Medication misuse in hospitalized patients with renal impairment

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Abstract

Objectives. The potential consequences of medication misuse in renal impairment have not been assessed in a population of in-patients. The purpose of this study was to determine the frequency and potential consequences of a lack of dosage adjustment in hospitalized patients with renal impairment.

Design. Order sheets for in-patients having a creatinine above 0.7 mg/dl were analysed. We considered the appropriateness of prescriptions for medications having potential nephrotoxicity and/or eliminated through renal excretion or metabolism (TEM medications) and having manufacturer’s guidelines for dosage adjustment in renal impairment.

Main measures. On the basis of these guidelines, each line of prescription was rated as ‘appropriate order’, ‘inappropriate dosage’, or ‘contra-indicated order’. Experts also rated prescriptions as potentially fatal or severe, serious, significant, or without potential for increased adverse effects.

Results. Two hundred and two order sheets were completed for 164 patients. They totalled 1469 lines of prescription, 85% of which were TEM medications, with guidelines for dosage adjustment for 71% of them (n = 886). Of these 886 prescriptions, 34% were inappropriate, 14% being contra-indicated and 20% with inappropriate dosage given the patient’s renal function. Among the 202 order sheets, 75% included at least one inappropriate prescription. Sixty-three per cent included at least one prescription with potentially adverse consequences, 3% of these having potentially fatal or severe consequences.

Conclusion. This study confirms that physicians do not take into account sufficiently patient renal function when prescribing. In light of these results, improving the quality of drug prescription in patients with renal impairment could be of importance for improving the quality of care.

Keywords: dosage adjustment, prescribing, quality of care, renal impairment

Most drugs and their active metabolites are eliminated through the kidneys and can sometimes induce nephrotoxicity. The high prevalence of renal failure [1–4] and the large number of drugs with renal elimination or potential nephrotoxicity suggest that physicians should consider renal function when prescribing [5–8]. For many drugs, dosage adjustment according to renal function is indicated in order to avoid overdosage and a iatrogenic risk of renal impairment or its aggravation [9]. The few studies that have assessed drug prescription in renal impairment show that adjustments are rarely made, but did not consider the consequences or potential consequences of this medication misuse [10–12].

The purpose of this study was (1) to assess the frequency of medication misuse in hospitalized patients having renal impairment, and (2) to consider the potential consequences of this medication misuse.

Methods

Setting

This prospective descriptive study was conducted in the Hôpital Pitié Salpêtrière (Assistance Publique, Hôpitaux de
Paris, Paris, France), a 2070-bed tertiary care hospital group. Formerly two distinct hospitals (until 1964), this teaching hospital group still encompasses two geographical areas. This study took place in one part of the group, Salpêtrière, which is composed of 12 medical departments and seven surgical departments. It includes 937 acute-care beds, 84 intensive-care beds and 265 medium- and long-stay beds, and receives about 39 500 in-patients per year.

**Study participants**

From September to December 1999, the laboratory department of the hospital listed daily the in-patients whose serum creatinine level was 1.7 mg/dl or above (normal range 0.7–1.4 mg/dl), and the orders for these patients were recorded. A patient whose serum creatinine level substantially fluctuated (increase or decrease of more than 1 mg/dl) could be recorded several times, since the medication order should have been reconsidered after such a change in creatinine level.

For each patient, medication orders were recorded 24 hours after the laboratory results were available.

** Appropriateness of order**

The reference chosen for assessment was the 1999 edition of the Vidal dictionary [13]. This dictionary pools the manufacturers’ Summaries of Product Characteristics (SmPC), is officially distributed by the French Regulatory Authorities, and is updated annually. It corresponds to the Physician’s Desk Reference and is the French reference for prescription. Commonly consulted by physicians, it may be used as formal evidence in legal procedures.

The assessment concerned medications with potential nephrotoxicity and/or elimination through renal excretion or metabolism (TEM medications), and for which the Vidal dictionary supplies a guideline for dosage adjustment in renal impairment (however detailed this guideline is).

For each order, the dose was considered according to the patient’s creatinine clearance (calculated using the Cockcroft and Gault formula [14]) and according to the Vidal dictionary. For each medication, prescriptions were rated as ‘appropriate’ when the dosage was appropriate to the patient’s renal function or when the treatment was discontinued. Prescriptions were rated as ‘inappropriate dosage’ when the dosage prescribed was not in conformity with the adjustment required in the SmPC with regard to the patient’s renal function. Prescriptions were rated as ‘contra-indicated’ if the SmPC mentioned a contra-indication due to renal impairment, or according to the patient’s renal function if this contra-indication was restricted, i.e. to severe renal impairment. Prescriptions rated as ‘inappropriate dosage’ and as ‘contra-indicated’ were both considered as inappropriate prescriptions.

