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Relevance of drug-drug Interaction in the ICU - Perceptions of Intensivists and Pharmacists

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Abstract. Relevancy of potential drug-drug interactions (pDDIs) is crucial in alerting system design. However, the way this relevancy is perceived is not well understood. The main objective of this study was to gauge and identify differences in perceptions of intensivists and pharmacists about pDDI relevancy in the ICU. Interactions were defined according to the national medication database using a computerized algorithm. Intensivists and pharmacists filled in a questionnaire to score their perceptions on relevancy of encountered pDDIs types. We conducted a focus group session to discuss pDDIs receiving markedly different relevancy scores. The questionnaire addressed 53 pDDI types. Pharmacists rated 29 pDDI types (54.7%) in the broad category "relevant" versus 16 (30.2%) for intensivists (p-value < 0.001). The pharmacists and intensivists gave the same scores for 23 pDDI types (12 as relevant, and 11 as not relevant), and scored 30 types differently. The focus group discussion resulted in a total of 36 relevant and 17 not relevant types. Compared to the pharmacists in this panel, the intensivists were less inclined to consider a pDDI type as relevant. It is important to tailor medication databases with information about evidence and severity of pDDIs to the environment in which they are used.

Keywords: Drug-drug interaction relevance, Intensive care, Alert systems

Introduction

Medication errors, such as adverse drug–drug interactions (DDIs), may compromise patient safety in the ICU. Computerized order entry and alerting systems provide an opportunity to identify and prevent medication errors [1]. Although these systems can be effective, studies showed that drug safety alerts are overridden frequently [2].

Some studies investigated factors affecting pDDI relevancy and improving alert acceptance [3;4]. DDI databases used for generating alerts should be considered in the context of the environment, including the users, in which the alerting systems operate [1]. Intensive care units (ICU) form a special environment in the hospitals due to the complex nature of the care processes provided to critically ill patients and the great reliance on medication. A recent study showed that interaction databases do not

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concord with pharmacists' assessment of severity of DDIs in the ICU settings [1]. No study, however, has elucidated the perception of intensivists on the relevance of DDIs in the ICU, and hence no comparisons exist with the pharmacists' perception.

The goal of this study was therefore to investigate which of the generated DDIs according to the Dutch national database were relevant in the perception of intensivists and pharmacists, how these perceptions differ among groups and with the national database in the ICU settings.

1. Methods

1.1. Settings

The adult ICU under study is 30-bed "closed format" department in an academic ICU in a large teaching hospital in the Netherlands, with medical/surgical patients (including cardiothoracic and neurosurgical patients). Since 2002, our ICU has been using a commercial patient data management system that runs on the MS Windows platform and includes computerized physician order entry. There was no alerting system available at the time of the study. The data on drug administration between 15-4-2002 and 15-12-2008 was extracted from this system.

1.2. Determining the relevant potential DDIs

To determine the DDIs based on their clinical importance and severity, we performed a retrospective study to find the potential DDIs based on a Dutch national pharmacology database (*G-standard*). This database includes all possible DDIs. They are classified on a six-point potential clinical relevance scale ranging from not very serious to potentially deadly (categories A-F), and on a five-point evidence scale, from not proven to clinically strongly proven (categories 0-4). A computerized algorithm has been developed that checks per patient whether one or more combinations of contraindicated medication recorded in the interaction database are present. Patient demographics, doses, routes of administration and severity ranking were not considered. A unique list of all the present combinations was constructed.

To focus on the clinically relevant drug interactions a questionnaire was sent to experts by email. Our panel consisted of 5 ICU specialists and 4 hospital pharmacists. From the unique interactions found, those combinations that had severity code D, E or F or of which the severity was unknown were selected. The clinicians were asked to score the relevancy (for the ICU) of each DDI using one of the following categories:

1. It is not relevant, as it has no consequent effect on the ICU patient;
2. It is relevant, but the consequences are acceptable for the ICU patient;
3. It is relevant but one can monitor the consequences through extra supplementary diagnose/ measurements;
4. It is relevant but the consequences of the interaction are treatable;
5. It is an absolute contraindications;
6. I do not know.

In the analysis, categories 1 and 2 were considered "not relevant" while categories 3, 4, and 5 were considered "relevant". Results were sorted for pharmacist, intensivists, and both combined. If the majority (66%) of the pharmacists and intensivists agreed that a pDDI was relevant or not relevant for the ICU then this was regarded as decisive.

