2

Preventing adverse drug events in hospital practice: an overview

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Summary

Adverse drug events (ADEs) are a considerable cause of morbidity and mortality in hospital practice. The precise frequency is unknown, but studies give an incidence number ranging from 2 until 52 ADEs per 100 patients. There are many different methods for definition, causality assessment, severity classification and detection of ADEs which make it difficult to compare the different studies. A substantial part (in some studies up to 70%) of ADEs can be prevented and it is important to, besides their detection, focus on the prevention of these ADEs. In this literature review we give an overview of methods for preventing ADEs. There are many different tools with different impact on a particular part of the distribution system which has the potential to prevent ADEs. A multifaceted approach is needed. Two interesting strategies of prevention, pharmacist participation on ward rounds and computerised physician order entry with clinical decision support systems (CDSS), are highlighted. Moreover, two promising CDSS are discussed in more detail, namely computer-based monitoring systems and information systems which link laboratory and pharmacy data.

Introduction

Drug use was the leading cause of adverse events, defined as an injury due to medical treatment, in the Medical Practice Study. These so-called Adverse Drug Events (ADEs) were accounting for 19.4% of the injuries found in this study [1]. Since then, ADEs have been a subject of intense research. There is an enormous amount of data about the incidences, detection and costs of ADEs. The precise frequency is unknown, but studies give an incidence number ranging from 2 until 52 ADEs per 100 patients [2-13].

The reported incidence figures of ADEs depend partly on different variables, such as definition, causality assessment, severity classification and detection methods. The World Health Organization (WHO) defines an ADE as 'any untoward medical occurrence that may be present during treatment with a medicine but which does not necessarily have a causal relationship with this treatment' [14]. This definition is often simplified to the more straightforward description 'an injury resulting from the use of a drug' [3,15].

ADEs can be divided into intrinsic and extrinsic harm. Intrinsic harm is the result of the pharmacological properties of the drug itself and is also called adverse drug reaction (ADR). Extrinsic harm is related to the manner the drugs are used and is also referred to as medication error. Potential ADEs, in contrast to actual ADEs, are medication errors with the potential to cause an injury but which do not necessarily cause any injury [15,16]. Different classification methods are described in the literature, varying in simplicity from NCC MERP medication error index to just mild, moderate and severe [3,5,16-19]. Also varying degrees of causality assessment are used [14,20-22]. Methods for the detection of ADEs are voluntary report, chart review and computer-based monitoring systems [3,5,12,19,23-26].

All these variables reduce the ability to make generalisations about the data on ADEs and make it difficult to compare the studies.

Besides these limitations it is the widespread impression that ADEs in hospitals are costly and prolong hospitalisation [6,27,28]. Most adverse events, including ADEs are preventable, particularly those due to error or negligence [3]. Theoretically, increasing the knowledge on ADEs and its understanding may turn into a higher proportion of ADEs becoming preventable.

Since a substantial proportion of ADEs can be prevented it is important to, after the detection, focus on the prevention of ADEs. An important step in reducing the incidence of adverse events is to identify the patients at highest risk for ADEs. However, in common hospital practice it is quite difficult to decide where and how to start. With this in mind, we have

reviewed the literature to provide our overview on different useful methods of prevention of ADEs. These useful and promising tools for detecting patients at risk for ADEs may contribute to an improvement of drug safety.

Methods

A literature search using Pubmed was performed to search for articles published between 1990 and February 2007. The search was done using the terms 'adverse drug events' in combination with 'prevention' and 'hospital'. The reference sections of all retrieved articles (in English) were manually searched for additional articles. Publications covering ADEs encompassing either medication errors and/or adverse drug reactions were included. Papers covering outpatient problems were excluded because we focus on hospital prevention of ADEs. Rather than exhaustively reviewing the literature on this topic, we selected papers that reflect exemplary current practice and suits our abilities and interest in relation to CPOE and CDSS and pharmacist ward participation as strategies to prevent ADEs.

Prevention of ADEs

Obviously, ADEs form an important and costly problem in the current health care system. As a considerable part of the ADEs are considered preventable, it seems logical to approach this problem by focusing on the preventable ADEs. In order to prevent ADEs it is important to detect them first. However, it is less clear where and how to start in a complex health care environment with a variety of clinical fields, medical professionals, types of patients and therapeutic options.

