Determination of Incidence and Characteristics of Preventable Adverse Drug Reactions : A Study in Phrae Hospital

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ABSTRACT

The characteristics of preventable adverse drug reaction (pADR) in hospitalized patients in Phrae Hospital were identified by a retrospective descriptive analysis. All ADR report forms of patient during fiscal year 2003 were explored. From 189 reports, 188 ADR reports were analyzed. Sixty-eight cases (36.17%) were classified with Schumock and Thornton criteria as pADR. Mean age of pADR patient was 42.97 years. Female was of the same number as male. Top- three underlying diseases were chronic renal failure, HIV and hypertension. Eight pADR (11.76%) were related to hospital admission and mostly (80.88%) considered non-serious ADR. Nine cases (13.24%) were considered severe to initial or prolonged hospitalization and required life-threatening management. The relationship of pADR to drug exposure was determined to be probable. Half of them occurred in skin and appendage system and body as a whole-general disorders system organ class of WHO. Most outcome (91.18%) was recovered without sequelae. "Antibiotics", "contrast media" and "miscellaneous" were top-three classes of drugs causing pADR. The third high-priority pADR code which accounted for 90% of all reports were (1) required therapeutic drug monitoring or other necessary laboratory tests were not performed or not performed frequently enough criteria (45.95%), (2) dose, route or frequency of administration was not appropriate for the patient's age, weight or disease criteria (24.32%), and (3) drugs involved were not appropriate for the patient's clinical condition criteria (19.82%). The data from this study reflected the importance and urgency for better understanding of pADRs in Thai-hospitalized patients and suggestion of the better interventions or model to prevent patients suffering from ADRs. Further nationwide studies are needed to determine ADR-associated factors and to develop strategies for prevention of pADR in hospitalized patients.

Key words: Characteristic, Incidence, Preventable Adverse drug reaction

INTRODUCTION

Adverse drug reaction (ADR) is an important type of drug-related problems resulting in undesirable effects in patients and discontinuation of medication. Epidemiological studies indicate that ADRs are the leading causes of admission

to hospital. The rate of reported admission resulting from ADRs ranks from 0.2 to 21.7%. Approximately 1.9 to 37% of in-patients experienced ADRs during hospitalization. Different types of ADR reporting systems and methods for identifying and resolving drug-related problems have been documented in the literature and shown that 30-80% of ADRs are preventable. ADRs cause not only morbidity and mortality but also prolongation of hospitalization and increased cost of treatment.

Although incidence of ADRs is still not exactly known, it affects patient's health and cost of treatment. Thus, prevention of ADRs will be encouraged in order to decrease these problems. It has been realized that all ADRs may not be avoided. However, 70 to 80% of ADRs are predictable and may be preventable. Currently, identification of preventable ADRs may be indistinct. Additionally, Schumock and Thornton (1992) reviewed process of ADRs from ADR reports. They found that preventable ADRs include allergic reactions where the allergy is previously known and / or documented; avoidable dose related reactions; idiosyncratic reactions that occurred previously; ADR secondary to drug interaction; requiring therapeutic drug monitoring or other necessary laboratory; and drug reaction associated with inappropriate compliance, prescribing, or administration. After that, they developed a set of questions that was useful in determining the preventability of ADRs.

Prospective studies in hospitalized patients in the incidence of ADRs in 21 selected Thai hospital project showed that total incidence of ADRs was 2.9% while the present at admission incidence was 1.6% and the occurring while hospitalized incidence was 1.3% (Hutongkabodee et al., 2002). Patients with ADRs were more likely to be female and had underlying disease or had a history of drug allergies. Most commonly affected system organ classes were skin and appendages and gastro-intestinal system. Drug classes most commonly implicated were other chemotherapeutics (i.e anti-neoplastic drugs, antituberculous drugs), neuro-muscular system drugs (i.e. antirheumatic, anti-inflammatory analgesics) and antibiotics (i.e. cephalosporins, penicillins).

