IDENTIFICATION OF SAFETY ALERT BY MONITORING ANALYTICAL PARAMETERS AND HIGH-RISK DRUGS

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ABSTRACT
Early detection of adverse drug reactions (ADR) increases patient safety. Our objective was to identify ADR by monitoring laboratory parameters and high-risk drugs. We carried out a two-month prospective observational study in a Internal Medicine Department, with daily recording of drugs prescribed and the following parameters: Na, K, Ca, serum creatinine, glomerular filtration rate (GFR), INR, glucose, haemoglobin, platelets, ALT, AST, bilirubin, GGT, alkaline phosphatase, TSH, T4, and blood digoxin. High-risk drugs were closely monitored. 52 patients included, of whom 46.2% experienced an ADR. We observed an association with drugs in 25.5%, as follows: reduction in GFR, 26.9% (associated with loop diuretics [41.7%], angiotensin-converting enzyme [ACE] inhibitors [33.3%], angiotensin II receptor blockers [ARB] [16.6%], and anti-diabetic drugs [8.3%]); hypokalemia, 22.3% (associated with loop diuretics [50.0%], potassium-free fluid [37.5%], and salbutamol [12.5%]); hyperkalemia, 14.4% (associated with ACE inhibitors [60.0%] and ARB [40.0%]); INR out of range, 10.8% (associated with drug interactions [66.7%]); hyperglycemia, 8.1% (associated with corticosteroids [66.7%] and anti-diabetic drugs [33.3%]); and other conditions, 18.8%. We concluded that patient safety could be improved by implementing warnings in electronic prescriptions in cases of a decrease in GFR or modification of potassium levels in patients who are prescribed loop diuretics, ACE inhibitors, or ARBs.

Key words: Adverse drug reaction, clinical decision support, high-risk drug, safety

INTRODUCTION
Patient safety and quality of healthcare are issues concerning professionals and authorities. In particular, drug-related adverse events (DRAE) represent an important problem which not only have significant social and healthcare consequences but also economic. A drug-related adverse event is any damage in health caused by the therapeutic use (including non-use) of a drug. Preventable adverse drug events are a consequence of a medication error, while non-preventable adverse drug events occur despite the proper use of medications. They are known as adverse drug reactions (ADRs), which are defined as any harmful and unwanted effect that occurs after the administration of a drug at the doses that are normally used in patients for prophylaxis, diagnosis or treatment of a disease, or in order to change its biological function (Otero et al., 2003).

In order to effectively prevent and detect these side effects early, many new technological advances are taking place. Due to its potential impact and ability to act at different stages of drug use, the assisted electronic prescription is one of the most important advances in this field (Kupcman et al., 2007; Silverman et al., 2004). The generation of warning messages in the electronic prescription in response to analytical parameters which can often be altered by drugs, contribute to the identification and prevention of DRAE by health care professionals.

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The objective of the study was to identify the largest number of ADRs in patients admitted to Internal Medicine by dual follow-up: monitoring of laboratory parameters (haematological and biochemical) and high-risk medications. Thus, we attempt to define security alerts to provide a more efficient monitoring of these variables in daily clinical practice.

**METHODOLOGY**

Prospective observational study conducted in patients hospitalized in an Internal Medicine Department with an average of 16 patients hospitalized, belonging to a 1500 bed tertiary hospital. All patients were included between the months of April and May 2011 and had been hospitalized for at least 24 hours in this unit. Biochemical and haematological parameters were reviewed daily as well as patient prescriptions. The main parameters that according to the literature are most likely to be altered by the use of medication were recorded (Kuperman et al., 2007; Silverman et al., 2004): serum electrolyte concentrations (sodium, potassium, calcium and magnesium), serum creatinine, estimated glomerular filtration rate (GFR) (MDRD-4 IDMS), hemoglobin levels (Hb), platelet count, glycerin, alkaline phosphatase, serum bilirubin, gamma glutamyl transpeptidase (GGT), aspartate amino-transferase (AST), alanine aminotransferase (ALT), international normalized ratio (INR), thyroxine-stimulating hormone (TSH), thyroxine (T4) and blood levels of digoxin (digoxinemia). Other variables recorded were age, sex, length of hospital stay and adverse drug reactions related to high-risk drugs (including the drug involved and the type and severity of the ADR).

