Potential drug-drug interactions in the intensive care

Frequency, clinical relevance and improvement strategy

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CHAPTER 1

General introduction

GENERAL INTRODUCTION

Medication safety

Drugs are prescribed as an important part of medical treatment for patients. During the process of medication prescribing, medication errors can occur. These errors can occur due to various reasons, on the human, environmental and organizational level, such as for example fatigue, staff shortages or inadequate training.[1,2] Medication errors can result in (severe) patient harm, disability and even death. Therefore, medication safety is a major concern in medical care.[3] In addition, the costs associated with medication errors are estimated at $42 billion USD yearly worldwide.[2]

When a medication error results in patient harm, we speak of an adverse drug event (ADE). An ADE is defined as any harm experienced by a patient resulting from the exposure to a drug. ADEs occur in 19% of hospitalized patients.[4] In a systematic review evaluating costs of ADEs in various countries, the costs of an ADE ranged from €702 to €40.273 for outpatients and from €943 to €7192 for inpatients.[5] Approximately, 16% of all ADEs in hospitalized patients are caused by a drug-drug interaction (DDI).[6]

A DDI occurs when two drugs are administered concomitantly and interact through pharmacokinetic or pharmacodynamic mechanisms, resulting in an unintended increased or decreased effect of one or both drugs. This can lead to toxicity or therapy failure, causing harm to the patient.[7] For instance, the concurrent use of corticosteroids and NSAIDs can lead to a gastrointestinal bleeding (a type of ADE), as both drugs individually increase the risk of bleeding, and when used together, this risk increases further.[8] DDIs that lead to an ADE are considered preventable, as the administration of two drugs known to potentially interact is considered a medication error.[9]

In the field of medication safety and this thesis, the administration of two drugs known to interact, resulting in the patient being exposed to both drugs simultaneously, is called a potential DDI (pDDI). The term "potential" implies that there is uncertainty about whether the exposure will cause a DDI in the patient's body, resulting in an ADE. Whether or not an actual DDI occurs, depends on various factors such as the patient's renal and liver function, drug dosage, and duration of the administration. Therefore, the term "potential" indicates the possibility of an ADE resulting from exposure to two drugs known to interact.

A clinically relevant pDDI is a pDDI that is considered clinically relevant within its clinical setting, due to the potential, clinically relevant consequences. In Chapter 5 we shifted to the term 'high-risk drug combination' instead of clinically relevant pDDI, but it means the same. We introduced this term to convey a clear message that the patient is certainly exposed to two drugs known to interact and this *may* result in clinically relevant consequences. Figure 1 provides an overview of the relations between these terms.

ICU setting

Intensive care units (ICUs) are specialized hospital wards that provide round-the-clock care for patients who are critically ill or at a high risk of becoming critically ill. ICU patients often require treatment for life-threatening conditions such as sepsis, trauma, heart failure, or respiratory failure. ICU care may also be required after major surgeries, such as heart surgery or neurosurgery, to monitor and manage potential complications.[10] Intensive care involves intensive treatment and close monitoring. Sophisticated equipment is used to monitor and support the vital signs and functions of ICU patients. For example, the heart rate and blood pressure are continuously monitored, a mechanical ventilator may be used to support the patient's breathing function, a form of dialysis may be used to the support kidney function, and intravenous lines and pumps are used to provide fluids, nutrition and medication to the patient.[11] As ICUs deal with complex processes and medical conditions, intensive care is expensive, vulnerable and prone to error.[12]

