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Nature, Occurrence and Consequences of Medication-Related Adverse Events During Hospitalization: A Retrospective Chart Review in the Netherlands

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ABSTRACT

Background: Medication-related adverse events (MRAEs) form a large proportion of all adverse events in hospitalized patients and are associated with considerable preventable harm. Detailed information on harm related to drugs administered during hospitalization is scarce. Knowledge of the nature and preventability ofMRAEs is needed to prioritize and improve medicationrelated patient safety.

Objective: To provide information on the nature, consequences and preventability of MRAEs occurring during hospitalization in the Netherlands.

Study Design: Analysis of MRAEs identified in a retrospective chart review of patients hospitalized during 2004.

Methods: The records of 7889 patients admitted to 21 hospitals in 2004 were reviewed by trained nurses and physicians using a three-stage process. For each hospital, patient records of 200 discharged and 200 deceased patients were randomly selected and reviewed. For each patient record, characteristics of the patient and the admission were collected. After identification of anMRAE the physician reviewers determined the type, severity, preventability, drug category and excess length of stay associated with the MRAE. Data on additional interventions or procedures related to MRAEs were obtained by linking our data to the national hospital registration database. The excess length of stay and the additional medical procedures were multiplied by unit costs to estimate the total excess direct medical costs associated with the MRAE.

Results: In total, 148 MRAEs occurred in 140 hospital admissions. The incidence of MRAEs was 0.9% (95% CI 0.7, 1.2) and the incidence of preventable MRAEs was 0.2%(95%CI 0.1, 0.4) per hospital admission. The majority of non-preventable MRAEs were adverse drug reactions caused by cancer chemotherapy. Preventable MRAEs were most often found in relation to anticoagulant treatment administered in combination with NSAIDs. Both non-preventable and preventable MRAEs resulted in considerable excess length of hospital stay and

costs. On average, MRAEs resulted in an excess length of stay of 6.2 days (95% CI 3.6, 8.8) and average additional costs of h2507 (95% CI 1520, 3773).

Conclusions: This study was the first to provide detailed information on MRAEs during hospital admissions in the Netherlands, which were associated with both considerable patient harm and additional medical costs. To increase patient safety, interventions need to be developed that reduce the burden of MRAEs. These interventions should target the areas with the highest risk of MRAEs, notably antibacterials, cancer treatment, anticoagulant treatment and drug therapy in elderly patients.

BACKGROUND

Patient safety, defined by the absence of healthcare-related adverse events (AEs) that harm patients, constitutes a prerequisite for good quality of care. An AE is defined as an unintended injury that results in temporary or permanent disability, death or prolonged hospital stay, and is caused by healthcare management rather than by the patient's underlying disease process.[1-3] It has been shown that AEs are generally associated with higher healthcare costs due to an excess length of hospital stay and the requirement for additional interventions.[1,4-8] It has been suggested that the financial consequences of these AEs in the US are in the range of $US30 and $US130 billion each year (1995 values).[4,6,9,10] After surgicalAEs,medicationrelated adverse events (MRAEs) are themost common healthcare-related AEs that occur during hospital admissions.[11,12] A systematic review showed that approximately 15% of all AEs were drug related.[11] This finding was recently confirmed by our study on AEs during hospitalizations in Dutch hospitals.[12] Although the incidence of MRAEs has been reported in many publications, detailed information on the nature, causes and consequences of MRAE is lacking.[1,2,4] Such detailed information on MRAEs has only been reported in an Australian patient record review published in 2003.[13] The results showed that the most common and high impact types of drugs associated with preventable errors were anticoagulants, anti-inflammatories and cardiovascular drugs. In addition, this study found a strong correlation between the increase of medication use and increase in medication errors.

The incidence and costs of MRAEs occurring outside the hospital that have led to hospitalization have been studied in the Netherlands.[14] However, no national data are available on MRAEs that occur during hospitalization. Therefore, in this study we aimed to provide a detailed analysis of the nature, type, preventability, causes, consequences and costs of MRAEs during hospitalizations in the Netherlands, in order to identify the main problem areas and opportunities for prevention.

