Overuse of acid suppressant drugs in patients with chronic renal failure

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Abstract
Background. Patients with chronic renal failure (CRF) have a high prevalence of gastrointestinal symptoms. The use of acid suppressive therapy (AST) in these patients is unexplored. We assessed the use of and indication for AST in CRF patients and compared them with hospitalized patients and patients with another chronic disease.

Methods. A total of 293 patients with CRF were compared with 261 hospitalized patients and 181 patients with another chronic disease. Information about AST, endoscopic investigations and indication for therapy were obtained by medical records and patient interviews.

Results. The use of AST was higher in CRF patients (41%, \(P < 0.001\)) compared with hospitalized patients (13%) and patients with a chronic lung disease (18%), but similar in patients with a rheumatic disease (34%). Inadequate use of AST was high in CRF patients (63%) and hospitalized patients (81%), but lower in patients with another chronic disease (32%, \(P < 0.01\)). Endoscopic investigations were performed in 41–46% of the patients. More than 90% of AST consisted of proton pump inhibitors (PPIs).

Conclusion. The majority of CRF patients had an inadequate indication for AST. Endoscopy seemed to be underused in these patients. PPIs were the dominating acid suppressive drug.

Keywords: acid suppressive therapy; chronic renal failure; oesophagogastroduodenoscopy; \(H_2\)-receptor antagonists; proton pump inhibitors

Introduction

Acid suppressive therapy (AST), including \(H_2\)-receptor antagonists and proton pump inhibitors (PPIs), is used frequently both in primary and secondary care. The costs of these medications have escalated during the last decade and constitute an important part of the expenses in the national medication budget in many countries [1]. The indications for their use in the treatment of peptic ulcer and for healing of oesophagitis are unequivocal. However, it has been suggested that acid suppressant drugs are often prescribed for minor symptoms without clear indications. Previous studies have demonstrated an overuse of AST among hospitalized patients and that a large proportion of this use was not indicated [2]. Also, studies in primary care have shown a high consumption of AST, often with no clear indication [3].

In a recent study from our group, we found that patients with chronic renal failure (CRF) have a high prevalence of gastrointestinal (GI) symptoms and we also noted a high consumption of AST among these patients [4]. The use of and indication for AST in CRF patients is unexplored and whether the therapy is preceded by oesophagogastroduodenoscopy (EGD) is also unclear.

The present study evaluated the prevalence and eligibility of gastric AST in CRF patients in dialysis. These patients were compared with hospitalized patients and patients with other chronic diseases (pulmonary diseases and rheumatic diseases). Eligibility of gastric AST included the indication for and length of AST and the proportion of endoscopic evaluation among the treated patients before the start of and during therapy. Furthermore, a secondary aim was to elucidate the proportion between \(H_2\)-receptor antagonists and PPIs.

Subjects and methods

Subjects

A total of 293 patients in dialysis were included in the study. All dialysis patients were recruited from the area around two cities, Gothenburg and Borås, in the western part of Sweden, with a total population of 700 000. They came from four haemodialysis units and two peritoneal dialysis units.
covering nearly all dialysis patients in this particular region. In Gothenburg, the patients came from a university hospital, a private hospital and a community hospital. In Borås, the dialysis patients came from Borås Hospital, a community hospital. One of the control groups consisted of hospitalized patients admitted consecutively to two internal medicine wards (coronary intensive ward and general internal medicine ward) at Borås Hospital over a 3-week period. Patients readmitted during the period were excluded. This group contained 261 patients. In the second control group there were 181 patients with a different chronic disease, either a pulmonary disease (95 patients) or a rheumatic disease (86 patients). These patients were recruited from two outpatient clinics at Borås Hospital during a 2-week period. The study was approved by the Ethics Committee of the University of Göteborg.

Experimental design

AST included H2-receptor antagonists and PPIs. By interviewing the patients and reviewing the medical records information about the use of AST, the indication for the medication was received. Use was defined as prescription of H2-receptor antagonists and PPIs regardless of dosage regimen. The duration of AST was noted. We divided the patients into two groups, one with AST shorter than 8 weeks (short-term therapy) and the second with AST for 8 weeks or longer (long-term therapy). We also noted whether the patient had undergone EGD and the result of it. Adequate indications for AST were those strongly supported by the medical literature and these are shown in Table 1. All other indications were considered inadequate.