Basically, known predisposing factors to ADRs are most important in classifying ADRs and developing the strategy for ADRs prevention. Factors predisposing to ADR may be categorized as the prescribing factors, the properties of the drug and the characteristics of patients. Moreover, if each patient could be prospectively assessed to determine the possibility of experiencing an ADR, this would provide valuable information for the health care team. Patients with a history of allergy are at the greatest risk. More or less, the high incidence and costs associated with ADRs have influenced health care policy and economics. To minimize this crisis, it is essential to gain knowledge of preventable ADRs. However, undesirable consequence resulting from ADRs is preventable, and it is essential to develop intervention programs to tackle this problem. Thus, it is of interest to push it work practically. Therefore, this study plans to set up researches to find out the extent of preventable ADRs in provincial hospital, Phrae Hospital, as the sample of the hospital in northern part of Thailand, using data in ADR report database in the same period as the prospective incidence of ADR studies in

hospitalized patients in 21 selected Thai hospital project as the research source.

The major aims of the study were to determine the incidence and characteristics of preventable ADR through the fiscal year 2003 ADR database of Phrae Hospital.

MATERIALS AND METHODS

All ADR report forms, 189 reports, through the fiscal year 2003 ADR database of Phrae Hospital were explored by a retrospective descriptive analysis. Each ADR report was assessed concurrently, using seven previously-published explicit criteria for preventability adapted from Schumock and Thornton (1992) and was classified as preventable or non- preventable. These data were analyzed to determine the incidence and characteristics associated with preventable ADR. The preventable ADR was categorized by drug or drug class, type of medication error, patient's demographic, ADR variables and hospital admission. Patients and drug therapy characteristics were evaluated to identify factors associated with preventable ADR. Preventable and non-preventable ADR were compared with respect to the patient's age, co-existing diseases, site of reaction, ADR severity and the probability that the reaction was drug-related.

Definition used in the study

Adverse drug reaction : WHO definition (1996) : Any response to a drug which was noxious and unintended, and which occurred at dose normally used in man for prophylaxis, diagnosis, or therapy of disease, or for the modification of physiological function.

Preventable adverse drug reaction was defined according to Schumock and Thornton (1992) as ADR which was preventable or avoidable. There were seven questions. Answering "YES" to one or more of the questions that an ADR was preventable.

1. Was the drug involved in the ADR not considered appropriate for the patient's clinical condition?
2. Was the dose, route, and frequency of administration not appropriate for the patient's age, weight and disease state?
3. Was required therapeutic drug monitoring or other necessary laboratory test not performed?
4. Was there a history of allergy or previous reactions to the drug?
5. Was a drug interaction involved in the reaction?
6. Was a toxic serum drug level documented?
7. Was poor compliance involved in the reaction?

RESULTS

Study period was during the fiscal year 2003, from October 1, 2002 to September 30, 2003. Of 189 ADR reports collected over the study period, 1 case was excluded because the data were incomplete. Therefore, 188 reports were

analyzed. From this group, sixty-eight reports (36.17%) were classified with seven previously-published explicit criteria for preventability of Schumock and Thornton (1992) as preventable ADRs (pADRs). Demographics associated with preventable and non-preventable ADRs are shown in Table l. The major age group of both was 41-60 years and mean age was 42.97 and 36.11, respectively. For pADRs, female was of the same number as male but twice for non-pADRs.

Table 1. Preventable and Non-preventable Adverse Drug Reaction (ADRs) Categorized by Patient and ADR Variables.

Variable	No.(%) Preventable ADR (n = 68, 36.17%)	No.(%) Non-preventable ADR (n = 120, 63.83%)
Age group		
≤20	8 (11.76)	32 (26.67)
21-40	20 (29.41)	35 (29.17)
41-60	27 (39.71)	36 (30.00)
61-80	11 (16.18)	16 (13.33)
≥81	2 (2.94)	1 (0.83)
Age		
Mean	42.97 years	36.11 years
Max	93 years	81 years
Min	1 months	3 days
Gender		
Male	33 (48.53)	48 (40.00)
Female	35 (51.47)	72 (60.00)
Type of patient		
Out-patient	34 (50.00)	66 (55.00)
In-patient	34 (50.00)	54 (45.00)

The analysis and categorization by preventability code are presented in Table 2 which suggested that three high-priority pADRs accounting for 90% of all reports were (1) required therapeutic drug monitoring or other necessary laboratory tests were not performed or not performed frequently enough criteria (45.95%), (2) dose, route, or frequency of administration was not appropriate for the patient's age, weight or disease criteria (24.32%), and (3) drugs involved were not appropriate for the patient's clinical condition criteria (19.82%).