METHODS

The methods of this study were based on the protocol of the Canadian Adverse Event Study,[1] which was originally developed by the Harvard Medical Practice Study Group.[7] The design and methods of this study, including modifications in comparison with the Canadian Adverse Event study protocol, have been described in detail elsewhere.[15]

Study Population

We performed a retrospective patient record review study in a random stratified sample of 7926 admissions in 21 of the 101 Dutch acutecare hospitals: 4 university and 17 general or tertiary medical teaching hospitals. The selected hospitals were representative of those throughout the Netherlands as verified based on hospitals in urban and rural settings. Furthermore, each eligible hospital had at least 200 beds, an emergency unit and an intensive care unit. In each hospital, records of a sample of approximately 200 discharged and 200 deceased patients admitted in 2004 were randomly selected and reviewed. Admissions in which the patient died were oversampled to facilitate assessment of preventable AEs associated with hospital deaths and to increase the efficiency of detecting AEs, since the incidence of AEs was expected to be higher in this group. The national weighted average incidence of adverse events in

Dutch hospitals in categories of preventability was calculated, corrected for oversampling of university hospitals and of patients who died during hospital admission.[15] For each admission coded, information on primary and secondary diagnoses (International Classification of Diseases 9th Edition – Dutch extension [ICD-9-DE]),[16] acute or non-acute admission, main and secondary interventions, expected length of stay (LOS),[17] the co-morbidity index of Charlson et al.,[18] and the reason for admission, was retrieved from the national hospital discharge register (HDR). Since 1986, all general and academic hospitals in the Netherlands participate in the HDR. For each hospital admission a new record is created in the HDR.[19] Thirty-seven (0.5%) of the hospital admissions could not be linked to the national HDR database because of non-unique or partially missing information on date of admission, date of birth and sex. Consequently, all presented analyses are based on 7889 patient records of hospital admissions.

Process of Identifying Medication-Related Adverse Events (MRAEs)

The patient records were reviewed in a threestage review process by trained nurses and physicians.

First, a nurse screened all the patient records using 18 criteria that indicated the potential presence of an AE (stage 1). The nurse indicated which of the four categories of physician specialty would be most appropriate to carry out stage 2 of the review. In stage 2, two physicians of the same specialty (internists, surgeons, neurologists or paediatricians) independently reviewed all the positively screened patient records using an extensive, standardized procedure (stage 2).[15] The determination of an AE was based on three criteria: (i) an unintended physical or mental injury, which (ii) resulted in prolongation of the hospital stay, temporary or permanent disability or death, and was (iii) caused by healthcare management rather than the underlying disease.[12] The physician reviewer assessed the nature, impact, location, responsible specialty, clinical procedure, causes and preventability of each identified AE.[12] The third stage involved reaching consensus.

If the two reviewers did not agree on fundamental questions (i.e. whether or not there was an MRAE or whether the MRAE was preventable), they discussed the case. If the two physicians could not reach consensus, a third physician reviewer with access to all the information made a final decision.

Judgements of the causality of healthcare and the preventability of theMRAE were implicit but based on supportive questions. Reviewers used their clinical experience and knowledge of professional standards as references to answer their questions.

AnMRAE was judged to be preventable if the harm caused by medication was the result of either not following the professional standard, or poor organization of care. The degree of preventability was measured on the following 6-point scale.

1. Almost no evidence for preventability.
2. Slight to modest evidence for preventability.
3. Modest preventability (<50/50, but borderline).
4. Modest-to-strong evidence of preventability (>50/50, but borderline).
5. Strong evidence of preventability.
6. Almost certain evidence of preventability.

All MRAEs that scored above 3 were considered preventable.

The inter-rater reliability between the two reviewers was ‘fair’ with regards to the determination of AEs (k 0.25 [95% CI 0.05, 0.45], 76% agreement), and ‘moderate’ with regards to the preventability of AEs (k 0.40 [95% CI 0.07, 0.73], 70% agreement).[20,21] An MRAE was defined as an AE related to the use of medication in the treatment of a patient if both physicians agreed. An exception was made for hair loss due to cytostatic treatment and medication-related neutropenia without fever, which were not counted as AEs in this study.