**Potential consequences**

To assess their potential consequences for patients, inappropriate prescriptions were jointly considered by a group of four experts including a nephrologist, an internist, a pharmacologist, and a pharmacist. Prescriptions were rated according to the Lesar classification for order errors, as potentially fatal or severe (A), potentially serious (B), potentially significant (C), or no toxic potential or potential for increased adverse effects (D) [15]. Prescriptions rated as A, B, or C were considered as having a clinically significant potential risk for the patient. Prescriptions rated as D were considered as inappropriate prescriptions with no or negligible potential for adverse consequences. To allow the experts to assess the potential clinical significance of inappropriate dosages, overdoses and underdoses were expressed as their equivalent in patients without renal impairment. For instance, an order of 2 g per day in a patient whose renal function would require half dosage according to creatinine clearance was considered similar to the prescription of 4 g per day to a patient with preserved renal function. When the experts disagreed, a consensus was obtained after group discussion.

The number of medications rated as having a potential for adverse consequences was therefore assessed. When several medications were prescribed in the same order sheet we considered that the results could be presented in two ways, the denominator being either the drug (line of prescription) or the patient (order sheet). As an example, when an order sheet included three lines of prescription, the first one having a potential for fatal consequences, the second one having a potential for significant adverse consequences, and the third one having no potential for adverse consequences, the results were expressed in two ways: (1) as a number of prescriptions (two medications out of three had a potential for adverse consequences, or one medication out of three had a potential for fatal consequences); and (2) as a number of order sheets, rated as the medication with the highest potential for adverse consequences among the prescriptions of that order (one order sheet with potential for fatal consequences).

**Analysis**

A descriptive analysis of data was made. A $\chi^2$ test of association was used to compare, in patients with severe versus mild renal impairment, (1) the frequency of prescriptions with an appropriate dosage, (2) the frequency of contra-indicated prescriptions, and (3) the frequency of overdose. To take into account multiple testing, the $P$ value was set at 1% instead of 5%.

**Results**

**Sociodemographic characteristics**

Among the approximately 9600 patients hospitalized at some point during the study, 164 were included. Of these, 69% were male, with a median age of 70 years, a median serum creatinine level of 2.0 mg/dl (range 1.7–5.7 mg/dl), and a median calculated clearance of 0.48 ml/s (minimum 0.1 ml/s, maximum 1.1 ml/s).
Orders

Two hundred and two consecutive order sheets prescribed for these 164 patients were analysed. They totalled 1469 lines of prescription (an average of seven drugs per order) and 295 different drugs. Eighty-five per cent of prescriptions (1243 of 1469) concerned TEM medications (Figure 1). The Vidal dictionary proposed a dosage adjustment for 71% (886 of 1243) of these prescriptions.

Conformity of orders

The appropriateness of these 886 prescriptions was assessed (Table 1). Thirty-four per cent (n = 301) were inappropriate, with 14% (n = 124) being contra-indicated orders and 20% (n = 177) indicating inappropriate dosage with regard to the patient’s renal function. Forty-six per cent of these 177 inappropriate dosages concerned anti-infectious drugs, which represented 24% of the prescriptions of TEM medications. No ‘over-adjustment’ (i.e. leading to underdosage) was observed.

Prescriptions were analysed according to the degree of renal impairment. Of the 202 order sheets analysed in this study, 110 concerned patients with severe renal impairment (creatinine clearance below 0.5 ml/s), with 614 prescriptions of TEM medications (an average of six drugs per order). Comparing the appropriateness of orders between patients with severe and with mild renal impairment, the frequency of overdose did not statistically differ (P = 0.3), whereas contra-indicated orders were more frequent in severe renal impairment (P = 0.00001) and appropriate orders were more frequent in mild renal impairment (P = 0.00001) (Table 1).

Potential consequences

Considering the 202 order sheets analysed in this study, 75% (n = 152) included at least one inappropriate prescription (i.e. a TEM medication prescribed at inappropriate dosage, or contra-indicated). Sixty-three per cent included at least one prescription with potentially adverse consequences (potentially serious or significant, such as the prescription of a full dosage of vancomycin to patients with, respectively, 25% and less than 50% of renal function), 3% of them being potentially fatal or severe (such as ordering a full dose of aldactazine to a patient with severe renal impairment).

The potential consequences of these inappropriate prescriptions are summarized in Table 2 for the 152 order sheets and for their 301 lines of prescription.

Discussion

Our study considered medication misuse in renal failure in a tertiary care hospital and its potential consequences.

### Table 1

<table>
<thead>
<tr>
<th>Level of appropriateness</th>
<th>Total n (%)</th>
<th>Mild1 n (%)</th>
<th>Severe2 n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Compliance with guidelines (or treatment interruption)</td>
<td>585 (66)</td>
<td>350 (75)</td>
<td>235 (56)</td>
</tr>
<tr>
<td>Overdosage</td>
<td>177 (20)</td>
<td>86 (19)</td>
<td>91 (21)</td>
</tr>
<tr>
<td>Contra-indicated medication</td>
<td>124 (14)</td>
<td>28 (6)</td>
<td>96 (23)</td>
</tr>
<tr>
<td>Total</td>
<td>886 (100)</td>
<td>464 (100)</td>
<td>422 (100)</td>
</tr>
</tbody>
</table>

