Impact of clinical pharmacy services on stress ulcer prophylaxis prescribing and related cost in patients with renal insufficiency

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Keywords
acid suppressive therapy; chronic kidney disease; clinical pharmacy; cost; stress ulcer prophylaxis

Abstract

Objectives Compared to the general population, chronic kidney disease patients are more vulnerable to gastrointestinal hemorrhage and its morbidity and mortality. Due to the fear of gastrointestinal bleeding consequences in these patients on the one hand, and the perception of general safety of acid suppressive medications on the other hand, inappropriate stress ulcer prophylaxis (SUP) seems to be encountered in nephrology wards. The objectives of this study were to evaluate appropriateness of acid suppression therapy in kidney disease patients and to assess the role of clinical pharmacists to decrease inappropriate SUP prescribing and related costs for these patients.

Methods All inpatients at nephrology wards of a teaching hospital were assessed regarding appropriate SUP prescribing during a 6-month pre-intervention phase of the study without any clinical pharmacists’ involvement in patients’ management. Thereafter, during a 6-month post-intervention phase clinical pharmacists provided local SUP protocol and educational classes for physicians regarding appropriate SUP prescribing and participated actively in the patient-care team.

Main findings The results showed significant relative reduction in inappropriate SUP prescribing and related cost in patients with renal insufficiency by about 44% and 67% respectively.

Conclusion This study showed that implementing institutional guidelines, and active involvement of clinical pharmacists in the nephrology healthcare team, could reduce inappropriate SUP prescribing and related costs for these patients.

Introduction

Preventing clinically significant gastrointestinal (GI) bleeding is the main goal of stress ulcer prophylaxis (SUP). Compared to the general population, end stage renal disease patients are more vulnerable to GI hemorrhage and its related morbidity and mortality. Uremic platelet dysfunction, intermittent heparin use during haemodialysis, and antiplatelet/anticoagulant medications administration have been proposed as possible reasons of bleeding tendency in patients with end stage renal diseases. These risk factors result in increased rate of GI bleeding in dialysis patients by at least 10 fold and poorer outcome in these patients compared to the general population. This estimation shows the importance of prevention and treatment of GI bleeding in these patients. The incidence of acid suppressive therapy (AST) in chronic kidney disease patients has been reported to be about 41%.

The American Society of Health-System Pharmacists (ASHP) have provided a SUP guideline in medical or surgical patients who were admitted to intensive-care units (ICU); however, this guideline currently does not recommend SUP routinely for general medical patients. Although acid suppression therapy (AST) causes relatively few and benign side-effects, there is increasing evidence that shows a probable AST-induced increased risk of pneumonia, delirium and hip fractures primarily in patients with renal insufficiency. These adverse effects may increase the risk of morbidity or mortality
in these subjects. Additionally, a relationship between administration of proton pump inhibitors (PPIs) and increasing risk of Clostridium difficile colitis has been reported.

Another concern regarding AST includes clinically significant drug–drug interactions. The PPIs may interfere with absorption of some drugs (e.g. ketoconazole, ampicillin, iron and digoxin) through inducing hypochlorhydria. Earlier PPIs (omeprazole, lansoprazole) inhibit hepatic cytochrome P450 that may result in increased serum concentrations of some drugs with narrow therapeutic indices such as warfarin or phenytoin. The PPIs, with the exception of pantoprazole, may be associated with reduced effectiveness of cimetidine and ranitidine.

Among H2-receptor antagonists, cimetidine and to a lesser extent ranitidine can also inhibit hepatic cytochrome P450, while famotidine and nizatidine do not. It seems that in patients who have chronic kidney disease (CKD), because of fear of GI bleeding consequences on the one hand and perception of the general safety of PPIs and H2-receptor antagonists on the other hand, inappropriate SUP prescribing is usually encountered in nephrology wards. Institutional-based clinical pharmacists can play a role in improving appropriate SUP prescribing and decreasing SUP-related costs. This study was designed to evaluate the appropriateness of AST in CKD patients at a teaching hospital in Iran, and to assess the role of clinical pharmacists in decreasing inappropriate SUP prescribing and related costs in this patient population.

**Methods**

Patients who were admitted to the nephrology wards of the Imam Khomeini Hospital Complex, affiliate to Tehran University of Medical Sciences, Iran, were enrolled in this survey. This study was conducted in four separate stages:

1. literature survey and preparing a local SUP prescribing protocol;
2. assessing SUP prescribing by physicians and related cost before the implementation of the SUP protocol (pre-intervention phase);
3. implementation of local SUP prescribing protocol;
4. evaluation of SUP prescribing and related cost after the implementation of the protocol (post-intervention phase).