If there was disagreement between the pharmacists and intensivists, the pDDI was marked for discussion in the focus group. A 2.5 hours focus group session consisting of 2 specialists and 2 pharmacists was planned to discuss any pDDIs classified differently by the two groups. The goal of the focus group was to reach consensus on relevancy of the indecisive scores. We used the Fisher exact test for testing the significance of the difference in scores between the pharmacists and the intensivists.

2. Results

Our computerized algorithm identified 2,662,230 record combinations with at least one pDDI corresponding to 3,892 admissions out of 9,644 admissions to the adult ICU during a 6 year period. The identified pDDIs corresponded to 85 pDDI types (unique administration with pDDIs) out of 330 possible types that appear in the *G-standard*.

After screening the 85 pDDI types based on the selected severity, 53 remained and were included in the survey. The survey was sent to nine local experts and the results showed that 12 pDDI types were scored similarly as relevant (23%) and 11 types not relevant (21%) by both groups. Thirty pDDI types (56%) remained indecisive. After the focus group session, from the 30 not decisive DDIs, 24 were rated as relevant for ICU patients and 6 as not relevant. Table 1 shows which pDDI types are considered relevant and those that were considered as not relevant. In total 36 pDDI types (68%) were scored as relevant and 17 (32%) as not-relevant. Interestingly, 18% (3 out of 17) of the pDDI types were rated as severe in the national database but not by our panel of experts for the ICU settings. 55% of the pDDIs were considered relevant by pharmacists and 30% by intensivists (p-value < 0.001). The results of the survey showed that 14 pDDI types (26%) were rated in the category 3 or 4 of the survey by the intensivists, while no pDDI types were rated by the majority of the pharmacists in groups 3 and 4 in the survey.

Table 1: Results of the survey(S) and focus groups (FG) tabulated for pharmacists and intensivists for the relevant and not-relevant DDI types.

Relevant DDI types					
Medication type 1	**Medication type 2**	**Intensi-vists (%)**	**Pharma-cists (%)**	**S/FG selection**	**Seve-rity**
Ace inhibitors	Diuretics	80	75	S	D
Raas inhibitors	Potassium-sparing diuretics	80	75	S	F
Coumarins	Serotonin reuptake inhibitors	80	100	S	D
Lithium	Diuretics	80	100	S	D
Coumarins	Protease inhibitors (excluding ritonavir) / efavirenz	80	100	S	*
Coumarins	Cefamandole	80	100	S	*
Coumarins	Fluconazole / voriconazole	80	100	S	F
Protease inhibitors	Efavirenz / nevirapine	80	100	S	*
Cyclosporine	Clindamycin	100	100	S	E
Lopinavir	Atovaquone/proguanil, fluconazole, ribavirin, probenecid, methadone, valproic acid	100	75	S	*
Lopinavir	Atovaquone/proguanil, bupropion lamotrigine , levothyroxine	75	100	S	*
Qt-prolonging drugs	Qt-prolonging drugs-(arizona)	100	100	S	F
Raas inhibitors	Nsaids	60	50	FG	D
Amino glycosides	Amphotericin b	80	50	FG	D

Amino glycosides	Cisplatin / carboplatin	40	100	FG	D
Lactam antibiotics	Tetracyclines	60	75	FG	F
Nonselective beta-adrenergic blocker	Insulin	60	100	FG	D
Coumarins	Allopurinol	40	100	FG	D
Coumarins	Amiodarone / propafenone	60	100	FG	D
Coumarins	Antibiotics (excluding cotrimoxazole / metronidazole / cefamandole)	60	50	FG	D
Coumarins	Metronidazole	60	100	FG	D
Potassium salts	Potassium-sparing diuretics	40	50	FG	F
Ketanserin	Potassium-losing diuretics (thiazides and loop-diuretics)	60	100	FG	D
Diuretica	Nsaids	40	50	FG	D
Tacrolimus	Nephrotoxic agents	25	50	FG	D
Cisapride	Fluoxetine / fluvoxamine / quinine	40	25	FG	D
Coumarins	Antithyroid agent	60	100	FG	*
Coumarins	Salicylates (< 100mg)	60	50	FG	F
Atazanavir / nelfinavir / indinavir / tipranavir	Proton pump inhibitors	20	100	FG	F
Efavirenz / nevirapine	P450 enzyme-inductors (excluding rifampicin)	25	100	FG	D
Lopinavir	P450-enzyme inductors	25	75	FG	*
Mycophenolic acid	Abacavir / didanosine	33	75	FG	*
Mycophenolic acid/ tacrolimus	Sevelamer	50	100	FG	*
Ssri's / venlafaxine	Thiazides	40	75	FG	*
Carbamazepine / oxcarbazepine	Diuretica	60	75	FG	*
Qt-prolonging drugs (non-arizona)	Qt-prolonging drugs (arizona)	75	25	FG	*

