Incidence of potential drug interactions in a transplant centre setting and relevance of electronic alerts for clinical practice support

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ABSTRACT

Background Adverse drug events may occur as a result of drug–drug interactions (DDIs). Information technology (IT) systems can be an important decision-making tool for healthcare workers to identify DDIs.

Objective The aim of the study is to analyse drug prescriptions in our main hospital units, in order to measure the incidence and severity of potential DDIs. The utility of clinical decision-support systems (CDSSs) and computerised physician order entry (CPOE) in term of alerts adherence was also assessed. DDIs were assessed using a Micromedex® healthcare series database.

Methods The system, adopted by the hospital, generates alerts for prescriptions with negative interactions and thanks to an ‘acknowledgement function’ it is possible to verify physician adherence to alerts. This function, although used previously, became mandatory from September 2010. Physician adherence to alerts and mean monthly incidence of potential DDIs in analysed units, before and after the mandatory ‘acknowledgement function’, were calculated.

Results The intensive care unit (ICU) registered the greatest incidence of potential DDIs (49.0%), followed by the abdominal surgery unit and dialysis (43.4 and 42.0%, respectively). The cardiothoracic surgery unit (41.6%), step-down unit (38.3%) and post-anaesthesia care unit (30.0%) were comparable. The operating theatre and endoscopy registered the fewest potential DDIs (28.2 and 22.7%, respectively). Adherence to alerts after the ‘acknowledgement function’ increased by 25.0% in the ICU, 54.0% in the cardiothoracic surgery unit, 52.5% in the abdominal surgery unit, 58.0% in the step-down unit, 67.0% in dialysis, 51.0% in endoscopy and 48.0% in the post-anaesthesia care unit. In the operating theatre, adherence to alerts decreased from 34.0 to 30.0%. The incidence of potential DDIs after mandatory use of the ‘acknowledgement function’ decreased slightly in endoscopy (–2.9%), the abdominal surgery unit (–2.7%), dialysis (–1.9%) and the step-down unit (–1.4%).

Conclusions Improving DDI alerts will improved patient safety by more appropriately alerting clinicians.

Keywords: clinical decision-support system, computerised physicians order entry, drug interactions
Introduction

Drug–drug interactions (DDIs) are a complex clinical problem that should draw the attention of all healthcare workers, especially physicians and pharmacists directly involved in choosing the right therapy for patients. Adverse drug events (ADEs) may occur as a result of potential DDIs (p-DDIs). Oftentimes they are predictable and preventable. These adverse events result in increased rates of hospitalisation, increased lengths of stay, and contribute to patient morbidity and mortality. Several factors can complicate the possibility of identifying and managing p-DDIs. For example, the use of polypharmacy, particularly common among older adults, increases the risk of having adverse drug reactions and/or interactions. A study of 4431 hospitalisations revealed an average of six drugs per patient. Another study, on 907 patients, revealed an average of 9.6 drugs per patient. The more associations there are among different drugs, the greater the chance that their safety profiles will be lowered.

Other factors, such as gender, age, genetics, comorbidities, and state of health are also linked to the risk of DDIs. The most vulnerable patients are those with chronic diseases that require long-term multitherapy; patients with liver or kidney failure who are using drugs included in the group at risk of interaction, and geriatric and paediatric patients, whose metabolic activity is significantly related to age. To ensure safe therapy for these patients, appropriate drug prescription is required. In the age of information technology (IT) systems, the use of electronic health records and computerised physician order entry (CPOE) can be an efficacy tool to promote patient safety. Clinical decision-support systems (CDSSs) are an additional component of CPOE systems that can be utilised and have been defined as ‘computer software employing a knowledgebase designed for use by a clinician involved in patient care, as a direct aid to clinical decision making’. CDSSs added to CPOE systems guide prescribers on appropriate dosing and alert them to duplicate therapies, drug allergies and DDIs. So patient safety, quality and efficiency of care can be improved.

Although CDSSs provide several benefits, there are also limitations as a result of which p-DDI alerts receive no response from physicians. Unclear clinical significance, alert fatigue and database rating inconsistencies can, at times, lead to low p-DDI alert acceptance by prescribers.

The goal of this study was to analyse drug prescriptions in our main hospital units, in order to measure the incidence and severity of p-DDIs. In addition, the utility of CDSS and CPOE in terms of alerts adherence was assessed.

Method

This retrospective observational study was carried out at ISMETT, a 90-bed transplant hospital in Palermo, Italy. All prescriptions in the intensive care unit (ICU), step-down unit (SDU), cardiothoracic surgery unit (CSU), abdominal surgery unit (ASU), dialysis, endoscopy, operating theatre (OT) and post-anaesthesia care unit (PACU), from June 2010 to December 2010, were analysed for p-DDIs. All interactions were assessed using the Micromedex Healthcare Series database, and severity of p-DDI was analysed according to the decisional support system classification (Table 1) in the Sunrise Eclipsys electronic medical record.