Two independent analyses of the data were performed. On the one hand, we studied the possible association between laboratory values out of range and the use of any medication by patients. On the other hand, we studied the association between the use of high-risk drugs and the emergence of ADR. The causal assessment between a drug and an ADR was established using the modified Karch-Lasagna algorithm, where the association is defined as: definite, probable, possible or conditional.

Drugs were considered of high risk as defined by the Institute for Safe Medication Practices (ISMP). These are drugs with a narrow therapeutic range, high incidence of adverse effects and high complexity of use. At the request of Internal Medicine, we also included two other drugs in this list: Angiotensin Receptor Blockers (ARBs) and Angiotensin Converting Enzyme (ACE) inhibitors.

The severity of ADRs were classified as mild (a trivial adverse effect not compromising the patient's clinical condition), moderate (an adverse effect prolonging hospitalization), severe (a potentially life threatening adverse effect) and lethal.

**RESULTS AND DISCUSSION**

The 52 patients (65.4% male) median age (interquartile range) was 72 (61.6, 82.7) years. Median hospital stay was 7.0 (4.8, 13.3) days.

Approximately 46.2% of the patients experienced an ADR during hospitalization. All of these ADR were classified as mild. According to causality, 52.9% were possible, 44.1% were probable and 2.9% were defined.

**High-risk drug monitoring**

There were 85.5% of the patients were prescribed at least one drug of high risk during hospitalization, with an average of 1.7 (SD: 1.2) drugs per patient. In table 1, the high-risk drugs prescribed and the identified ADR associated with their use are shown.

Drugs that required dose adjustment according to GFR were: levofloxacin (60.0%), meropenem (20.0%) and enoxaparin (20.0%).

**Haematologic and blood biochemistry monitoring**

That it was found an average of 2.94 (SD: 2.37) altered biochemical and haematological parameters per patient. 79.1% of these alterations were present on admission. Of those, 25.3% were associated with drug use. These alterations were reduction of GFR: 26.9% (probable association with ARBs: 8.3%, possible association with loop diuretics: 41.7%, possible association with ACE inhibitors: 33.3%, possible association with ARBs: 8.3% and possible association with oral antidiabetics: 8.3%), hypokalemia: 22.3%, of which 22.9%
### Table I. High-risk drugs prescribed and associated ADR

<table>
<thead>
<tr>
<th>High-risk drug</th>
<th>Percentage of patients with the drug and an ADR</th>
<th>Description of the ADR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Enoxaparin (69.2%)</td>
<td>0%</td>
<td>No ADR identified</td>
</tr>
<tr>
<td>ACE inhibitors (21.2%)</td>
<td>34.8%</td>
<td>Reduction in GFR and hyperkalemia</td>
</tr>
<tr>
<td>Rapid-acting insulin SC (19.2%)</td>
<td>29.7%</td>
<td>Alterations in glycemia</td>
</tr>
<tr>
<td>Atenolol (15.4%)</td>
<td>23.8%</td>
<td>INR out of range, in the 66.7% due to drug interactions</td>
</tr>
<tr>
<td>Digoxin (9.6%)</td>
<td>40.0%</td>
<td>Non-therapeutic levels of digoxin in blood</td>
</tr>
<tr>
<td>ARBs (3.8%)</td>
<td>33.3%</td>
<td>Reduction in GFR and hyperkalemia</td>
</tr>
<tr>
<td>Oral antidiabetics (3.8%)</td>
<td>50%</td>
<td>Reduction in GFR</td>
</tr>
<tr>
<td>Morphine, IV (3.8%)</td>
<td>0%</td>
<td>No ADR identified</td>
</tr>
<tr>
<td>Transdermal Fentanyl (3.8%)</td>
<td>0%</td>
<td>No ADR identified</td>
</tr>
<tr>
<td>Metoclopramide, oral (1.9%)</td>
<td>0%</td>
<td>No ADR identified</td>
</tr>
</tbody>
</table>

ADR: Adverse drug reaction; ACE inhibitors: Angiotensin Converting Enzyme inhibitors; GFR: glomerular filtration rate; ARBs: Angiotensin receptor blockers.