To describe the nature of theMRAE, questions were developed and agreed upon by a member of the Dutch Association of Hospital Pharmacists.

These questions concerned drug category, route of administration (e.g. oral, subcutaneous), process factors (e.g. prescribing, dispensing or administration factors) and whether patient harm occurred during use of the drug at a normal dosage and in the normal setting (often called an adverse drug reaction or side effect).

Causes ofMRAEs were assessed and classified as technical, organizational, healthcare workerrelated and patient-related. Finally, potential improvement strategies were identified by the physician reviewers.

Cost Measurement

Direct medical costs attributable to MRAEs were considered to be those incurred by excess LOS during the sampled admission and re-admission, and by additional medical procedures required as a consequence of the MRAEs.

Excess LOS attributable to MRAEs during the sampled admission was calculated by taking the average of two estimates of excess LOS made independently by the physician reviewers, and rounding this value upwards to the closest whole day value.The mean difference between the two physician reviewers was 1.23 days (range 0–16 days, median 0 days). If the physician reviewers were unable to determine excess LOS (in 7 of the 148 admissions during which MRAEs occurred), we imputed the excess LOS based on national hospital registration data, notably the difference between expected and observed LOS, which was determined for each sampled admission based on the patients' age, sex and diagnosis at admission.

We imputed a zero LOS if this difference was negative, that is if the observed LOS was less than the expected LOS. The estimates varied from no extra bed days (if theMRAE was mild) to all bed days of the sampled admission (if the MRAE occurred in a previous hospital admission and resulted in the sampled admission). For re-admissions after MRAEs in the sampled admission, we imputed the national average LOS in 2004 (7.3 days).

Additional medical procedures attributable to MRAEs were those considered by the physician reviewers to be required as a result of theMRAE.

Cost Valuation

The excess LOS and the additional medical procedures were multiplied by unit costs to estimate the total excess direct medical costs. A similar approach was used to calculate costs of MRAES as that used in the study on all AEs.[8] Dutch guideline prices of 2003 were used to estimate the costs of one hospital day, distinguishing between standard care and intensive care in university and general hospitals (table I).[23] The guideline prices were corrected with price indices for 2004. No unit costs for tertiary medical teaching hospitals were available; therefore, guideline prices for general hospitals were used.[22,24] The unit costs included costs of medical and nursing staff, drugs, consumables equipment, inpatient stay and overheads.

The costs of excessmedical procedures were estimated bymultiplying the number of procedures with the price used for public health insurance, maintained by the Dutch Healthcare Authority.

[TABLE 1]

DATA ANALYSIS

Since our study population included an artificially large sample of deceased patients, incidence rates and 95% CIs representative for the Netherlands were obtained after weighting for the sampling frame. The weighting factor was the inverse of the probability of being included in the sample
and was calculated by dividing the representation of a group in the population by the representation of this group in the study.[12] The weighing factor was not used in the analyses to describe MRAEs, since baseline characteristics, such as age, sex, admission department and medication type did not show statistically significant differences between the deceased patients and those discharged alive.

The distribution of the excess LOS and costs were positively skewed. We used non-parametric bootstrapping, adjusting for the sampling frame, to calculate the CI of cost estimates.[25] Nonparametric bootstrap is the preferred method to estimate 95% CIs around cost estimates because it uses the distribution of the often skewed cost data instead of assuming a normal distribution.[26] To assess differences between preventable and non-preventable MRAEs, Chi-square tests for dichotomous variables and Student's t-tests for continuous variables were used to estimate differences in excess LOS and hospitalization costs.

Statistical analyses were performed using SPSS forWindows version 15.0, except non-parametric bootstrapping, which was performed in Microsoft Excel_ 2003.

In order to get an impression of the risk of MRAEs per medication type we obtained data on the frequency of prescribed medication during hospitalizations of ten hospital pharmacies, which were collected by the Institute of Drug Outcomes Research PHARMO, Utrecht, the Netherlands (www.pharmo.nl), since national data are currently not available. Data were available on the frequency of prescriptions for the main groups of the Anatomical Therapeutic Chemical (ATC) classification system.