Non-relevant DDI types

Medication type 1	**Medication type 2**	**Intensivists (%)**	**Pharmacists (%)**	**S/FG selection**	**Severity**
Amino glycosides	Loop diuretics	80	100	S	*
Bisacodyl oral	Antacids	100	100	S	*
Tacrolimus	Quinolones	100	75	S	*
Coumarins	Phytomenadione	80	75	S	D
Alpha-adrenergic blockers	Raas inhibitors/ diuretics	100	100	S	*
Quinolones	Nsaids	100	100	S	*
Clopidogrel	Acetylsalicylic acid	80	100	S	*
Tolcapone / entacapone	Various substances[$]	100	100	S	*
Cyclophosphamide	Various substances[$]	100	75	S	*
Methotrexate / fluorouracil / cyclophosphamide	Thiazides	100	75	S	*
Methotrexate methotrexate	Various substances[#]	100	100	S	*
Corticosteroids	P450-enzyme inductors	50	25	FG	D
Acetazolamide	Thiazides & loop diuretics	80	50	FG	*
Lopinavir	Special agents[!]	25	75	FG	*
Selective beta-adrenergic blockers	Beta-adrenergic agonists	40	25	FG	*
Zidovudine	Special agents[!]	25	75	FG	*
Theophylline	Allopurinol / disulfiram	40	100	FG	D

D: Long period (>168 hours) or lasting symptoms, or disablement; E: Potential failure of life saving therapy, arrhythmia, rhabdomyoysis, malignant hypertension, pseudo feochromocytome, multi-organ failure; F: Death, torsade de pointes ventricular arrhythmia, myocardial infarction, serotonin syndrome, hyperpyrexia (42°C));*: no severity known; $: Amiodarone, benzodiazepines, bupropion, captopril, ceftriaxone, chloramphenicol, chlorpromazine, chloroquine,dapsone, indomethacin, insulin, metronidazole, morphine, nifedipine, sulphonylureas; !: Atovaquone/proguanil, fluconazole, ribavirin, probenecid, methadone, valproic acid; #: Allopurinol, amiodarone, ascorbic acid, chloramphenicol, furosemide, haloperidol, hydrocortisone, prednisone,tolbutamide, triamterene.

3. Discussion

Identification and prevention of potential DDIs is an important aspect of patient safety. Computerized decision support systems (CDSS) have been devised to alert on and reduce the number of pDDIs. The DDI databases that are used in designing the alerting systems are mostly designed by the pharmacists and are based on the literature and are not environment specific. The results of our study however showed that the intensivists are less inclined to label a DDI as important for ICU patients compared to pharmacists and to interaction databases. Using such databases for alert-design without considering relevancy can lead to alert fatigue. Intensivists are aware of the consequences of prescribing two interacting drugs but because they continuously monitor patient vital parameters they are able to control or treat the consequences of pDDI in the ICU. In addition, the text of the alert could also be adapted based on the perception of the intensivists per pDDI type. Instead of only reminding them about pDDI occurrence, the alert system should tell them how to manage and treat a DDI when needed.

This study is the first eliciting intensivists' opinion on pDDI relevance at the ICU and investigating differences with pharmacists' perceptions. Our study has some limitations. First, it was performed in a single centre ICU. The measured relevance of the pDDI types has a certain level of subjectivity as is inherent to the reliance on a focus group. Finally, the algorithm was uninformed about patient demographics, doses, and routes of administration.

In general, our findings showed a discrepancy in the theoretical relevance of pDDIs as expressed in the *G-standard* and the practical relevance as perceived by the pharmacists and intensivists. We believe that our findings can contribute to a better alert acceptance and in consequence a greater trust by users.

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