; 1969; Mózsik, 1969a).
This clinical pharmacological methodology was applied in the medical evaluation of different anticholinergic agents (drugs) before their clinical applications.

Recently, the pharmacological basic research offered a possibility to introduce new anticholinergic agents into the medical practice. The experts working in the field of experimental pharmacology showed that the actions of these anticholinergic agents can be enhanced on the autonomic nervous system by the changes in their chemical structures (perhaps by the production of quaternary ammonium compounds instead of only tertiary quaternary ammonium compounds) (Gyermek, 1951; 1953; Gyermek and Nádor, 1952; 1953 a, b; György et al., 1961).

The Gastropin® is one of the most representative quaternary ammonium compounds, which was introduced into the medical treatment in the 1960s. We were clearly able to prove that the Gastropin® does not absorb from the gastrointestinal tract. We were not able to detect any drug levels in the serum and urine of patients when the patients were orally given 1000 pills; however, these parameters were well detectable after it was injected in the same patients.

The established clinical pharmacological methods were widely used in the evaluation of different anticholinergic agents (Mózsik, 1969a).

Many clinical pharmacological studies (from human phase I to III) were carried out by our work team who were working on different drugs [(tertiary amine, oxyphen cylamine), muscarinic receptor blocking (gastrozepin), histamine₂ receptor blocking (first to fourth generation), proton pump inhibitors and other components] for patients with peptic ulcer (Mózsik et al., 1965b; Mózsik, 1969a; Jávor et al., 1967; Garamszegi et al., 1997; Nagy et al., 1997; Tárnok et al., 1979, 1997).

2.4. Comparative clinical pharmacology of anticholinergic drugs

Different clinical pharmacological studies were carried out in patients with peptic ulcer to compare the detectable concentrations in the sera, excretion in the urine and bile, inhibitory actions on the salivary secretion, gastric acid secretion, necessary dose rate to decrease glandular secretion and gastric motility, detectability of drug to proteins and the excretion time. The results are summarized in Table 3.

<table>
<thead>
<tr>
<th>Oral – parenteral dose rate</th>
<th>Atropine</th>
<th>Novatropine</th>
<th>Isopropamide</th>
</tr>
</thead>
<tbody>
<tr>
<td>Detectable in serum</td>
<td>+</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>Detectable in urine</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Detectable in saliva</td>
<td>-</td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td>Detectable in bile</td>
<td>-</td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td>Necessary dose rate to decreased glandular secretion and the gastric motility</td>
<td>1 : 2</td>
<td>1 : 2</td>
<td>1 : 2</td>
</tr>
<tr>
<td></td>
<td>Atropine</td>
<td>Novatropine</td>
<td>Isopropamide</td>
</tr>
<tr>
<td>--------------------------</td>
<td>----------</td>
<td>-------------</td>
<td>--------------</td>
</tr>
<tr>
<td>Inhibitory effect on salivary secretion</td>
<td>+</td>
<td>++</td>
<td>-</td>
</tr>
<tr>
<td>Inhibitory effect of gastric secretion</td>
<td>+</td>
<td>++</td>
<td>++</td>
</tr>
<tr>
<td>Inhibitory effect of gastric emptying in decreasing dose of glandular secretion</td>
<td>-</td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td>Duration of inhibitory effect on the salivary secretion</td>
<td>3-4 hours</td>
<td>6-8 hours</td>
<td>10-15 hours</td>
</tr>
<tr>
<td>Excretion in urine up</td>
<td>3-4 hours</td>
<td>6-8 hours</td>
<td>10-15 hours</td>
</tr>
<tr>
<td>detectable protein binding of the drug in serum</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>


Figure 2. The schematic presentation of the measured serum levels of different parasympatholytic drugs in peptic ulcer patients. The ordinate shows the level of parasympatholytic drugs (toxic, effective and ineffective); the abscissa demonstrates the time after administration of these drugs. a: atropine; N: Novatropine; I: isopropamide. [Mózsik, Vizi, Jávor: Recent Advances in Gastroenterology. The 3rd World Congress of Gastroenterology, Tokyo, 1967, 681–683 (with kind permission).]
2.5. Clinical evidence of the existence of gastrointestinal protection differs from the decrease of gastric acid secretion (Gastric cytoprotection)

The results of our observation of chronic atropine treatment in DU patients were given in detail previously.