Sensitivity Analysis of the Excess Length of Stay and Costs of MRAEs

To test the reliability of the estimates of excess LOS and consequently the costs of MRAEs, we performed a sensitivity analysis. As it is sometimes difficult to determine the excess LOS due to the MRAEs based on patient record review, we used a different approach in calculating excess LOS. For each individual admission in our sample we obtained the expected LOS from the HDR.Within the HDR, for each hospital admission, the expected LOS is calculated based on the following characteristics of the patient and the national mean LOS that is associated with these characteristics: age, primary ICD-9 – Clinical Modification (ICD-9-CM) diagnosis (approximately 1000 diagnoses) and procedures.[17] Excess LOS was estimated as the difference between the expected and the observed LOS, using HDR data. Previous research has shown that the excess LOS based on the national hospital registration data showed similar results to the excess LOS based on the reviewers expert opinion.[8]

RESULTS

In the retrospective patient record review, 744 AEs were observed in 7926 patient records.

Thirty-seven were excluded because no data from the HDR could be collected; therefore, the total number of patient records used in the analyses were 7889. Of the 744 AEs, 157 were classified by the physician reviewers as MRAEs.[12] Detailed information on costs of all AEs have been previously published.[8] Nine AEs were excluded from the analysis because they did not meet the criteria for an MRAE: five AEs involved blood products and fluids rather than drugs, two AEs involved graft-versus-host disease and two AEs appeared to be misclassified. Therefore, a total of 148 MRAEs were included in the analysis, which occurred in 140 patients. Six patients had two MRAEs and one patient had three MRAEs. The 148 MRAEs could be divided into 60 preventable MRAEs (41%) and 88 non-preventable MRAEs (59%). The 148 MRAEs occurred in 31 patients discharged alive and 109 patients who died in hospital.

The incidence of MRAEs was 0.9% (95% CI 0.7, 1.2) per hospital admission, and the incidence of preventable MRAEs was 0.2% (95% CI 0.1, 0.4) per hospital admission. There were no statistically significant differences in incidence between university hospitals and general or tertiary teaching hospitals (table II).

With regard to age, a greater proportion of MRAEs in patients over 65 years of age were preventable than those in younger patients. Comparing medication categories, MRAEs associated with anticoagulants resulted in permanent disability (23%) or death (21%) more frequently than other drug types. Over 50% of all MRAEs related to antithrombotic treatment (antiplatelets,NSAIDs, anticoagulants) were considered preventable by the reviewers (table III). Use of antibacterials contributed to both preventable and unpreventable MRAEs.

Cancer chemotherapy was responsible for 96% of non-preventable MRAEs. With regard to the medication process, prescription errors were the cause of the majority (44%) of preventable MRAEs. Prescription errors mainly consisted of wrong dosage of the medication (either too much or too little). Over 50% of prescription errors were considered preventable. PreventableMRAEs also included dispensing errors (3% of preventable MRAEs), all of which were considered preventable.

Non-preventable MRAEs consisted of patient harm caused by the use of the drug at a normal dose or in the normal setting and constituted 53% of MRAEs. In the majority of MRAEs, human error played a role.Organizational and technical factors were seldom identified.

The average excess LOS associated withMRAEs was 6.2 days (95% CI 3.6, 8.8) and the average excess costs ofMRAEs were h2507 (95%CI 1519, 3773) [table IV]. Preventable MRAEs had approximately 25% greater excess costs than nonpreventable MRAEs.

The average costs of non-preventable MRAEs were higher for patients younger than 65 years of age, whereas the costs of preventable MRAEs were higher in patients older than 65 years. The average excess LOS of patients under 65 years of age who experienced a preventable MRAE was 4.2 days, while the excess costs were h2851 per preventable MRAE. The average excess LOS of patients over 65 years of age who experienced a preventableMRAE was 7.2 days, while the excess costs were h3097 per preventableMRAE (table IV).

