Incidence of Adverse Drug Reactions in Adult Medical Inpatients

Lee Bowman, Bruce C. Carlstedt and Curtis D. Black

ABSTRACT

This study was a prospective observational study of ADR occurrence and evaluation in adult internal medicine inpatients conducted over a 120-day period. Clinical pharmacists screened for ADRs at a county hospital in Indianapolis, IN. Patient information was reviewed on admission, every four days during hospitalization, and at discharge. ADRs occurring after hospital admission were assessed for causality, severity, pharmacological type (i.e., augmented pharmacology versus idiosyncratic reaction) and affected organ system. Nurse and pharmacist reports, incident reports, physician consults, patient transfers to critical care units, and serum drug concentration reports were additional means of ADR identification.

Overall, 23.1% of patients experienced an ADR while 2.6% of the 11,702 drug exposures resulted in an ADR. Patients aged greater than 65 years (29.6% vs. 20.5% for younger patients) and females (26.2% vs. 20% for males) were at higher risk for ADR development ($p<0.05$). Length of hospital stay was longer (13.3 days vs. 6.7 days; $p<0.05$) and drug exposures more frequent for patients experiencing ADRs ($p<0.001$).

Furosemide elicited the most ADRs with 36 in 244 patient exposures (14.7%). Diltiazem, enalapril, heparin, trimterene/hydrochlorothiazide combination and captopril were also frequently implicated. ADRs were classified as mild (35.9%), moderate (52.6%), and severe (10.2%). Organ systems most commonly affected were the metabolic/hematologic (32.9%), gastrointestinal (17.8%), genitourinary (11.8%), and cardiovascular (10.5%). Over 30% of events were idiosyncratic reactions. ADR incidence was consistent with previous literature. Many frequently implicated medications were newer agents and the severity of events was less than previously reported.

Key words: *Adverse drug reaction*

RÉSUMÉ

Cette étude, menée sur une période de 120 jours, consistait en une étude prospective d'observation de la survenue des réactions indésirable (R.I.) et de leur évaluation chez les patients adultes hospitalisés en médecine interne. Des pharmaciens en pharmacie clinique ont observé les patients, dans un hôpital régional d'Indianapolis, en Indiana, à la recherche de R.I. Les renseignements recueillis sur les patients ont été revus à l'admission, puis tous les quatre jours durant le séjour à l'hôpital, et avant le congé. Les R.I. qui sont survenues après l'admission à l'hôpital ont été évaluées afin de déterminer leur cause, leur gravité, le lien pharmacologique (c.-à-d. un effet pharmacologique accru vs une réaction idiosyncrasique) et les fonctions ou le ou les systèmes ou appareils touchés. Les rapports des pharmaciens et des infirmières, les rapports d'événements indésirables, les consultations medicales, les informations sur les transferts des patients à l'unité de soins intensifs et les rapports sur les concentrations sériques des médicaments constituaient un moyen additionnel d'identifier les réactions indésirables.

Dans l'ensemble, 23,1 % des patients ont éprouvé des R.I.; 2,6 % des 11 702 expositions des patients à un médicament ont été associées à une R.I. Les patients de plus de 65 ans (29,6 % vs 20,5 % pour les patients plus jeunes) et ceux de sexe féminin (26,2 % vs 20 % de sexe masculin) présentaient un risque accru d'éprouver des R.I. ($p<0,05$). Le séjour à l'hôpital était plus long (13,3 jours vs 6,7 jours; $p<0,05$) et la fréquence d'administration des médicaments était plus élevée chez les patients qui ont éprouvé des R.I. ($p<0,001$).

Le furosémide a entraîné une plus grande fréquence de R.I., soit 36 cas de R.I. sur 244 expositions (14,7 %). Le diltiazem, l'énalapril, l'héparine, l'association triamtérène-hydrochlorothiazide et le captopril ont aussi été fréquemment mis en cause. Les R.I. ont été classées comme légères (35,9 %), modérées (52,6 %) ou graves (10,2 %). Les fonctions, systèmes ou appareils les plus couramment touchés étaient les fonctions métabolique/hématologique (32,9 %), l'appareil digestif (17,8 %), l'appareil génito-urinaire (11,8 %) et l'appareil cardio-vasculaire (10,5 %). Plus de 30 % des réactions indésirables étaient de type idiosyncrasique. L'incidence des R.I. corroborait les résultats déjà cités dans la littérature. Un grand nombre de médicaments qui ont entraîné les réactions indésirables était moindre que ce qui avait déjà été rapporté.

