Table 8 Prevalence of substandard drug samples by location

	Rural			Urban		
	N	%	95% CI*	N	%	95% CI*
Substandard	69	17.8	14.1, 22.0	112	13.2	11.0, 15.7
Acceptable	319	82.2	78.0, 85.9	736	86.8	84.3, 89.0
Total	388	100		848	100	

*CI: confidence interval.

Table 10 Substandard samples by location and registration status

	Substandard		Acceptable		Total	
Rural provinces	N	%	N	%	N	% Substandard
Unregistered	35	9.0	50	12.9	85	41.2
Registered	34	8.8	269	69.3	303	11.2
All provinces	69	17.8	319	82.2	388	
Urban districts	N	%	N	%	N	% Substandard
Unregistered	18	2.1	132	15.6	150	12.0
Registered	94	11.1	604	71.2	698	13.5
All districts	112	13.2	736	86.8	848	

excluding drug samples from the unlicensed market, where the prevalence of substandard drugs has found to be significantly higher (Almuzaini et al. 2013). Another potential issue is that the biochemical analysis was performed at 3 different drug testing laboratories in Mongolia. Although they all used the same Pharmacoepeia standards, the possibility of variability in testing between facilities exists. In order to confirm the accuracy of the results, we had planned to send 10% of the samples to an outside lab for verification. Because of budgetary constraints, only 4 substandard samples (2.2%) were actually sent for testing at an outside reference laboratory (National Institute of Drug Quality Control of Vietnam, Hanoi, Vietnam). These 4 samples were all verified as correctly classified, but it is not a large enough number and did not include any acceptable samples, therefore we cannot claim to validate our findings by outside reference laboratory testing.

Another important limitation of our study is that it does not provide any details about the degree of variation from the threshold requirements of the Pharmacopeia quality standards. Our study also does not provide any information about the presence of harmful ingredients. Because of this, our ability to make any inferences about the potential clinical, safety, or economic impact of the substandard drugs in Mongolia is limited, but it does support the need for increased pharmacovigilance and review of drug regulatory policies. Further details of the biochemical analysis of the substandard samples, particularly the degree and direction of the deviation of the samples failing the assay, could provide additional valuable insight into the public health impact of poor drug quality.

Conclusions

Our findings indicate that the presence of substandard drugs raise a genuine concern in both urban and rural

Table 9 Prevalence of unregistered drug samples by location

	Rural			Urban		
	N	%	95% CI*	N	%	95% CI*
Unregistered	85	21.9	18.0, 26.3	150	17.7	15.2, 20.4
Registered	303	78.1	73.6,82.1	698	82.3	79.6, 84.8
Total	388	100		848	100	

*CI: confidence interval.

areas of Mongolia. In addition, we found that unregistered drugs are common in both areas, with a significant association between substandard and unregistered drugs in the rural provinces. This highlights an important opportunity to improve the quality of the drug supply in Mongolia by reviewing and enforcing drug registration and inspection polices. Improving drug storage conditions and importation monitoring at borders are other interventions that can potentially improve drug supply quality, especially in rural provinces. Other areas for further investigation to better understand the quality of the drug supply in Mongolia would be to determine the degree of variation in the assay results for substandard drug samples, sampling the unlicensed market, and investigating the drug supply chain, especially in the provinces. Another important area for further study of the public health impact of substandard drugs is evaluating the patterns of antibiotic resistance and health outcomes for people living in areas with a high prevalence of substandard drugs.

study design; in the collection, analysis, and interpretation of data; writing of the manuscript; and the decision to submit the manuscript for publication.

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References
Abdelkrim S (2009) Quality Control and Quality Assurance of Medicines in Mongolia. World Bank, Health Sciences University of Mongolia, Available from Mongolia Ministry of Health
Almuzaini T, Choonara I, Sammons H (2013) Substandard and counterfeit medicines: a systematic review of the literature. BMJ Open 3:e002923
Attaran A, Barry D, Basheer S, Bate R, Ben-ton D, Chauvin J, Garrett L, Kickbusch I, Kohler JC, Midha K, Newton PN, Nishtar S, Orhii P, McKee M (2012) How to achieve international action on falsified and substandard medicines. BMJ (Clinical research ed) 345:e7381, http://researchonline.lshtm.ac.uk/768540/1/bmj.e7381.full.pdf (Accessed October 21, 2014)
British Pharmacopoeia Vol. 2 (2001) Stationery Office, London
Caudron JM, Ford N, Henkens M, Macé C, Kiddle-Monroe R, Pinel J (2008) Substandard medicines in resource-poor settings: a problem that can no longer be ignored. Trop Med Int Health 13;1062–1072
Cockburn R, Newton PN, Agyarko EK, Akunyili D, White NJ (2005) The global threat of counterfeit drugs: why industry and governments must communicate the dangers. PLoS Med 2:e100
Fernandez FM, Hostetler D, Powell K, Kaur H, Green MD, Mildenhall DC, Newton PN (2011) Poor quality drugs: grand challenges in high throughput detection, countrywide sampling, and forensics in developing countries. Analyst 136:3073–3082
Mongolia Ministry of Health (2006) Report on Intensive Surveillance of Counterfeit Medicines in Mongolia. Available from http://moh.mn/moh%20db/healthreports.nsf/32fe9f3e7452a6f3c8256d1b0013e24e/a85f8ce2676c2376c825712600245fbc/$FILE/Report.counterfiet.08.02.06.pdf. Accessed Feb 2014
Mongolian National Pharmacopeia (2011), 1st edn. Ministry of Health, Mongolia, Ulaanbaatar
National Pharmacopeia Committee (2005) Pharmacopeia of the People's Republic of China. Chemical Industry Press, Beijing
Newton PN, Lee SJ, Goodman C, Fernández FM, Yeung S, Phanouvong S, Kaur H, Amin A, Whitty C, Kokwao G, Lindegardh N, Lukulay P, White L, Day N, Green M, White N (2009) Guidelines for field surveys of the quality of medicines: a proposal. PLoS Med 6:e1000052
Newton PN, Green MD, Fernández FM (2010) Impact of poor-quality medicines in the 'developing' world. Trends Pharmacol Sci 31:99–101
Sabartova J, Toumi A, Ondari C (2011a) Survey of the quality of selected antimalarial medicines circulating in six countries of sub-Saharan Africa. http://www.WHO.int/medicines/publications/WHO_QAMSA (Accessed 5 December 2014)
Sabartova J, Nathanson E, Polishchuk O (2011b) Survey of the quality of anti-tuberculosis medicines circulating in selected newly independent states of the former Soviet Union. http://apps.who.int/prequal/info_applicants/qclabs/monitoring_documents/TBQuality-Survey_ (accessed December 5, 2014)
Tsetsegmaa S (2008) Assessment of the Transparency in Mongolian Pharmaceutical System (Registration, Control of Medicine Promotion, Inspection of Establishment, Selection, and Procurement of Medicines) Health Sciences University of Mongolia. Health Sciences University of Mongolia, Available from Mongolian Ministry of Health, 2006 and Progress Report
Wondemagegnehu E (1999) Counterfeit and substandard drugs in Myanmar and Vietnam. http://apps.who.int/medicinedocs/pdf/s2276e/s2276e.pdf (accessed October 21, 2014)
World Health Organization (1999) Counterfeit Drugs: Guidelines for the Development of Measures to Combat Counterfeit Drugs. Combat, http://whqlibdoc.who.int/hq/1999/WHO_EDM_QSM_99.1.pdf. Accessed Oct 2014

An individual patient data meta-analysis on factors associated with adverse drug events in surgical and non-surgical inpatients

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WHAT IS ALREADY KNOWN ABOUT THE SUBJECT

- Adverse drug events cause serious morbidity and mortality in hospitalized patients.
- The admission pathway of surgical and non-surgical patients differs.
- Drug use is associated with an increased risk of post-operative complications.

WHAT THIS STUDY ADDS

- Individual patient data analysis of patient characteristics and types of medication associated with (preventable) adverse drug events (ADEs) during admission with a substantial increase of statistical power.
- Difference in occurrence of ADEs in surgical and non-surgical patients.
- Suggestions for focused interventions for preventing ADEs in surgical and non-surgical patients.

AIM

The incidence of adverse drug events (ADEs) in surgical and non-surgical patients may differ. This individual patient data meta-analysis (IPDMA) identifies patient characteristics and types of medication most associated with patients experiencing ADEs and suggests target areas for reducing harm and implementing focused interventions.

METHODS

Authors of eligible studies on preventable ADEs (pADEs) were approached for collaboration. For assessment of differences among (non-)surgical patients and identification of associated factors descriptive statistics, Pearson chi-square, Poisson and logistic regression analyses were performed. For identification of high risk drugs (HRDs), a model was developed based on frequency, severity and preventability of medication related to ADEs.

RESULTS

Included were 5367 patients from four studies. Patients aged ≥ 77 years experienced more ADEs and pADEs compared with patients aged ≤ 52 years (odds ratios (OR) 2.12 (95% CI 1.70, 2.65) and 2.55 (95% CI 1.70, 3.84), respectively, both $P < 0.05$). Polypharmacy on admission also increased the risk of ADEs (OR 1.21 (95% CI 1.03, 1.44), $P < 0.05$) and pADEs (OR 1.85 (95% CI 1.34, 2.56), $P < 0.05$). pADEs were associated with more severe harm than non-preventable ADEs (54% vs. 32%, $P < 0.05$). The top five HRDs were antibiotics, sedatives, anticoagulants, diuretics and antihypertensives. Events associated with HRDs included diarrhoea or constipation, abnormal liver function test and central nervous system events. Most pADEs resulted from prescribing errors (90%).

CONCLUSION

Elderly patients with polypharmacy on admission and receiving antibiotics, sedatives, anticoagulants, diuretics or antihypertensives were more prone to experiencing ADEs. Efficiency in prevention of ADEs may be improved by targeted vigilance systems for alertness of physicians and pharmacists.