Table V shows the distribution of MRAEs and the distribution of prescriptions during hospitalizations according to ATC categories. Antithrombotic drugs were included in the categories ‘blood and

bloodforming organs' and 'cardiovascular system'. MRAEs in these drug groups occurred at rates proportional to prescribing practice.

The ATC categories in which most MRAEs occurred were 'anti-infectives for systemic use' (21%) and 'antineoplastics and immunomodulating agents' (27%). As these two ATC categories form only 12% of prescriptions during hospitalization (8 and 4%, respectively), the risk of anMRAE seems relatively high compared with other ATC categories.

The sensitivity analysis of excess LOS and costs showed similar results to the excess LOS and costs determined by the reviewers for all MRAEs, as well as similar results for preventable and nonpreventable MRAEs. The MRAEs showed an excess LOS of 7.7 days (95% CI 1.9, 11.6) and excess costs of h2841 (95% CI 1404, 4404).

Extrapolation of the costs of MRAEs to a national level resulted in a cost of approximately h30 million (95% CI 24, 40) annually.

[TABLE 2, 3]

DISCUSSION

MRAEs during hospitalization form a large proportion of all AEs. An in-depth analysis showed that 59% of the MRAEs were non-preventable.

Most of these were adverse effects of drug therapy.

A large proportion of these were associated with cancer chemotherapy.

PreventableMRAEs were responsible for 41% of theMRAEs and mainly consisted of dispensing errors, which were all considered preventable, and prescribing errors, of which over 50% were considered preventable. Our results support the results of two prior studies on hospital admissions resulting frompreventable MRAEs, which showed that anticoagulants, anti-infectives, antineoplastics and immunosuppressants were associated with relatively high risks for medication-related hospitalization.[27,28] The most common errors were too high or too low dosage, poorly controlled prescriptions of anticoagulants (the dosages were not appropriately adjusted in line with laboratory parameters) and poorly controlled laboratory parameters such as the International Normalized Ratio.[14,29] With an aging population in the Netherlands, the frequency of prescriptions of anticoagulants will increase. Successful interventions are needed to reduce the chance of MRAEs in association with anticoagulant treatment.[30] [table 4, 5] MRAEs in patients over 65 years of age were more often preventable compared with patients under 65 years of age. In contrast with other studies, in our study this could not be explained by the more complex health situation and comorbidities of elderly patients.[2,14,31,32] Of the patients in our study, 66% had no or minor co-morbidity (Charlson's co-morbidity index of 0 or 1); this was similar among patients younger and older than 65 years.

The excess LOS was the cost driver in both preventable and non-preventable MRAEs. Patients under 65 years of age who encountered a preventable MRAE received more additional interventions in an attempt to reduce the damage after a preventable MRAE.

A proportion of all medication errors result in patient harm and MRAEs. Medication errors result from not only prescribed drugs but also over-the-counter drugs and vitamins, and other supplements that patients may take. Therefore, medication errors andMRAEs occur at every stage of the medication process, from the prescribing stage to the patient's response to the drug involved.

Our study was limited toMRAEs causing harm during hospitalization. Studies such as ours that evaluate MRAEs find much lower incidence rates than studies using broader endpoints such as medication errors. However, when the aim is to increase the sense of urgency around the prevention of MRAEs, insight in the burden of MRAEs is of great importance. Unintended events resulting in harm may be considered the most relevant part of the medication errors. A second limitation is that only information reported in the medical and nursing records was available. This may have led to underestimation of MRAE rates because not all information regarding the medication process was recorded (forms of medication administration that were not electronically recorded may be missing). Nevertheless, this study found thatMRAEs during hospitalization resulted in considerable harm to the patients, and medication-related patient safety in hospitals needs to be improved.

Third, data on the distribution of prescriptions during hospitalization by type of medication were not available on a national level. However, we were able to obtain surrogate data, which gave an indication of

prescriptions during hospital admissions. By comparing the distribution of prescribed medication in hospitals with the distribution of MRAEs, both anti-infectives (antibacterials) and antineoplastic agents appear to be associated with a larger risk for MRAEs. Although drugs with antithrombotic effects cause the largest number ofMRAEs, this seems to be in proportion with the number of prescriptions.

