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Adverse Reactions During Hospitalization

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ADVERSE reactions during hospitalization have become recognized as part of the price that must be paid for more complicated diagnostic techniques and more potent and effective drugs. In spite of greater awareness of the risks of hospital care, there has been only one recent study of these undesirable events.[1] Several epidemiological studies of reactions to drugs emphasize the need for continuing study of these special hazards.[2-4] This study includes an analysis of the frequency and severity of all risks of hospitalization.

METHODS

All patients admitted to a public medical ward of The Montreal General Hospital, a teaching centre of McGill University, between July 1, 1965, and June 30, 1966, were studied. Patients with general medical illnesses were admitted to this 35-bed ward. One of the authors (R.I.O.) was resident physician on the ward throughout the study.

In addition to age and sex, patients were characterized by the type of illness which prompted their admission. Three categories were used: patients with an illness of short duration, who had not been ill previously, were considered to have an "acute illness"; patients with an illness of short duration superimposed on a more chronic disorder were considered to have an "acute and chronic illness"; and patients with an illness of long duration without a recent acute exacerbation were considered to have a "chronic illness".

An adverse reaction to hospitalization was defined as any undesired or unintended consequence of investigation or care of the patient while he was in hospital. Failure to achieve an expected therapeutic result was not considered an adverse reaction. Psychiatric disturbances arising in hospital were not included because of the difficulty in interpreting cause and effect in such events. Reactions which were present at the time a patient was admitted to hospital were recorded but were not included in the total incidence of adverse reactions during hospitalization.

The house staff and nursing staff reported the adverse effects. Interns and residents were asked to report all adverse reactions by writing the patient's name, the suspected drug or procedure, and the type of reaction on a printed form placed on the patient chart carrier which was used for their daily bedside rounds. The nursing staff were instructed in the recognition of adverse reactions, and nurses on each of the three daily shifts listed the following information on three separate forms: the names of patients who had their drug therapy cancelled, diminished in dose or substituted by another drug, or the route of administration changed; all diagnostic and therapeutic procedures carried out on patients and any adverse effects of these; and all adverse reactions recognized during the shift. The first list was usually completed by the "medications" nurse, the second by the "charge" nurse, and the third was made up of the reports of all nursing personnel during "nursing report" at the time of changes in shift. In order to encourage adequate

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Canad. Med. Ass. J.
Dec. 9, 1967, vol. 97

completion of each list, the nurses, in the same way as the house staff, were asked to record only the name of the patient, the suspected procedure or drug, and one word describing the reaction. A two-week pilot study was carried out before the 12-month study.

Reactions reported daily by these methods were evaluated, studied and recorded by the resident (R.I.O.). At the time of discharge from hospital, the chart of every patient who had had an adverse reaction was reviewed and a summary of the patient's stay in hospital and the reactions were recorded. The severity of the reaction was estimated and contributing factors were studied. The charts and autopsy reports of all patients who had died on the ward were reviewed for unrecognized adverse reactions that may have contributed to death. The severity of reactions was categorized in a manner similar to that described by Schimmel:[1]

1. A minor event—one having a short course and subsiding without specific treatment.

2. An event of moderate severity—one which prolonged hospital stay more than one day or required specific treatment.

3. A major event—one which was life-threatening, or lethal, or contributed to death, or which caused continuing effects at the time of discharge.

Statistical significance was determined using the Student "t" and the chi square tests.

RESULTS

During the 12-month period, 731 patients were admitted to the study; 177 patients (24%) had suffered one or more adverse reactions; and a total of 261 reactions were recorded. The types of reactions are shown in Table I.

TABLE I.—VARIOUS TYPES OF ADVERSE REACTIONS (731 PATIENTS)

Reactions	*Number*	*% of total*
To miscellaneous hazards	13	5.0
To transfusion	15	5.7
To therapeutic procedures	21	8.0
Acquired infections	24	9.2
To diagnostic procedures	26	10.0
To therapeutic drugs	162	62.1
	261	100.0

Types of Reactions

Thirteen reactions to miscellaneous hazards were recorded in 13 patients (5.0% of all reactions). Four patients developed foot-drop, two after intramuscular injections, one after a period of unconsciousness and the use of vessels in the affected limb for hemodialysis, and one probably due to leg-crossing and peroneal nerve ischemia. A "zero-calorie" diet induced hyperuricemia and acute gout in one patient. Prolonged bed rest in two patients was associated with phlebitis of calf veins. One of these patients had a non-fatal pulmonary embolus. Skin abrasions due to adhesive tape or bed linen accounted for the remainder of these reactions.