The data required to evaluate SUP prescribing appropriateness was extracted from patient medical records and chart review.

**Preparing stress ulcer prophylaxis prescribing protocol and evaluation form**

The local SUP prescribing protocol (Table 1) was developed following an extensive review of the literature and mainly based on the ASHP SUP guidelines. A specific form was designed to gather patients’ demographic data (including age, gender and weight), serum creatinine concentration, medical diagnosis at admission, any underlying disease, reason and duration of SUP prescription and type of prescribed AST. Prophylaxis was defined as sustained (>1 day) administration of an acid-suppressive medicine (H2 blocker or PPIs) in the absence of active GI bleeding, based on medical record review.

**Patient exclusion criteria**

Patients who needed AST due to active GI bleeding of any cause, peptic ulcer or gastric-oesophageal disease, or Zollinger–Ellison syndrome, were excluded from the study in both phases of the study.

**Pre-intervention study**

In order to assess baseline SUP prescribing patterns by physicians, clinical pharmacists retrospectively collected clinical and laboratory data, as defined above, by chart review of patients who were admitted to nephrology wards from the beginning of July 2009 until end of December 2009.

**Implementation of local stress ulcer prophylaxis instruction**

Based on the literature review, and specifically on the ASHP guideline and a locally prepared protocol on SUP in
infectious disease wards of the same hospital, a SUP prescribing protocol was developed by clinical pharmacists. This protocol was implemented over 2–3 months in the nephrology wards. The protocol was approved by the head of the nephrology department and registered by the Tehran University of Medical Sciences (registration number 89-04-33–11924). Additionally, clinical pharmacists provided educational classes for medical doctors working on the nephrology wards regarding appropriate SUP prescribing. Clinical pharmacists recommended AST when the patient had at least one primary (‘absolute’) risk factor or at least two secondary (‘relative’) risk factors as presented in Table 1.

Post-intervention study
During the post-intervention phase of the study, medical doctors working on the nephrology wards were asked to prescribe SUP based on the protocol. Clinical pharmacists accompanied physicians on the ward rounds and advised on starting or stopping SUP. Post-intervention data were collected from the beginning of July 2010 to the end of December 2010.

Measures
The outcome measures were the percentage of patients who did not receive SUP when they needed it and the percentage of patients who were prescribed SUP without appropriate indication.

Economic outcome
Costs due to inappropriate AST therapy were calculated as the total direct pharmacy (drugs and materials) costs incurred by patients. These were based on the costs of the SUP medications (unitary cost) and disposable materials (needles, syringe, and alcohol-pad) using average wholesale-price data from the 2010 Annual Pharma Statistics from the Ministry of Health and Medical Education of Iran. The average cost per patient during hospitalization for each group is reported (1 US dollar = 11000 Iranian rials).

Ethics
Study protocol was approved by local ethics committee of the Tehran University of Medical Sciences.

Data analysis
The Statistical Package for Social Sciences (SPSS, Chicago, Illinois; now owned by IBM, Armonk, USA) version 11.5 was used for data analysis. Descriptive tests were used to report the percentage of patients who received SUP prescribing appropriately or conversely inappropriately in the pre- and post-intervention periods of the study. The Pearson chi-squared test was used to compare the pre- and post-intervention phases with an a priori statistical significance level of 0.05.

Results
During the two 6-month phases of the study, 629 patients were admitted to nephrology wards; 18 patients were excluded from data analysis (Figure 1). Three hundred and eighty seven patients in the pre-intervention phase and 242 subjects in the post-intervention phase completed the study.

Table 2 summarizes the demographic and clinical data of the patients including sex, age, underlying disease resulting in renal insufficiency, indication for SUP prescribing and duration of AST administration.

Based on the protocol, 32% of subjects in pre-intervention phase and 39.8% of patients in post-intervention period of the study had an appropriate indication for SUP prescribing. The percentage of patients who received SUP inappropriately decreased from 60% in the pre-intervention to 33.6% in the post-intervention phase of the study; this is a significant relative reduction of 44% in inappropriate SUP prescription ($P = 0.005$) and an average relative cost reduction per patient of 67.2%; conversely, the percentage of patients who were prescribed SUP appropriately increased significantly from 46% in the pre-intervention to 66.4% in the post-intervention period of the study ($P = 0.006$). These data are summarized in Table 3.

