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Cost Evaluation of Adverse Drug Reactions in Hospitalized Patients in Taiwan: A Prospective, Descriptive, Observational Study

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ABSTRACT

BACKGROUND: Adverse drug reactions (ADRs) are a leading cause of morbidity and mortality. In the United States, ADR-related morbidity and mortality costs have been estimated at US $30 billion to US $130 billion annually.

OBJECTIVES: The aim of this study was to evaluate the incidence of ADRs in Taiwan, to identify the drug classes that are most commonly related to ADRs, and to determine the direct medical costs to hospitals associated with prolonged hospitalizations due to ADRs.

METHODS: In this prospective, descriptive, observational study, patients who experienced ADRs during their hospitalization at a Taiwan teaching hospital or who were admitted due to an ADR from January 1, 2002, through December 31, 2004, were included in the study. The patients were identified actively by clinical pharmacists and passively by physicians and nurses who reported ADRs. The World Health Organization (WHO) definition of ADR severity was adopted, and degrees of probability for each ADR were determined using the Naranjo algorithm. The direct medical costs incurred to the hospital in the treatment of ADRs that prolonged hospitalization were calculated (ie, costs of emergency department [ED] visits, intensive care unit visits, extra days of hospitalization, monitoring and laboratory studies, pharmacist dispensing fees, physician fees, room charges, ED charges).

RESULTS: During the study period, 43 of the 142,295 hospitalized patients (0.03%) were admitted because of an ADR. A total of 564 (0.40%) of the hospitalized patients were verified to have ADRs. Three hundred eighteen of the patients (56.4%) with ADRs were male and the overall mean (SD) age was 66 (2) years. The most common drug classes associated with the ADRs were antibiotics (219 patients [38.8%]), analgesics (62 [11.0%]), and cardiovascular agents (56 [9.9%]). The systems most commonly involved in ADRs were cutaneous (296 patients [52.5%]), hematologic

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(61 [10.8%]), and cardiovascular (54 [9.6%]). The causes of the ADRs were anaphylactic (464 patients [82.3%]), drug overdose (78 [13.8%]), and drug–drug interactions (22 [3.9%]). Of the ADRs, 474 (84.0%) were idiosyncratic type B reactions (predictable). ADR-related costs, estimated at US $3489/ADR, were mostly due to prolonged length of stay. Based on the WHO definition, of the 564 ADRs, 330 (58.5%) and 40 (7.1%) were classified as moderate and severe, respectively. Two patients died of ADRs associated with allopurinol.

CONCLUSION: In this hospital, 0.40% of patients were identified as having ADRs that were associated with high direct costs, mostly due to extended hospitalizations. (*Curr Ther Res Clin Exp.* 2008;69:118–129) © 2008 Excerpta Medica Inc.

KEY WORDS: direct medical cost, adverse drug reactions.

INTRODUCTION

Adverse drug reactions (ADRs) are a leading cause of morbidity and mortality.[1,2] ADRs have been estimated to account for up to 106,000 deaths annually in the United States.[1,2] Additionally, ADRs are the cause of hospital admission in 3% to 6% of patients of all ages[3,4] and 3% to 24% of elderly patients.[5] The incidence of fatal ADRs has been found to be 0.15% to 0.41% in Western countries.[1,4] In the United States, ADR-related morbidity and mortality costs have been estimated at US $30 billion to US $130 billion annually.[6,7]

ADRs are generally defined as any undesirable effect of a drug beyond its anticipated therapeutic effect that occurs during clinical use.[8] Although many ADRs are mild and disappear when the causative drug is discontinued or the dose is reduced, some are serious and permanent. Therefore, ADRs might increase not only morbidity and mortality but also health care costs.

A nationwide ADR reporting system was established in Taiwan in 1986, but no statistical analysis data have been previously reported. Although the clinical pharmacy departments in all hospitals in Taiwan contribute to the ADR reporting and monitoring programs, the reporting rate of physicians remains low (0.003%),[9] compared with rates reported in the United States (0.19%)[9] and Australia (1.09%).[10]

The aim of this study was to analyze the characteristics of all ADRs reported in our hospital, including the incidence of ADRs, the classes of drugs that were most commonly associated with ADRs, the relation of the drugs with the ADRs, the type and severity of each ADR, and the direct medical costs to the hospital.