Table 2. Distribution of Preventability Code.

Preventability Code	Criteria	No. of times code used (% total uses)
1	Drugs involved were not appropriate for the patient's clinical condition.	22 (19.82)
2	Dose, route, or frequency of administration was not appropriate for the patient's age, weight or disease.	27 (24.32)
3	Required therapeutic drug monitoring or other necessary laboratory tests were not performed or not performed frequently enough.	51 (45.95)
4	Patient has a history of allergy or previous reaction to the drug.	8 (7.21)
5	A known drug interaction was the s uspected cause of the reaction.	0* (0.00)
6	A serum drug concentration above the therapeutic range was documented.	0* (0.00)
7	Noncompliance was associated with the reaction.	3 (2.70)

*No case was classified in this code.

Focus on the concurrent diseases in patients developed ADR in this study, it was found that the commonest underlying diseases of both preventable and non-preventable ADRs were chronic renal failure, AIDs and hypertension. The others are listed in Table 3.

Table 3. Preventable and Non-preventable Adverse Drug Reaction (ADRs) Categorized by Underlying Disease.

Variable	No.(%) Preventable ADR	No.(%) Non-preventable ADR
Underlying Disease		
Hypertension	11 (8.53)	16 (12.21)
Diabetes Mellitus	7 (5.43)	10 (7.63)
Tuberculosis	5 (3.88)	1 (0.76)
Chronic Renal Failure	19 (14.73)	1 (0.76)
Gout	3 (2.33)	1 (0.76)
Cardiovascular Accident	3 (2.33)	2 (1.53)
Cancer	0 (0.00)	1 (0.76)
Acquired Immunodeficiency Syndrome; AIDs	12 (9.30)	6 (4.58)
Epilepsy	3 (2.33)	(0.00)
Dyslipidemia	3 (2.33)	3 (2.29)
None	61 (47.29)	90 (68.70)

Eight (11.76 %) reports of pADRs were related to hospital admission. The most cases of pADRs and non- pADRs had no drug allergy history as shown in Table 4.

Table 4. Preventable and Non-preventable Adverse Drug Reaction (ADRs) Categorized by Admissions due to ADR and Drug Allergy History.

Variable	No.(%) Preventable ADR (n = 68, 36.17%)	No.(%) Non-preventable ADR (n = 120, 63.83%)
Admissions due to ADR		
Yes	8 (11.76)	4 (3.33)
No	60 (88.24)	116 (96.67)
Drug Allergy History		
Yes	13 (9.12)	4 (3.33)
No	55 (80.88)	116 (96.67)

With reference to severity, both groups were considered non-severe. Most of patients recovered without sequelae. Serious with life-threatening adverse drug event was more likely to be preventable than less severe events. For serious with initial or prolonged hospitalization adverse drug event was more likely to be non-preventable than other events. Disability distribution of severity and outcome are summarized in Table 5.

Table 5. Preventable and Non-preventable Adverse Drug Reaction (ADRs) Categorized by Severity and Outcome of ADR.

Variable	No.(%) Preventable ADR	No.(%) Non-preventable ADR
Severity of ADR		
Non-serious	55 (80.88)	99 (82.50)
Serious - Death	0 (0.00)	0 (0.00)
- Life threatening	5 (7.36)	2 (1.67)
- Initial or prolonged hospitalization	4 (5.88)	17 (14.16)
- Disability	0 (0.00)	0 (0.00)
- Require Intervention to prevent permanent impairment	4 (5.88)	2 (1.67)
Outcome of ADR		
1. Recovered without sequelae	62 (91.18)	110 (91.67)
2. Recovered with sequelae	1 (1.46)	2 (1.67)
3. Not yet recovered	5 (7.36)	8 (6.67)
4. Died-due to ADR	0 (0.00)	0 (0.00)
5. Died-drug may be contributory	0 (0.00)	0 (0.00)
6. Died-unrelated to drug	0 (0.00)	0 (0.00)