21

Introduction

Adverse drug events (ADEs) constitute a considerable cause of morbidity and mortality in hospitalized patients [1]. Most studies on the occurrence and preventability of ADEs were performed in cohorts of non-surgical patients such as paediatric, medical and intensive care patients [2]. A study on risk factors associated with drug-related admissions to the hospital focused on the drug groups, based on frequency of events [3]. Another review on medication errors or ADEs in hospitalized patients concluded a wide variability of the occurrence of medication errors and adverse events or reactions. Important risk factors for errors included the insufficient pharmacological knowledge of health care professionals. Polypharmacy, female gender, drugs with a narrow therapeutic range, renal elimination of drugs, age over 65 years and use of anticoagulants or diuretics are important risk factors for adverse events [4]. Differences in the admission process of surgical and non-surgical patients may affect the risk for ADEs during hospitalization. For instance, during the surgical process many patient handovers associated with the intervention take place [5]. Handovers between physicians in hospitals are routinely mediated through a verbal or written 'sign-out'. Important information is often not transmitted at sign-out [6]. These failures in communication can lead to uncertainty in patient care decisions resulting in patient harm [7]. A paper by Kennedy et al. demonstrated that regular drug use for co-morbidity was associated with increased risk of post-operative complications related to the co-morbidity at hand. Moreover, if the length of a paucity in medication use in preparation for the surgery increased, then the complication rate increased as well. Hence, the increased risk certainly reflects the severity of co-morbidity as a confounder. These authors further suggested that the patients' needs for drugs to withstand the stresses of the post-operative period of an operation might also contribute to an increased risk of complications [8]. On the other hand, non-surgical patients may be older and often use more kinds of medication during their admission. All these aspects can affect the occurrence of ADEs in both groups. It would be interesting to know if the admission to a surgical or to a non-surgical ward differentially associates with the occurrence of in-hospital (p)ADEs.

Different means for improving patient safety have been advocated through the years. The recent development in patient safety improvement is to provide individual care systems. A system approach is based on patient characteristics as well. Our study group is developing a medication safety programme using a combination of a system approach and an individual care approach tailored by patient characteristics [9].

A meta-analysis of individual patient data was used to provide more detailed information on factors associated with ADEs during admission of patients to hospital.

Another major advantage of an individual patient data meta-analysis (IPDMA) was a substantial increase in statistical power. It allowed subgroup analyses and enabled correction for potential effect modifiers or confounders.

This IPDMA aimed to identify patient characteristics and types of medication associated with (preventable) ADEs during admission, focusing on surgical and non-surgical patients. If these factors can be identified, interventions can be developed to prevent patients from having ADEs during admission or to detect ADEs as early as possible.

Methods

Search and study selection

To identify studies that registered ADEs in adult hospitalized patients a literature search was conducted on PubMed and Embase (from 2000 to April 2011). The combined search term consisted of the following keywords in the title or abstract regarding ADEs: 'adverse drug events', 'ADE', 'medication related problems', 'adverse drug reaction reporting system' or 'drug therapy/adverse effects'. In order to find studies that included surgical patients as well as non-surgical patients, to specify surgical patients, 'surgical', 'surgery', 'operation', 'pre-operative', 'peri-operative' or 'post-operative' were added. Then the terms 'hospitalized' or 'hospitalised', 'hospitalization' or 'hospitalisation', 'hospital' or 'inpatients' were included in order to retrieve studies on hospitalized patients, i.e. studies that included ADEs during admission. Lastly the keywords 'frequency', 'incidence' or 'epidemiology' were added to include epidemiological studies. No language restrictions were used.

To exclude children and incidents registered in the emergency department, study titles containing the terms 'child', 'children', 'paediatrics' or 'emergency' were excluded. A manual cross-reference search of eligible papers was performed to identify other relevant articles. Two studies on ADEs from research groups at our hospital, one in surgical patients and one in medical patients using the same methodology, also met the inclusion criteria [10, 11].

After completion of the study and study manuscript we updated the search in August 2014 to make sure that in the meantime no vital studies had been published while the current study was running.

Data collection process

The corresponding authors of the studies meeting the inclusion criteria of the present IPDMA were approached by e-mail, including the research protocol, to collaborate on this project. When collaboration was confirmed, available variables in the datasets were compared. Variables were considered for harmonization if included in at least two studies. After this step, a definite list of the IPDMA

variables was created. With respect to privacy, the transferred databases and cumulative database did not contain identifiable personal data, only unique study numbers. All data were handled and stored anonymously in the IPDMA database.

Data items

The data items were defined before article selection. Item definitions had to be comparable in two or more studies. Moreover, data items could only be included and merged if the definitions were similar. The included items and their definitions were relevant items and used widely in patient and medication safety studies. The selection of patient characteristics in the final analysis consisted of age, gender, clinical service (surgical or non-surgical), urgency of admission (acute or planned) and polypharmacy. Age was categorized in four age categories: ≤52 years, 53–64 years, 65–76 years and ≥77 years. Age was first categorized in under and over 65 years old and each category subsequently separated in two subcategories based on their median ages (52 and 77 years, respectively). Information on urgency of admission was available in three studies. In the fourth dataset the urgency was assessed based on the reason for admission. Polypharmacy was dichotomized to include all studies in the analysis and defined as more than five drugs used on admission. One study (de Boer *et al.*) only supplied the dichotomous variable. In the literature, this cut-off point is commonly used [12, 13]. A study by Linjakumpu *et al.* concluded that using five or more drugs was associated with poor physical and psychic health [13]. The selected ADE variables were trigger used for ADE detection, causality, severity, preventability, type of medication accountable for the ADE, type of event and type of medication error. Triggers used for identification of ADEs were classified as laboratory values, clinical symptoms or both. Assessment of the probability for a causal relationship between an adverse event and a drug was classified as certain, probable/likely and possible. For assessment of the severity of ADEs, the Common Terminology Criteria for Adverse Events (CTCAE) classification was used [14]. The CTCAE identifies five categories: mild, moderate, severe, life-threatening and death. For the purpose of this IPDMA, these five categories were recoded into two categories, mild and moderate were recoded as mild and severe, life-threatening and death were recoded as severe. Medication accountable for ADEs was categorized based on major medication groups or, in the case of high number of ADEs, on subgroups. ADEs caused by medication errors were deemed preventable (pADEs). To all pADEs a stage of medication error was attributed. The categorization consisted of five error stages: prescribing (including ordering and monitoring), transcribing, dispensing, administering and across stage. ADEs not caused by medication errors were considered non-preventable ADEs.

For quality assessment, the Methodological Index for Non-randomized Studies (MINORS)-checklist was used,

developed by Slim *et al.* This checklist was developed to assess the methodological quality in comparative and non-comparative studies. The checklist consists out of 12 items, eight for non-comparative studies and four additional items for comparative studies, including the risk of bias. The items were scored on a three point scale, ranging from 0–2. The maximum score was 16 for non-comparative studies and 24 for comparative studies, with higher scores indicating better quality [15].

Summary measures and synthesis of results

After pooling the datasets, occurrences of ADEs and pADEs per 100 admissions (and their 95% confidence intervals) were calculated with a Poisson regression analysis. Furthermore the risk factors for ADEs in surgical and non-surgical patients were identified. The associations of patient characteristics with ADE occurrence were expressed as odds ratios (and their 95% confidence intervals) following uni- and multivariable binary logistic regression analyses with candidate factors for the multivariable analyses selected from the univariable analyses with $P > = 0.10$ as the removal criterion. Study participants were listwise deleted in regression analyses, in the case of missing data on any variable of the predictor sets. If, due to this set-up, adding a variable to a regression model excluded a whole site, then the previous regression model without the added variable was assessed with and without data from the excluded site(s) to assess the potential bias resulting from the complete case analyses.

In a second step of the analysis we assessed whether the heterogeneity among studies in the pooled dataset had an impact on the identification of factors significantly associated with (p)ADEs by adding 'Study' to the final multivariable models and observing if the associations remained significant. Steps in model building were fully documented.

For the assessment of medications accountable for ADEs, i.e. high-risk drugs (HRDs), a weighing model was applied. This model was based on the fraction of all ADEs related to the type of medication (fADE), the medication-related proportion of severe ADEs (pS), the relative weight of severe (wS) compared with mild ADEs, and the medication-related proportions of preventable severe (prevS) and mild (prevM) ADEs: $fADE*(pS*wS*prevS + (1 - pS)*prevM)$. All parameters except wS stem from the included data. The relative weight of severe vs. mild ADEs (wS) was arbitrarily set at 5 (severe ADEs being five times as worse as mild ADEs). The medications were ranked according to their weight based on this formula and the top five were considered HRDs. Because the relative weight of 5 was set arbitrarily, it was varied within a range from 2 to 10 in an additional scenario analysis in order to assess the robustness of this ranking.

Analysis of the triggers for detecting the ADEs and of type of medication errors in the different wards were performed with Pearson's Chi-square. The level of signifi-

cance was set at $P < 0.05$. Statistical analyses were performed using SPSS, version 19.0.

Results

Study selection and characteristics

The literature search in 2011 yielded 1280 titles. After screening title and abstract, 47 papers were eligible and their full text was retrieved. Only two studies fulfilled the inclusion criteria and provided information on ADEs and their preventability in surgical as well as non-surgical patients. Their data were combined with two eligible studies performed in our centre [10, 11, 16, 17] (Figure I). All four included studies were prospective observational multicentre studies. The methodological quality of the studies, based on the MINORS criteria, was good, and scored in the upper quartile of the quality score range (13–15 points, possible maximum score was 16 points). The characteristics of the included studies are shown in Table 1.

The Japan Adverse Drug Events (JADE) study by Morimoto and colleagues investigated the incidence and preventability of ADEs and medication errors in Japan [17]. This study provided data of 1469 surgical patients and 1531 non-surgical patients. Another 459 patients admitted to the ICU ward were excluded for this analysis.

The Ward-oriented pharmacy In Newly admitted Geriatric Seniors (WINGS) study by Klopotowska and colleagues investigated the incidence and preventability of ADEs in hospitalized seniors (>65 years) [11]. Chart review enhanced by a modified Institute for Healthcare Improvement (IHI) trigger-tool was used to identify ADEs [18]. An expert team (physician and pharmacist) conducted the ADE assessment. For the purpose of the IPDMA only ADEs detected by the modified IHI ADE trigger-tool were included in the analyses. ADEs not related to triggers (i.e. detected by chart review only) were excluded.