Fifteen reactions to transfusions occurred in 14 patients (5.7% of all reactions). Febrile episodes were recorded in two patients, pruritus and urticaria in 10 and circulatory overload in two. The latter two patients were considered to have suffered life-threatening reactions. No mismatched transfusions were recorded.

Twenty-one reactions to therapeutic procedures were recorded in 17 patients (8.0% of all reactions). Four were life-threatening. Gastric lavage of an intoxicated semicomatose patient, without previous endotracheal intubation, resulted in severe aspiration pneumonitis. In another patient, failure to clear the pharynx adequately before inserting an airway resulted in airway obstruction. An 8-cm. length of plastic intravenous catheter was severed during a convulsion and lodged in the right pulmonary artery of a 63-year-old survivor of an acute myocardial infarction. Nasogastric tube feeding of a patient with Guillain-Barré syndrome caused diarrhea which was complicated by severe hypokalemia, and this aggravated the paralysis and respiratory difficulty. Other therapeutic procedures which were complicated by adverse reactions included venous "cut-downs", urinary bladder catheterization, nasal packing, enemas and irradiation.

Twenty-four infections that had been acquired in hospital were recognized in 24 patients (9.2% of all reactions). Seven patients developed cystitis during bladder drainage with a retention catheter, and one had bacteremia after urethral dilatation. One patient with pancytopenia after cancer chemotherapy was admitted for "protective isolation", at which time all bacterial cultures were negative. Eight days later a sputum specimen culture grew penicillin-resistant *Staphylococcus aureus* and *Klebsiella pneumoniae,* and signs of pneumonia were present.

Most acquired infections were superinfections while patients were receiving broad-spectrum antibiotics. There were four fatal superinfections and a further four life-threatening infections, and three patients had persistent infections at time of discharge from the hospital. *Staphylococcus aureus* was cultured in 11 cases, gram-negative organisms in nine and *Candida albicans* in two cases.

Twenty-six adverse reactions to diagnostic procedures were recorded in 26 patients (10.0% of all reactions). Six of these reactions were life-threatening. An augmented histamine gastric analysis was followed by severe hypotension in one patient and by a profuse upper gastrointestinal hemorrhage in another. Ventricular fibrillation induced during coronary angiography was successfully reverted to sinus rhythm. A tension pneumothorax followed scalene node biopsy. Severe laryngospasm and laryngeal edema followed lidocaine spray locally for bronchography. Apnea and hypoxia due to respiratory-centre depression followed general anesthesia for bronchoscopy. Other types of reactions in this category included skin necrosis after tuberculin testing, allergic reactions to radiographic dyes, pneumothorax after thoracentesis, headache after lumbar puncture, and cardiac arrhythmia after edrophonium chloride was used as a test of the adequacy of treatment of myasthenia gravis. Over one-half of all reactions to diagnostic procedures were reactions to drugs which had been used in diagnosis.

One hundred and sixty-two reactions to therapeutic drugs occurred in 102 patients (62.1% of all reactions). In addition, 18 reactions to drugs used in diagnostic procedures occurred in 17 patients, and 13 acquired infections occurred in 13 patients receiving antibacterial drugs. Thus, there was a total of 193 reactions to drugs in 132 patients (74.0% of all reactions). Reactions to all classes of drugs occurred in 18.0% of the patients studied. These reactions will be described in another paper.[5]

TABLE II.—DURATION OF STAY IN HOSPITAL UNTIL FIRST ADVERSE REACTION

Reactions	*Average interval (days ± S.D.)*
To miscellaneous hazards	7.1 ± 5.3
To transfusion	3.2 ± 2.3
To therapeutic procedures	4.7 ± 2.8
Acquired infections	13.5 ± 5.3*
To diagnostic procedures	8.0 ± 3.5
To therapeutic drugs	6.8 ± 6.0
All adverse reactions	7.1 ± 9.2

*The average stay in hospital until the onset of the acquired infection as the first reaction differs from the average stay until the first reaction of all other reactors ($p < 0.05$). The other intervals are not significantly different from the average stay until the first reaction of all other reactors.