PATIENTS AND METHODS

This prospective, descriptive, observational study was conducted from January 1, 2002, to December 31, 2004, at the 1083-bed Chi Mei Medical Center, a tertiary teaching hospital in Tainan, Taiwan. Institutional review board approval was not required for this study. Patient confidentiality was maintained throughout the course of the study. The medications associated with the ADRs were classified in accordance with the hospital formulary. *ADRs* were defined according to the World Health Organization as "any response to a drug which is noxious and unintended, and which occurs at doses

normally used in humans for prophylaxis, diagnosis, or therapy of disease, or for the modification of physiological function."[8]

Patients who experienced ADRs during their hospital stay or were admitted due to ADRs were identified and included in the study. The ADR reporting system involves both active and passive methods routinely conducted in Taiwanese hospitals. Active methods included the identification, by clinical pharmacists, of any suspected ADRs through ward rounds and prescribed drugs (eg, naloxone for the reversal of narcotic depression). The passive method was spontaneous reports from pharmacists, physicians, and nurses (hereafter called reporters) of suspected ADRs using a computerized automatic reporting system or paper ADR reporting forms. All cases were reviewed by clinical pharmacists to exclude ADRs reported in duplicate through the 2 reporting methods. Any suspected ADRs were reported by entering the name of reporter and units, patients' brief data, the name of suspected drugs, and suspected ADR. Patients who developed an ADR during hospitalization and patients whose admission resulted from an ADR were assessed by a clinical pharmacist and their responsible physicians on receipt of the ADR reporting form using the Naranjo algorithm.[11] ADRs were classified as *definite* (score = 9 or 10), *probable* (5–8), *possible* (1–4), or *doubtful* (0) in regard to their relation with a particular drug. ADR severity was assessed according to the criteria developed by Hartwig et al.[12] This scale categorized each ADR as mild, moderate, or severe.

A probability category for each ADR was assigned according to the Naranjo scale.[11] The cause of an ADR was considered type A (augmented pharmacologic effects) or B (idiosyncratic).[13] ADRs were defined as *mild* if they were self-limiting, resolved over time without treatment, and did not affect the length of hospitalization. *Moderate* ADRs were those that required therapeutic intervention, prolonged hospitalization by 1 day, or caused the patient to be admitted to the hospital. *Severe* ADRs were those that were life threatening, carcinogenic, or permanently disabling, prolonged hospitalization by >1 day, or caused death.[8] Patient ADR outcomes were reported as follows: fully recovered; not fully recovered; death; or unknown.

To measure the impact of ADRs on direct medical costs and length of stay, data were collected from the hospital's claims database. The extra days of stay associated with ADRs were marked as the difference between the beginning and end of the ADR. The beginning of the ADR was the date of hospital admission due to the ADR or, if the event occurred during hospitalization, the date of the clinical or biological diagnosis of the ADR. The end of the ADR was the date of hospital discharge or the date of normalization of the effect, including the date of laboratory examination with normal results or the disappearance of clinical symptoms reported by physicians during hospitalization. The direct medical cost incurred in treating the ADRs was calculated for each medical service, physician fee, and laboratory test (by day rate) based on the hospital's claims data system. For ADRs requiring discontinuation of the suspected drugs, the cost for treatment was considered as zero. When ADRs required extra medications, treatments, or laboratory tests, the costs of these (eg, all drug costs, physician fees, pharmacist dispensing fees, laboratory test fees, room charges) were included in calculating the cost incurred by the patient.

STATISTICAL ANALYSIS

Descriptive analysis was conducted for quantitative variables. Mean values and the χ^2 test were used to compare the distributions of categorical variables. Data are presented as mean (SD). Categorical variables are expressed as a percentage of the total number of ADRs. $P \leq 0.05$ was considered statistically significant.

RESULTS

During the study period, 43 of the 142,295 hospitalized patients (0.03%) were admitted because of an ADR. A total of 564 (0.40%) of the hospitalized patients were verified to have ADRs (318 males [56.4%]; mean [SD] age, 66 [2] years). The age distribution of patients with ADRs and of the general population of hospitalized patients is shown in **Table I**.

The correlation of ADR rate with gender was not statistically significant (**Table II**). ADR rates increased with age from 1.34/1000 patients for the age range of 0 to 10 years to 6.95/1000 patients for the age range of 71 to 100 years ($P < 0.001$) (**Table III**).

All 564 ADRs were detected by either the active or the passive ADR reporting system. Clinical pharmacists reported 257 of the ADRs (45.6%), nurses reported 204 (36.2%), and physicians reported 85 (15.1%). The remaining 18 (3.2%) were reported by the patient or a family member.