Mots clés: *réaction indésirables à un médicament*

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INTRODUCTION

Potential complications from medicines and health care in general have been referred to as "the price we pay" for modern medical care.[1] However, in attempts to minimize this "price", newer medications are developed to achieve efficacy while avoiding unwanted side effects. Since the advent of many of these agents, (e.g., calcium channel blockers and angiotensin converting enzyme inhibitors) no comprehensive surveillance of inpatients has been published to identify the occurrence of adverse drug reactions (ADRs). This study was conducted to identify and categorize ADRs in the hospitalized internal medicine patient through a definitive chart review process, and to characterize the occurrence of ADRs in an urban county hospital.

METHODS

ADR Detection

This prospective, observational study evaluated all patient admissions (1,024 patients) to the internal medicine wards at a 350-bed county, general hospital in Indianapolis, IN during a four-month period. These wards included three intensive care units.

An ADR was defined as any adverse experience associated with the use of the drug including any side effect, injury, toxicity, sensitivity or reaction. This definition had been reviewed and approved by the hospital's Pharmacy and Therapeutics committee as part of the institution's ADR monitoring policy. Collection and evaluation of the ADR data were performed via chart review by one of two clinical pharmacists. All patients' charts were reviewed at admission, every three to four days during the patient stay, and again at discharge. The chart review strategy was enhanced by identifying a number of potential indicators or "flags" for ADR occurrence. Among those utilized were spontaneous physician, nursing, and pharmacist reports. In addition to spontaneous ADR reports, other indicators included incident reports; off-service physician consultations (dermatology, cardiology, gastrointestinal, infectious disease, nephrology, neurology, orthopedics, pulmonary and others); targeted drug orders (diphenhydramine, loperamide, benztropine, diazepam, diphenoxylate/atropine, oral vancomycin, hydrocortisone, epinephrine, phytonadione, protamine and laxatives); "stat", "now" and "hold" orders; abnormal serum drug concentrations; and patient transfers to the critical care units and deaths. All potential ADRs validated during the chart review process were documented and then evaluated according to four different ADR classification schemes.

ADR Evaluation

ADRs were classified according to causality, severity, pharmacological type, and affected organ system. If a patient problem had a potential drug association not documented in the chart (as determined by the clinical pharmacist review), the reviewer contacted the satellite pharmacist on the ward, explained the basis for the potential adverse reaction, and requested that the pharmacist contact the patient's physician regarding the patient problem. All patient problems that were associated with a drug effect were documented as ADRs for this study, unless the physician later "ruled out" a drug etiology for the specific patient problem.

Causality was assessed using the Naranjo scale.[2] This scale scores the probability of an event being drug-related in two ways; using a point system and using a four-level ordinal categorization, (i.e., doubtful, possible, probable, and definite). The Naranjo scale was chosen because of its ease of use, previous validation, and common acceptance. The evaluation of severity was performed by using modified severity descriptors attributed to Venulet.[3] The descriptions for the severity classifications of mild, moderate, and severe were broken down into individual statements to aid in uniform classification.

ADRs were also classified in a manner relating to adverse event to the drug's pharmacology. According to Rawlins, an ADR can be either "Type A" (an Augmentation or extension of the drug's pharmacology, e.g., beta-blocker inducing a bradyarrhythmia) or "Type B" (a Bizarre or idiosyncratic reaction that is not related to the pharmacology, e.g., ampicillin inducing a rash).[4] The classification of ADRs by affected organ system provides a means to easily classify adverse drug events without a narrative description. This classification scheme closely resembles the "review of systems" format used for charting a patient's history and physical exam.