Time of Reactions

The time of recognition of adverse reactions of various types, expressed as days from admission to hospital until the reporting of the first event, is shown in Table II. Most reactors had their first reaction within eight days of admission to hospital. The only exceptions were acquired infections which occurred in patients towards the end of the second week.

Characteristics of Patients with Adverse Reactions

The average age of the patients having adverse reactions was not different from that of all other patients (Table III). The mean age of patients with various types of reactions was compared to the mean age of all reactors. A significant difference in age was found for one group only. Patients who acquired infections were older ($p < 0.05$) than other reactors.

The incidence of adverse reactions was 25.0% in male patients and 23.3% in female patients ($p < 0.7$).

TABLE III.—AGE OF PATIENTS

Type of patient	*Number*	*Average age (years ± S.D.)*
Total population	731	57.0 ± 23.1
Non-reactors	544	56.6 ± 22.5
All reactors	177	57.8 ± 16.2
Patients with reactions		
To miscellaneous hazards	13	51.9 ± 16.8
To transfusion	14	55.1 ± 18.0
To therapeutic procedures	17	62.0 ± 13.0
Acquired infections	24	65.4 ± 13.9*
To diagnostic procedures	26	52.5 ± 17.2
To all drugs	132	57.9 ± 15.8

*The average age of patients with acquired infections differs from the average age of all reactors ($p < 0.05$). Other ages are not significantly different from the average age.

The incidence of a second reaction was studied by assessing the occurrence of more than one reaction in patients during their hospital course as well as by assessing the incidence of reactions in hospital in those patients who had been admitted to hospital with a reaction. The data in Table IV show that of 177 patients who suffered reactions during hospitalization, 32% had a second reaction while of 60 patients admitted with a reaction 37% had a subsequent reaction in hospital. These rates were both higher than the 24% rate of a first reaction in hospital ($p < 0.001$).

In 53 of the 60 patients admitted with a reaction, the reaction was directly responsible for admission. None of these reactions was included in the total incidence.

There was a difference in the incidence of adverse reactions in patients in the three admission categories: 38.5% of patients were admitted with an acute illness, of whom 24.5% had adverse reactions; 29.2% of patients were ad-

Canad. Med. Ass. J.
Dec. 9, 1967, vol. 97

TABLE IV.—INCIDENCE OF SECOND ADVERSE REACTION

	Number	*Per cent*
Patients suffering a reaction during hospital stay:		
One reaction only	120	68
More than one reaction	57	32
Total	177	100
Patients admitted with an adverse reaction:		
No further reaction	38	63
Further reactions during hospitalization	22	37
Total	60	100

mitted with a chronic illness, of whom 16.4% had adverse reactions; and 32.3% of patients were admitted with both an acute and chronic illness, of whom 31% ($p < 0.01$) had adverse reactions.

Effect of the Adverse Reaction on the Patient

The stay in hospital of non-reactors and reactors is shown in Table V. While all patients averaged a hospital stay of 13.7 days, non-reactors averaged 11.6 and reactors 20.5 days.

TABLE V.—STAY IN HOSPITAL

	Average stay (days ± S.D.)	
	Present study 1965 - 1966	*Schimmel 1960 - 1961*
Total patient population	13.7 ± 10.3	12.0
Non-reactors	11.6 ± 7.8	11.4
Reactors during hospitalization	20.5 ± 13.6*	28.7

*Average stay of reactor differs from that of non-reactor ($p < 0.001$).

The severity of reactions is shown in Table VI. Most reactions were major or moderate in severity. Of the 86 major reactions, 20 had continuing effects on the patient at the time of discharge from the study, 49 were life-threatening, and 17 were lethal.

Sixty-seven of the patients studied died in hospital. Seventeen of these were thought to have died of fatal adverse reactions, all of which were reactions to drugs. Twelve patients died of digitalis toxicity, four of antibiotic-induced superinfection and one of respiratory arrest caused by morphine sulfate. Details are given elsewhere.[5]

TABLE VI.—SEVERITY OF ADVERSE REACTIONS

	Present study 1965 - 1966		*Schimmel 1960 - 1961*	
Severity	*Number*	*Per cent*	*Number*	*Per cent*
Minor	73	28	110	46
Moderate	102	39	82	34
Major	86	33	48	20
Total	261	100	240	100
Fatal reactions	17	6.5	16	6.7

Recognition and Reporting of Reactions

None of the methods used provided complete reporting of results. Of the three systems used—voluntary house staff recording, voluntary nursing staff recording, or using medication changes as an alerting system—none reported more than 60% of the total adverse reactions. The nursing staff was more efficient in reporting minor events and events of moderate severity than the house staff. One-third of all adverse reactions were reported only by the nurses and one-third only by the house staff.