The updated literature search in 2014 yielded 45 titles and abstracts. Just one additional study, with data on (p)ADEs in Saudi Arabia, was identified and we decided to reflect upon its outcomes in the discussion section below [19].
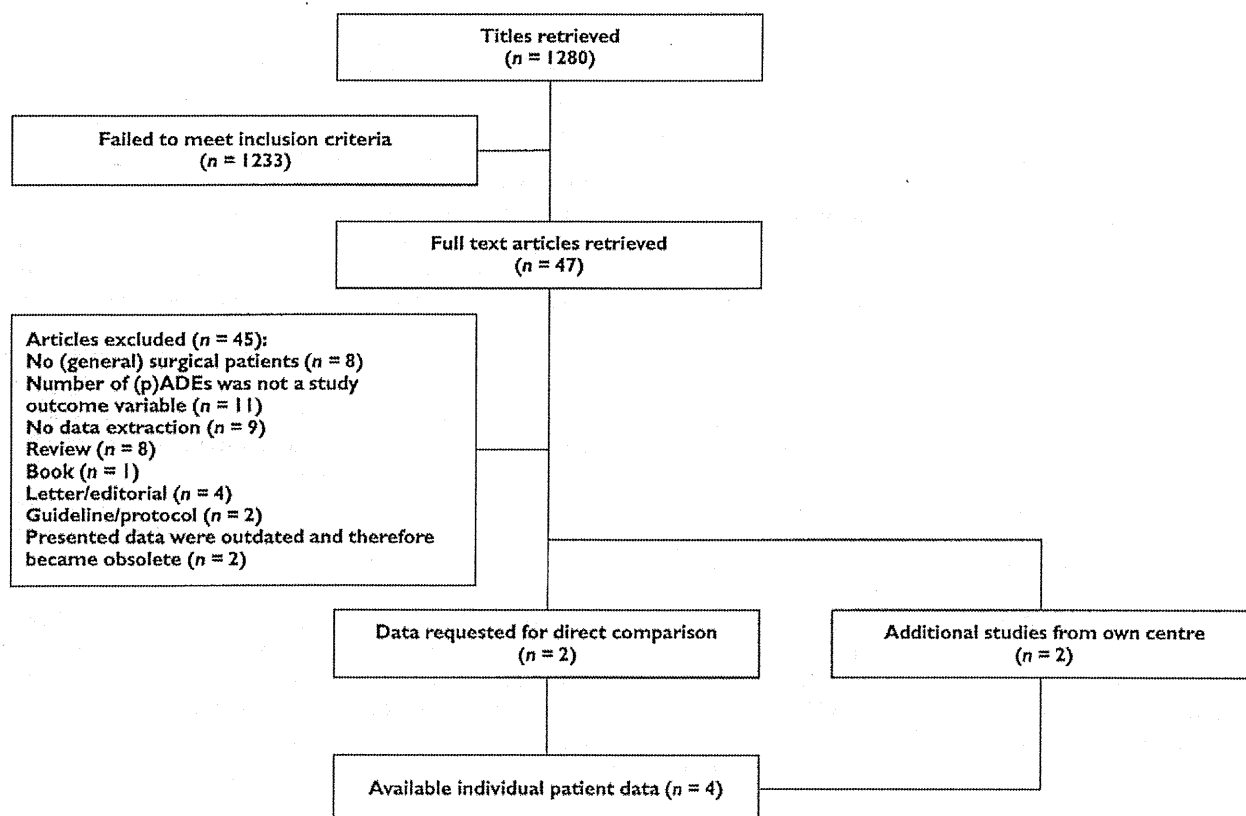

Figure 1

Flow chart article selection

Table 1

Study and patient characteristics per included cohort

		de Boer et al. [10]	Klopotowska et al. [11]	Morimoto et al. [17]	Berga Culleré et al. [16]
Trial design characteristics					
Publication year		2013	2013	2010	2009
Cohort year		2009	2007	2004	2007
Quality score (maximum 16)		13	14	14	15
Number of hospitals		3	3	5	5
Number of patients		567	250	3 000	1550
	Surgical	567	–	1 469	775
	Non-surgical	–	250	1531	775
Patient days					
	Surgical	5367		30 457	5876
	Non-surgical	–	2151	25 751	7252
Method of ADE detection		Chart review based on selected triggers; assessment by an expert panel	Chart review enhanced by a IHI trigger tool; assessment by an expert panel	Chart review, direct observation and voluntary incident reports; assessment by physician reviewers	Chart review based on selected warning signs and daily observation; assessment by the research team
Patient characteristics					
Age (%)	≤52 years	130 (23)	0	572 (19)	336 (22)
	53–64 years	172 (30)	0	549 (18)	259 (17)
	65–76 years	173 (31)	126 (50)	995 (33)	397 (26)
	≥77 years	92 (16)	124 (50)	884 (29)	558 (36)
Gender (%)	Male	278 (49)	117 (47)	1 668 (56)	894 (58)
	Female	289 (51)	133 (53)	1 332 (44)	656 (42)
Medication on admission (%)	≤5	392 (69)	82 (33)	2 288 (76)	–
n = 4271	>6	170 (30)	168 (67)	712 (24)	–
Urgency of admission (%) n = 5754	Planned	567 (100)	37 (15)	1 561 (52)	465 (30)
	Acute	-	213 (85)	1 439 (48)	1013 (65)
Patients with ADE (%)		130 (23)	36 (14)	656 (22)	159 (10)
Patients with pADE (%)		23 (4)	21 (8)	116 (4)	81 (5)

Summary measures and synthesis of results

Data from a total of 5367 admitted patients were available for the present IPDMA, 2811 surgical and 2556 non-surgical patients. The overall number of ADEs was 1304 of which 265 (20%) were preventable. Per 100 admissions, 24.3 (95% CI 22.8, 25.9) ADEs and 4.9 (95% CI 4.3, 5.6) pADEs were counted. ADEs occurred less frequently in surgical patients compared with non-surgical patients without reaching statistical significance (P value = 0.061), with 22.9 (95% CI 20.9, 25.1) ADEs per 100 admissions vs. 25.9 (95% CI 23.6, 28.3). The occurrence of pADEs was significantly lower in surgical patients, with 4.2 (95% CI 3.5, 5.1) pADEs per 100 admissions vs. 5.7 (95% CI 4.8, 6.8) in non-surgical patients (P value = 0.024).

Patient factors associated with ADEs All patients were evaluated to define factors associated with one or more ADEs using a univariable and multivariable analysis. In the univariable analysis, the variables age and polypharmacy on admission significantly contributed to the occurrence of ADEs and pADEs. In line with the higher occurrence of pADEs in non-surgical patients, a non-surgical service was identified as a factor associated with pADEs as well (Table 2). In a multivariable logistic regression analysis, age

was the only identified factor associated with ADEs, while age and polypharmacy on admission were both factors associated with pADEs. Equal results were found in a subgroup analysis in patients over 65 years (Table 2).

The variable 'Study' did not affect the identification of factors associated with (p)ADEs in the hierarchical regression model for the whole group, as well as the senior group.

Detection and nature of ADEs All studies used triggers such as clinical symptoms, laboratory values or a combination of both to detect ADEs. The greater part of the ADEs was detected by clinical symptoms, 937 of 1304 ADEs (72%). The role of laboratory values in detecting ADEs and pADEs was significantly higher in the severe ADE severity category (P < 0.001) (Table 3).

The probability of a causal relationship between adverse event and an administered drug was deemed certain in 12%, probable/likely in 42% and possible in 46% of the ADEs. Causality was significantly more often certain in pADEs compared with non-preventable ADEs (30% vs. 9%, P < 0.05) [10, 11, 17].

Next, the focus was on the type of medication accountable for ADEs [10, 11, 16, 17]. For the additional analysis,

Table 2

Factors associated with (preventable) ADEs

Factors		All patients				Patients > 65 years			
		OR (95% CI) ADE	P value	OR (95% CI) pADE	P value	OR (95% CI) ADE	P value	OR (95% CI) pADE	P value
Age (years)	≤ 52 years	1		1		–		–	
	53–64 years	1.62 (1.26, 2.08)	0.000	0.84 (0.49, 1.45)	0.540	–		–	
	65–76 years	1.75 (1.40, 2.19)	0.000	1.45 (0.94, 2.24)	0.093	1		1	
	≥ 77 years	2.12 (1.70, 2.65)	0.000	2.55 (1.69, 3.84)	0.000	1.21 (1.02, 1.43)	0.027	1.76 (1.30, 2.38)	0.000
Gender	Male	1		1		1		1	
	Female	1.09(0.95, 1.25)	0.242	1.07 (0.82, 1.38)	0.616	0.99 (0.83, 1.17)	0.875	1.02 (0.76, 1.38)	0.874
Clinical service	Surgical	1		1		1		1	
	Non-surgical	1.04 (0.91, 1.20)	0.534	1.30 (1.01, 1.69)	0.045	0.92 (0.77, 1.08)	0.306	1.05 (0.78, 1.41)	0.751
Urgency of admission	Planned	1		1		1		1	
(n = 5295)	Acute	0.94 (0.82, 1.08)	0.367	1.22 (0.94, 1.58)	0.137	0.97 (0.82, 1.14)	0.687	1.16 (0.86, 1.56)	0.330
Polypharmacy *	No	1		1		1		1	
(n = 3812)	Yes	1.21 (1.03, 1.44)	0.024	1.85 (1.34, 2.56)	0.000	1.10 (0.90, 1.35)	0.335	1.58 (1.10, 2.27)	0.013

Crude odds ratios (OR) are presented based on logistic regression analysis. ADEs, adverse drug events; pADEs, preventable adverse drug events. *Data from three studies [10, 11, 17].

Table 3

Triggers identifying ADEs

	Severity*			Preventability		
	Mild (%)	Severe (%)	P value	No (%)	Yes (%)	P value
Clinical	596 (83)	212 (54)		767 (74)	170 (64)	
Laboratory	116 (16)	159 (40)	0.000	253 (24)	82 (31)	0.001
Both	3 (0)	21 (5)		19 (2)	13 (5)	

ADEs, adverse drug events. Results are calculated using a chi-square test. *Data from three studies [10, 11, 17].

data from only three studies were used [10, 11, 17], since one study had only analyzed the severity on pADEs [16]. Applying the weighing model as described in the methods section, resulted in a top five of HRDs: antibiotics, sedatives, anticoagulants, diuretics and antihypertensives (Table 4).

The type of events associated with HRDs in the various medication groups was evaluated [10, 11, 17]. An overview of all event types, the preventability and severity of the events can be found in Table 5 [10, 11, 16, 17]. The events were ordered based on their association with HRDs. The event types associated with HRDs were often associated with abnormal laboratory values, such as abnormal liver function tests (19%) or impaired haemostasis (4%). Other event types were diarrhoea or constipation (35%), central nervous system event (18%) and skin and/or allergic reaction (11%).

A non-significantly higher proportion of pADEs in non-surgical patients was identified, 146 of 661 non-surgical ADEs (22%) vs. 119 of 643 surgical ADEs (19%, P = 0.108). A total of 13 ADEs directly contributed to the death of a patient, seven of which were judged as preventable. Significantly more pADEs were classified severe compared with the non-preventable ADEs (55% vs. 32%, P < 0.001; in

data from three cohorts [10, 11, 17]). Furthermore, more severe ADEs were seen in non-surgical patients compared with the surgical patients (43% vs. 28%, P < 0.001).