The mean incidence of p-DDIs for each unit was calculated. The value was obtained by dividing the mean number of p-DDIs for each unit by the mean number of drug prescriptions in that unit for each period of evaluation.

The program developed and adopted by our hospital allows physicians to obtain helpful information on drug prescriptions. It also generates alerts in case of active agents with negative interactions. It is possible to verify adherence to p-DDI alerts through the electronic medical record. This verification was made
possible thanks to an ‘acknowledgement function’, which carries the electronic signature of the physician (statement read yes/no) indicating his or her acknowledgement of the interactions. Statement read ‘yes’ means the physician displayed and read the alert and is aware that the combination drug choice is potentially harmful for the patient. This function, in the first period of study, was not required, so physicians could proceed with the prescription without responding to any alert. Beginning in September 2010, the ‘acknowledgement function’ became mandatory, prompting physicians to consider the alert. ‘Acknowledgement function’ can aid physicians to choose, when possible, a therapeutic alternative. For each unit, the adherence to alerts on the part of physicians and the incidence of p-DDIs, before and after introduction of the ‘acknowledgement function’, were compared to verify the function suitability as a strategy for improving quality of the process.

A pivot table was used as an analytical and reporting instrument in which the available data were processed by type of drug, unit and number of p-DDIs, and physician adherence to the alerts.

### Results

The ICU registered a mean of 1053 p-DDIs for a mean of 2152 prescriptions per month (49.0%), followed by ASU and dialysis with an average of 604 and 15.6 p-DDIs, respectively, for a mean of 1390 and 37 prescriptions (43.4 and 42.0%, respectively). CSU registered a mean of 520 p-DDIs for a mean of 1248 prescriptions monthly (41.6%), SDU registered a mean of 596 p-DDIs for a mean of 1555 prescriptions monthly (38.3%) and PACU registered a mean of 99 p-DDIs for a mean of 332 prescriptions per month (30.0%).

OT and endoscopy, the smallest units, registered a mean of 166 p-DDIs for a mean of 588 prescriptions monthly (28.2%), and 8.8 p-DDIs for a mean of 39 prescriptions monthly (22.6%), respectively. Overall analysis of prescriptions identified the top five drugs responsible for p-DDIs in the main units in our hospital: furosemide (1768 p-DDIs), tacrolimus (1496 p-DDIs), omeprazole (801 p-DDIs), sodium-fructose-1.6-diphosphate (428 p-DDIs) and warfarin (395 p-DDIs). Although these interactions are known in the literature, the subject is so vast and growing both for mechanisms that determine p-DDIs and appearance on the market of new drugs, that remembering their importance is never enough.

In the first period of study (June 2010 to August 2010) adherence to alerts was 70.0% in the ICU, 41.0% in the CSU, 43.0% in the ASU, 36.0% in the SDU, 29.0% in dialysis, 10.0% in endoscopy and 42.0% in the PACU. From September 2010 to December 2010, after introduction of the mandatory reading of alerts for physicians, a marked improvement was found: 95.0% in the ICU, 95.0% in the CSU, 95.5% in the ASU, 94.0% in the SDU, 96.0% in dialysis, 61.0% in endoscopy and 90% in the PACU. In OT adherence to alerts decreased from 34.0 to 30.0%. A positive trend was observed (reduction of p-DDIs) in four units, which might be due to the greater adherence to warning systems. The better results were in endoscopy and ASU with a reduction of 2.9 and 2.7%, respectively, followed by dialysis and SDU with a reduction of 1.9 and 1.4%, respectively (Table 2).

Considering the total number of drug prescriptions (51 393) in the study period (seven months), the total number of p-DDIs was 21 447, or 41.7%.

### Table 1 Multum drug database of alert severity levels

<table>
<thead>
<tr>
<th>Alert severity levels</th>
<th>Definitions</th>
<th>Reported lesions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Major</td>
<td>Monitor closely Contraindicated Generally avoid</td>
<td>Death or life-threatening lesions</td>
</tr>
<tr>
<td>Moderate</td>
<td>Monitor Generally avoid Adjust dosing interval Adjust dosing Additional contraception recommended</td>
<td>Severe lesions, not lethal</td>
</tr>
<tr>
<td>Minor</td>
<td>None</td>
<td>Clinical effects insignificant, minor or favourable</td>
</tr>
</tbody>
</table>

Example of table 1 showing the Multum drug database of alert severity levels with different severity levels and definitions along with reported lesions.
Discussion

Principal findings

DDIs are a complex and controversial part of pharmacology. Our study showed that almost 42.0% of drugs prescribed in the analysed period and in the units reviewed interacted with other drugs prescribed for therapy. This may be because many of our patients are seriously ill and require multidrug therapies. Of the eight units evaluated, the ICU registered the greatest number of p-DDIs, followed by ASU and dialysis. CSU, SDU and PACU are comparable with the larger units in terms of number and type of interactions, whereas OT and endoscopy registered the fewest p-DDIs.