Several factors may have led to under- or overestimation of the MRAE rate. Hindsight bias is a general weakness of retrospective studies.[33] Knowing the outcome and its severity may influence judgement of causation and preventability.

This may have led to an overestimation of preventable MRAEs that contributed to the patient's death judged by the reviewers.

On the other hand, MRAEs may have been underestimated due to the fact that not all information regarding the medication is written in the medical or nursing records.

Furthermore, the interrater reliability of the determination of AEs was only fair, and the interrater reliability for the determination of the preventability of AEs was moderate. However, the circumstances in which the study took place, and the highly motivated and trained reviewers support the idea that the estimation of the incidence ofMRAEs during hospital admissions was good.

Finally, there are several reasons to assume that our cost estimation is conservative. The most important reason is that other research has shown that due to inefficiencies once AEs occur, the average costs of a hospital day becomes more expensive after an AE or an MRAE.[34] Because of the study design we were only able to use the same guideline unit price for hospitalization days before and after AEs.

It is difficult to compare the results of our study of MRAEs with previously published studies of medication errors, adverse drug reactions and adverse drug events for several reasons. First, the differences in definitions lead to unreliable comparisons. For example, the review of Yu et al.[35] found 32 definitions of 'adverse event' resulting in eight different definitions and three different functional meanings. Second, the determination or reporting of MRAEs leads to methodological differences and outcome differences compared with our study where MRAEs are detected by patient record review. Voluntary reporting led to lower estimations of medication errors; a group of anaesthesiologists reported administering wrong drugs 1.5 times during their career,[27] while automated pharmacy signals and other prospective methods result in much higher estimations of medication errors. The incidence of adverse drug reactions occurring in-hospital in the meta-analysis of Lazarou et al.[36] was 10.9%.

There are a few studies based on record review, but these were performed more than 10 years ago, or used different definitions. Suh et al.[37] showed, in a case-control study, that 2.1% of all patients encountered an adverse drug reaction and these patients had an additional LOS of 3.8 days.

Leape et al.[38] showed an increase in adverse drug reactions with age from 1.4% in newborn infants to 5.7% in patients aged 65 years and older. In our study, the number of MRAEs was not large enough to separate into more than two categories (below and above 65 years of age). Third, the studies have been performed in differing populations.

For example, the exclusion of psychiatric patients, obstetric departments and patients younger than 1 year of age in this study prevents direct comparison with the study of Bates et al.,[39] which only included adults but allowed patients from all hospital departments. This study found an adverse drug event rate of 6.5 per 100 admissions, and a potential adverse drug event rate of 5.5 per 100 admissions.[39] Consequently, incidence rates may vary across studies. However, in all countries and settings, the incidences of MRAEs have been shown to be high and this should increase awareness and, thereby, patient safety.

A Dutch study into MRAEs resulting in hospital admissions conducted in a similar time period to this study showed a high percentage of preventable admissions caused by anticoagulants, NSAIDs and vitamin K antagonists, or combinations of these drugs. The yearly excess cost of these MRAEs that resulted in hospital admissions was h85 million annually.[14] In addition to the costs of the MRAEs resulting in hospital admissions, the costs of MRAE during hospital admission assessed in this study resulted in h30 million annually, which makes the total annual costs of MRAEs leading to or occurring during hospitalization h115 million. This is approximately 0.8% of the annual hospital budget of h14.5 billion in 2004. In the Netherlands, the total burden of MRAEs resulting in hospitalization and during hospitalization is high. Therefore, it is important to improve awareness of medicationrelated patient safety among clinicians and to develop initiatives to improve patient safety in primary and secondary care.

The problem of medication-related errors is not new and interventions such as the computerized physician order entry system (CPOE) have only been developed during the last decade. Until now, these interventions have not produced the expected results; that is, they have not reduced the number of medication errors. A recent review of the literature on CPOE systems concluded that there is no evidence that using a CPOE system reduces medication errors.[40] Recently, studies have evaluated other innovative interventions for reducing MRAEs or improving hospital patient safety, such as electronic trigger tools,[41] scanning of bar codes in pharmacies,[42] analysis of spontaneous reporting[43] and root-cause analysis.[44,45] A review by Karnon et al.[46] showed that these solutions probably do not lead to positive net benefits. However, these authors suggested that if the monetary value of lost health could be included, interventions would probably produce a positive net benefit on preventable medication errors. On the other hand, the study of van den Bemt et al.[47] showed favourable cost-benefit associated with reducing prescribing errors.