For the 265 pADEs associated with medication errors, the medication error stage could be determined in 264 of the 265 pADEs. The majority of medication errors were found in the prescribing stage (90%). A slightly higher number of prescribing errors occurred in surgical patients (94%), compared with non-surgical patients (87%), but just failed to reach significance (P = 0.055). Importantly, in the severe pADE severity category 96% of the errors were associated with prescribing errors.

Discussion

The overall occurrence of ADEs and more specific pADEs constitutes a serious problem in hospitalized patients. The patients and/or drugs factors associated with the occurrence of a (p)ADE as provided by the present IPDMA can be used to target tailored interventions aimed at reducing ADEs. Non-surgical, elderly patients with polypharmacy on admission and/or receiving HRDs (antibiotics, sedatives,

Table 4

Medication accountable for ADEs

Type of medication	Frequency (% of all ADEs n = 1304)	Severe*† All (% of all severe ADEs)	Preventable	Mild*† All (% of all mild ADEs)	Preventable	Ranking HRDs*‡
Sedatives	89 (7)	81 (21)	24	7 (1)	1	1 (0.109)
Antibiotics	375 (29)	89 (23)	12	252 (35)	9	2 (0.062)
Antithrombotics– anticoagulants	41 (3)	22 (6)	9	13 (2)	5	3 (0.045)
Diuretics	35 (3)	18 (5)	7	9 (1)	2	4 (0.033)
Antihypertensives	56 (4)	24 (6)	6	26 (4)	5	5 (0.032)
Electrolytes or fluids	28 (2)	2 (1)	2	24 (3)	23	6 (0.030)
Antidiabetics	25 (2)	11 (3)	6	8 (1)	2	7 (0.029)
Analgesics – opioids	143 (11)	21 (5)	4	101(14)	6	8 (0.024)
Analgesics – NSAIDs	90 (7)	40 (10)	4	35 (5)	6	9 (0.023)
Other drugs	163 (13)	34 (9)	3	73 (10)	9	10 (0.022)
Antipsychotics	26 (2)	17 (4)	3	6 (1)	1	11 (0.014)
Cardiovascular drugs	25 (2)	8 (2)	2	8 (1)	0	12 (0.009)
Gastrointestinal drugs	123 (9)	13 (3)	0	103 (14)	4	13 (0.004)
Antithrombotics–antiplatelets	19 (1)	5 (1)	0	13 (2)	2	14 (0.002)
Nutritional agents and vitamins	13 (1)	1 (0)	0	8 (1)	2	15 (0.002)
Anaesthetics	21 (2)	2 (1)	0	11 (2)	0	16 (0)
Antiepileptics	13 (1)	4 (1)	0	6 (1)	0	17 (0)
Combination of medication	12 (1)	0	0	10 (1)	0	18 (0)
Antifungals	4 (0)	0	0	2 (0)	0	19 (0)

ADEs, adverse drug events; HRDs, high risk drugs; NSAIDs, non-steroidal anti-inflammatory drugs. *Data from three studies [10, 11, 17]. †n = 1107, severity was not assessable in three cases. ‡Weighing algorithm based on the fraction of all ADEs related to the type of medication (fADE), the medication-related proportion of severe ADEs (pS), the relative weight of severe (wS) compared with mild ADEs, and the medication-related proportions of preventable severe (prevS) and mild (prevM) ADEs: fADE*(pS*wS*prevS + (1 − pS)*prevM). wS was set at 5 in this calculation.

Table 5

ADE classification

Type of ADE	Frequency (% of all ADEs n = 1304)	Preventable (% of all pADEs n = 265)	Severe (% of all severe ADEs)*†	Associated with high risk drugs (%)
Diarrhoea or constipation	345 (26)	16 (6)	24 (7)	188 (35)
Abnormal liver function tests	161 (12)	5 (2)	79 (52)	101 (19)
Central nervous system event	184 (14)	48 (18)	133 (83)	96 (18)
Skin and/or allergic reaction	156 (12)	42 (16)	7 (5)	62 (11)
Impaired haemostasis	23 (2)	13 (5)	13 (65)	19 (4)
Renal function disorder	38 (3)	16 (6)	20 (69)	18 (3)
Cardiovascular event	58 (4)	28 (11)	16 (43)	13 (2)
Other	85 (7)	28 (11)	20 (47)	12 (2)
Haemorrhage	65 (5)	19 (7)	50 (79)	11 (2)
Electrolyte imbalance	32 (2)	22 (8)	3 (23)	8 (1)
Respiratory insufficiency	12 (1)	5 (2)	9 (90)	7 (1)
Nausea and/or vomiting	131 (10)	13 (5)	10 (9)	6 (1)
Thromboembolic event	3 (0)	3 (1)	0	0
Hypoglycaemia	11 (1)	7 (3)	8 (80)	0

ADEs, adverse drug events. *Data from three studies [10, 11, 17]. †n = 1107, severity was not assessable in three cases.

anticoagulants, diuretics and antihypertensives) require increased alertness.

This IPDMA led us to conclude that non-surgical patients are the ones who have a higher risk of pADEs compared with surgical patients. An explanation for this conclusion may be the age difference in both groups. Non-surgical patients in the included studies were older than surgical patients. This age difference remained when excluding the WINGS study that was conducted exclusively in elderly patients. Other grounds for this contrast might be the urgency of admission and length of hospital stay. Surgical admissions were more frequently planned admissions, whereas internal medicine has more acute admissions. The length of stay could increase the risk for

developing pADEs as the longer the hospital stay, the more time patients are exposed to possible errors and their adverse effects. However, in the IPDMA, hospital stay of surgical admissions was comparable with non-surgical admissions.

Previous studies determined patient factors associated with ADEs in ambulatory care, nursing home residents and adult hospitalized patients. They concluded that age, gender, number of drugs, comorbidity and medical (non-surgical) service are important factors [20–23]. These studies were performed 20 years ago and perhaps are now outdated. Moreover, most of these studies were case-control studies that have a high risk of bias in comparison with prospective studies. One prospective cohort study was found. However, it relied on patient interviews for identifying ADEs and was entirely lacking objective measurements, which leads to highly biased results [21]. This IPDMA is comprised exclusively of prospective patient data. Therefore, this large international dataset has an explicit additional value in determining the genuine factors associated with ADEs.

Next to identification of patient groups with an increased risk of developing (p)ADEs, medication types seem another important focus in identifying ADE risks. The 5 Million Lives Campaign by the Institute of Healthcare Improvement focused on specific high ADE risk medication groups. In that campaign 12 interventions aimed to reduce morbidity and mortality due to medication errors were proposed. One of these interventions was 'Prevent Harm from High-Alert Medications . . . starting with a focus on anticoagulants, sedatives, narcotics and insulin' [24]. The campaign focused on prevention of all harm caused by medication, not solely harm perceived as preventable. The necessity of increased alertness when prescribing anticoagulants and sedatives was confirmed by the present IPDMA. According to this IPDMA, antibiotics, diuretics and antihypertensives should be considered as high risk drugs as well. To label certain categories of drugs as high risk drugs, here not only frequency of ADEs was taken into account but also the severity and the preventability of them. A robust model was used for ranking types of drugs, attributing a higher weight to those types causing severe ADEs. It may nevertheless still be worthwhile to put more effort into determining quantitative severity weights for different ADEs among groups of professionals and patients in future research.

Most errors in the medication order process occurred at the prescribing stage. The stage of prescribing is the most well documented stage of the medication order process. Also errors at this stage are the root of most errors. Nurses or anyone else will not likely intercept a wrong prescription. Kale et al. estimated that in a hospital where 6 million doses a year were administrated, more than 4200 preventable ADEs attributable to medication administration errors occur annually. The costs could range anywhere between \$25 and \$33 million in a 700-bed teaching hospital annually [25]. Another study concluded that the most important factor resulting in errors was the number of items on a prescription [26].

The important value of this IPDMA compared with single observational studies is the availability of ADE data from very diverse and large patient populations. Therefore, we were able to identify factors that can contribute to an ADE based on patient characteristics and medication type. The originating countries and baseline characteristics of the included studies were heterogeneous, meaning that identified factors associated with ADEs likely apply to various patient populations. If tailored intervention strategies to prevent ADEs are based on these factors they likely apply to any setting. The Agency for Healthcare Research and Quality (AHRQ) reported that 'Adverse drug events cannot be predicted by patient characteristics or drug type' [27]. With this IPDMA, however, due to the large population it was deemed possible to predict ADEs based on patient characteristics or drug type. On the other hand the diversity of studies unfortunately is a limitation as well. The population size varied. About half (56%) of the study population in this IPDMA consisted of patients from the JADE study [17]. Moreover, due to the minor differences in study design and recorded variables, only a small number of corresponding variables could be included in this IPDMA. In doing so, some more specific patient factors that presumably influence the risk for an ADE might have been left out in this analysis. For example the health status of the admitted patient, based on comorbidities and expressed as ASA classification, the body mass index or social class could not be retrieved from all studies and were therefore not included. These potential confounders, if known, could have influenced the observed association patterns. Hence, further differentiation in targeting areas for future interventions like elderly people with particular morbidity or disease statuses is well conceivable. For now, the IPDMA focused on information that is known for most patients on admission and thereby readily available for involved caregivers.

The study by Berga Culleré et al. focused on pADEs and while variables regarding these events were fairly complete, data on severity of non-preventable ADEs were absent [16]. The urgency of admission was manually determined based on the reason for admission, if sufficient information was available. The study by Berga Culleré et al. was excluded from analysis whenever the missing variables were required for that specific analysis, such as analysis of severity for non-preventable as well as preventable ADEs. Fortunately data from the Berga Culleré et al. study could be used in analyses for appointing patient characteristics that could be an indicator for the occurrence of (p)ADEs. To prevent bias due to their missing values, an additional patient risk factor analysis was performed, while excluding the Berga Culleré et al. study. It did not appear to be a confounding factor, since factors associated with

(p)ADEs in this analysis (age and polypharmacy on admission) remained unchanged.

Some limitations of the data analysis must be noted as well. It was originally intended to include the variable 'length of hospital stay' in the multivariable analysis of factors associated with (p)ADEs. However, it was necessary to exclude this variable as a prospective risk factor for two main reasons: causality and unfitness for use as a predictor. First, it is difficult to discriminate between long hospital stays resulting in more time and opportunities for ADEs to take place on the one hand and prolonged hospitals stay resulting from experiencing an ADE on the other hand. Secondly, the length of hospital stay cannot be used as a predictive factor, since this factor develops during hospital stay and is not yet available on admission.