In a system analysis of ADEs, Leape et al. [29] found 16 major system failures as the underlying causes of the errors. The most common system failure was in the dissemination of drug knowledge, particularly to physicians, accounting for 29% of the errors. Physicians made many prescribing errors that appeared to be due to deficiencies of knowledge of the drug and how it should be used. These included incorrect doses, dosage forms, dosage regimens and routes of administration, as well as errors in the choice of drugs. The systems for verifying that the proper drug is delivered in the proper dose sometimes failed in both the pharmacy at dispensing and nursing at administrating the drug. A significant cause of identity errors was look-alike packing and sound-alike names for drugs. Inadequate availability of patient information was associated with 18% of errors. Information about the patients' condition, results of laboratory tests, current medications and recent doses were

sometimes not easily accessible when it was needed, leading to prescribing errors as well as inappropriate administration of ordered drugs. Pharmacists sometimes lacked information about clinical characteristics of patients and results of laboratory tests that would have enabled them to intercept an improper order. Other system failures were order transcription, allergy defence, medication order tracking and interservice communication [29]. Bates et al. [30] proposed a risk stratification model for patients likely to experience an ADE using a cohort analysis and a case-control study. However, almost none of the proposed 'risk factors', such as age, multiple drug therapy and impaired renal function, were actually associated with a substantially elevated risk of developing an ADE. No major drug class was responsible for a disproportionate share of the ADEs, with the possible exception of analgesics. They concluded that rather than targeting patients at high risk of experiencing an ADE, prevention strategies should focus on improving medication systems [30], for example implementing a patient safety program [30-32] or performing risk assessment with multidisciplinary teams [33]. In a paediatric setting, Fortescue et al. [34] analysed 10 medication error prevention strategies for their potential effectiveness in reducing both overall error rates and potentially harmful error rates. These10 strategies included: (1) basic computerised physician order entry (CPOE); (2) CPOE with clinical decision support systems (CDSS) including checks of drug ordering and patient factors; (3) a clinical pharmacist on physician rounds or monitoring medication ordering, transcribing and delivery; (4) changes in communication; (5) computerised medication administration records; (6) robots in drug dispensing; (7) 'smart' intravenous devices for performing dilutions; (8) barcoding of drugs and patients; (9) automated bedside dispensing devices and (10) unit-based dosing. They found that three interventions might have prevented 98.5% of all potentially harmful errors being CPOE with CDSS, ward-based clinical pharmacists monitoring ordering, transcribing and administering and improved communication among physicians, nurses and pharmacists [34].

A study from Evans et al. [35] was designed to identify inpatient risk factors for ADEs. Conditional logistic regression was used to analyse all pharmacist-verified ADEs by therapeutic class of drugs and severity during a 10-year study period in a 520-bed teaching hospital. Each case patient was matched with up to 16 control patients. They found four classes of drugs causing the majority of the ADEs: analgesics, anti-infectives, cardiovascular agents and anti-coagulants. They also showed that female gender was a uniformly significant risk factor for ADEs, while age was not. Creatinine clearance was a prominent risk factor only in the cardiovascular drug category. Increased dose, number of co morbidities and parenteral routes of administration were found to be a significant risk factor for ADE in nearly every drug category. They conclude that the four high-risk drug classes should be

closely monitored based on patient characteristics (gender, age, weight, creatinine clearance, number of comorbidities) and drug administration (dosage, administration route, number of concomitant drugs) [35].

Clearly, there are many different tools which have the potential to prevent ADEs but with different impact. Each tool has its impact on a particular part of the drug distribution system, for example barcode scanning of drugs and patients will only prevent administration errors and not other kinds of ADEs. Thus, a multifaceted approach, such as that Silverman et al. [36] has described for their institution, seems to be the best option to reduce preventable ADEs.

Two strategies of such a multifaceted approach to prevent ADEs we have special interests in and will be highlighted. These interventions are: (1) pharmacists participation on ward rounds and (2) CPOE with CDSS. Two of these CDSS we are working on as well and are discussed in more detail, namely (A) computer-based monitoring system with alerts and (B) linking laboratory and pharmacy information systems.

Pharmacist participating on ward rounds

Fortescue et al. [34] proposed clinical pharmacists on ward rounds as a potential strategy to reduce ADEs. Leape et al. [37] conducted a controlled clinical trial to estimate the effect of pharmacist participation on medical rounds in the ICU on the rate of preventable ADEs caused by medication ordering errors. During a 6 month period in a large urban teaching hospital a senior pharmacist participated on rounds with the ICU team and remained in the ICU for consultation in the morning and was available on call throughout the day. The rate of preventable prescribing ADEs decreased by 66% from 10.4 per 1000 patient days (95% CI, 7–14) before the intervention to 3.5 (95% CI, 1–5; $p < 0.001$) after the intervention. In another unit, which served as a control, the rate was essentially unchanged during the same period. The pharmacist made 366 recommendations related to drug ordering, of which 362 (99%) were accepted by physicians. The recommendations varied from clarification or correction of the medication order, provision of drug information to recommendation of alternative therapy and identification of drug–drug interactions [37]. Similarly, Kucukarslan et al. [38] studied during a 3 month period the effect of pharmacists on rounding teams in a general medicine unit. The services of the clinical pharmacist included rounding, documenting pharmacotherapy history and providing discharge counselling. The rate of preventable ADEs was reduced by 78%, from 26.5 per 1000 hospital days to 5.7 per 1000 hospital days. They documented 150 interventions, of which 147 were accepted by the team. The most common interventions were dosing-related changes and recommendations to add a drug to