Statistics

Variable distribution is given as medians with interquartile ranges (IQR). For comparisons of AST use, the frequency of adequate/inadequate AST, proportion of EGD and length of AST between the different patient groups, Fisher’s Exact test was used. Two-tailed P-values of 0.05 were considered statistically significant.

Results

Patient characteristics

Of the total of 293 patients in dialysis, 202 were in haemodialysis (HD) and 91 were in peritoneal dialysis (PD). Gender distribution, mean age and age range for the different groups are shown in Table 2. Admitting diagnoses for hospitalized patients are shown in Table 3. Chronic obstructive pulmonary disease was dominating among pulmonary disease patients present in 46/94 (49%) and rheumatoid arthritis was the most common diagnosis in patients with a rheumatic disease (60/84, 70%).

Use of acid suppressive therapy

Of the 293 patients in dialysis, 119 (41%) received PPIs or H2-receptor antagonists. There was no significant difference between HD and PD patients in the use of AST (data not shown). In the hospitalized patients group, 35 out of 261 (13%) patients used AST with no clear difference between the patients staying at the two different internal medicine wards (21/182 vs 15/79 patients, NS). Patients with rheumatic diseases had a higher consumption of AST than patients with a chronic pulmonary disease (29/86 vs 15/95, P < 0.01). Dialysis patients had a higher use of AST compared with hospitalized patients (119/293 vs 36/261, P < 0.001) and patients with chronic pulmonary disease (119/293 vs 15/95, P < 0.001). There was no clear difference in use of AST between dialysis patients and patients with a rheumatic disease (119/293 vs 29/86, NS). Gender did not have any impact on the use of AST in the different groups (data not shown).

Indications for acid suppressive therapy

Figure 1 shows the proportion of adequate and inadequate indications for AST in the three different patient groups in our study. Patients with CRF and hospitalized patients had a significantly higher

<table>
<thead>
<tr>
<th>Table 1. Adequate indications for AST</th>
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- Peptic ulcer (gastric and duodenal).
- Long-term treatment of chronic, non-HP related peptic ulcers.
- GERD with and without oesophagitis. Prevention of NSAID-induced ulcers and NSAID-related symptoms.
- Symptomatic treatment of ulcer-like symptoms (before endoscopy).
- Upper GI bleeding.

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Number of patients (%)</th>
</tr>
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<tbody>
<tr>
<td>coronary artery disease</td>
<td>54 (21%)</td>
</tr>
<tr>
<td>Others*</td>
<td>50 (19%)</td>
</tr>
<tr>
<td>Other heart diseases</td>
<td>33 (13%)</td>
</tr>
<tr>
<td>Infections in respiratory and urinary tract</td>
<td>27 (11%)</td>
</tr>
<tr>
<td>Chest pain</td>
<td>25 (10%)</td>
</tr>
<tr>
<td>Neurologic disease</td>
<td>18 (7%)</td>
</tr>
<tr>
<td>Congestive heart failure</td>
<td>16 (6%)</td>
</tr>
<tr>
<td>Pulmonary disease</td>
<td>13 (5%)</td>
</tr>
<tr>
<td>GI disease</td>
<td>7 (3%)</td>
</tr>
<tr>
<td>Anaemia</td>
<td>6 (2%)</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>4 (1%)</td>
</tr>
<tr>
<td>Intoxication</td>
<td>3 (1%)</td>
</tr>
<tr>
<td>Renal disease</td>
<td>1 (&lt;1%)</td>
</tr>
</tbody>
</table>

*Other diagnosis included malignant diseases, elderly patients with unclear symptoms and other infections.
proportion of inadequate indications for AST than patients with another chronic disease. In this group, patients with a rheumatic disease had the highest level of appropriate use of AST, with non-steroidal anti-inflammatory drugs (NSAID) prophylaxis as the dominating indication. Figures 2 and 3 show the adequate and inadequate indications for AST in the three different groups, respectively. There was no gender difference in the indication for AST (data not shown).