"Antibiotics", "Contras Media", "Antidotes, detoxifying agents & drug used in substance dependence" and "miscellaneous" were most top three classes of drugs (MIMS classification), causing pADRs while of non-preventable ADRs were "Antibiotics", "Neuro-muscular system" and "Cardiovascular & Hematopoietic system". The relationship of ADRs to drug exposure using Naranjo's algorithm was mostly determined to be probable (Naranjo et al., 1981). Half of pADRs and non-preventable ADRs occurred in skin and appendage disorders. Details of the site of ADRs and drug classes responsible for ADRs are shown in Table 6.

Table 6. Preventable and Non-preventable Adverse Drug Reaction (ADRs) Categorized by System Organ Class (WHO) of ADR, Class of drugs (MIMS classification) causing ADR and Probability of being drug-related.

Variable	No. (%) Preventable ADR	No. (%) Non-preventable ADR
System Organ Class (WHO) of ADR		
Skin and appendages disorders	84 (43.52)	119 (61.34)
Gastro-intestinal system disorders	25 (12.95)	6 (3.09)
Central & peripheral nervous system disorders	2 (1.04)	2 (1.03)
Liver and biliary system disorders	6 (3.11)	1 (0.52)
Body as a whole-general disorders	30 (15.54)	40 (20.62)
Heart rate and rhythm disorders	5 (2.59)	3 (1.55)
Platelet, bleeding & clotting disorders	2 (1.04)	0 (0.00)
Cardiovascular disorders, general	2 (1.04)	0 (0.00)
Vascular (Extracardiac) disorders	0 (0.00)	1 (0.52)
Psychiatric disorders	0 (0.00)	1 (0.52)
Respiratory system disorders	21 (10.88)	12 (6.19)
Application site disorders	9 (4.66)	1 (0.52)
Autonomic nervous system disorders	0 (0.00)	1 (0.52)
Hearing and vestibular disorders	0 (0.00)	1 (0.52)
Special sense other, disorders	7 (3.63)	6 (3.09)
Class of drugs (MIMS classification) causing ADR		
Neuro-muscular system	4 (5.97)	11 (9.40)
Antibiotics	32 (47.76)	75 (64.10)
Cardiovascular & hematopoietic system	1 (1.49)	9 (7.69)
Metabolism	1 (1.49)	4 (3.42)
Miscellaneous	5 (7.46)	3 (2.56)
Respiratory system	0 (0.00)	6 (5.13)
Alimentary system	0 (0.00)	4 (3.42)
Contras media	19 (28.36)	0 (0.00)

Variable	No. (%) Preventable ADR	No. (%) Non-preventable ADR
Dermatologicals	0 (0.00)	0 (0.00)
Antidotes,detoxifying agents & drug used in substance dependence	5 (7.46)	2 (1.71)
Probability of being drug-related		
Doubtful	0 (0.00)	0 (0.00)
Probable	52 (76.47)	102 (85.00)
Possible	7 (10.29)	16 (13.33)
Definite	9 (13.24)	2 (1.67)