The therapeutic classes of the drugs associated with the ADRs are shown in **Table IV**. Antibiotics were the most frequent cause of ADRs, with 219 patients (38.8%) experiencing an ADR associated with this drug class.

The most common clinical manifestations of the ADRs are listed in **Table V**. The most common ADRs with clinical manifestations were cutaneous (296 patients [52.5%]) and hematologic (61 [10.8%]) (**Table VI**). Among the most frequently observed ADRs were rash (172 patients [30.5%]) and local rash at the injection site (37 [6.6%]) (**Table V**), with most cases being classified as mild, resolved with the highest recovery rates (75%), and caused by the first-generation cephalosporin cephazolin. The most severe dermatologic ADR was Stevens-Johnson syndrome; 2 patients experiencing this reaction died. Hematologic ADRs were the second most frequently rated as severe in intensity (11/61 [18%]); thrombocytopenia was the most frequently occurring (6.9%). Regarding the probability of ADRs, 413 of ADRs (73.2%) reported were identified as probable, indicating that they were more likely to be associated with the suspected drug, according to the Naranjo probability scale.[11] Two reported ADRs (0.4%) were considered doubtful. The majority of ADRs (474 [84.0%]) reported were considered predictable, type B reactions (**Table VII**).

Gastrointestinal ADRs had the lowest recovery rates (1/28 [3.6%]), because most of the patients experienced vomiting and diarrhea and were not fully recovered before discharge; however, none of these reactions resulted in death (**Table VIII**).

Hospitalizations or extensions of hospitalization due to ADRs accounted for a total of 530 additional days of hospitalization (**Table IX**). The total cost of treating ADR-related illness collected from the hospital claims data was estimated to be US $150,027.14 (**Table X**). The cost of treating each ADR that was associated with extended hospitalization (n = 42) was estimated to be US $3489.00.

Table I. Age distribution of Taiwanese patients with adverse drug reactions (ADRs) and the general hospitalized population by sex. Data are no. of patients unless specified otherwise.

	Age Group, y										
Variable	0–10	11–20	21–30	31–40	41–50	51–60	61–70	71–80	81–90	91–100	Total
Patients with ADRs											
Male	12	19	25	19	42	44	47	74	35	1	318
Female	8	7	17	17	25	28	38	67	33	6	246
Total	20	26	42	36	67	72	85	141	68	7	564
Admitted patients											
Male	8516	3331	5909	6991	10,694	10,978	13,517	12,658	4116	177	76,887
Female	6419	2201	8078	7700	7684	8225	10,956	9714	4191	240	65,408
Total	14,935	5532	13,987	14,691	18,378	19,203	24,473	22,372	8307	417	142,295
ADR rate (per 1000 patients)											
Male	1.41	5.70	4.23	2.72	3.93	4.01	3.48	5.85	8.50	5.65	4.14
Female	1.25	3.18	2.10	2.21	3.25	3.40	3.47	6.90	7.87	25.00	3.76
Total	1.34	4.70	3.00	2.45	3.65	3.75	3.47	6.30	8.19	16.79	3.96
Male/Female	1.13	1.79	2.01	1.23	1.21	1.18	1.00	0.85	1.08	0.23	1.10

Table II. Correlation of adverse drug reaction (ADR)-related hospitalizations with sex in Taiwanese patients.*

Sex	ADR-Related	Not ADR-Related	Total
Male			
No.	318	76,569	76,887
Rate (per 1000 patients)	4.14	995.86	
Female			
No.	246	65,162	65,408
Rate (per 1000 patients)	3.76	996.24	
Total	564	141,731	142,295

*No significant between-gender differences were observed.

Table III. Correlation of adverse drug reaction (ADR)-related hospitalizations by age group in Taiwanese patients.

	Age Group, y					
Variable	0–10	11–20	21–40	41–70	71–100	Total
No. of patients (ADR-related hospitalization)	20	26	78	224	216	564
Rate (per 1000 patients)	1.34	4.70	2.72	3.61	6.95*	3.96
No. of patients (non-ADR–related hospitalization)	14,915	5506	28,600	61,830	30,880	141,731
Rate (per 1000 patients)	998.7	995.3	997.3	996.4	993.1	996.0
Total no. of patients	14,935	5532	28,678	62,054	31,096	142,295

*$P < 0.001$ versus all other age groups.