In 1978, we found that the GI anti-ulcer effects of atropine, cimetidine and carbenoxolone were superior to placebo in a multiclinical, randomized, prospective and comparative study in DU patients. However, no significant difference was obtained in the beneficial effects of atropine versus cimetidine versus carbenoxolone (Tárnok et al., 1979). Since carbenoxolone has no inhibitory action on the gastric acid secretion in DU patients, the ulcer-healing effects (due to stimulation of mucus) could be considered independent of any effects on gastric acid secretion.

Thus, these clinical observations during 1960–1970 were performed before the classical concept of “gastric cytoprotection” was formulated and published by André Robert (Robert et al., 1979).

![Figure 3. A prospective multiclinical study comparing the effects of placebo, carbenoxolone, atropine and cimetidine in patients with duodenal ulcer (4 weeks' study). [Tárnok et al., Drugs Exp. Clin. Res. 5: 157–166, 1979 and Mózsik, Szabó, Czimmer, Curr. Pharm. Des. 17: 1556–1572, 2011 (with kind permission).]

Our clinical pharmacological studies (1965) (Mózsik et al., 1965b; 1967 a, b, c, d; Mózsik and Jávor, 1968 a, b; Mózsik, 1969a; Tárnok et al., 1979) as well as randomized, prospective, multiclinical and comparative studies (1978) are clear even now in retrospect that we had been observing acid-independent gastroduodenal protection with atropine and other drugs before André Robert had defined the existence of “gastric cytoprotection” (Mózsik, 2010; Mózsik et al., 2011).

During 1965–1970, the existence of “gastric cytoprotection” was not reported; conversely, the clinical importance of gastric acid secretion had only been emphasized. Chaudhury and Jacobson (1978) were the first to indicate that the gastric mucosal damage could be prevented without inhibition of gastric secretion.

The existence of “gastric cytoprotection” has been widely accepted after the work of Robert et al. (1979) in animal experiments. The clinical applicability of gastric cytoprotection was later
accepted for patients with gastroduodenal ulcer (with the exception of our previously carried out observations in DU patients).

2.6. Randomized, multiclinical, prospective and multicentric study of treatment of chronic gastric ulcer patients with vitamin A

Later, we demonstrated in multiclinical, multicentric, prospective and randomized study the ulcer-healing effect of vitamin A (as scavenger component) in patients with gastric ulcer (Patty et al., 1982; 1983). However, no gastric acid inhibitory action of the vitamin A exists in humans (Jávor et al., 1983 a, b; Mózsik et al., 1986; 2001; 2005; 2007; Rumi et al., 2001 a, b).

Fifty-six patients with chronic gastric ulcer were examined for this multiclinical, multicentric, randomized and prospective study (Patty et al., 1982; 1983).

The patients were divided into three groups: group A (16 patients) received only antacids; group B (18 patients) were treated with antacids plus vitamin A (3 × 50,000 IU orally) and group C (22 patients) received antacids, vitamin A (3 × 50,000 IU orally) and cyproheptadine (Peritol®). The observations were carried out in 4 weeks’ time.

Endoscopic measurements, and clinical and laboratory parameters were carried out at the beginning and at the end (2nd and 4th week) of the treatment of these patients (Figure 4).

The parameters in Figure 4 help us to evaluate the different objective (planimetric measurement of ulcer sizes, presence or absence of gastric ulcer – at the beginning and end of different treatments – and states of ulcer) and subjective (changes in complaints of patients and...
consumption of antacids) events of the process of ulcer healing (including the possible roles of drug actions). The obtained results are summarized in Figures 5–8.