Another limitation might be that the factors potentially associated with (p)ADEs were all selected from available and accessible data from the included studies. Potential confounders like morbidity and disease status were not assessed, but could have influenced the observed association patterns, if known. Hence, further differentiation in targeting areas for future interventions like elderly people with particular morbidity or disease statuses is well conceivable.

Furthermore, two datasets from different studies at our centre were used. These studies were included because the methodology was similar, albeit not fully equal. In the WINGS study, the experts conducted a full chart review using the trigger-tool only as an aid and not for patient pre-selection [11]. In the Surepill study, a trigger tool was used to pre-select patients [10]. Only patients with identified triggers in their charts were further assessed by an expert team for ADEs [28]. For the purpose of this IPDMA, only ADEs that were identified by the trigger tool in the WINGS study were included, to optimize the comparability with the Surepill study. When using trigger tools to identify ADEs, ADEs not related to triggers can be missed [29].

The updated literature search yielded one prospective cohort study on the occurrence and nature of (p)ADEs in Saudi Arabia [19]. The study included 496 medical (nonsurgical), 306 surgical and 175 ICU patients. The overall incidence of ADEs was 8.5 (95% CI 6.8, 10.4) and preventable ADEs 2.6 (95% CI 1.6, 3.7) per 100 admissions. The stage of errors was most frequent at the prescribing stage of the medication use process. The most frequent preventable ADEs according to drug classes were antibiotics, anticoagulants and antihypertensives. Significant factors associated with an increased odds ratio for ADEs were age, ICU, number of medications at admission and comorbidity. Surgical wards had a significantly lower odds ratio for ADEs.

In conclusion this IPDMA provided patient, drug and event characteristics that are associated with the occurrence of (p)ADEs. In particular elderly patients with polypharmacy on admission and use of high risk drugs are prone to experience ADEs. Efficiency in the prevention of ADEs can be improved by targeting vigilance systems for alertness of physicians and pharmacists.

Competing Interests

REFERENCES

1 Kohn LT, Corrigan JM, Donaldson MS. To Err Is Human: Building A Safer Health System. New York: National Academies Press, 1999.

2 Cano FG, Rozenfeld S. Adverse drug events in hospitals: a systematic review. Cad. saúde pública / Ministério da Saúde, Fundação Oswaldo Cruz, Esc. Nac. Saúde Pública 2009; 25: (Suppl. 3): S360–72.

3 Howard RL, Avery J, Slavenburg S, Royal S, Pipe G, Lucassen P, Pirmohamed M. Which drugs cause preventable admissions to hospital? A systematic review. Br J Clin Pharmacol 2007; 63: 136–47.

4 Krähenbühl-Melcher A, Schlienger R, Lampert M, Haschke M, Drewe J, Krähenbühl S. Drug-related problems in hospitals: a review of the recent literature. Drug Saf 2007; 30: 379–407.

5 De Vries EN, Prins HA, Crolla RMPH, den Outer AJ, van Andel G, van Helden SH, Schlack WS, van Putten MA, Gouma DJ, Dijkgraaf MG, Smorenburg SM, Boermeester MA. Effect of a comprehensive surgical safety system on patient outcomes. N Engl J Med 2010; 363: 1928–37.

6 Borowitz SM, Waggoner-Fountain L, Bass EJ, Sledd RM. Adequacy of information transferred at resident sign-out (in-hospital handover of care): a prospective survey. Qual Saf Health Care 2008; 17: 6–10.

7 Arora V, Johnson J, Lovinger D, Humphrey HJ, Meltzer DO. Communication failures in patient sign-out and suggestions for improvement: a critical incident analysis. Qual Saf Health Care 2005; 14: 401–7.

8 Kennedy JM, van Rij AM, Spears GF, Pettigrew RA, Tucker IG. Polypharmacy in a general surgical unit and consequences of drug withdrawal. Br J Clin Pharmacol 2000; 49: 353–62.

9 Ramrattan MA, Boeker EB, Ram K, Burgers DMT, de Boer M, Lie-A-Huen L, Mulder WM, Boermeester MA. Evidence based

development of bedside clinical drug rules for surgical patients. Int J Clin Pharm 2014; 36: 581–8.

10 De Boer M, Boeker EB, Ramrattan MA, Kiewiet JJS, Dijkgraaf MGW, Boermeester MA, Lie-A-Huen L. Adverse drug events in surgical patients: an observational multicentre study. Int J Clin Pharm 2013; 35: 744–52.

11 Klopotowska JE, Wierenga PC, Smorenburg SM, Stuijt CCM, Arisz L, Kuks PFM, Lie-A-Huen L. Recognition of adverse drug events in older hospitalized medical patients. Eur J Clin Pharmacol 2012; 69: 75–85.

12 Veehof LJG, Steward RE, Haaijer-Ruskamp FM, Meyboom-de Jong B. The development of polypharmacy. A longitudinal study. Fam Pract 2000; 17: 261–7.

13 Linjakumpu T, Hartikainen S, Klaukka T, Veijola J, Kivelä S-L, Isoaho R. Use of medications and polypharmacy are increasing among the elderly. J Clin Epidemiol 2002; 55: 809–17.

14 National Cancer Institute. Common Terminology Criteria for Adverse Events v.3.0and v.4.0 (CTCAE). [Internet]. Available at http://ctep.cancer.gov/protocolDevelopment/ electronic_applications/ctc.htm (last accessed 18 December 2012).

15 Slim K, Nini E, Forestier D, Kwiatkowski F, Panis Y, Chipponi J. Methodological index for non-randomized studies (minors): development and validation of a new instrument. ANZ J Surg 2003; 73: 712–6.

16 Berga Culleré C, Gorgas Torner MQ, Altimiras Ruiz J, Tuset Creus M, Besalduch Martin MT, Capdevila Sunyer M, Torres Gubert M, Casajoana Cortinas MT, Baró Sabaté E, Fernández Solà JR, Moron i Besolí A, Òdena Estradé E, Serrais Benavente J, Vitales Farrero MT, Codina Jané C. Detecting adverse drug events during hospital stay. Farm Hosp 2009; 33: 312–23.

17 Morimoto T, Sakuma M, Matsui K, Kuramoto N, Toshiro J, Murakami J, Fukui T, Saito M, Hiraide A, Bates DW. Incidence of adverse drug events and medication errors in Japan: the JADE study. J Gen Intern Med 2011; 26: 148–53.

18 Griffin F, Resar R. IHI global trigger tool for measuring adverse events (second edition). IHI Innov. Ser. White Pap. 2009. Available at www.IHI.org (last accessed 18 December 2012).

19 Aljadhey H, Mahmoud M, Mayet A, Alshaikh M, Ahmed Y, Murray MD, Bates DW. Incidence of adverse drug events in an academic hospital: a prospective cohort study. Int J Qual Health Care 2013; 25: 648–55.

20 Bates DW, Miller EB, Cullen DJ, Burdick L, Williams L, Laird N, Petersen LA, Small SD, Sweitzer BJ, Vander Vliet M, Leape LL. Patient risk factors for adverse drug events in hospitalized patients. ADE Prevention Study Group. Arch Intern Med 1999; 159: 2553–60.

21 Gandhi TK, Weingart SN, Borus J, Seger AC. Adverse drug events in ambulatory care. N Engl J Med 2003; 348: 1556–64.

22 Bates DW, Leape LL, Petrycki S. Incidence and preventability of adverse drug events in hospitalized adults. J Gen Intern Med 1993; 8: 289–94.

23 Field TS, Gurwitz JH, Avorn J, McCormick D, Jain S, Eckler M, Benser M, Bates DW. Risk factors for adverse drug events among nursing home residents. Arch Intern Med 2001; 161: 1629–34.

24 Federico F. Preventing harm from high-alert medications. Jt Comm J Qual Patient Saf 2007; 33: 537–42.

25 Kale A, Keohane C, Maviglia S, Gandhi TK, Poon EG. Adverse drug events caused by serious medication administration errors. BMJ Qual Saf 2012; 21: 933–8.

26 Seden K, Kirkham JJ, Kennedy T, Lloyd M, James S, McManus A, Ritchings A, Simpson J, Thornton D, Gill A, Coleman C, Thorpe B, Khoo SH. Cross-sectional study of prescribing errors in patients admitted to nine hospitals across North West England. BMJ Open 2013; 3: 1–14.

27 Agency for Healthcare Research and Quality, Rockville M. Reducing and preventing adverse drug events to decrease hospital costs: research in action. Issue 1. 2001. Available at http://www.ahrq.gov/research/findings/factsheets/errors -safety/aderia/index.html (last accessed 18 December 2012).

28 De Boer M, Kiewiet JJS, Boeker EB, Ramrattan MA, Dijkgraaf MGW, Lie-A-Huen L, Boermeester MA. A targeted method for standardized assessment of adverse drug events in surgical patients. J Eval Clin Pract 2013; 19: 1073–82.

29 Franklin BD, Birch S, Schachter M, Barber N. Testing a trigger tool as a method of detecting harm from medication errors in a UK hospital: a pilot study. Int J Pharm Pract 2010; 18: 305–11.

Adverse drug events and medication errors in Japanese paediatric inpatients: a retrospective cohort study

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ABSTRACT

Objectives Knowledge about the epidemiology of adverse drug events (ADEs) and medication errors in paediatric inpatients is limited outside Western countries. To improve paediatric patient safety worldwide, assessing local epidemiology is essential.

Design The Japan Adverse Drug Events (JADE) Study was a cohort study.

Setting Paediatric inpatients at two tertiary care teaching hospitals in Japan.

Main outcome measures ADEs and medication errors identified by onsite review of all medical charts, incident reports and prescription queries by pharmacists. Two independent physicians reviewed all incidents and classified ADEs and medication errors, as well as their severity and preventability.

Results We enrolled 1189 admissions which included 12 691 patient-days during the study period, and identified 480 ADEs and 826 medication errors. The incidence of ADEs was 37.8 (95% CI 34.4 to 41.2) per 1000 patient-days and that of medication errors was 65.1 (95% CI 60.6 to 69.5) per 1000 patient-days. Among ADEs, 4%, 23% and 73% were fatal or life-threatening, serious and significant, respectively. Among the 480 ADEs, 36 (8%) were considered to be preventable which accounted for 4% of all medication errors, while 668 (81%) of all medication errors were judged to have the potential to cause harm to patients. The most common error stage for preventable ADEs was monitoring (78%) whereas 95% of potential ADEs occurred at the ordering stage.