DISCUSSION

Several studies of some of the risks of hospital care have been reported recently,[2, 3, 6-8] but only Schimmel,[1] in 1960, studied all of the untoward reactions suffered by patients in hospital. Because of the frequency and severity of adverse reactions reported by Schimmel, it was thought that another study of all of the hazards of hospitalization should be made. In order that comparisons could be made between the two studies, similar methods were used in our study. However, because of our interest in testing ways of reporting of adverse reactions, our surveillance methods included reports by nurses as well as interns.

Many of the results in our study confirm those of Schimmel. Adverse reactions to hospitalization were frequent. Twenty-four per cent of our patients suffered an adverse reaction, while 20% of all patients were affected in the earlier study. The frequency of various types of reactions was similar in the two groups except for a somewhat more frequent incidence of drug reactions in our patients. This difference may be the result of differences in the patient populations, in monitoring programs and in medical practice or because of a change in drug use since 1960. Adverse drug reactions were the most frequent untoward events (74% of all reactions) and are discussed elsewhere.[5] Reactions to transfusions, to diagnostic and to therapeutic procedures and acquired infections each affected less than 3.5% of the patients.

None of the reactions experienced by our patients were particularly unusual. Most physicians have observed similar untoward events in

their patients. Because they are commonplace, these risks are sometimes forgotten when decisions about diagnosis and therapy are made. Their severity is not adequately realized. Seventy-two per cent of the reactions in our patients were of major or moderate severity; that is, specific treatment of the reaction was required, hospital stay was prolonged by the reaction, or the reaction was life-threatening, contributed to death or was lethal. Fifty-four per cent of Schimmel's patients suffered reactions of this severity (Table VI).

An attempt was made to characterize the patient who was susceptible to adverse reactions. The reactor did not differ in age or sex from the non-reactor except that patients who suffered an acquired infection were older. Patients who had suffered one reaction were more likely to have another. Patients with acute and chronic illnesses had a higher incidence of reactions than patients with an acute illness alone. Patients with a chronic illness alone showed the lowest incidence. These differences in host characteristics are difficult to explain. It seems likely that patients with a high incidence of reactions were exposed to more drugs, therapeutic and diagnostic procedures and other hazards. No attempt was made to study the incidence rate in relationship to the exposure rate, but such an inquiry might clarify some of these inexplicable differences in host characteristics.

Schimmel[1] proposed that a long hospital stay predisposed patients to adverse reactions, but our study does not support this thesis. The average stay in hospital of all our patients was 13.7 days, while the stay of reactors was 20.5 days (Table V). If this long stay had an important effect, it would be expected that the mean time of occurrence of adverse reactions would be at a time beyond the average hospital stay of patients. However, the mean time in hospital for patients until first adverse reaction was 7.1 days. First reactions accounted for 65% of all reactions. The impression that prolonged hospital stay predisposes patients to adverse reactions may be due to the higher incidence of second reactions in reactors than first reactions in the total population.

Evaluation of the incidence of adverse reactions is dependent upon accurate recognition and complete reporting of these events. Most studies have relied upon the intern and resident staff as reporters of adverse reactions. Unfortunately, these physicians, already overburdened with forms to complete, are unreliable in a comprehensive reporting system. The nursing staff have been traditionally trained to recognize and report adverse events but their efforts in "nursing reports" have been largely neglected.

None of the alerting systems used in this study identified more than 60% of the total reactions recognized. Nurses reported reactions of a mild nature more often than did interns. If complete reporting of incidents of this type is desired, several alerting systems should be used.

Summary The incidence of adverse reactions to hospitalization among patients on a 35-bed ward over a 12-month period was 24%. Drugs were the main hazard and accounted for 74% of reactions. Less frequently, reactions occurred to diagnostic and therapeutic procedures, to transfusions and to miscellaneous hazards.