Six out of 387 patients (1.6%) in the pre-intervention phase of the study experienced active GI bleeding; none of these patients had received SUP before their GI bleeding episodes. During the post-intervention phase of the study active GI bleeding did not occur in any patient.

As shown in Table 4, risk factors for SUP were comparable in the pre-intervention and post-intervention periods with coagulopathy ranked the highest in both phases of the study. A history of non-steroidal anti inflammatory drug (NSAID) use for more than 3 months was the most prevalent relative risk factor for SUP. In this study, omeprazole was the most frequently used AST (83.5% and 86.7% in pre- and post-intervention phases respectively) (Figure 1).

Discussion
Based on the findings of this study, implementing a SUP protocol by clinical pharmacists reduced inappropriate AST prescribing and related cost by about 44% and 70% respectively. Additionally, there was about a 70% relative reduction in missed SUP prescribing for CKD patients who needed AST. These results show marked improvement in appropriate
Post-test phase

Patients admitted to the nephrology wards
(n = 242)

Excluded (n = 6): all were on acid-suppressive therapy before admission
of these, 202 received stress ulcer prophylaxis

Patient data available for analysis (n = 236): of these, 134 received stress ulcer prophylaxis

Excluded (n = 12): on acid-suppressive therapy before admission
(n = 4); active gastrointestinal bleeding at time of hospital admission or during in hospital stay
(n = 6); missing or insufficient records (2)

Pre-test phase

Patients admitted to the nephrology wards
(n = 387)

Patient data available for analysis (n = 375): of these, 202 received stress ulcer prophylaxis

Excluded (n = 6): all were on acid-suppressive therapy before admission

Figure 1 Patient selection flow chart.

Table 2 Demographic and clinical characteristics of patients who completed each phase of the study

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Pre-test phase</th>
<th>Post-test phase</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total patients</td>
<td>Number 375</td>
<td>236</td>
</tr>
<tr>
<td>Male/female</td>
<td>Number (%)</td>
<td>213 (56.8)/162 (43.2)%</td>
</tr>
<tr>
<td>Age, years</td>
<td>Mean ± SD (range)</td>
<td>51.2 ± 18.3 (13–90)</td>
</tr>
<tr>
<td>Presence of indication for SUP based on protocol</td>
<td>Number (%)</td>
<td>120 (32)</td>
</tr>
<tr>
<td>Duration of AST (days)</td>
<td>Mean (range)</td>
<td>11.5 (2–37)</td>
</tr>
<tr>
<td>eGFR (ml/min)</td>
<td>Mean</td>
<td>28</td>
</tr>
<tr>
<td>Underlying disease</td>
<td></td>
<td></td>
</tr>
<tr>
<td>DM</td>
<td>43%</td>
<td>40.5%</td>
</tr>
<tr>
<td>Hypertension</td>
<td>50.6%</td>
<td>51.7%</td>
</tr>
</tbody>
</table>

AST, acid suppressive therapy; DM, diabetes mellitus; eGFR, estimated glomerular filtration rate; SD, standard deviation; SUP, stress ulcer prophylaxis.

Table 3 Comparing stress ulcer prophylaxis appropriateness and related costs during pre-test and post-test phases of the study

<table>
<thead>
<tr>
<th></th>
<th>Pre-test phase</th>
<th>Post-test phase</th>
<th>Change (%)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total patients who received SUP</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Appropriately</td>
<td>202 (46.0)</td>
<td>134 (66.4)</td>
<td>44.3</td>
<td>&lt;0.006</td>
</tr>
<tr>
<td>Cost per patient for appropriate SUP administration (US$)</td>
<td>12.5</td>
<td>18.2</td>
<td>31.2</td>
<td></td>
</tr>
<tr>
<td>Inappropriately</td>
<td>109 (60)</td>
<td>45 (33.6)</td>
<td>−44</td>
<td>&lt;0.005</td>
</tr>
<tr>
<td>Cost per patient for inappropriate SUP administration (US$)</td>
<td>18.2</td>
<td>8.0</td>
<td>−67.2</td>
<td></td>
</tr>
<tr>
<td>Total patients who did not receive SUP</td>
<td>173 (84.4)</td>
<td>102 (33.6)</td>
<td>12.7</td>
<td>&lt;0.009</td>
</tr>
<tr>
<td>Appropriately</td>
<td>146 (84.4)</td>
<td>97 (55.1)</td>
<td>12.7</td>
<td>&lt;0.009</td>
</tr>
<tr>
<td>Inappropriately</td>
<td>27 (16.6)</td>
<td>5 (4.9)</td>
<td>−68.6</td>
<td>&lt;0.006</td>
</tr>
</tbody>
</table>