1Mild impairment, creatinine clearance ≥ 0.5 ml/s.
2Severe impairment, creatinine clearance < 0.5 ml/s.
Table 2 Potential consequences of the misuse, in renal impairment, of medications with potential for nephrotoxicity and/or elimination through renal excretion or metabolism, according to the Lesar classification [15]

<table>
<thead>
<tr>
<th></th>
<th>All orders</th>
<th>Inappropriate orders</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Order sheets</td>
<td>Lines of Prescription</td>
</tr>
<tr>
<td></td>
<td>$n = 202$</td>
<td>$n = 886$</td>
</tr>
<tr>
<td>Inappropriate</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Potentially fatal or severe</td>
<td>7 (3)</td>
<td>8 (1)</td>
</tr>
<tr>
<td>Potentially serious</td>
<td>25 (12)</td>
<td>27 (3)</td>
</tr>
<tr>
<td>Potentially significant</td>
<td>96 (48)</td>
<td>173 (20)</td>
</tr>
<tr>
<td>No toxic potential nor potential for increased adverse effects</td>
<td>24 (12)</td>
<td>93 (10)</td>
</tr>
<tr>
<td>Total</td>
<td>152 (75)</td>
<td>301 (34)</td>
</tr>
<tr>
<td>Appropriate</td>
<td>50 (25)</td>
<td>585 (66)</td>
</tr>
</tbody>
</table>

Thirty-four per cent of the prescriptions of TEM medications were inappropriate and 75% of order sheets included at least one inappropriate prescription. Of the 202 order sheets analysed in this study, 63% included a drug prescription rated by experts as having a potential for adverse consequences and 3% included a prescription rated as having a potential for fatal or severe consequences.

Few data are available on medication misuse and contra-indicated orders in hospitalized patients, particularly concerning patients with renal impairment. Our study showed that the frequency of overdose did not differ in mild and in severe (and more obvious) renal impairment. Contra-indicated orders were more frequent in severe renal impairment and appropriate orders were more frequent in mild renal impairment (Table 1). This difference may be explained by the guidelines themselves rather than by the quality of orders. For a given medication contra-indicated in severe renal impairment, the same order would be rated as appropriate in a patient with mild renal impairment and as contra-indicated in a patient with severe renal impairment.

Considering TEM medications having a guideline in renal impairment (whatever the guideline and however detailed it was), misuse was observed in 34% of prescriptions. This frequency of inappropriate prescriptions is high, and in addition is probably underestimated, because: (1) patients with serum creatinine level less than 1.7 mg/dl were not considered, although their creatinine clearance might have required dosage adjustment; (2) prescriptions were rated as ‘appropriate’ whenever a treatment was discontinued; and (3) 29% of TEM medication prescriptions, having no mention of dosage adjustment in the SmPC, were not analysed.

Despite this possible overestimation of appropriate orders, our results are consistent with those of a study made among elderly patients with renal impairment, where 35% of the prescriptions contradicted the British National Formulary guidelines [11]. In another study considering a list of selected medications (depending on renal function for elimination and either costly or with a narrow therapeutic index), 44% of prescriptions exceeded the manufacturer’s dosage recommendations [10].

Several explanations may be advanced for this lack of adjustment. These include physicians’ underestimation of the consequences of mild renal impairment in terms of subsequent iatrogenic risk [16] or their poor knowledge of the medications requiring adjustment in renal impairment. Although used in daily practice, serum creatinine level is often inappropriate to assess actual renal function and leads to underestimation of renal impairment, particularly in the elderly. The assessment of creatinine clearance requires a 24-hour urine collection which is often difficult to perform, but its estimation with the Cockcroft and Gault formula, taking into account patient’s weight, age, and serum creatinine level, also provides an accurate assessment of renal function [14]. Another explanation would be that physicians who do not calculate creatinine clearance underestimate the necessity of adjusting medication dosage.

Most medications prescribed in this study (225 of 295) were TEM drugs. Memorizing the adjustments required at each stage of renal impairment seems unfeasible, and it would be time consuming to consult the Vidal dictionary for 85% of the prescriptions in patients with renal impairment. Therefore, implementing a computing system with reminders at the time of prescription could have great interest. Several hospitals have reported the implementation of computing systems that screen for inappropriate dosage of renally eliminated drugs [17–20]. In hospitals with no computerized register of medication orders, such as ours, such procedures are more difficult to implement. Yet laboratory computers can provide prescribers with more accurate data to assess renal function, such as calculated creatinine clearance, and generate alerts adapted to patients’ serum creatinine level, e.g. a list of selected medications. Such alerts are probably less efficient than the intervention of pharmacists, but few means of action are possible in hospitals without a computerized...
register of prescriptions, i.e. most French hospitals. Therefore, assessing the efficiency of such alerts could be of great interest.

Conclusion
This study confirmed that physicians do not pay enough attention to the drugs prescribed in patients with renal impairment. Three per cent of the orders in these patients contained a medication misuse considered as potentially lethal or severe. With regard to these results, the quality of drug prescription in patients with renal impairment is an important field for quality improvement.

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References

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