DISCUSSION

In this study, we found that 0.03% (43/142295) of hospitalized patients were admitted because of an ADR. A total of 564 (0.40%) hospitalized patients experienced an ADR during their hospital stay. These figures appear much lower than data from published studies from other countries (2.9%–35.0%).[3,4,14]

Physicians in Taiwan may underreport ADRs, even though most medical centers have a well-established ADR reporting system connected to the central reporting center. Clinical pharmacists also promote ADR reporting through presentations about ADRs at physicians' morning meetings and through promotional materials and a newsletter. Additionally, ADR reporting is a basic requirement of hospital accreditation in Taiwan. However, the ADR reporting rate remains low (0.003%), possibly due to physicians' concerns about liability. This phenomenon may also occur in Western countries.[15] One study reported that their ADR-reporting method supported the observation of traditional ADRs reporting are markedly underreported in hospitalized patients because the reporting system is physician dependent.[16]

Table IV. Therapeutic classes of drugs associated with adverse drug reactions in Taiwanese patients (N = 564).

Drug Class	Patients, No. (%)
Antibiotic	219 (38.8)
Analgesic	62 (11.0)
Cardiovascular	56 (9.9)
NSAID	32 (5.7)
Anticonvulsant	29 (5.1)
Anticoagulant	27 (4.8)
Gastrointestinal	17 (3.0)
Antituberculosis	14 (2.5)
Respiratory system	14 (2.5)
Antidiabetic	13 (2.3)
Antigout	13 (2.3)
Chemotherapy	13 (2.3)
Central nervous system	9 (1.6)
Metabolic	6 (1.1)
Antipyretic	4 (0.7)
Muscle relaxant	4 (0.7)
Narcotic	4 (0.7)
Hormone	3 (0.5)
Steroid	3 (0.5)
Antineoplastic	2 (0.4)
Antiplatelet	1 (0.2)
Dermatology	1 (0.2)
Other	18 (3.2)

Table V. Clinical manifestations of the adverse drug reactions (ADRs) in Taiwanese patients (N = 564).

ADR	Patients, No. (%)*
Rash	172 (30.5)
Thrombocytopenia	39 (6.9)
Local rash at injection site	37 (6.6)
Increased GOT/GPT	26 (4.6)
Bleeding	25 (4.4)
Bradycardia	23 (4.1)
Neutropenia	20 (3.6)
Diarrhea	14 (2.5)
Tremors	10 (1.8)
Other	198 (35.1)

GOT = glutamate oxaloacetate transaminase; GPT = glutamic-pyruvic transaminase.
*Totals may not sum to 100% due to rounding.

Table VI. Frequency of the adverse drug reactions by organ system and cause in Taiwanese patients (N = 564).

Variable	Patients, No. (%)*
Organ system	
Cutaneous	296 (52.5)
Hematologic	61 (10.8)
Cardiovascular	54 (9.6)
Hepatic	33 (5.9)
Gastrointestinal	28 (5.0)
Other	92 (16.3)
Cause	
Anaphylactic	464 (82.3)
Drug overdose, duration too long	78 (13.8)
Drug–drug interaction	22 (3.9)

*Totals may not sum to 100% due to rounding.

Table VII. Frequency of adverse drug reactions in Taiwanese patients by probability, type, and severity as defined by the World Health Organization.[8]

Variable	Reactions, No. (%)
Probability[11]	
Definite	23 (4.1)
Probable	413 (73.2)
Possible	126 (22.3)
Doubtful	2 (0.4)
Type	
Type A	90 (16.0)
Type B	474 (84.0)
Severity	
Mild	194 (34.4)
Moderate	330 (58.5)
Severe	40 (7.1)

We found that the proportion of ADR-related hospitalizations increased with age from 0.22% in patients aged <21 years to 0.69% in patients aged ≥71 years, which confirms a previous study that found that older patients have significantly more ADR-related problems.[17] This observation suggests that increasing age is a risk factor for the occurrence of ADRs, which might be related to the increased number of drugs elderly patients receive, the use of drugs that are inappropriate for elderly patients, and the number of previous illnesses.[17,18]

ADR rates did not vary significantly by gender in our study, which differed from the findings of previous studies.[19,20] They found that female sex was associated with a greater number of ADR-related problems.

Table VIII. Affected organ systems by the intensity of the adverse drug reactions (ADRs) and outcomes in Taiwanese patients (N = 564).