**Oesophagastroduodenoscopy prior to or during acid suppressive therapy**

Of the 199 patients using AST in our study, 83 (42%) had EGD performed. The proportion of EGD was similar in CRF patients 49/119 (42%), in hospitalized patients 16/36 (46%) and in patients with another chronic disease 18/44 (41%). There were no significant differences within the control groups (data not shown).
The results of the EGD are shown in Table 4. Peptic ulcer and oesophagitis were found in 33/83 (40%) of the EGDs.

### Duration of acid suppressive therapy

The majority of patients with a chronic illness—CRF, pulmonary disease or rheumatic disease—were on long-term AST. Among the hospitalized patients, ~50% had been treated for 8 weeks or longer, but in a high proportion of patients in this group the duration of AST was unclear (Figure 4).

### Type of acid suppressive therapy

Of the two types of drugs studied, a total of 185 patients (93%) received PPIs and only 14 (7%) received H2-receptor antagonists.

### Discussion

Information of the use of AST in patients with chronic diseases is limited, especially in patients with CRF. Previous studies have focused on general practice settings and hospitalized patients in general and have demonstrated a large and often inappropriate prescription of AST [1–3]. In none of these previous studies was the use of and the indication for AST according to the underlying chronic disease taken into consideration.

The present study shows a high consumption of AST in patients with CRF in dialysis and the use of AST had, in the majority of cases, no adequate indication. These findings are consistent with previous reports in hospitalized patients and patients in primary care [2,3]. In comparison with patients with two other chronic disease groups, we found a similar use among patients with a rheumatic disease. The proportion of adequate indications for this patient group were, however, significantly higher. Many of the patients with a rheumatic disease had NSAID prescribed with a risk of developing peptic ulcers. NSAID prophylaxis is an adequate indication for using PPIs and have shown prophylactic efficacy with PPIs in patients using NSAID [5]. However, not all NSAID users need PPI as ulcer prophylaxis and certain risk factors have been identified such as previous ulcers, old age, concomitant anti-coagulant therapy and treatment with corticosteroids [6]. In the present study, we did not take into account the risk factors, but only regarded indications as adequate or inadequate. Patients with a chronic pulmonary disease had a lower use of AST compared with the other two groups with a chronic disease. The lower consumption among these patients might be explained by a conscious prescription by the lung doctors in this hospital or that the patients visiting the outpatient clinic have a milder disease than patients requiring hospital care. The use of AST in hospitalized patients was also significantly lower compared with CRF patients. However, Nardino et al. [2] demonstrated a higher consumption of AST in hospitalized patients.

#### Table 4. The result of endoscopy

<table>
<thead>
<tr>
<th>Endoscopic diagnosis</th>
<th>Number of patients (n = 83)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peptic ulcer</td>
<td>28</td>
</tr>
<tr>
<td>Normal</td>
<td>28</td>
</tr>
<tr>
<td>Others</td>
<td>15</td>
</tr>
<tr>
<td>Oesophagitis</td>
<td>5</td>
</tr>
<tr>
<td>Vascular malformations</td>
<td>3</td>
</tr>
<tr>
<td>Not known</td>
<td>3</td>
</tr>
<tr>
<td>Erosions</td>
<td>1</td>
</tr>
</tbody>
</table>
Ala-Kaila [7] reported a high prevalence of superficial gastritis, duodenitis and peptic ulcer in patients with CRF. In our study, peptic ulcer was a rather uncommon clinical indication for AST in CRF patients. The peptic ulcer diagnosis was confirmed by EGD in all patients. However, the majority of these patients had been on long-term therapy, 78% of CRF patients, and after initial EGD the treatment with acid suppressive drugs was continued in many cases as ulcer prophylaxis without any re-investigation. Ryder et al. [3] found similar results among patients in general practice. For some of the patients, the AST as peptic ulcer prophylaxis is adequate in case of peptic ulcer not related to *Helicobacter pylori*, but a substantial number of patients are probably taking these drugs unnecessarily. It has recently been demonstrated that successful *H. pylori* eradication in peptic ulcer patients almost completely eliminates the need for AST [8].

We have recently demonstrated an increased prevalence of gastro-oesophageal reflux symptoms in PD patients [4]. These findings are in line with the results in this study, gastro-oesophageal reflux disease (GERD) was the indication for AST in 40% of the PD patients compared with 20% of the HD patients.