In 2007, a national programme (www.VMSZ org.nl) was launched in the Netherlands to reduce unintended events in Dutch hospitals by 50% by 2012. This programme has ten themes, of which three involve drug safety: (i) reducing events that involve high risk medication; (ii) reducing medication errors on admission and discharge; and (iii) reducing medication errors in the frail elderly.

Although the safety programme does not directly target the main problem areas shown in our study, it may have indirect beneficial effects. In addition, many hospitals have their own improvement plans that often involve ensuring the correct and safe administration of cancer chemotherapy, anticoagulants and antibacterials. Benchmarking hospitals with regard to these themes may illuminate best practices.

This study showed that the burden ofMRAEs during hospitalization is high. MRAEs are associated with excess LOS and high excess costs. To improve patient safety, interventions need to be developed that reduce the burden of MRAEs during hospitalization. These interventions should target the areas with the highest risk of MRAEs, i.e. antibacterial, anticoagulant and cancer treatment, and drug administration in elderly patients.

The use of a CPOE could reduce the risk of wrong doses for patients on anticoagulant therapy;[48] likewise, implementation of pharmacist consultation services have been shown to have positive effects on both patient outcomes and costs.[30] However, these interventions target potentially preventable MRAEs, and non-preventable MRAEs, such as many of the AEs associated with medications used in cancer treatment, require a different approach. For example, both preventable and non-preventable MRAEs could be reduced by introducing multidisciplinary teams in which the patient is closely monitored, implementing surveillance systems monitoring the distribution of cancer medication[49] or the development of drugs with fewer adverse effects.

Research into the drug interactions occurring from antineoplastic treatment in combination with other medication used to treat co-morbidities is needed.[50] Data are often insufficient to accurately determine all costs associated withMRAEs from a societal perspective. In particular, a valid estimate of the indirect costs associated with MRAEs is lacking. Future studies should include an evaluation for estimation of indirect costs.

By doing so, the sense of urgency as well as the impact on patient safety will become even more apparent.

[TABLE 4, 5]

CONCLUSIONS

This study was the first to provide detailed information on MRAEs during hospital admissions in the Netherlands, which were associated with both considerable patient harm and additional medical costs. To increase patient safety, interventions need to be developed that reduce the burden ofMRAEs. These interventions should target the areas with the highest risk of MRAEs, notably antibacterials, cancer treatment, anticoagulant treatment and drug therapy in elderly patients.

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[TABLES]

Table I. Hospital day unit cost prices 2004[22]

Resource	Cost (€)[a]
Academic hospital day	48 163
General hospital day[b]	34 099
Intensive care day[b]	170 392

a Corrected for 2004.

b From an economic perspective, the costs in tertiary teaching hospitals are the same as in general hospitals. Costs for intensive care days are across all hospital types.

Table II. Weighted incidence medication-related adverse events (MRAEs)[a] in patients admitted to Dutch hospitals in 2004 by hospital type for the total sample (discharged patients and deceased patients)

Parameters	Hospital type		
	university hospital	general or tertiary teaching hospitals	total sample
All events			
No. of patient records reviewed	1378	6511	7889
No. of patient records with MRAE	48	92	140
Weighted MRAE incidence [% (95% CI)]	1.1 (0.6, 2.1)	0.9 (0.6, 1.2)	0.9 (0.7, 1.2)
Preventable			
No. of patient records with preventable MRAE	7	38	45
Weighted preventable MRAE incidence [% (95% CI)]	0.2 (0.04, 0.9)	0.2 (0.1, 0.4)	0.2 (0.1, 0.4)

a Incidence rates and 95% CIs were weighted for oversampling of deceased patients and patients admitted to a university hospital.