Statistical analyses for categorical association were performed using the Chi Square statistic. For continuous variables, tests of sample means were performed utilizing the Wilcoxon rank sums test with correction for multiple hypothesis testing using a sharper Bonferroni adjustment.

RESULTS

Rate of ADRs per patient stay

1,024 patients experienced 366 ADRs during the total 1,225 admissions (i.e., some patients were admitted two or more times

during the four-month period). In subsequent hospitalizations, patients likely possess medication profiles similar to their previous admission and this may violate the assumptions of independence for statistical analyses. By restricting analysis to first admissions, the number of ADRs observed was reduced to 304. These 304 ADRs were experienced by 237 (23.1%) patients. A number of patients experienced multiple ADRs during their hospital stay (Figure 1). The ADR rate per patient for first admissions is nearly the same (29.7%) as when the multiple admissions are included (29.8%). However, patients having repeat admissions have higher rates of ADRs (31.58%) than patients overall (23.14%). Table I provides a summary of ADR frequency for the population with and without the patient's subsequent admissions.

One hundred and ten different drug entities were implicated in the 304 adverse effects available for final analysis. Many drugs were associated with ADRs many times. When evaluating the importance of these events, one must also consider the number of exposures for each drug. Overall, 11,702 patient drug exposures resulted in 304 ADRs or 2.6% of drug exposures.

Table II demonstrates the top five drugs most commonly observed to be associated with adverse events. Subsequent to the list of top five agents, the rest of the medications are presented. Drugs associated with severe reactions are so designated. Table II provides information regarding an individual drug's percent ADR occurrence to exposure, as well as the percentage of overall ADR occurrences. It is interesting to note that although furosemide accounts for a high number of ADRs, the percent ADR occurrence to exposure is much lower than that associated with, for example, amphotericin B (14.7% vs. 71.4%, respectively).

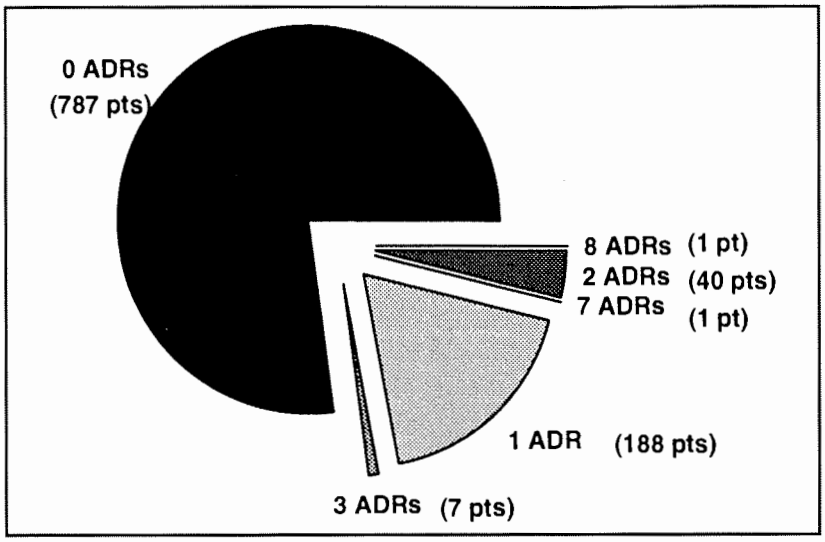

Figure 1: Frequency of ADR occurrence in 1024 admissions.

TABLE I: Summary of ADR frequency

	# of Units	# with ADRs	% with ADRs	# of ADRs	ADRs per 1000 Units
Drug Exposures (1st Admissions)	11,702	304	2.6%	304	25.9/1000
Admissions (All)	1,225	285	23.18%	366	298.8/1000
1st Admissions	1,024	237	23.14%	304	296.9/1000
Repeat Admissions	201	48	23.83%	62	308.5/1000
Patients (All Admissions)	1,024	237	23.14%	366	357.4/1000
Patients (with Repeat Admissions)	152	48	31.58%	62	407.9/1000

The therapeutic class of the involved medications was also evaluated. Cardiovascular agents (antihypertensives, antiarrhythmics, etc.) and diuretics were the two most frequently implicated drug classes, each accounting for 15.8% (58 ADRs) of the total ADRs observed. Antibiotics and psychotropic medications were the two next most commonly implicated drug classes accounting for 13.8% and 6.6%, respectively. Of the 58 ADRs identified in the cardiovascular class, 39 of those events were associated with calcium channel blockers and angiotensin converting enzyme inhibitors.