Conclusions ADEs and medication errors were common in paediatric inpatients in Japan, though the proportion of ADEs that were preventable was low. The ordering and monitoring stages appeared most important for improving safety.

INTRODUCTION

Adverse drug events (ADEs) are injuries due to medication use[1]. ADEs represent a serious problem in healthcare because they are the most frequent cause of injuries due to medical care in hospitals in developed countries[2 3] and are associated with substantial increases in morbidity and mortality.[2 4-6]

Paediatric inpatients are also vulnerable to ADEs and medication errors.[7] Physiologically, they often have limited reserves with respect to metabolism and/or fluid volume. Preschoolers and younger children are even more vulnerable, because they cannot describe their symptoms and they also vary substantially in terms of weight. Several studies of ADEs and medication errors in paediatric inpatients have been done,[7-12] and in addition a few studies of medication error prevention strategies have been performed in paediatric inpatients.[13-16] However, most of these studies were from Western countries and their results cannot be extrapolated to other settings globally without basic data from other parts of the world.[17]

Thus, we conducted the Japan Adverse Drug Events (JADE) Study, a multicentre cohort study in several settings in Japan.[6] The JADE Study for paediatrics was conducted in a historical cohort study fashion to estimate the epidemiology and nature of ADEs and medication errors in paediatric inpatients in Japan.

METHODS

Study design and patient population
We conducted this JADE Study in the paediatric inpatient setting in two tertiary

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31

care teaching hospitals in Japan. The total number of beds in these two hospitals is 1754 and 152 beds among them were for paediatric inpatients. One hospital had an electronic medical record with an alert system for a drug-drug interaction and duplicate prescriptions. Another hospital did not have either an electronic medical record or any alert system but had only computerised order entry for simple drug prescriptions, blood tests and radiographs. The study used a cohort study design.

Both hospitals care for adult and paediatric patients. Some paediatric patients were admitted to units including adults such as the regular intensive care units (ICUs), emergent care units or subspecialty wards, such as otolaryngology, a practice which is common in Japan. Others were admitted to the neonatal ICUs (NICUs), the paediatric ICUs (PICUs) or general paediatric wards. A few adult patients were also cared for by paediatricians and admitted to the paediatric ward, though this group comprised less than 1% of the admissions to these units. They generally had complex long-term medical conditions, such as congenital diseases (eg, metabolic disease or cerebral palsy) or multiple disabilities.

There are only a few independent children's hospitals in Japan and they generally have more complex patients in terms of severity than general hospitals, but we did not include any of these hospitals in this study. However, one of the hospitals in this study was a university affiliated hospital which does have very complex patients.

We studied all paediatric wards including the NICU and the PICU. We also studied the ICU, the emergent care unit, and the general adult ward when paediatric patients (≤15 years old) were admitted. Thus, we included all patients aged ≤15 years admitted to any ward and patients aged >15 years old who were admitted to any of the paediatric wards over a 3 month study period in 2009.

We had 'well baby nurseries' in both hospitals. However, neonates at the well baby nursery were excluded from this study because they were healthy and were not cared for by paediatricians. Instead, if neonates at birth had a problem such as temporary dyspnoea or mild cyanosis of the limbs, they were admitted to the NICU and cared for by neonatologists. Therefore, the NICU included relatively healthy neonates as well as critically ill neonates. Because of this dichotomy, we elected to classify neonates in the NICU into two categories according to birth weight; low birthweight (LBW) neonates weighing <2500 g and non-LBW neonates weighing ≥2500 g. The main units of evaluation were patient-day and number of admission. The institutional review boards of the two participating hospitals approved the study. Because all data were obtained as part of routine daily practice, informed consent was waived by the institutional review board.

Definitions

The primary outcome of the study was the ADE, defined as an injury due to a medication use.[1] For example, a rash in a patient receiving ampicillin without another obvious cause was considered an ADE. We also identified medication errors, which were defined as any deviation from appropriate use of medication in any step of the medication use process including ordering, transcribing, dispensing, administering or monitoring.[1] Some ADEs were associated with a medication error and were considered preventable (preventable ADEs), while some were not associated with a medication error and were considered non-preventable. Preventable ADEs included ameliorable ADEs: ameliorable ADEs occurred when care was otherwise appropriate but the patient developed issues that could have been addressed sooner; such injury could be ameliorable when appropriate action was taken during the monitoring stage. An event that had potential for harm but did not result in injury was considered a potential ADE. If potential ADEs were intercepted before reaching the patient, they were considered an intercepted potential ADE. An example would be if a physician ordered ampicillin in a patient with known penicillin allergy, but that order was intercepted and corrected by a pharmacist. A non-intercepted potential ADE would be when a physician administered ampicillin to a patient known to be allergic to penicillin without interception, but nothing occurred by chance.

Data collection and review process

Trained reviewers were based at each participating hospital and reviewed all medical charts along with laboratories, incident reports and prescription queries by pharmacists. The trained reviewers consisted of a board-certified paediatrician, paediatric nurses and a dietitian, and the paediatrician trained all reviewers in a standard manner, as reported elsewhere.[1] They collected the characteristics and administrative data for all enrolled patients in the cohort. Then, they identified incidents such as ADEs, potential ADEs and medication errors, as well as the details of those incidents. Data collected for incidents included the name, dose, route and class of the drug, the details of symptoms if the incidents were ADEs, and the details of errors such as stage, persons who were in charge, or causes if the incidents were errors.

Two independent physician reviewers evaluated all incidents collected by the research assistants and classified them as ADEs, potential ADEs, medication errors and exclusions. The physician reviewers rated ADEs and potential ADEs according to the severity of injuries or potential injuries to the patient using a 4-point scale as well as their preventability using a 5-point scale. Categories of severity were fatal, life-threatening, serious and significant. Fatal ADEs resulted in death; life-threatening ADEs caused such

831

issues as transfers to ICU or anaphylactic shock, serious ADEs included gastrointestinal bleeding, altered mental status, excessive sedation, increased creatine or a decrease in blood pressure, and significant ADEs included cases with rash, diarrhoea or nausea, for example. Reviewers considered ADEs as preventable or ameliorable if they were due to an error.

If a medication error was found, the type of error and the error stage in the process where it occurred were classified. The stages of the medication use process were classified into ordering by physicians, transcription by nurses, dispensing by pharmacists or nurses, administration by nurses, patients themselves or caregivers, and monitoring by physicians or other health professionals. When disagreement affected the classification of an incident, the physician reviewers reached consensus through discussion.

Statistical analyses

The incidence per 1000 patient-days, the rates per 100 admissions and the 95% CIs were calculated as a whole, by age group (neonates, infants, preschoolers, school-age children, teenagers or adults) and by ward category (the paediatric general ward, the NICU, the PICU, the ICU, the emergent care unit or the adult ward), respectively. Continuous variables are presented as means with SDs or medians with IQRs, and categorical variables are shown as numbers and percentages. We calculated inter-rater reliabilities using the κ statistics. We carried out all analyses using JMP V.8.0 (SAS Institute, Cary, North Carolina, USA) software.

RESULTS

We enrolled 1189 admissions with 12 691 patient-days on the study wards. The median age was 2 (IQR 0–7) years and 55% (649/1189) were male. The median hospital stay was 5 (IQR 3–9) days, and the median number of medications administered to a patient on admission was 4 (IQR 2–6) (table 1). The patients included 252 (21%) neonates, 174 (14%) infants, 465 (39%) preschoolers, 189 (16%) school-age children, 98 (8%) teenagers and 11 (0.9%) adults (table 2). We had more patients with cancer in the teenagers' group than in other age groups (N=6, 6%). Overall, 169 patients were admitted to the NICU, where 69 (41%) were LBW neonates and 100 (59%) were non-LBW neonates (table 2). The hospital stay was longer in the

LBW neonates and more medications were prescribed to the LBW neonates on admission than non-LBW neonates (median hospital stay; 26 days vs 4 days, the median number of medications on admission; 4 vs 2). Among the 37 patients admitted to the ICU, 35 patients (95%) had had an operation and came to the ICU directly after a procedure, and 15 of these 35 patients were transferred to the PICU from the ICU as a step to be back to the general paediatric ward. Thus, 83% (15/18) of the PICU-admitted patients were transferred from the ICU. Physician reviewers had moderate to excellent agreement with κ statistics of 0.31–0.86.

Adverse drug events

The onsite research assistants identified 1767 incidents during the study period. Among these incidents, physician reviewers judged that there were 480 ADEs in 234 patients (20%), for the incidence of 37.8 (95% CI 34.4 to 41.2) per 1000 patient-days and the rate per 100 admissions of 40.4 (95% CI 36.8 to 44.0) (figure 1). Among those 234 patients who had ADEs, 26 patients (11%) had three or more ADEs.

The incidence of ADEs was the highest in teenagers (table 2). Among neonates, incidence was lower in non-LBW neonates in the NICU than LBW neonates in the NICU and neonates in the general paediatric ward (table 2). The incidence in infants, preschoolers and school-age children were almost similar, and those age groups accounted for 70% of all patients. The incidence by ward category was the highest in the ICU and the lowest in non-LBW neonates in the NICU (table 2).

Seventeen fatal or life-threatening ADEs occurred in 15 patients during their hospital stay, which accounted for 3.5% of the 480 ADEs. Fatal or life-threatening ADEs included respiratory depressions, allergic reactions with dyspnoea, sepsis, airway bleeding and hypoglycaemia. Among the 17 fatal or life-threatening ADEs, 6 ADEs involved sedatives, 4 narcotics and 3 antibiotics. Serious ADEs and significant ADEs accounted for 23% and 73% of all ADEs, respectively.

Regarding organ systems affected by ADEs, gastrointestinal were most frequent, accounting for 45% of all ADEs followed by allergic or skin symptoms (12%) and metabolic or liver dysfunction (11%) (table 3).

Among drug classes, antitumour agents and antibiotics accounted for 31% and 30% of all ADEs, respectively. Narcotics and steroids were the next leading

Table 1 The number of medications on admission according to the ward category

	Total	Paediatric ward	NICU LBW neonates	Non-LBW neonates	PICU	ICU	Emergent care unit	Adult ward
The number of medications on admission, median (25, 75%)	4 (2, 6)	4 (2, 6)	3 (2, 4) 4 (3, 6)	2 (2, 3)	6 (5, 7)	7 (4, 10)	5 (4, 7)	3 (1, 6)

ICU, intensive care unit; LBW, low birth weight; NICU, neonatal intensive care unit; PICU, paediatric intensive care unit.