Patients who suffered reactions did not differ in age and sex from the average hospital patient, although patients admitted with an acute and chronic illness were more likely to suffer a reaction than those with an acute illness only. Patients with a chronic illness showed the lowest incidence. There was a higher incidence of a second reaction in reactors than a first reaction in the total population. Seventeen of 67 patients who died were believed to have suffered fatal adverse reactions during hospitalization; all were drug reactions. Most reactions were major or moderate in severity. Reactors stayed in hospital almost twice as long as non-reactors.

None of the alerting systems used in this study identified more than 60% of the total reactions recognized.

Résumé Dans une salle de 35 lits d'un hôpital général, la fréquence de réactions défavorables des malades à l'hospitalisation s'est élevée à 24%. Les médicaments ont constitué le risque principal et comptaient pour 74% des réactions. On a observé moins souvent des réactions liées au diagnostic, aux moyens thérapeutiques, aux transfusions et à divers risques.

Les malades qui ont présenté des réactions ne différaient pas sensiblement, aux points de vue âge et sexe, du malade hospitalisé moyen, mais on a noté que les malades hospitalisés pour une maladie aiguë et chronique avaient plus de chance de présenter une réaction que ceux qui avaient été admis pour une maladie aiguë uniquement. La plus faible proportion de réactions a été notée chez les chroniques. Chez les malades ayant réagi défavorablement, la fréquence d'une seconde réaction a été plus élevée qu'une première réaction dans l'ensemble de la population. Il a été estimé que 17 des 67 décès pouvaient être attribués à des réactions fatales pendant leur séjour à l'hôpital, toutes étant des réactions médicamenteuses. La majorité des réactions étaient d'une gravité élevée ou modérée. La durée de séjour des malades ayant mal réagi a été le double de celle des malades n'ayant pas présenté de réactions.

Canad. Med. Ass. J.
Dec. 9, 1967, vol. 97

Aucune des méthodes d'alarme employées durant cette étude n'a permis d'identifier plus de 60% du total des réactions diagnostiquées.

ADDENDUM

Since completion of the above report, McLamb and Huntley[9] have reported a one-month study of adverse reactions during hospitalization, with comparable results.

We wish to thank the resident and nursing staffs for their co-operation throughout this study.

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Adverse Drug Reactions During Hospitalization

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SEVERAL studies of adverse drug reactions have been reported recently,[1-4] each emphasizing the need for physician recognition of this hazard of medical care. Some of the epidemiological factors have been ascertained. The reported incidence of reactions is variable, reflecting the different methods of surveillance, populations under study, and habits of medical care. The results of our survey of all hazards of hospitalization have been reported.[5] This report details the findings of one hazard, drug therapy.

METHODS

The methods used are described elsewhere.[5] For a 12-month period from July 1965, all patients admitted to a public medical service of The Montreal General Hospital were surveyed for adverse drug reactions occurring during their hospital stay. An adverse drug reaction was defined as any undesired consequence of drug therapy. Failure to achieve an expected therapeutic result was not considered an adverse reaction. Reports of possible reactions were made in writing by the resident and nursing staffs. Each shift of nurses listed the following information on separate forms: medication alterations; diagnostic and therapeutic procedures, and adverse reactions observed. These reports were used as a daily alerting system whereby one of the authors (R.I.O.) could further investigate, evaluate and record the events. During the study period, the evaluator was resident physician on the ward.

The severity of reactions was classified using a system modified after Schimmel.[1] A minor event was one having a short course and subsiding without specific treatment; an event of moderate severity was one which required specific treatment or prolonged hospitalization; and a major event was one which had continuing effects on the host at the time of discharge, or was life-threatening or fatal.

Reactions were classified according to two types.

I. Adverse reactions due to the action of the drug.

(a) Overdosage—an exaggeration of the desired pharmacological effect of the drug.

(b) Side effect—an undesired pharmacological effect of the drug.

(c) Cytotoxic effect—an effect of the drug causing unwanted morphological changes in tissues.

All of Type I events are quantitative abnormalities in drug effects, usually dose-related and predictable. Host factors determining the concentration of drug at the site of drug action may exaggerate these adverse reactions, but special predisposing factors are not necessary for their production.

II. Adverse reactions due to a combination of the effect of the drug and special predisposing factors:

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