The number of concurrent drugs that a patient received during their hospitalization was wide ranging. The range was from one up to 72 different drugs while the mean number was 11.4 ± 6.8 (sd) drugs. The mean number of drug exposures was 15.8 for patients experiencing ADRs and 10.1 for patients having experienced no adverse event, ($p<0.001$).

Demographics

The demographic patient variables tabulated in this study were age,

gender, and race. Although age is a continuous variable, much literature has pointed to an increased risk of ADR development in patients over 65 years of age. The association of age with ADR occurrence is in itself a topic of debate[5]. Nevertheless, age, gender, and race underwent categorical analysis. A Chi Square statistic was used to determine the association between these patient characteristics and ADR occurrence. Age was treated as a dichotomy of those less than 65 years versus those older. Those greater than 65 experienced an ADR 29.6% of the time versus 20.5% for those younger, ($p<0.01$). Similar statistical significance for age was found when evaluated as a continuous variable. Patient's race was categorized as black, caucasian or other. Caucasian patients experienced ADRs in 20% of admissions while black patients experienced adverse events in 25.7% of admissions. "Other" races possessed the highest percentage of ADRs with 27.3%. The difference in these rates of occurrence was not found to be statistically significant, ($p>0.05$). ADRs occurred in 26.2% of females versus 20% of males, ($p<0.05$).

TABLE II: Drugs producing severe and/or frequent ADRs

DRUG	# of ADRs	# of Exposures	% of Exposures	% all ADRs
Furosemide (*)	36	244	14.7	11.8
Diltiazem (*)	11	61	18.0	3.6
Enalapril	10	97	10.3	3.2
Heparin	10	662	1.5	3.2
HCTZ/triamterene	10	39	25.6	3.2
Aminophylline	1	53	1.9	0.3
Amphotericin B (*)	5	7	71.4	1.6
Captopril	9	109	8.3	3.0
Ceftazidime	1	20	5.0	0.3
Ceftriaxone	6	205	2.9	2.0
Chlorpromazine	1	16	6.2	0.3
Cimetidine	4	236	1.7	1.3
Clonidine	3	84	3.6	1.0
Cotrimoxazole DS	7	96	7.3	2.3
Darvocet	1	142	0.7	0.3
Desipramine	1	7	14.3	0.3
Digoxin	3	128	2.3	1.0
Diphenhydramine	2	154	1.3	0.7
Erythromycin	7	41	17.1	2.3
Gentamicin (**)	6	30	20.0	2.0
Hydrochlorothiazide	7	65	10.8	2.3
Indomethacin	4	8	50.0	1.3
Insulin (all types)	4	214	1.9	1.3
Isoniazid	3	19	15.8	1.0
Isosorbide dinitrate	5	210	2.4	1.6
IVP dye	1	-	-	0.3
Levothyroxine	1	3	33.3	0.3
Lorazepam	7	184	3.8	2.3
Meperidine	1	140	0.7	0.3
Methocarbamol	1	4	25.0	0.3
Methylprednisone	5	59	8.5	1.6
Metolazone	3	8	37.5	1.0
Metoprolol	5	46	10.9	1.6
Midazolam	3	38	7.9	1.0
Morphine	4	101	4.0	1.3
Nalbuphine	1	2	50.0	0.3
Nifedipine	7	112	6.2	2.3
Pentamidine	1	3	33.3	0.3
Phenytoin	4	60	6.7	1.3
Prednisone	3	105	2.8	1.0
Propranolol	1	15	6.7	0.3
Pyrazinamide	3	7	42.9	1.0
Vasopressin	3	6	50.0	1.0

The five drugs most frequently associated with adverse events are listed first.
"-" designates an unknown number of exposures.
Bold type designates one or more severe events.
* designates 2 severe events.
** designates 3 severe events.