The dynamism of the ulcer healing can be scientifically studied by the changes of ulcer sizes at 2 and 4 weeks after beginning the treatment (Figure 8). It was surprising to note that the healing rate differed significantly at 2 weeks; however, this value was the same at 4 weeks.

![Figure 5. Changes in the antacid consumption in the different groups of patients with chronic gastric ulcer. [Patty et al., Lancet II, 872, 1982; Int. J. Tiss. React. 5: 301–307, 1983 (with kind permission).]](image)

![Figure 6. Changes of gastric ulcer indices in patients treated with antacids (A); antacids plus vitamin A (B) and antacids, vitamin A and Peritol® (C) during 4 weeks of treatment. [Patty et al., Lancet II, 872, 1982; Patty et al., Int. J. Tiss. React. 5: 301–307, 1983 (with kind permission).]](image)
2.7. Comparative clinical pharmacology of “cytoprotective” and “anti-secretory” drugs (multiclinical, randomized, prospective and multicentric studies) in patients with chronic gastric and duodenal ulcers

Our work team participated in the clinical pharmacological studies of peptic ulcer patients (including different international studies as well as ours). After our previously performed studies, our attention focused on the results of clinical pharmacological studies with “cytoprotective” and “anti-secretory” drugs in patients with chronic gastric and duodenal ulcers.

In this subchapter, we summarized the results of clinical pharmacological studies of 441 chronic gastric and duodenal ulcers. The patients treated with nonsteroidal, anti-inflammatory drugs, steroids, antihypertensive drugs (e.g., Reserpine) and those who underwent some stress, burns or trauma were excluded from this comparative study. These patients were divided into different groups and were treated with different drugs: placebo (calcium carbonicum, magnesium trisilicate and sodium bicarbonate in equal portion), atropine (1.0 mg/os), cimetidine (1000 mg/day orally), ranitidine (300 mg/day orally), famotidine (80 mg/day orally), pirenzepine (150 mg/day orally), sucralfate (1000 mg/day orally), vitamin A (3 × 50,000 IU/day orally) alone or in combination with cyproheptadine chloratum (3 × 4 mg/
day orally), DE-NOL (3 × 5 mL/day orally) and Tisacid® (Al–Mg–antacidum 3 × 1 g/day orally). The antacids in composition mentioned above were applied with the so-called active compounds. Twenty patients were allocated into each group. The treatments were carried out for 4 or 6 weeks. (These results are reused with the permission of Wiley publisher.)

Endoscopy (estimation of ulcer size), laboratory measurements (blood count, urine, kidney and liver functions), pH status, medical examinations, summed pain score (expressed in percentage of original values) and antacid consumption were evaluated at the beginning, during 2nd, 4th and 6th week (if the treatment extends) and after the treatment.

The aims of this study are as follows:

1. To compare the efficiencies of ulcer treatments by cytoprotective (Tisacid®, sucralfate, DE-NOL and vitamin A) and anti-secretory (atropine, pirenzepine, cimetidine, ranitidine, famotidine) drugs in a short-term study (4–6 weeks);
2. To evaluate the dynamism of ulcer healing in unhealed gastric and duodenal patients;
3. To evaluate the summed pain score and antacid consumption in GU and DU patients;
4. To compare the different results (ulcer healing, laboratory parameters, summed pain score and antacids) obtained in healed and unhealed GU and DU patients.