SUP, stress ulcer prophylaxis.
SUP in these wards. However, this study suffers some main limitations, including assessment of the intervention in a limited number of patients in a single nephrology centre. Additionally, in this study, the influence of the clinical pharmacist-implemented programme was evaluated during a pre- and post-intervention study without including a control group.

Overuse of AST in non-critically ill patients has been reported by several investigators.\[^{8,17,18}\] Since chronic kidney disease has been proposed as a condition that increases the risk of GI bleeding,\[^{2–7}\] we suggested that AST is initiated inappropriately in the vast majority of CKD patients who are admitted to nephrology wards due to fear of GI bleedings and its related morbidity and mortality. The results of the study showed that the suggestion is correct, by showing that more than half of the CKD patients who received AST at the initiation of the study had no appropriate SUP indication.

In a Swedish study that compared AST in dialysis patients compared with other hospitalized and chronic diseases patients, AST was significantly higher in dialysis patients compared with hospitalized patients and chronic lung disease patients but similar to patients with rheumatic diseases.\[^{9}\] Based on their findings, the majority of the dialysis patients had inadequate indication for AST.\[^{10}\] Conversely, it seems that inadequate use of AST is also higher in CKD patients.\[^{11}\] In the present study about 16% of patients who did not receive AST needed it, based on the protocol, and missed being prescribed for SUP.

The results of the present study showed a significant reduction of unnecessary AST following clinical pharmacists’ interventions in the nephrology wards. In a pre- and post-clinical pharmacists’ intervention study in infectious diseases wards of the same hospital, overall use of AST significantly reduced from about 81% in the pre-intervention period to about 47% in post-intervention phase.\[^{16}\] Our results are also similar to the findings of Hatch \etal\ who studied the role of pharmacists in reducing inappropriate continuation of SUP in ICU patients upon discharge, or transferring to the general care-unit, and found that the reduction was more than 60%.\[^{19}\] Coursol and Sanzari assessed the influence of a pharmacist-provided algorithm in the appropriateness of SUP prescribing in ICU patients. In their study, implementation of the SUP algorithm reduced inappropriate SUP from 95.7 to 88.2% with a significant reduction of SUP cost. The presence of active GI bleeding was similar in pre- and post-intervention phases of their study.\[^{20}\] In another pre-/post-intervention study by Hughes \etal,\ pharmacist intervention reduced inappropriate AST in non-ICU patients by about 50% at discharge time.\[^{21}\]

An enormous drug cost burden on patients and insurances relates to inappropriate PPI administration for SUP purposes.\[^{22}\] Clinical pharmacist participation in patient management may decrease SUP-related expenditures without having a detrimental impact on quality of care.\[^{23–26}\] In the present study, pharmacists’ intervention reduced relative the SUP cost by about 70%.

Similarly to other studies, our study found that PPIs were widely used drugs for the prophylaxis of stress ulcers.\[^{8,10,26}\] Possible reasons for the widespread use of PPIs in our hospital were low rate of side effects associated with these medications and no need for dose adjustment in patients with