Time to ADR onset and length of hospital stay

The time elapsed from admission to ADR occurrence was highly variable. ADRs occurred on the first day of hospitalization and up to 57 days later. The most common day for ADR occurrence was the first day of hospitalization which accounted for 18.8% of all ADRs. The average day of ADR occurrence was the seventh day while the median was day four. By the eighth hospital day, 75% of all ADRs detected had occurred. The length of hospital stay for patients with ADRs versus patients without ADRs was also evaluated. The mean length of stay (in days) for patients without ADRs was 6.7 while those with ADRs was 13.3, ($p<0.001$).

Casuality

Upon examination of the continuous Naranjo causality score, Figure 2 demonstrates a rather wide range and somewhat bimodal distribution of values. Because this system allows for scoring a value of zero when a particular characteristic measured by the scale is unknown, these scores and subsequent categorizations may at times reflect the

prescribers initiative (or lack thereof) in investigating the ADR rather than a true estimate of positive causality.

Severity

The distribution of ADR severity as measured by the modified Venulet classification scheme is demonstrated in Figure 3. The 31 severe ADRs observed were associated with 26 different drugs. Although the individual reactions cannot be examined fully in this space, Table II identifies the drugs associated with severe events with bold print and designates the number of severe events. It should be noted that three of these agents, (amphotericin B, diltiazem, and furosemide) resulted in severe reactions twice while gentamicin was implicated in three severe events. Although no severe reaction is trivial (e.g., nephrotoxicity, heart failure, etc.), the frequency of severe events with regard to furosemide and diltiazem is perhaps understandable in light of their high use and relatively high rate of ADRs. However, patient exposure to amphotericin B and gentamicin is much less frequent and severe events comprised 40% and 50% of their total ADRs, respectively. Therefore, these four agents should bear close individual scrutiny in later drug utilization evaluations.

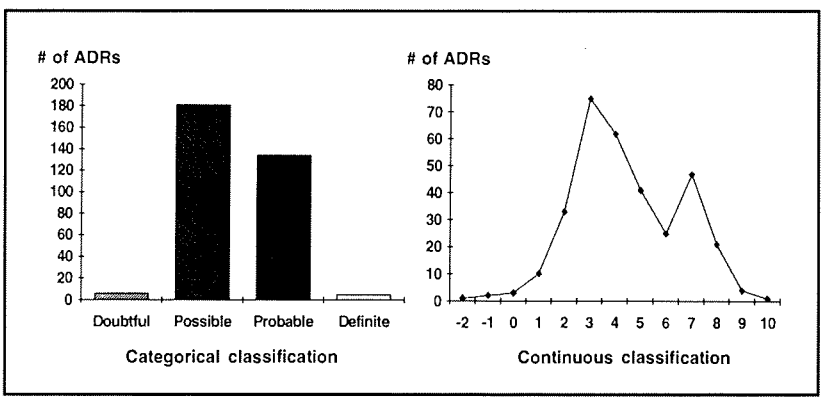

Figure 2: Naranjo causality scores.