Figure 8. Dynamism of ulcer-healing effect of vitamin A in patients with chronic gastric ulcer, indicating the changes of ulcer size in unhealed patients (in 4 weeks of treatment). [Patty et al., Lancet II, 872, 1982; Patty et al., Int. J. Tiss. React. 5: 301–307, 1983 (with kind permission).]
<table>
<thead>
<tr>
<th>Treatment</th>
<th>Number of Patients</th>
<th>Number of Unhealed Patients (%)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antacid</td>
<td>40</td>
<td>30(75)</td>
<td>-</td>
</tr>
<tr>
<td>Al-Mg-hydroxy- Carbonate (Tisacid®)</td>
<td>15</td>
<td>10(66.7)</td>
<td>NS</td>
</tr>
<tr>
<td>Vitamin A</td>
<td>18</td>
<td>11(61.1)</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Vitamin A and cyproheptadine</td>
<td>22</td>
<td>14(63.9)</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>DE-NOL</td>
<td>16</td>
<td>5 (31.2)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Sucralfate</td>
<td>19</td>
<td>14(73.7)</td>
<td>NS</td>
</tr>
<tr>
<td>Gastrozepine</td>
<td>16</td>
<td>9 (56.2)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Cimetidine</td>
<td>30</td>
<td>8 (26.7)</td>
<td>&lt;0.01</td>
</tr>
</tbody>
</table>

Table 4. Changes in the incidence of gastric ulcer (GU) healing during 4 weeks of treatment with different groups of patients compared with antacid. The numbers in parentheses are calculated in percentage. NS: not significant [Mózsik et al., J. Gastroenterol. Hepatol 9: S88–S92, 1994 (with kind permission)].

![Figure 9](attachment:image.png)

Figure 9. Changes in ulcer-healing rate during the different therapies in patients with chronic gastric ulcer (4 weeks). The results are expressed as means; n indicates the number of patients. P-values between the groups treated with antacids (placebo) and different groups. *: P < 0.05; **: P < 0.01; NS: not significant. [Mózsik et al., J. Gastroenterol. Hepatol 9: S88–S92, 1994 (with kind permission).]
Table 5. Changes in the incidence of duodenal ulcer healing during 4 weeks of treatment in different groups of patients compared with antacid. The numbers in parentheses are calculated in percentage. [Mózsik et al., J. Gastroenterol. Hepatol 9: S88–S92, 1994 (with kind permission).]
Figure 11. Changes in ulcer-healing rate in chronic duodenal ulcer patients treated with different drugs. $P$-values are between antacid (placebo) and treated groups at 4 and 6 weeks. *: $P < 0.05$; **: $P < 0.001$; NS: not significant. [Mózsik et al., J. Gastroenterol. Hepatol 9: S88–S92, 1994 (with kind permission)].

Figure 12. Changes in ulcer size in patients with incompletely healed duodenal ulcer after 4 weeks of treatment. Ulcer size before treatment = 1. [Mózsik et al., J. Gastroenterol. Hepatol 9: S88–S92, 1994 (with kind permission).]
2.8. General conclusion(s) of clinical pharmacological studies in patients with peptic ulcer

Returning the results of our earlier clinical pharmacological studies in patients with duodenal ulcer (see before), our final conclusion was that we have no any correct knowledge on the principle biochemical cellular and extracellular changes (mechanisms) are present in the keeping the normal homeostasis of the GI mucosa, and in time of development of GI mucosal damage and protection neither in animal experiments nor in humans (patients).

In addition to these, the discovery of “gastric cytoprotection” represented a new challenge to us in answer to the scientific problem mentioned above.

The results of these observations helped us to start a new scale of examinations in the field of peptic ulcer disease. We wanted to start with biochemical examinations in this field, but, unfortunately, nobody worked on it. Consequently, we have to learn the principal points of the general biochemical research to introduce it into the field of peptic ulcer research.

We have to emphasize that scientific problems and their knowledge have been changing over the past few decades, and many new scientific results are published.

Four well-known scientists were awarded the Nobel Prize [Jens Christian Skou (Department of Physiology, Aarhus University, Denmark) in chemistry, 1997; Earl W. Sutherland (Department of Physiology, Vanderbilt University, Nashville, TN, USA) in physiology (medicine), 1971; and Barry James Marshall and J. Robin Warren (Royal Perth Hospital, Australia) in physiology (medicine), 2005]. Their results inspired us to study these fields in our peptic ulcer research in animals and humans.

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Membrane-bound Atp-dependent Energy Systems and the Gastrointestinal Mucosal Damage and Protection