Table 2   Incidence of adverse drug events and medication errors

Adverse drug events	N	Patient-days	ADEs	Incidence*	95% CI	Rate†	95% CI
Total	1189	12 691	480	37.8	34.4 to 41.2	40.4	36.8 to 44.0
Age category							
Neonates (<1 month)	252	4757	53	11.1	8.1 to 14.1	21.0	15.4 to 26.7
LBW neonates, NICU	69	3270	44	13.5	9.5 to 17.4	63.8	44.9 to 82.6
Non-LBW neonates, NICU	100	944	2	2.1	0.26 to 7.7	2.0	0.24 to 7.2
General paediatric ward	83	543	7	12.9	5.2 to 26.6	8.4	3.4 to 17.4
Infants (1 month=< <1 year)	174	1923	84	43.7	34.3 to 53.0	48.3	38.0 to 58.6
Preschoolers (1 year =< <7 year s)	465	3425	157	45.8	38.7 to 53.0	33.8	28.5 to 39.0
School-age children (7 years=< <13 years)	189	1459	73	50.0	38.6 to 61.5	38.6	29.8 to 47.5
Teenagers (13 years=< <19 years)	98	1081	112	103.6	84.4 to 122.8	114.3	93.1 to 135.5
Adults (19 years=<)	11	46	1	21.7	0.55 to 121.1	9.1	0.23 to 50.7
Ward category							
Paediatric ward	704	7007	364	51.9	46.6 to 57.3	51.7	46.4 to 57.0
NICU	169	4214	46	10.9	7.8 to 14.1	27.2	19.4 to 35.1
LBW neonates	69	3270	44	13.5	9.5 to 17.4	63.8	44.9 to 82.6
Non-LBW neonates	100	944	2	2.1	0.26 to 7.7	2.0	0.24 to 7.2
PICU	18	157	2	12.7	1.5 to 46.0	11.1	1.3 to 40.1
ICU	37	107	9	84.1	38.5 to 159.7	24.3	11.1 to 46.2
Emergent care unit	98	197	11	55.8	22.8 to 88.8	11.2	4.6 to 17.9
Adult ward	163	1009	48	47.6	34.1 to 61.0	29.4	21.1 to 37.8

Medication errors	N	Patient-days	Medication errors	Incidence*	95% CI	Rate†	95% CI
Total	1189	12 691	826	65.1	60.6 to 69.5	69.5	64.7 to 74.2
Age category							
Neonates (<1 month)	252	4757	161	33.8	28.6 to 39.1	63.9	54.0 to 73.8
LBW neonates, NICU	69	3270	112	34.3	27.9 to 40.6	162.3	132.3 to 192.4
Non-LBW neonates, NICU	100	944	36	38.1	25.7 to 50.6	36.0	24.2 to 47.8
General paediatric ward	83	543	13	23.9	10.9 to 37.0	15.7	7.1 to 24.2
Infants (1 month=< <1 year)	174	1923	70	36.4	27.9 to 44.9	40.2	30.8 to 49.7
Preschoolers (1 year =< <7 year)	465	3425	283	82.6	73.0 to 92.3	60.9	53.8 to 68.0
School-age children (7 year=< <13 year)	189	1459	175	119.9	102.2 to 137.7	92.6	78.9 to 106.3
Teenagers (13 year=< < 19 year)	98	1081	125	115.6	95.4 to 135.9	127.6	105.2 to 149.9
Adults (19 year=<)	11	46	12	260.9	113.3 to 408.5	109.1	47.4 to 170.8
Ward category							
Paediatric ward	704	7007	440	62.8	56.9 to 68.7	62.5	56.7 to 68.3
NICU	169	4214	148	35.1	29.5 to 40.8	87.6	73.5 to 101.7
LBW neonates	69	3270	112	34.3	27.9 to 40.6	162.3	132.3 to 192.4
Non-LBW neonates	100	944	36	38.1	25.7 to 50.6	36.0	24.2 to 47.8
PICU	18	157	1	6.4	0.16 to 35.5	5.6	0.14 to 31.0
ICU	37	107	15	140.2	69.2 to 211.1	40.5	20.0 to 61.1
Emergent care unit	98	197	82	416.2	326.1 to 506.3	83.7	65.6 to 101.8
Adult ward	163	1009	140	138.8	115.8 to 161.7	85.9	71.7 to 100.1

ADEs, adverse drug events; ICU, intensive care unit; LBW, low birth weight; NICU, neonatal intensive care unit; PICU, paediatric intensive care unit.
*Per 1000 patient-days.
†Per 100 admissions.

categories at 9% and 7%. Other drug classes accounted for less than 5% of all ADEs.

Medication errors and potential adverse drug events
We identified 826 medication errors among 349 patients (29%): the incidence was 65.1 (95% CI 60.6 to 69.5) per 1000 patient-days, and the rate was 69.5 (95% CI 64.7 to 74.2) per 100 admissions. Among those 349 patients who had medication errors, 102 patients (29%) had three or more medication errors.

The incidence was higher in older age groups: adults had the highest incidence followed by school-age children and teenagers, and the lowest in neonates. Among different wards, the incidence was the
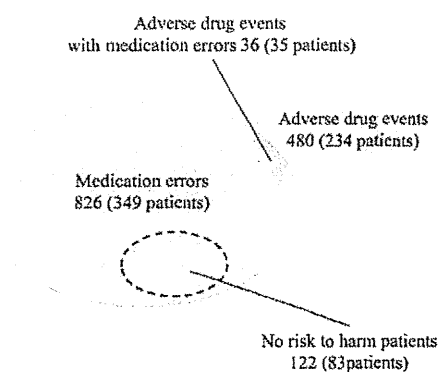
833

34

Adverse drug events
with medication errors 36 (35 patients)

Adverse drug events
480 (234 patients)

Medication errors
826 (349 patients)

No risk to harm patients
122 (83 patients)

Figure 1 Relationship between adverse drug events and medication errors.

Table 4 The details of preventable adverse drug events

Error stage	The number of ADEs (%)	Examples of event
Ordering	7 (19)	Excessive sedation, tachycardia by overdosing or rash by administration of medication with the past history of allergy
Administering	1 (3)	Worsen a symptom by forgetting to administer the medication
Monitoring	28 (78)	Prolonged sever eczema due to diarrhoea by antibiotics, prolonged rash by medication or intravenous administration related extravasations with tissue damages

ADEs, adverse drug events.

highest in the emergent care unit followed by the ICU and the adult ward. On the other hand, the incidence was lower in the PICU and the NICU (table 2).

Among the 826 medication errors, 36 (4%) resulted in ADEs, so that 8% of all 480 ADEs were considered preventable. Twenty-eight ADEs of these 36 preventable ADEs (78%) occurred at the monitoring stage—ordering and administration were appropriate, but patients had prolonged symptoms related to the medications that were not addressed promptly. Thus, they were classified as preventable ADEs in terms of duration or severity (table 4). Of the remaining 790 medication errors, 668 (81%) had the potential to cause harm for patients, and were thus potential ADEs (figure 1). The incidence of preventable ADEs was 2.8 (95% CI 1.9 to 3.8) and that of potential ADEs was 52.6 (95% CI 48.6 to 56.6) per 1000 patient-days. Nineteen per cent of potential ADEs were intercepted before a drug was administered to a patient, and thus, they were considered intercepted potential ADEs. The remaining 538 potential ADEs were non-intercepted potential ADEs: the patient did not actually take the drug in 113 cases (21%) and took the drug but no injuries occurred in 425 cases (79%). The incidence of intercepted and non-intercepted potential ADEs were 10.2 (95% CI 8.5 to 12.0) and 42.4 (95% CI 38.8 to 46.0) per 1000 patient-days,

Table 3 Symptoms of adverse drug events

Symptoms	ADEs (%)
Bleeding	10 (2)
Central nervous	46 (9)
Allergic/skin	57 (12)
Metabolic/liver	51 (11)
Cardiovascular	16 (3)
Gastrointestinal	214 (45)
Renal	16 (3)
Respiratory	19 (4)
Bone marrow	38 (8)
Others	13 (3)

ADEs, adverse drug events.

respectively. The remaining 122 (15%) medication errors had very low potential to harm patients. The most common stage for preventable ADEs was the monitoring stage (78%) whereas 95% of potential ADEs arose at the ordering stage (table 5).

The most common drug class involved in preventable ADEs was antibiotics (58%) while laxatives was the most common in potential ADEs (18%). Although antitumour agents were the most frequent drug class associated with ADEs, only one case was judged preventable.

DISCUSSION

We found that ADEs were frequent in the paediatric inpatient setting in Japan, with an ADE incidence of 38 per 1000 patient-days, though most were not preventable. There were also 65 medication errors per 1000 patient-days.

The present study used the same methodology as a study in the paediatric inpatient setting by Kaushal et al[7] as well as the studies in adult settings in Japan and the USA.[5][6] Kaushal et al reported an incidence of ADEs of 7 per 1000 patient-days, about a fifth the rate in this study, and an incidence of medication errors of 157 per 1000 patient-days, which was twice the rate in this study. Other studies have also reported the incidence of ADEs: Holdsworth et al[8] reported 8 ADEs per 1000 patient-days; Takata et al. reported 22 ADEs per 1000 patient-days,[9] Kunac et al[10] reported 22 ADEs per 1000 patient-days, and Agarwal et al[18] reported 49 ADEs per 1000 patient-days in PICUs. These incidences were generally similar, but more recent studies reported higher incidences (table 6). The reasons for the higher recent incidences are unclear, but potential hypotheses could be that techniques for finding ADEs have improved, or more drugs might be being used. The differences of patients' demographics and physicians' practice in each study setting also could be related to the incidence because they influenced the class of and the number of medications administered to patients. For example, patients with cancer need chemotherapy, which cause more

35

Table 5 Stages of primary errors associated with preventable and potential adverse drug events

Event	Ordering n (%)	Transcription n (%)	Dispensing n (%)	Administration n (%)	Monitoring n (%)
Preventable ADEs	7 (19)	0 (0)	0 (0)	1 (3)	28 (78)
Intercepted potential ADEs	130 (100)	0 (0)	0 (0)	0 (0)	0 (0)
Non-intercepted potential ADEs	503 (93)	0 (0)	1 (0.2)	27 (5)	7 (1)
All above events	640 (91)	0 (0)	1 (0.1)	28 (4)	35 (5)

ADEs, adverse drug events.