Another important result that emerged from the data was the increasing adherence on the part of physicians to the software alerts. More specifically, ASU, SDU and dialysis are among the units where there is more adherence. Effectively, in these units, there was a decrease, although low, in the incidence of p-DDIs from 42 to 39%. The exception was the OT in which adherence is very low. It was assumed that this may be due to unforeseen emergency situations that often occur. It is right, also, to remember that in the OT there is always an anaesthetist present to carefully monitor the patient. This study has identified the five drugs more involved in p-DDIs in our hospital, this could be a starting point for all healthcare workers responsible for medication safety.

It is hard to predict the clinical impact of p-DDIs. As a result, the rational and appropriate use of multidrug therapies is a key factor of prevention. Often p-DDIs cannot be avoided because of the need to use drugs in combination, especially when there are no therapeutic alternatives. This limitation is mitigated by constant patient monitoring of vital signs and drug blood levels. Despite a small reduction in p-DDIs, implementing computerised alerts can be an effective way of supporting clinical decision making, allowing clinicians to see all possible p-DDIs and evaluate their impact in terms of potential risks and benefits. Introducing alerts does not replace physician assessment: patients cannot be deprived of therapies based solely on the risk of interactions, but all alternatives must be taken into account. In conclusion, it is important to make alerts as effective as possible. In this context new technologies can aid physicians and improve prescribing safety. However, there is yet the need to determine the most effective way to deliver alerts in order to eliminate possible unnecessary alerts.

Implications for practice

Although a slight decrease in the incidence of p-DDIs was observed, development of the ‘acknowledgement function’ has increased physician adherence to alerts. This is an important starting point for advanced forms of CDSSs that should support the physician in identifying important p-DDIs without generating clinically irrelevant alerts.

Comparisons with the literature

As widely addressed by Vaziri et al., the prescribing alert systems used in primary care practice often have

| Table 2 Incidence of potential DDIs before and after introducing the ‘acknowledgement function’ |
|----------------------------------|----------------------------------|----------------------------------|
|                                 | June/July/August interactions (%) | September/October/November/December interactions (%) | Δ (%) |
| ICU                             | 47.0                             | 50.4                             | 3.4   |
| SDU                             | 39.2                             | 37.8                             | −1.4  |
| CTU                             | 41.0                             | 42.4                             | 1.4   |
| ASU                             | 45.0                             | 42.3                             | −2.7  |
| OT                              | 27.2                             | 28.7                             | 1.5   |
| PACU                            | 27.1                             | 31.9                             | 4.8   |
| Dialysis                        | 43.4                             | 41.5                             | −1.9  |
| Endoscopy                       | 24.4                             | 21.5                             | −2.9  |
low specificity and low utility. In fact, alerts are often ignored, or viewed uncritically by physicians, who rely on their experience, and on a careful monitoring of patients. Healthcare IT leaders are working to resolve this important issue to everyone’s benefit, increasingly implementing systems that put out only effective alerts or apply alerting strategies.

Limitations of the method
Alerts for interaction have a number of important limitations. Checking drug interactions can generate large numbers of clinically insignificant alerts (low severity) that clinicians might ignore. We experienced this at our hospital because too many p-DDIs of low priority were displayed, leading the user to reject the entire application. We urgently need better evidence on which p-DDIs are important. The strength of the alerts should be related to the severity and importance of the interactions, only in this way ‘alert fatigue’ may decrease.

Calls for further research
CDSSs must support rather than impede, clinical work-flows through speedy, available and usable algorithms that provide parsimonious, clear, concise and actionable warnings and advice. A potential solution beyond using alerts in or not in this situation would be continuing to deliver decision support but, when alerting, ask clinicians explicitly whether the patient has an infection that requires treatment for which there is no other good option. Alerts should present the names of the interacting drugs, a brief description of the interaction, optional link to more detailed information and a menu for appropriate actions in response to the alert.

Conclusion
p-DDIs might cause an important amount of harm, which is largely preventable. The main goal for all healthcare workers is to participate in a system that ensures patient safety, and this should include evaluation of severe p-DDIs. There is a need for modification of DDI alerting systems to increase alert acceptance and maximise the benefits of this technology. For this reason, the optimisation of resources by improving DDI alerts through careful and constant monitoring of therapies can ensure safer and more appropriate prescriptions.

ETHICAL APPROVAL
This study was approved by the Institutional Review Board and Ethic Committee of ISMETT.

CONFLICTS OF INTEREST
None.

REFERENCES
13 Obreli Neto PR, Nobili A, de Lyra DP Jr et al. Incidence and predictors of adverse drug reactions caused by


29 Vaziri A, Connor E, Shepherd I, Jones RT, Chan T and de Lusignan S. Are we setting about improving the safety of computerised prescribing in the right way? A workshop report. Informatics in Primary Care 2009;17:73–82.


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