DISCUSSION AND CONCLUSION

The percentage of pADRs (36.17%) is consistent with values previously reported as being preventable (28-80%) (Pearson et al., 1994; Bates et al., 1995; Leape et al., 1995; Seeger et al., 1998; Gholami et al., 1999). The percentage of admissions that were classified as preventable found in this study is 11.76%. Female was of the same number as male. Three high-priority pADRs which accounted for 90% of all reports were (1) required therapeutic drug monitoring or other necessary laboratory tests were not performed or not performed frequently enough criteria, (2) dose, route, or frequency of administration was not appropriate for the patient's age, weight or disease criteria, and (3) drugs involved were not appropriate for the patient's clinical condition criteria. The most cases of pADRs and non-pADRs had no drug allergy history. "Antibiotics", "Contras Media", "Antidotes, detoxifying agents & drug used in substance dependence" and "miscellaneous" were most top four classes of drugs causing pADRs. Although it is difficult to directly compare event rates observed in the present study with studies performed in other clinical settings involving different patient populations, some comparisons are of interest. In the incidence of ADRs studies in hospitalized patients in 21 selected Thai hospital project, 363 ADRs reports during February 1, 2002 to March 8, 2002 were analyzed (Hutongkabodee et al., 2002). From this group, 114 (31.4%) were classified pADRs. Female was twice more than male. 71.1% pADRs were related to hospital admission and 71.9% considered severe to initial or prolonged hospitalization. The relationship of pADRs to drug exposure was determined to be probable or possible in 100%. It was found that "other chemotherapeutics", "metabolism" and "miscellaneous" were most top three classes of drugs causing pADRs. The four high-priority preventable ADRs code accounted for 89% of all reports were (1) required therapeutic drug monitoring or other necessary laboratory tests were not performed or not performed frequently enough criteria, (2) dose, route, or frequency of administration was not appropriate for the patient's age, weight or disease criteria, (3) drugs involved were not appropriate for the patient's clinical condition criteria and (4) noncompliance was associated with the reaction criteria. Bates et al., (1995) identified adverse drug events occurring in 2 Boston tertiary care hospitals during a 6-month period. Of the 247 adverse drug events

identified in that study (6.5 adverse drug events per 100 admissions), 1% were fatal, 12% were life-threatening, 30% were serious, and 57% were significant; and 28% of these were judged preventable. Of the serious and life-threatening adverse events, 42% were judged preventable compared with 18% of significant adverse drug events. Gurwitz et al., (2000) identified adverse drug events during nursing home resident-years of observation (227 adverse drug events per 1000 resident-years) in 18 Massachusetts nursing homes. Of the adverse drug events, 1 was fatal, 6% were life-threatening, 38% were serious, and 56% were significant; and 51% of these were judged preventable. Of the serious, life-threatening, and fatal events, 72% were judged preventable compared with 34% of the significant events. In the ambulatory setting, the percentage of adverse drug events that were deemed preventable more closely mirrored the hospital setting (28%). Consistent with both the hospital and nursing home settings, more serious events were more likely to be judged preventable.

This discrepancy may be attributed to variations in ADR reporting practices or differences in the definition of an ADR. Our data were taken from a formalized retrospective ADR report review rather than a concurrent ADR report. By focusing on hospital admissions directly related to an ADR, our study included actual occurrences of ADRs. This differs from the study by Bates et al. (1995), which reported an adverse drug event (ADE) preventability rate of 28%, but included both actual (56%) and potential (44%) ADEs. Bates et al., also focused on ADEs that occurred while the patient was hospitalized. We must also keep in mind that the term ADE encompasses several subsets of events, including ADRs, medication errors, adverse drug withdrawal events, therapeutic failures, and intentional drug overdose. Bates et al., (1995) seemed to focus on the medication error subset of ADEs. while this study focused on the ADR subset of ADEs, but only on ADRs that were considered preventable.

Preventability characteristics revealed that the required therapeutic drug monitoring or other necessary laboratory tests were not performed or not performed frequently enough criteria was the major class of pADRs. Most ADR report associated with pADRs occurred at the prescribing and monitoring stages. While most antibiotic-associated ADRs were characterized as non-preventable, it is widely recognized that these agents are commonly overused, particularly in the ambulatory setting. Many antibiotic-associated ADRs, for example, rashes and diarrhea, might have been deemed preventable if the decision to implement therapy had been more rigidly scrutinized. Some studies determined preventability according to expert panel review, whereas we applied published criteria. The relationship between preventability as assessed by the criteria and by an expert panel is unknown. This may have produced some degree of misclassification bias in this assessment.

However, the ADR database does not represent the universe of preventable ADEs and may not omit other equally important areas. Moreover, ADR reports may represent only about 5-10% of all ADR occurrences. The decision to report events might depend on the severity of the ADR or litigation concerns. Spontaneous reporting of ADRs and errors is also biased toward causal associations

between drugs and events that are known and well established. It is important to note that ADR database usually include only errors of commission, omission errors are not well represented, even though they have been found to contribute substantially to pADRs.

From this and other researches, it suggests that an ADR report is useful in characterizing pADRs and there is a need for further studies to identify. Factors associated with and develop strategies for preventing ADRs in hospitalized patient population.

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