ADEs. Similarly, physicians in a certain hospital or country may be more likely to order more medications than others. We found that the epidemiological characteristics of ADEs and medication errors between these previous reports and the present study were fairly similar, such as the severity of ADEs,[7][8][10] the drug classes related to ADEs,[8] the proportion of preventable ADEs[7][9] and stages for which medication errors were most frequent.[7-9]

We also compared the results of the present study with our study in the adult inpatient setting.[6] The incidence of ADEs was higher in paediatric than adult patients (37.8 vs 17.0 per 1000 patient-days) while the incidence of medication errors was about eight times higher in this paediatric study than in our adult study (65.1 vs 8.7 per 1000 patient-days). The higher incidence of medication errors in paediatrics could be because of specific complexities in the drug ordering and delivery process in children; individual drug dosage calculation is needed according to age and weight, which can increase opportunities for error with a high risk of 10-fold errors at the ordering stage,[19][20] and young children cannot report to caregivers or healthcare professionals about their symptoms due to ADEs, causing more frequent monitoring errors in the paediatric setting. On the other hand, medication errors were most prevalent in adults in this study, perhaps because they are relatively infrequent in general paediatric wards. School-age children and teenagers also had a higher incidence than younger children. When physicians prescribed medicine for older children and adults, they often made errors in directions around dose and frequency.

We had more patients with cancer in the teenager group than in other age groups, and these patients had received chemotherapy, which resulted in the higher incidence of ADEs in teenagers. Among neonates, non-LBW neonates in the NICU had a lower ADE incidence than LBW neonates in the NICU and neonates in the general paediatric ward because they are relatively healthy. In the PICU, 83% of patients were transferred from the ICU as an interim location before returning to the general paediatric ward for postoperative care. This practice likely differs from that in most Western PICUs which may be the reason that the ADE incidence in the PICU was relatively low in our study.[18] Not surprisingly, ADE incidence was higher in ICUs than in general care units.

In this study, only 8% of ADEs were considered preventable, in that few were associated with an obvious error. This lower proportion of preventable ADEs compared with the previous studies is probably in part due to the high proportion of patients who received chemotherapy in this study; a third of the ADEs were associated with antitumour agents and they occurred due to its high toxicity without errors except one judged as preventable. This situation decreased the proportion of preventable ADEs overall. Except chemotherapy related ADEs, preventable ADEs accounted for 11%, which was consistent with the previous studies.[6][7] From the safety perspective, preventable and non-preventable ADEs are important because those ADEs which are not judged preventable today may be preventable in the future, and both result in harm.

Several studies have reported that interventions with information technologies including computerised physician order entry[21][22], as well as pharmacist participation in physician rounds, have been effective to reduce medication errors in adult inpatient settings.[23] A few studies have reported that the interventions above would be effective to reduce medication errors in paediatric inpatient setting as well.[13-16][24-26] Our finding showing the common epidemiological characteristics of ADEs and medication errors between Japan and Western countries may suggest that such interventions for reducing the medication errors could be beneficial in most developed countries.

Our study has several limitations. We conducted this paediatric study at two tertiary care teaching hospitals. Therefore, our results may not be generalisable to non-tertiary care teaching hospitals where most children received their medical care in Japan. Some ADEs may not have been noted in the charts and may thus have not been detected, which would make our estimates a lower bound. However, more robust alternatives to measure ADEs and medication errors have not yet been developed, so the approach we used is the current standard one.

CONCLUSION

We found that ADEs and medication errors were common in paediatric inpatients in Japan, and that there was a similar nature of ADEs and medication errors to those arising in the paediatric settings in Western countries. The proportion of preventable

Table 6 The comparison of epidemiology of adverse drug events among paediatric settings

Study	JADE study	Agarwal S[18]	Takata GS[9]	Kunac DL[16]	Holdsworth MT[8]	Kaushal R[7]
Country and studied year	Japan, 2012	U.S., 2005	U.S., 2003	New Zealand, 2002	U.S., 2000	U.S., 2000
Patients and setting	All patients admitted at two teaching hospitals	Randomly selected patients from 15 hospitals	5 hospitals participating in the California Paediatric Patient Safety Initiative	All patients admitted at a university-affiliated urban general hospital	All patient admitted at a large metropolitan tertiary care centre	All patient admitted at 2 academic institutions
Wards	Paediatric medical/surgical wards, two NICUs and a PICU*	15 PICUs	Paediatric wards, PICUs, and NICUs	A paediatric ward, a NICU and a postnatal ward	A paediatric ward and a PICU	9 ward including paediatric medical/surgical wards, NICUs, PICUs, and short-stay medical ward
Number of admissions	1189	734	Not available	520	1197	1120
Data acquisition method	Reviewers, historical cohort study	Cross sectional retrospective review with trigger methods	Trigger methods	Review by the principal investigator, prospective cohort study	A reviewer, Prospective cohort study	Reviewers, Prospective cohort study
Incidence of ADEs (ADEs/1000 patient days)	37.8	49	22.3	22.1	7.5	6.6
Rate of ADEs (ADEs/100 admissions)	40.4	34.9	11.2	12.9	6	2.3
Rate of patients who had at least one ADE	20%	Not available	9%	Not available	Not available	Not available

*Studied the patients admitted at the ICU, the emergent care unit and the general adult ward when paediatric patients ($\leq$15 years old) were admitted.
ADEs, adverse drug events; JADE, Japan Adverse Drug Events; NICU, neonatal intensive care unit; PICU, paediatric intensive care unit.

ADEs and potential ADEs among all medication errors was substantial, and most of the errors occurred at the ordering and the monitoring stages. Interventions to support healthcare providers focusing on ordering to and monitoring patients may improve medication safety among paediatric inpatients, although more testing of the potential benefits of these strategies would be valuable in a variety of settings.

REFERENCES

1 Morimoto T, Gandhi TK, Seger AC, et al. Adverse drug events and medication errors: detection and classification methods. Qual Saf Health Care 2004;13:306–14.

2 Leape LL, Brennan TA, Laird N, et al. The nature of adverse events in hospitalized patients. Results of the Harvard Medical Practice Study II. N Engl J Med 1991;324:377–84.

3 Jha AK, Prasopa-Plaizier N, Larizgoitia I, et al. Patient safety research: an overview of the global evidence. Qual Saf Health Care 2010;19:42–7.

4 Brennan TA, Leape LL, Laird NM, et al. Incidence of adverse events and negligence in hospitalized patients. Results of the Harvard Medical Practice Study I. N Engl J Med 1991;324:370–6.

5 Bates DW, Cullen DJ, Laird N, et al. Incidence of adverse drug events and potential adverse drug events. Implications for prevention. ADE Prevention Study Group. JAMA 1995;274:29–34.

6 Morimoto T, Sakuma M, Matsui K, et al. Incidence of adverse drug events and medication errors in Japan: the JADE study. J Gen Intern Med 2011;26:148–53.

7 Kaushal R, Bates DW, Landrigan C, et al. Medication errors and adverse drug events in pediatric inpatients. JAMA 2001;285:2114–20.

8 Holdsworth MT, Fichtl RE, Behta M, et al. Incidence and impact of adverse drug events in pediatric inpatients. Arch Pediatr Adolesc Med 2003;157:60–5.

9 Takata GS, Taketomo CK, Waite S. Characteristics of medication errors and adverse drug events in hospitals participating in the California Pediatric Patient Safety Initiative. Am J Health Syst Pharm 2008;65:2036–44.

10 Kunac DL, Kennedy J, Austin N, et al. Incidence, preventability, and impact of Adverse Drug Events (ADEs) and potential ADEs in hospitalized children in New Zealand: a prospective observational cohort study. Paediatr Drugs 2009;11:153–60.

11 Takata GS, Mason W, Taketomo C, et al. Development, testing, and findings of a pediatric-focused trigger tool to identify medication-related harm in US children's hospitals. Pediatrics 2008;121:e927–35.

12 Ghaleb MA, Barber N, Franklin BD, et al. Systematic review of medication errors in pediatric patients. Ann Pharmacother 2006;40:1766–76.

13 Mullett CJ, Evans RS, Christenson JC, et al. Development and impact of a computerized pediatric antiinfective decision support program. Pediatrics 2001;108:E75.

14 Lehmann CU, Conner KG, Cox JM. Preventing provider errors: online total parenteral nutrition calculator. Pediatrics 2004;113:748–53.

15 Potts AL, Barr FE, Gregory DF, et al. Computerized physician order entry and medication errors in a pediatric critical care unit. Pediatrics 2004;113(1 Pt 1):59–63.

16 King WJ, Paice N, Rangrej J, et al. The effect of computerized physician order entry on medication errors and adverse drug events in pediatric inpatients. Pediatrics 2003;112(3 Pt 1):506–9.

17 Morimoto T, Fukui T, Lee TH, et al. Application of U.S. guidelines in other countries: aspirin for the primary prevention of cardiovascular events in Japan. Am J Med 2004;117:459–68.

18 Agarwal S, Classen D, Larsen G, et al. Prevalence of adverse events in pediatric intensive care units in the United States. Pediatr Crit Care Med 2010;11:568–78.

19 Koren G, Barzilay Z, Greenwald M. Tenfold errors in administration of drug doses: a neglected iatrogenic disease in pediatrics. Pediatrics 1986;77:848–9.

20 Poole RL, Benitz WE. Medication errors in children. JAMA 2001;286:915; author reply -6. Epub 2001/08/31.

21 Bates DW, Cohen M, Leape LL, et al. Reducing the frequency of errors in medicine using information technology. J Am Med Inform Assoc 2001;8:299–308.

22 Bates DW, Leape LL, Cullen DJ, et al. Effect of computerized physician order entry and a team intervention on prevention of serious medication errors. JAMA 1998;280:1311–16.

23 Leape LL, Cullen DJ, Clapp MD, et al. Pharmacist participation on physician rounds and adverse drug events in the intensive care unit. JAMA 1999;282:267–70.

24 Folli HL, Poole RL, Benitz WE, et al. Medication error prevention by clinical pharmacists in two children's hospitals. Pediatrics 1987;79:718–22.

25 Fortescue EB, Kaushal R, Landrigan CP, et al. Prioritizing strategies for preventing medication errors and adverse drug events in pediatric inpatients. Pediatrics 2003;111(4 Pt 1): 722–9.

26 Wang JK, Herzog NS, Kaushal R, et al. Prevention of pediatric medication errors by hospital pharmacists and the potential benefit of computerized physician order entry. Pediatrics 2007;119:e77–85.