therapy [38]. A systematic review of Kaboli et al. [39] evaluated the published literature on the effects of clinical pharmacist interventions in controlled trials in hospitalised patients. In 36 studies, three different types of clinical pharmacist services were reviewed: (1) patient care unit pharmacist participation on rounds (10 studies); (2) admission or discharge medication reconciliation (11 studies) and (3) drug class-specific pharmacist services (i.e. inpatient anti-coagulation services, antibiotic therapy and infectious disease counselling and therapeutic drug monitoring services; 15 studies). Different outcome measures were used. For example 7 of 12 studies reported a reduction of ADEs, ADRs or medication errors and 5 reported no differences. Hospital length of stay was reduced in 9 of 17 trials and readmission rates, ICU transfers, test use and costs were either reduced or not affected. Mortality was evaluated in eight trials. One showed a significant reduction. Of the other seven studies, three demonstrated lower mortality and four demonstrated higher mortality in the intervention group, but these differences were not significant. The overall conclusion was that the addition of clinical pharmacist services in the care of the inpatients generally resulted in improved care, with no evidence of harm [39]. Finally, in a 84 beds paediatric academic setting, Wang et al. [40] quantified the harmful medication errors and ADEs that occurred during a 3 month period and judged whether or not these were intercepted by the clinical pharmacist system and if not whether it would have been captured by CPOE. They found 865 medication errors, including 687 non harmful medication errors, 162 near misses and 16 preventable ADEs, and also 36 non preventable ADEs. Of all potential harmful medication errors 54% were intercepted by the clinical pharmacist system. This included 78% of prescribing errors but none of the administration errors. An idealised paediatric CPOE with CDSS could capture additional prescribing errors (78% vs. 93%; $p = 0.002$), but not administration errors [40].

The positive effect of pharmacist participation on rounds on improving medication safety is obvious; however, data on cost effectiveness are currently lacking. In the study of Leape et al. the total commitment of the clinical pharmacist was approximately half of the pharmacist's time [37]. This means that having clinical pharmacists available on all hospital wards may be unrealistic also because of shortage in pharmacists in many countries.

CPOE with CDSS

One intervention that has our interest and has substantial potential for improving the medication ordering process is CPOE in which physicians write orders online [41,42]. It has been recommended by the Leapfrog group as one of the first leaps to be implemented as a major step to improve patient safety in the USA [43]. CPOE ensures complete, legible, standardised

and clear orders. CDSS are built into almost all CPOE systems to varying degrees and have the ability to improve patient safety. Basic clinical decision support provides computerised advice regarding drug dose, routes and frequencies, and more sophisticated CDSS can perform drug allergy checks, drug-laboratory value checks and drug–drug interaction checks and can provide reminders about corollary orders or drug guidelines [44-46]. In his systematic review Kaushal et al. [44] evaluated five studies regarding CPOE with CDSS. Of these studies two demonstrated a marked decrease in the serious medication error rate, one an improvement in corollary orders, one a prescribing improvement in dose and frequency of drugs and one an improvement in dose and frequency prescription of nephrotoxic drugs. For example, two studies from Bates et al. [47,48] showed a 55% and 86% decrease in preventable and non-intercepted potential ADEs, respectively. The first study showed a decline from 10.7 events per 1000 patient days to 4.68 events ($p = 0.01$). The rate of ordering errors decreased 19% overall, the number of transcription errors fell by 84% and the rates of dispensing and administration errors fell by 68% and 59%, respectively [47]. The event rate in the second study fell from 7.6 per 1000 patient days to 7.3 per 1000 patient days after implementing CPOE and further to 1.1 per 1000 patient days after improving drug allergy checking, potassium ordering and drug–drug interaction checking [48]. A more recent study in the ICU, conducted during a 5 week period, comparing two paper-based units with one unit with CPOE, found a relative reduction of 86.7% for all types of errors associated with medication ordering. The incidence of non-intercepted potential ADEs and ADEs together was significantly lower in de CPOE unit ($n = 23$) compared with the paper-based unit ($n = 60$) [49]. However, there have also been some negative reports on CPOE. Han et al. found an unexpected increase in mortality coincident with CPOE implementation [50]. Moreover, Koppel et al. [51] reported that a widely used CPOE system facilitated 22 types of medication error risks, mainly systems integration failure and human-machine interface flaws, and as Wang et al. [40] judged, CPOE captures mostly prescribing and transcription errors, but not administration errors.