Table III. Characteristics of medication-related adverse events by age, sex, drug category, route of administration of the medication and point in the medication process

Parameter	Cases [n (%)]	Weighted cases [n (%)]	Permanent impairment[a] (%)	Death[a] (%)	High preventability (%)[a]
Age (y)[b]					
1–18	2 (1.4)	4 (4.7)	0	0	54
19–40	2 (1.4)	0 (0.2)	0	0	0
41–65	50 (34)	22 (29)	2	9	4
66–79	62 (42)	32 (43)	6	11	30
>80	32 (22)	18 (24)	0	9	38
Sex					
Male	60 (46.5)	31 (40)	0	13	23
Female	69 (53.5)	45 (60)	4	7	27
Drug category					
Anticoagulants	27 (18)	8 (11)	23	21	54
antiplatelet	6 (4.1)	1 (0.7)	0	15	15
NSAID	4 (2.7)	1 (0.7)	0	50	75
antiplatelet + NSAID	2 (1.4)	4 (5.1)	0	0	50
chemotherapy	42 (28)	20 (26)	0	13	4
Morphine/opioids	8 (5.4)	3 (4)	0	5	15
Antibacterials	19 (12.8)	16 (21)	0	3	13
Other	40 (27.5)	23 (30)			
Route of administration					
Intravenous	71 (48)	30 (40)	1	15	6
Oral	67 (45)	38 (50)	5	7	27
Subcutaneous	5 (3)	6 (8)	0	1	97
Point in medication process					
Adverse drug reaction	79 (53)	41 (55)	1	8	1
Prescription error	65 (44)	32 (42)	6	11	52
Dispensing error	4 (3)	2 (3)	0	11	100

a Proportions were weighted for oversampling of deceased patients and of patients admitted to a university hospital.

b Mean age in years (±SD) of weighted cases was 68 (±15) and for weighted cases was 66 (±19).

Table IV Excess length of stay and excess costs of medication-related adverse events (MRAEs), non-preventable MRAEs and preventable MRAEs (2004 values)

Age group	MRAE	Non-preventable	Preventable
Excess length of stay [days (95% CI[a])]			
All	6.2 (3.6, 8.8)	5.8 (2.2, 9.2)	6.9 (2.2, 7.8)
Age <65 y	6.4 (1.9, 11.9)	6.9 (1.4, 8.1)	4.2 (0, 7.7)
Age ≥65 y	6.1 (3.6, 8.6)	4.9 (1.6, 6.4)	7.2 (5.5, 17.7)
Excess hospitalization costs [€ (95% CI[a])]			
All	2507 (1519, 3773)	2272 (1006, 3959)	2876 (976, 5080)
Age <65 y	2365 (797, 4265)	2521 (614, 3785)	2851 (127, 5845)
Age ≥65 y	2580 (1603, 4037)	2066 (796, 2841)	3097 (2796, 13908)

a As cost-data are skewed to the right, we used non-parametric bootstrapping, adjusting for the sampling frame, to calculate the 95% CIs.

Table V. Distribution of Anatomical Therapeutic Chemical (ATC) groups of drugs amongst prescriptions dispensed in ten hospital pharmacies in the Netherlands in relation to the distribution of medication-related adverse events (MRAEs) in 2004

ATC main groups[a]	Distribution in 2004 (%)	MRAEs (%)[b]
Alimentary tract and metabolism	15	11
Blood and blood forming organs	16	12
Cardiovascular system	18	11
Dermatologicals	1	NR
Genito-urinary tract system and sex hormones	1	NR
Systemic hormonal preparation, excluding sex hormones and insulins	4	0
Anti-infectives for systemic use	8	21
Antineoplastic and immunomodulating agents	4	27
Musculoskeletal system	5	3
Nervous system	21	14
Antiparasitic products, insecticides and repellents	0	NR
Respiratory system	6	0
Sensory organs	1	0
Various	1	NR

a ATC main groups: the ATC classification system is used for the classification of drugs, controlled by the WHO.

b Percentages were weighted for oversampling of deceased patients and of patients admitted to a university hospital.

NR = none reported.