Parameter	ADR Frequency	Intensity			Outcome			
		Mild	Moderate	Severe	Fully Recovered	Not Fully Recovered	Death	Unknown
System, no. (%)								
Cutaneous	296 (52.5)	74 (25.0)	204 (68.9)	18 (6.1)	78 (26.4)	195 (65.9)	2 (0.7)	21 (7.1)
Hematologic	61 (10.8)	12 (19.7)	38 (62.3)	11 (18.0)	9 (14.8)	49 (80.3)	–	3 (4.9)
Cardiovascular	54 (9.6)	11 (20.4)	34 (63.0)	9 (16.7)	12 (22.2)	40 (74.1)	–	2 (3.7)
Hepatic	33 (5.9)	9 (27.3)	24 (72.7)	–	8 (24.2)	24 (72.7)	–	1 (3.0)
Gastrointestinal	28 (5.0)	13 (46.4)	15 (53.6)	–	1 (3.6)	27 (96.4)	–	–
Other	92 (16.3)	75 (81.5)	15 (16.3)	2 (2.2)	26 (28.3)	64 (69.6)	–	2 (2.2)
Total	564 (100.0)*	194 (34.4)	330 (58.5)	40 (7.1)	134 (23.8)	399 (70.7)	2 (0.4)	29 (5.1)

*Total percentages may not sum to 100% due to rounding.

Table IX. Costs associated with adverse drug reactions (ADRs) by drug class in Taiwanese patients. All costs are in 2006 US $.

Drug/ Drug Class	ADRs, n	ED Visits, n	ICU Visits, n	Extra Days of Hospitalization, n	Drug Costs	Monitoring and Laboratory Costs
Antibiotics	6	6	0	118	109,294.60	903,796.00
Sedative/hypnotic	0	0	0	0	0	0
Antiepileptic	12	11	3	159	93,649.42	422,229.00
Antipsychotics	0	0	0	0	0	0
Antidepressant	0	0	0	0	0	0
Cardiovascular	8	6	0	78	20,495.89	98,837.00
Endocrine drugs	4	4	2	80	140,799.30	1,088,692.00
Immunosuppressant	0	0	0	0	0	0
Gastrointestinal	1	0	0	0	2064.20	9140.00
Miscellaneous	12	10	3	95	352,523.60	531,972.00
Total	43	37	8	530	22,323.80	94,865.40

ED = emergency department; ICU = intensive care unit.

Table X. Total cost associated with adverse drug reactions (ADRs) in Taiwanese patients. All costs are in 2006 US $.

	Pharmacist Dispensing Fee	Physician Fee	Room Charges	ED Charges	Total Cost (US $1 = NT $32.2)
Total Cost	1172.42	5158.88	25,932.11	574.53	150,027.14
Average cost/ADR					3489.00

ED = emergency department; NT $ = Taiwanese new dollar

As reported in previous studies,[21] the most commonly affected organ system associated with ADRs in our study was the skin (52.5%). Two patients died of allopurinol-related Stevens-Johnson syndrome, which is the second most common drug associated with fatal ADRs.[22]

Consistent with published studies,[20,21] the ADRs in our study were most frequently associated with antibiotics (38.8%), analgesics (11.0%), and cardiovascular drugs (9.9%). The most common ADR was rash related to treatment with cephazolin.

A probability category for each ADR was assigned based on the Naranjo scale.[11] The results of the assessment were submitted to the Pharmaceutical and Therapeutic (P&T) Committee of our hospital for further evaluation. The results of the P&T evaluation were then reported to the National Adverse Drug Reporting Center of Taiwan.

Our hospital incurred a mean of US $283 for 1 additional length of stay associated with an ADR. One study[23] identified longer hospital stays as directly contributing to increased ADR costs. Two studies[2,23] concluded that the increase in the cost of hospitalization for an ADR was US $3800 and US $3200, respectively. Another study[24] found that the mean additional cost of hospitalization for an ADR was US $1400. In our study, the mean cost of an ADR associated with extended hospitalization was US $3489. The higher costs determined by some previous studies might be due to the severity of the ADRs, as patients with cardiovascular and hemorrhagic ADRs related to cardiovascular or anticoagulant drugs may be transferred to the intensive care unit.[25] However, the severe ADRs in our study were hematologic and cutaneous (ie, Stevens-Johnson syndrome, neutropenia, thrombocytopenia).

A limitation of this study was that the rate of ADR-related hospitalization was probably an underestimate because of underreporting or misclassification, because all ADRs possibly were not identified.[26] The actual number of ADRs in our patients might also have been higher than the number of ADRs detected during hospitalization because of the relatively short length of stay in our hospital (mean, 7 days). Therefore, some ADRs triggered by the drugs used during hospitalization may have occurred in the outpatient department.

CONCLUSION

In this hospital, 0.40% of patients were identified as having ADRs that were associated with high direct costs, mostly due to extended hospitalizations.

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