Overall, CPOE has many benefits beyond medication safety and is a useful tool to prevent ADEs. It is good to realize that not every CPOE (with CDSS) is the same and that there are important differences between the systems used in different countries. Overall, it is here to stay, but needs continuous monitoring and fixing [52].

Computer-based monitoring system with alerts

One example of CPOE with CDSS to prevent ADEs is the use of computer-based monitoring systems, also called clinical event monitoring systems or clinical event monitors. These systems can use any data available in electronic form to detect adverse drug events. These

can be administrative data, like coded data (ICD-9-CM), free text trigger words, drug prescription, or multiple data like combination of sources using queries, rules or algorithms [19,23,24,53]. We focus on systems that monitor clinical laboratory data, demographic patient data and physician orders within a CPOE system by using defined clinical rules. These clinical rules or algorithms are based on identifiers searching for specific medication orders, patient characteristics and/or laboratory values [5,25,54,55].

Raschke et al. [54] developed a computer alert system to correct errors that might lead to ADEs and to detect ADEs before maximum injury occurs. In a prospective case series 37 drug-specific ADEs were targeted. During the last 6 months of 1997 the alert system fired 1116 times and 596 (53%) were true-positive alerts (defined as in which the physician wrote orders consistent with the alert recommendation). The alerts identified opportunities to prevent patient injury secondary to ADEs at a rate of 64 per 1000 admissions [54]. Likewise, Silverman et al. [55] used a computer-based detection system with rules that identify actionable events (excluded identification of ADE after it has occurred). In 3 different periods they used 58 rules and performed 169, 452 and 792 interventions based on these rules respectively. The rules were continually assessed by evaluating the positive predicted value. Of these interventions by pharmacists, 133 (78.7%), 411 (90.9%) and 730 (92.2%) were accepted by the physician in each period, respectively. The most efficient rules in terms of intervention were a quinidine level above 5 mg/dl and a theophylline level above 20 mg/dl [55]. It is essential that the CDSS provide the user with relevant guidance regarding prescribing and monitoring decisions without overwhelming the user with irrelevant alerts; if too many low-level alerts are delivered, prescribers may disregard important warning messages [56]. A problem that might occur with CDSS is 'alert fatigue'. In their review, Van der Sijs et al. [56] mention that in 49% to 96% of cases, drug safety alerts in CPOE are overridden by clinicians. They warn for error-producing conditions of the alert system, like low specificity, low sensitivity, unclear information content, unnecessary workflow disruptions and unsafe and inefficient handling. One explanation may be that medication control is one of the tasks of the complex function of the physician, whereas medication control is the core business of the pharmacist. Therefore a broader range of warnings can still be displayed to the pharmacist, for example after prescribing but before dispensing.

Linking laboratory and pharmacy information systems

Many of the clinical rules used in computer-based monitoring systems consist of a combination of drug and laboratory algorithms. Laboratory and pharmacy functions are closely related. Drug choice and dosing often depend on laboratory information such as

therapeutic drug levels and biochemical and other physiologic parameters. Despite this relation between laboratory and pharmacy, connection between their information systems is often suboptimal or non-existent [57]. ADEs that may be prevented by use of such a CDSS are for example wrong dosing of drugs which are eliminated by the kidney in patients with impaired renal function [58,59], prescribing potassium to patients despite high plasma potassium level [60] and lack of monitoring at initiation of drug therapy [61]. Several studies have demonstrated that drug- laboratory combinations are one of the best tools for identifying (potential) ADEs [5,19,25,62]. Schiff et al. [57] describe in their review 10 ways in which laboratory and pharmacy data can be related to improve patient care. Their knowledge-based rules are for example linking laboratory findings with drug selection (indication or contraindication), with drug dosing, drug use with laboratory monitoring for toxicity and also drug use and interference with laboratory measurements. The linking between tests and treatments can be retrospective, linking downloaded laboratory and pharmacy files, or real-time via CPOE with CDSS [57].

Information technology can reduce the frequency of ADEs. The main classes of strategies for this prevention include tools that can improve communication, make knowledge more readily accessible, require key pieces of information, perform checks in real time, assist with monitoring and provide decision support. However in today's systems, many important warnings are ignored and there are too many unimportant warnings. Thus, pre-screening by the pharmacist can be useful [45,63].

Conclusion

ADEs in hospital practice cause considerable morbidity and even mortality albeit its precise frequency is yet unknown. Since a substantial proportion of the detected ADEs can be prevented we find it important to focus on the prevention of ADEs. It is suggested to follow a systems approach, involving multiple strategies, such as CPOE with sophisticated CDSS and patient-oriented pharmacy services, to adequately encounter the problem of ADEs in hospital settings. Linking pharmacy and laboratory data is a good way to start. Information technology can be very helpful to reach this goal.

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