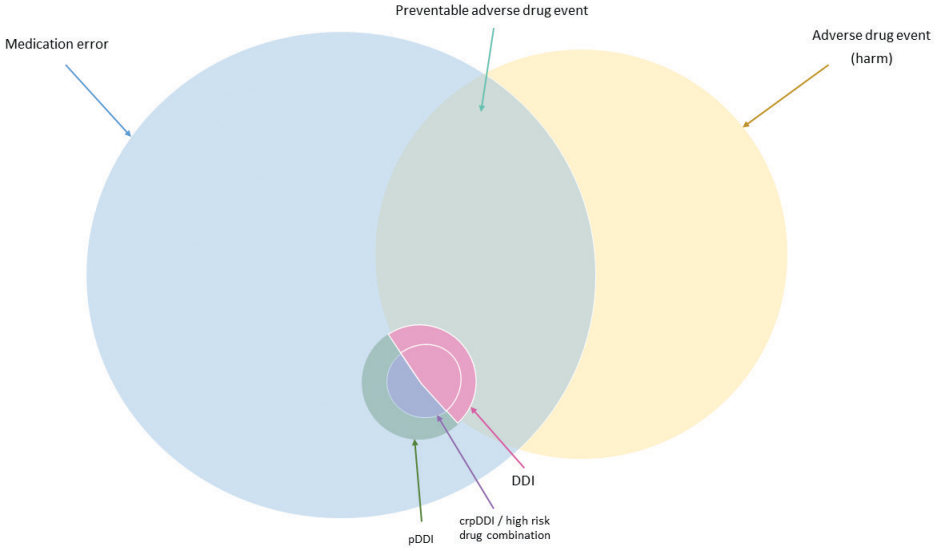

Figure 1 Overview of terminology and relation between terms

In the ICU, medication is an important part of the patient's treatment, and it is common practice to use multiple medications concomitantly. In the ICU, patients are more likely to be exposed to and experience harm from DDIs. A recent systematic review estimated that 58% of the ICU patients are exposed to a pDDI, which is twice as much as in general wards. [3,13,14]

The use of multiple drugs (polypharmacy) increases the risk of being exposed to a pDDI. On average, ICU patients receive 30 different medications during their stay, with each intravenous medication administered increasing the risk of an ADE by 3%.[13,15] In addition, ICU patients are in a critical condition and administration of drugs known to interact may be necessary for the patient to survive, despite the risk of harm. Furthermore, ICU patients are at a higher risk to

experience harm from a DDI resulting in an ADE, because of often-present impaired absorption, diminished renal and hepatic function influencing drug elimination and clearance.[16,17] On the other hand, ICU patients are extensively and continuously monitored, facilitating effective and timely risk management. If a pDDI cannot be avoided, monitoring can prevent or ameliorate harm. Monitoring may include monitoring laboratory values, making electrocardiograms (ECGs), checking for symptoms of harm, and monitoring the plasma concentration of a drug.

CDSS

Computerized decision support systems (CDSSs) are systems that link patient data with domain knowledge (e.g. medical guidelines, medical handbooks, scientific literature) to support clinicians in their decision making process, and are applied in many aspects of care, including prescribing.[18] Several studies have shown the potential of CDSSs to help prevent pDDIs. [19,20] Such CDSSs support clinicians to prescribe medication safely by showing alerts for pDDIs during drug order entry. When a pDDI alert is shown, the clinician can decide to cancel the prescription of one or both drugs involved, or continue while monitoring the patient.

However, current CDSSs generate an overload of irrelevant pDDI alerts. In the ICU, around 90% of the pDDI alerts are overridden, and most of these overrides seem appropriate, as these alerts warn for pDDIs that are not perceived as clinically relevant.[16,21] Therefore, the clinical relevance of pDDIs is essential for the acceptance of CDSSs and their effective use in supporting safe prescribing.[18]

If the majority of alerts is overridden there is a serious chance of alert fatigue. Van der Sijs et al. applied Reason's model of accident causation to drug safety alerting.[22] The model shows that when the system produces irrelevant alerts, this desensitizes clinicians and leads to alert fatigue, which leads to overriding alerts. In turn, high override rates increase the risk of missing the alerts that *are* clinically relevant, and missing those may compromise patient safety.[22,23]

Lack of a fit between the clinical setting and pDDI alerts can be a cause of irrelevant alerts.[22] We hypothesize that tailoring pDDI alerts to the ICU setting by showing alerts only for clinically relevant pDDIs would improve the fit between the ICU setting and pDDI alerts, reduce alert fatigue and alert overrides, and ultimately enhance the effectiveness of CDSSs. This, in turn, would decrease the occurrence of clinically relevant pDDIs, i.e. reduce patients' exposure to high-risk drug combinations.

The research questions of this thesis therefore are:

1. What is the frequency of pDDIs and high-risk drug combinations in the ICU, and which pDDIs are clinically relevant in the ICU setting, in the sense that they require regimen change or monitoring?
2. Does tailoring pDDI alerts to the ICU setting reduce the frequency of administering high-risk drug combinations?

Aim and outline of this thesis

To contribute to answering the first research question, in Chapter 2 we performed a systematic review on the identification and reporting of pDDI frequency in the ICU setting. In Chapter 3, we described the rationale and protocol for the studies discussed in the following chapters. To answer the first research question, in Chapter 4 we identified which pDDIs are considered clinically relevant for the ICU setting through a standardized and rigorous Delphi procedure with a national expert panel of intensivists and hospital pharmacists. In Chapter 5, we described the frequency of these clinically relevant pDDIs (high-risk drug combinations) in 13 Dutch ICUs, based on a large retrospective observational multicenter dataset. To answer the second research question, we used the resulting set of clinically relevant pDDIs to tailor alerts in the ICU. In Chapter 6, we evaluated the effect of this tailoring strategy on the frequency and monitoring of high-risk drug combinations in the ICU, in a multicenter cluster randomized stepped-wedge trial.

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