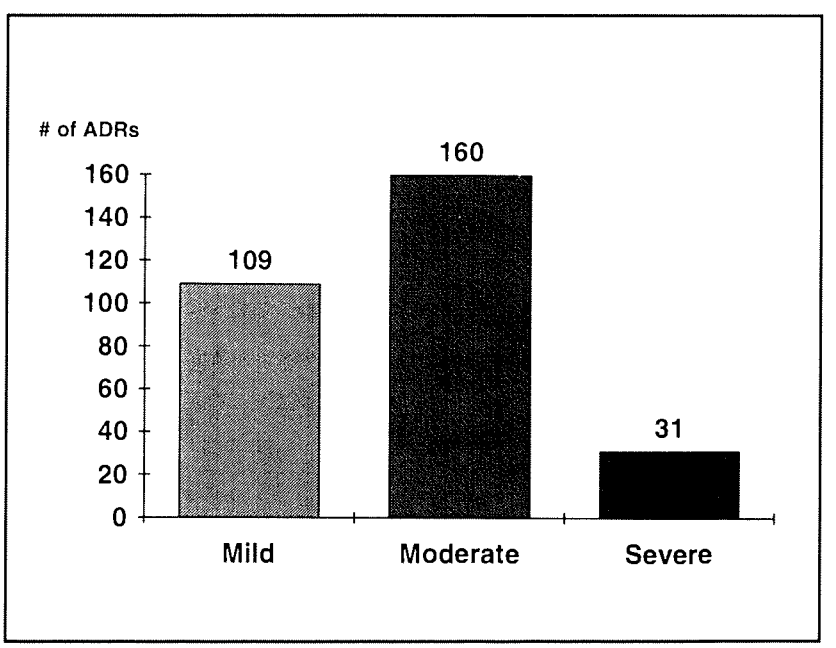

Figure 3: Overall severity of ADRs.

Pharmacological type and organ system classification

"Type A" reactions accounted for 212 (69.7%) of the 304 total ADRs. The remaining 92 (30.3%) adverse events were considered idiosyncratic or "Type B".

The ADR distribution according to organ system classification is given in Figure 4. The most commonly affected organ system identified in this study was the hematologic/metabolic system. This classification includes not only drug-induced changes in blood cells, but also changes in serum electrolytes and serum blood glucose.

DISCUSSION

Comparisons to the literature: Demographics

The percent of ADR occurrence detected in this study was approximately 23% of hospitalizations. This value falls within the 10 to 50% range documented in the literature.[6-13] A higher rate of ADR occurrence in reference to the number of patient drug exposures has been documented by others (3.6%[8,9] and 5.7%[3]). This study demonstrated a lower rate of 2.6%. Two reasons for this difference are hypothesized. Perhaps an increase in overall drug exposure in our patient population has inflated the denominator in the ADR occurrence ratio. Alternatively, evolvement of the hospital formulary system may have reduced the availability of agents with high risk-to-benefit ratios. If the latter is true, this might be evidence of formulary development contributing to better utilization of drugs rather than just utilization of cheaper drugs as is sometimes perceived.[14] Finally, in accordance with the literature[10] the

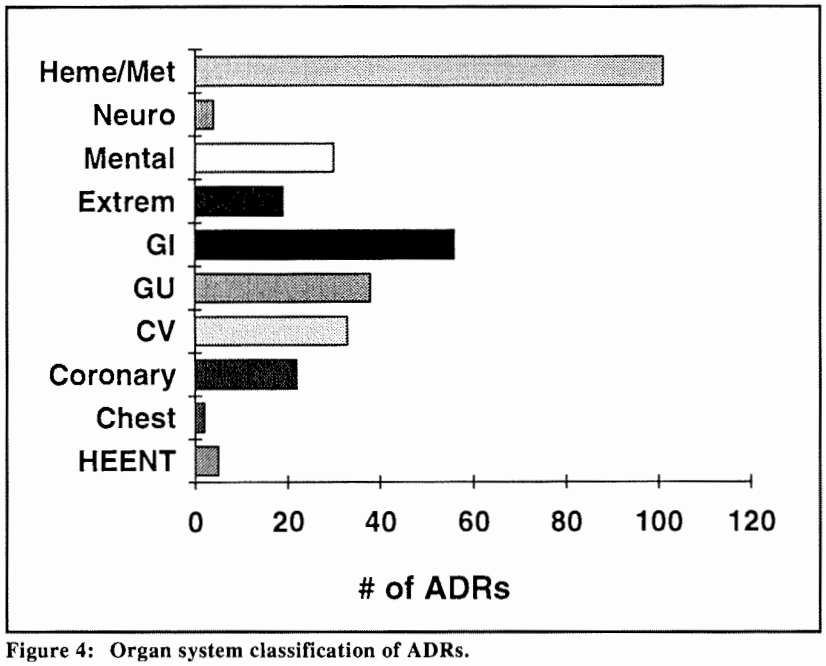

Figure 4: Organ system classification of ADRs.