Reported leg cramps (probable association with loop diuretics: 50.0%, probable association with potassium-free fluid: 25.0%, probable association with salbutamol: 12.5% and possible association with potassium-free fluid: 12.5%), hyperkalemia (14.4% (probable association with ARBs: 20.0%, possible association with ACE inhibitors: 60.0% and possible association with ARBs: 20.0%), INR out of range during hospitalization: 10.8% (possible association with drug interactions: 66.7%), hyperglycemia: 8.1% (probable association with corticosteroids: 66.7% and probable association with error in medication reconciliation at admission: 33.3%), hypoglycemia (5.2%: probable association with slow-acting insulin), fatty liver: 2.7% (possible association with antibiotics: 100%), hypothyroidism: 2.7% (defined association with high doses of methimazole: 100%), hyperthyroidism: 2.7% (probable association with high-dose thyroxine: 100%), hyperkalemia: 2.7% (probable association with loop diuretics: 100%).

Low molecular weight heparins were the most commonly used high-risk drugs, although they were not associated with the occurrence of any ADR. 69.2% of patients were prescribed enoxaparin, whose primary indication was DVT prophylaxis. Among the drugs that were associated with laboratory abnormalities were ACE inhibitors (reduction in GFR and hyperkalemia), subcutaneous rapid insulin (changes in blood glucose), aenocumarol (INR alterations, mainly due to drug interactions), digoxin (non-therapeutic levels) and ARBs (GFR reduction and hyperkalemia).

The current interest in DRAE began following the publication of the study *To err is human: Building a safer health system* (Kohn et al., 2004), which highlights the high morbidity attributed to drug use in hospitalized patients. The largest study to date in Spain on adverse effects related to hospitalization (ENEAS, 2005) shows an incidence of 9.3% of adverse events in hospitalized patients, with DRAE being the main type of adverse effect, since it represented a 37.4% of all adverse events detected.

In our study, 46.2% of the patients experienced some ADR during hospitalization. This data differs greatly from those obtained in other studies, where its incidence is usually between 4.5-9.0% (ENEAS, 2005; Berga et al., 2009; Gaviria et al., 2010). Two reasons may contribute to this difference: the first being that the cohort studies cited are retrospective, where there is a bias to underreporting. *Mainz Trenor et al.* (2010) in a prospective study, reported a higher incidence of ADR (51%) in patients admitted to Internal Medicine. The second reason may be that the two strategies in place...
to identify ADR (monitoring of laboratory parameters and high-risk drugs) are not methods used in most studies, and this new approach may have contributed to an increase in the sensitivity of ADR detection.

Age and number of drugs are directly associated with the appearance of DRAE. (Fernández-Regueiro et al., 2011), both being characteristics of patients hospitalized in Internal Medicine. The most frequently described ADRs are gastrointestinal problems and skin disorders, the main drugs involved being corticosteroids, anticoagulants, ENEAS, 2005; Berga et al., 2009; García et al., 2010; Sánchez et al., 2010). These ADRs were not identified in this study as our goal was to identify only those that cause alterations in biochemical and haematological parameters and are induced by high-risk drugs. The most frequent ADRs were: GFR reduction due to loop diuretics, ACE inhibitors and ARBs, hypokalemia due to loop diuretics and hyperkalemia due to ACE inhibitors and ARBs.

The severity of ADRs reported in the literature is usually mild or moderate. However, some may compromise the patient’s life. The percentage of serious reactions is between 4.4 and 18% (ENAES, 2005; Berga et al., 2009; Zapatero et al., 2010), among which are those associated with anticoagulants (bleeding), digoxin (arrhythmias), oral hypoglycemic agents and insulin (hypoglycemia). All ADRs identified in our study were mild, which could also be due to their rapid detection by close monitoring.

Modification of serum potassium levels associated with the use of drugs occurs in 6-10% of hospitalized patients (Esther et al., 2011). It has been published showing that patients with GFR < 50 are at increased risk of hyperkalemia. This study recommended an increase in the frequency of monitoring of serum potassium levels when certain drugs (such as potassium supplements, potassium-sparing diuretics, ACE inhibitors and ARBs), highlighting the importance of methods to support the prescription. For example, the reminder in the prescription every 3-4 days of potassium levels in patients receiving two or more of the above prescribed drugs.

CONCLUSION

Close monitoring of potassium levels as well as GFR in patients treated with loop diuretics, ARBs and ACE inhibitors may result in improved efficiency of ADR detection. Therefore, the implementation in electronic prescription of such warning messages would assist physicians in a more efficient management of resources in order to ensure patient safety.

CONFLICTS OF INTEREST

The authors declare no conflicts of interest.

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