Non-specific symptoms as dyspepsia and abdominal pain were the most frequent inadequate indications among CRF patients and hospitalized patients. These findings are consistent with previous reports [3]. Recent studies suggest that empiric PPI treatment of uninvestigated dyspepsia in patients younger than 45 years old without alarm symptoms is a cost-effective and safe approach [9]. In the current study, AST without EGD was considered adequate in short-term treatment of ulcer-like GI symptoms. However, most patients with CRF are older than 45 years and the mean age in our study among these patients was 65 years. This supports a different treatment strategy with a more frequent use of EGD in these patients before starting AST. Patients in dialysis are often prescribed many different drugs for conditions accompanied with their renal disease or other co-existing diseases. GI symptoms are regarded as common side effects of many drugs. This multipharmacy can partly explain the overuse of AST. However, Hallas and Bytzer [10] did not find evidence for drug-related dyspepsia as an important factor for dyspepsia in general. Van Vlem et al. [11] have shown a correlation between delayed gastric emptying and dyspepsia in CRF patients.

Previously, use of corticosteroids was considered associated with development of peptic ulcer [12]. However, it has now been well documented that corticosteroids do not increase the risk of peptic ulcer [13]. Piper et al. [14] found that only patients treated concomitantly with NSAIDs had an increased risk for peptic ulcer. In our study, corticosteroid therapy was a common inadequate indication for AST in patients with chronic diseases, especially in patients with a chronic pulmonary disease, but also in CRF patients. The reason for this is probably the long living steroid ulcer myth.

The majority of the patients in our study have been treated with AST for a long period of time and there are many possible explanations for this. One simple explanation could be that many physicians are involved in the treatment of the patient and none of them take responsibility for evaluating the need for long-term treatment and perhaps discontinuing the AST. Many nephrologists have had the experience that patients with an inadequate indication for long-term AST want to restart therapy that has recently been discontinued. A possible explanation for this could be rebound acid hypersecretion leading to reintroduction of AST. This is a well-established phenomenon for
both H2-receptor antagonists and PPIs [15,16]. Smith et al. [16] have demonstrated that this rebound acid hypersecretion was associated with development of dyspeptic symptoms in healthy subjects. Hypergastrinaemia is a well-known phenomenon among patients with CRF, mostly due to their renal insufficiency [17]. When these patients stop AST, the rebound hypergastrinaemia might add to the hypergastrinaemia related to the renal insufficiency and lead to a more pronounced acid hypersecretion compared with patients without renal insufficiency. However, the importance of rebound acid hypersecretion in CRF patients is obviously speculative and clearly warrants further studies.

Whether the proportion of CRF patients investigated with endoscopy prior to or during AST in the present study is questionable. In the Genval Workshop Report 1999, it was concluded that medical history and PPI test for a short period were good diagnostic tools for GERD, but if there were symptoms recurrence after withdrawal of initial drug therapy, an EGD should be performed [18]. Gastro-oesophageal reflux was a common indication for AST among CRF patients in our study and the majority of them were on long-term treatment. In patients older than 50–55 years presenting with new onset dyspepsia, EGD is recommended to rule out serious disease [19]. Patients with CRF are often old and the mean age in CRF patients in our study was 65 years. These findings in our study do support a more frequent use of EGD in CRF patients with GI symptoms having AST. Therefore, the proportion of endoscopy in our study prior to or during AST in CRF patients might be too low.

Long-term acid suppression with PPIs rarely produces adverse events [20] and PPIs are considered safe in the treatment of patients with end-stage renal disease [21]. This is probably another reason for the high use of PPIs in CRF patients.

In conclusion, we have demonstrated an overuse of AST in CRF patients. The majority of these patients have an inadequate indication for these drugs and endoscopic investigation before and during therapy is insufficient. The reasons for this overuse of acid suppressive drugs are probably multifactorial. PPIs were the dominating acid suppressive drugs. Discontinuation of inappropriately prescribed PPIs and H2-receptor antagonists during CRF patients frequent hospital visits would have great economic implications leading to a reduced economic burden for health care providers.

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References