Heme/Met = Hematological/metabolic, Neuro = neurological, Extrem = Extremities, GI = Gastrointestinal, GU = Genitourinary, CV = Cardiovascular, HEENT = Head-Ears-Eyes-Nose-Throat.

mean number of drugs was much higher for those patients who experienced an ADR (15.8) than for those who did not experience an ADR (10.1).

The therapeutic class of the implicated agents was similar to that seen in previous studies of ADR epidemiology. Cardiovascular agents have been the most frequently implicated class associated with adverse events in several studies.[6,17,18] Antimicrobial agents also possessed a high rate of adverse events and this has also been well demonstrated in the hospitalized patient.[6,15-18] Perhaps our most unusual finding is the high rate of adverse events associated with diuretics. Although many of these events are considered mild or moderate, the overall impact is difficult to assess. Although an adverse event (e.g., electrolyte imbalance) is perhaps expected, it is, nevertheless, unintended and adverse. Subsequent laboratory tests to monitor correction of the abnormality may be initiated and costs may thereby be increased. The high rate of ADRs discovered may reflect the over-aggressive use of diuretics or perhaps an overwhelming need for diuresis in these patients. Undoubtedly, this high occurrence indicates the need for further review of diuretic use by the institution.

The more novel pharmacotherapies (calcium channel blockers and ACE-inhibitors) have demonstrated substantial toxicity as well (e.g., arrhythmias, hyperkalemia, etc.). These accounted for 39 of the 58 adverse events ascribed to cardiovascular agents. However, it is again difficult to differentiate between the associated adverse effects of these agents and the severity of the disease for which they have been prescribed. If patients receiving these agents are more severely ill, they perhaps have a greater predisposition to ADRs.

The population demographics were partially in agreement with the literature. Female gender was found to be a risk factor for ADR development and accounted for 57% of ADRs. This was consistent with the literature.[18-20]

Our findings for the effect of race seem to disagree with the literature. Our study found no statistical significance in effect of race on ADR occurrence. Non-whites tended to experience more ADRs; other studies have tended to find the opposite.[6-8] There is no apparent explanation for this difference. The lack of statistical significance may be secondary to Type II error. However, our findings may be unique to the population served by the institution. Larger and more complete studies including information on population socioeconomic status would need to be performed to evaluate this interesting but statistically equivocal finding.

ADRs occurred relatively early in the hospital stay. The most common day for ADR occurrence was the first day (18.8%) with 75% of all ADRs having occurred by the eighth day. Although this would seem to disagree with earlier studies stating 63% of ADRs occurred by the third hospital day[14], it does appear more consistent with later studies that reported 62% of ADRs occurred by the eighth day.[17,18]

The association of length of stay with ADR occurrence was consistent with earlier literature.[1] Although length of stay is associated with ADR occurrence, the former may not be a result of ADR occurrence because of the apparent lack of severe reactions which by definition[3] prolong hospital stay. One third of all reactions occurred in the first two days so one would have had to observe a large number of quite severe reactions to lengthen hospital stay from 10 to 15 days. This was not the case. The alternative relationship would be that increased length of stay provides more time for drug

exposure and subsequent ADR occurrence. However, this argument also fails because of the large number of ADRs occurring early in the hospital stay. Both of these time elements may be covariates of an indicator of disease severity. For example, a patient who is admitted in the most severe stages of illness is more likely to receive many drugs early in the hospitalization and then stay a prolonged period for recuperation. Efforts toward monitoring and preventing ADRs may best be directed toward the first days of hospitalization in order to minimize the occurrence and perhaps severity of ADRs. Further study is needed to characterize these relationships.