<table>
<thead>
<tr>
<th>Risk factors</th>
<th>Indication</th>
<th>Control phase (n = 375)</th>
<th>Intervention phase (n = 236)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Coagulopathy</td>
<td>Absolute</td>
<td>46 (12.3%)</td>
<td>21 (7.9%)</td>
</tr>
<tr>
<td>Mechanical ventilation more than 48h</td>
<td>Absolute</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Evidence of GI bleeding</td>
<td>Absolute</td>
<td>5 (1.3%)</td>
<td>1 (0.4%)</td>
</tr>
<tr>
<td>Sepsis</td>
<td>Relative</td>
<td>23 (6.1%)</td>
<td>16 (6.8%)</td>
</tr>
<tr>
<td>Acute kidney injury</td>
<td>Relative</td>
<td>19 (5.1%)</td>
<td>14 (5.9%)</td>
</tr>
<tr>
<td>Respiratory failure</td>
<td>Relative</td>
<td>1 (0.3%)</td>
<td>4 (1.7%)</td>
</tr>
<tr>
<td>Enteral feeding</td>
<td>Relative</td>
<td>4 (1.1%)</td>
<td>2 (0.8%)</td>
</tr>
<tr>
<td>Glucocorticoids (hydrocortisone or equivalent&gt; 250 mg per day)</td>
<td>Relative</td>
<td>31 (8.3%)</td>
<td>21 (8.9%)</td>
</tr>
<tr>
<td>low molecular weight unfractionated or Heparin (therapeutic dose)</td>
<td>Relative</td>
<td>4 (1.1%)</td>
<td>6 (2.5%)</td>
</tr>
<tr>
<td>Warfarin</td>
<td>Relative</td>
<td>17 (4.5%)</td>
<td>9 (3.8%)</td>
</tr>
<tr>
<td>Hepatic impairment</td>
<td>Relative</td>
<td>3 (0.8%)</td>
<td>7 (3%)</td>
</tr>
<tr>
<td>History of NSAID use &gt;3 months</td>
<td>Relative</td>
<td>27 (7.2%)</td>
<td>28 (11.9%)</td>
</tr>
<tr>
<td>An ICU stay of more than 1 week</td>
<td>Relative</td>
<td>0</td>
<td>1 (0.4%)</td>
</tr>
<tr>
<td>Early organ transplant</td>
<td>Relative</td>
<td>18 (4.8%)</td>
<td>10 (4.2%)</td>
</tr>
<tr>
<td>Hypotension</td>
<td>Relative</td>
<td>3 (0.8%)</td>
<td>9 (3.8%)</td>
</tr>
<tr>
<td>History of gastrointestinal bleeding or peptic ulcer disease within 1 year</td>
<td>Relative</td>
<td>25 (6.7%)</td>
<td>25 (10.6%)</td>
</tr>
<tr>
<td>total patients</td>
<td></td>
<td>375</td>
<td>236</td>
</tr>
</tbody>
</table>
impaired kidney function.\textsuperscript{[11]} However, most PPIs are more expensive than H2-receptor antagonists, and some propose their administration when H2-receptor antagonists are not successful in CKD patients.\textsuperscript{[28]} Administration of H2-blockers should be adjusted according to kidney function. Lack of attention to ranitidine dose adjustment in patients with declined renal function, may increase 1-year all-cause mortality.\textsuperscript{[27]}

Pilotto \textit{et al.} reported higher risk of GI bleeding in acute rather than chronic NSAID or aspirin users.\textsuperscript{[20]} Co-treatment with PPIs, but not with H2-blockers, in symptomatic elderly patients who need to be treated with a NSAID and/or aspirin for a short period of time, may reduce the risk of GI bleeding.\textsuperscript{[26,30]} According to the above-mentioned trials,\textsuperscript{[26,29,30]} and since large percentage of our CKD patients used aspirin owing to underlying diseases, most nephrologists in our wards considered PPIs, especially omeprazole, to be the first-choice AST for their patients (Figure 1).

This interventional study has shown the remarkable impact that clinical pharmacy services can have on improving SUP prescribing for patients with renal insufficiency, who are a major population vulnerable to stress ulcer and drug side effects. In order to confirm the value of the pharmacist’s role in improving appropriate SUP prescribing for hospitalized patients, the design and implementation of case-control studies on larger numbers of patients with the assessment of patients’ outcomes (such as duration of hospitalization and whole treatment costs) are highly recommended. Moreover, similar studies on other medical patients who are supposed to be vulnerable to stress ulcer, such as rheumatologic patients on long-term NSAIDs administration, would be of great value.

\section*{Conclusion}

This study has shown that preparing an institutional protocol, together with the active involvement of clinical pharmacists in the nephrology healthcare team, could significantly reduce inappropriate AST prescribing and related costs in patients with kidney diseases.

\section*{Declarations}

\section*{Conflict of interest}

The Authors declare that they have no conflicts of interest to disclose.

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\section*{Authors’ contributions}

Providing the idea, designing the study and implementing the SUP protocol in the nephrology ward, data gathering and manuscript drafting, analysis and patients’ monitoring were performed by Dr Hossein Khalili, Dr Simin Dashti-Khavidaki, Dr Maryam Mousavi, Dr Amir Farshchi, Dr Mansoor Gatmiri respectively. All Authors state that they had complete access to the study data that support the publication.

\section*{References}