Comparisons to the literature: ADR Evaluation

The Naranjo Causality evaluation demonstrated a wide and relatively bimodal dispersion in the numerical scoring of ADRs. The categorical assessments were similarly grouped into the two middle categories: possible and probable. These two categories accounted for over 97% of the ADRs. The potential reasons for this are twofold. First, information from the chart review was the primary source for confirming a suspected ADR occurrence. Because the physicians were not responsible for completing the Naranjo form, much of the specific information pertinent to establishing causation was not documented. Therefore, determining likelihood for a drug etiology was difficult. Secondly, the difficulty in establishing a doubtful categorization is likely to be found in the bias of the physician. The physician will not routinely rule out a drug etiology for each patient problem and document this process in the chart. For the Naranjo instrument to work most reliably, each patient problem should be evaluated for a potential drug association and for each drug exposure. However, the number of causality evaluations necessary would dramatically increase for this type of evaluation. The assumption made for this study was that the negligible increase in meaningful ADRs identified would not warrant such an expenditure of time and resources.

The evaluation of ADR severity was performed in as standard a manner as was available. The distribution of reactions across categories was slightly different than that reported in the literature but nevertheless fell within the extremes. One study documented major, moderate, and minor reactions at 25, 54, and 20%, respectively.[12] While another demonstrated percentages of severe, moderate, and minor at 4, 80 and 16% respectively[15,16]. Our study demonstrated a slightly skewed distribution. Severe, moderate, and mild were demonstrated to be at 10.3, 53.3, and 36.3%, respectively. The summed percentage of moderate and severe reactions (10.3% + 53.3% = 63.6%) seems to be much lower than previous literature reports (79 and 84%, respectively)[12,15,16] and moderate/severe reactions have the greatest impact on health care. A reasonable explanation is difficult to identify. Development of drugs with improved safety profiles and changing prescribing patterns may account for the relative decrease in moderate and severe ADRs. The evolvement of the hospital formulary system, drug utilization programs or perhaps the patients' severity of illness may have also shared in this effect.

An evaluation of the pharmacological mechanism of ADR occurrence revealed a 70:30 ratio of "Type A" reactions to "Type B". This is slightly lower than the 80:20 ratio previously reported in the literature[3]. Although our 30% figure for "Type B" reactions is slightly higher than that previously reported, pharmacological classification may be biased by poor attribution of a patient problem to an ADR. For instance, if a chart review reveals an ADR and the causal relationship is quite weak, then the reaction would be documented although a probable mechanism is unknown. This reaction would be classified as "Type B". In our study, 16.7% of the ADRs reported were at a Naranjo causality score of 2 or less. If a large fraction of these events were inappropriately attributed to a drug etiology, the pharmacological support for the reaction might be suspect and lead to an increase "Type B" classifications. Interestingly of the 51 events of weak numerical causality, 42% of them were Type B while only 30% of total ADRs were Type B. Although speculative, this relationship may explain our relatively higher percentage of idiosyncratic-type reactions.

The organ system classification demonstrated that those systems most affected were the hematologic/metabolic, GI, GU, and cardiovascular systems. This scheme is quite consistent with Hurwitz's results[13,14] with an under-reporting of neuromuscular events in this study. Similarly, our results are consistent with those shown by Seidl et al[4] and Rosenberg[14]. The most apparent discrepancy with these two studies is the under-reporting of skin-related events in our study. This may be due to the paucity of ADR reports by the nursing service. Also, the number of GU classifications (primarily renal

toxicities) was slightly higher and may be indicative of increased renal toxicity or the increased hemodynamic effects of the newer medications such as angiotensin converting enzyme inhibitors and calcium channel blockers.

The results of ADR evaluation for our population are in many ways similar to those demonstrated in the literature. Although causality was not routinely assessed in the early epidemiological studies of ADR occurrence, this assessment does help in formulating a rationale for the slight differences in the distribution of events for pharmacological and severity classifications. The overall rate of ADR occurrence seems little altered in the past 30 years. Although the rate of ADR occurrence seem unchanged, the ADRs reported tended to be less severe in this study; but still not innocuous. It is unknown as to whether the decreased severity is an artifact of this study or related to modified provision of pharmacy services or related to the newer medications themselves. Periodic evaluation of the overall occurrence of ADRs in hospitalized patients allows for a refocusing of drug therapy monitoring, formulation of drug utilization evaluation strategies, and enhanced patient care.

All data collection forms are available upon request from the corresponding author.

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