Original Articles

Drug-Related Cardiac Iatrogenic Illness as the Cause for Admission to the Intensive Cardiac Care Unit

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Abstract

Background: Iatrogenic illness, defined as a disease that results from a diagnostic procedure or from any form of therapy, is a well-recognized phenomenon in clinical practice.

Objectives: To study and evaluate major cardiac iatrogenic disease as the cause of admission to the intensive cardiac care unit in the modern era.

Methods: We assessed 64 critically ill patients suffering from major cardiac iatrogenic problems among a total of 2,559 patients admitted to the intensive cardiac care unit during 3 years. Iatrogenic illness was defined as any problem that resulted from therapy. Only cardiac problems were included in the study. Complications of interventional cardiovascular procedures, suicide attempts or accidental intoxications were excluded.

Results: There was evidence of a major cardiac iatrogenic problem as the cause for admission in 64 patients (2.5%): 58 (91%) suffered from arrhythmias (mainly bradyarrhythmias) secondary to beta-blockers, amiodarone, calcium antagonists, electrolyte imbalance or a combination, and 6 (9%) had non-arrhythmic events (hypotension, syncope or acute heart failure). In 41 patients (64%) the iatrogenic event was considered preventable

Conclusions: Major cardiac iatrogenic complications are an important factor among patients admitted to the intensive cardiac care unit. Most of the events are bradyarrhythmias related to anti-arrhythmic agents. Almost two-thirds of events are preventable.

IMAJ 2000;2:577–579

Iatrogenic illness is a well-recognized phenomenon in clinical practice. Defined as a disease that results from a diagnostic procedure or from any form of therapy, iatrogenicity can also be designated as diseases that would not have occurred if sound therapeutic procedures had been employed. A study published in 1981 reported that 36% of patients in a general medical service of a university hospital had an iatrogenic illness. In 2% of the patients the iatrogenic illness was believed to have contributed to the death of the patient [1]. The incidence of iatrogenicity in outpatient consultations is between 2 and 10% [2] and accounts for 3–7% of hospital admissions [3,4].

Adverse drug reactions are the most common cause of iatrogenic illness and are extremely high among hospitalized patients. Iatrogenic events may be life threatening and are associated with fatality. In a large meta-analysis the overall incidence of serious adverse drug reactions was found to be 6.7% with a fatality rate of 0.32% among hospitalized patients [5].

During the past few years diagnostic procedures and therapy have developed and changed rapidly, the population has aged, and patients are frequently exposed to a myriad of potent drugs. In view of the major advances in cardiac therapy, we chose to study and evaluate major cardiac iatrogenic problems as the cause of admission to the intensive cardiac care unit in the modern era.

Materials and Methods

Our basic approach was to assess consecutively all patients admitted to the Intensive Cardiac Care Unit between July 1994 and June 1997. The study was conducted in the ICCU, which is a 9 bed unit in a 900 bed general university hospital.

For the purpose of our study, we defined iatrogenic complication as any adverse event that resulted from therapy, modified according to the criteria of Karch and Lasagna [6]. We included only reactions that followed a reasonable temporal sequence from drug administration and with a known response pattern to the suspected therapy that could not be explained by the patient's condition. Only patients with major cardiac events were included in the study. A major iatrogenic event was defined

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ICCU = intensive cardiac care unit

as either a life-threatening problem or one serious enough to warrant specific therapy or intensive care and monitoring.

Two board-certified cardiologists performed screening, and the diagnosis of an iatrogenic problem was made by consensus. If consensus was not reached, the patient was not included in the study. If there was even the slightest reason to believe that the event reflected the natural course of a disease, it was excluded from the study. Minor iatrogenic problems that resolved without specific therapy were dismissed. Complications of interventional cardio-vascular procedures or non-cardiac complications as a result of cardiac therapy (e.g., bleeding) were not included in the study. Suicide attempts or accidental intoxications were excluded.

A preventable event was defined as an event that could have been avoided if the prescription of therapy had respected the art of medical practice. It was sometimes hard to define such an event, especially when an unexpected adverse reaction occurred. In the event of the possibility that an event was unavoidable, it was not considered preventable.

Results

Of the 2,559 admissions to the ICCU between July 1994 and June 1997, 64 were due to major cardiac iatrogenic events, accounting for 2.5% of all ICCU admissions. The age of the patients was 72 ± 8 (mean $\pm$ SEM). The male:female ratio was 0:56. Fifty-eight patients (91%) suffered mainly from arrhythmias and 6 (9%) from non-arrhythmic events, mainly hypotension, syncope or acute heart failure.

Most of the patients in the iatrogenic group (n=57, 89%) suffered from ischemic heart disease. In 7 patients (11%) there was evidence of cardiomyopathy; 42 patients (66%) suffered from heart failure (functional class 3 or 4), and 24 (38%) from hypertension. Nineteen patients (30%) had diabetes mellitus and 15 (23%) had renal failure.

Commonly used cardiovascular-related drugs among patients suffering from iatrogenicity are listed in Table 1. All patients but one (98%) were treated by some combina-tion of drugs. The most common drug combinations related to iatrogenic events were beta-blockers and calcium antagonists in 22 patients (34%), and amiodarone and beta-blockers or calcium antagonists in 14 (22%). Verapamil was the most commonly involved calcium antagonist in 19 patients and diltiazem in the remaining 9 patients. Angiotensin-converting enzyme inhibitors were responsible for iatrogenicity in 7 (11%), most of them in combination with diuretics. In another 5 cases (8%), ACE inhibitors were combined with spironolactone. All patients with ACE inhibitors, which were iatrogenically related, suffered from renal failure and exhibited serious electro-lyte imbalance.

Most of the arrhythmic events were bradyarrhythmias, namely sinus bradycardia, sino-atrial blocks, atrioventricu-lar blocks, atrioventricular rhythms and atrial fibrillation with slow ventricular rate. One patient had polymorphous ventricular tachycardia due to QT prolongation secondary to a tricyclic antidepressant agent. One patient developed ventricular fibrillation [Table 2]. Among the 56 patients with sinus bradycardia, 22 (39.3%) received a combination of a beta-blocker agent and a calcium antagonist, 12 (21.4%) received a beta-blocker and 10 (17.9%) a combi-nation of amiodarone and a beta-blocker. Six patients (10.7%) received amiodarone, 3 (5.4%) a calcium antago-nist, and 3 (5.4%) amiodarone and a calcium antagonist. A temporary pacemaker was implanted in 39 patients (61%). The iatrogenic event was considered preventable in 41 patients (64%); all were arrhythmias.

Discussion

Major cardiac iatrogenic events play an important role among patients admitted to the ICCU in a general univer-sity hospital. All of our patients, but one, were treated by a combination of drugs, most them known to have a syner-gistic or additive effect with each other (e.g., beta-blockers and calcium antagonists or amiodarone, ACE inhibitors and spironolactone). Since the combination of multiple drugs is a known risk factor for iatrogenicity, one way to reduce preventable adverse events is to reduce the

Table 1. Cardiac related drugs

Drug	Patients
Beta-blockers	44 (68.8%)
Calcium antagonists	28 (43.8%)
Amiodarone	19 (29.7%)
ACE inhibitors	29 (45.3%)
Vasodilators	11 (17.2%)
Nitrates	49 (76.6%)
Diuretics	45 (70.3%)
Spironolactone	5 (8.0%)
Digoxin*	3
Tricyclic antidepressants	1

*Laboratory evidence of digitoxicity was found in one patient

Table 2. Arrhythmias related to iatrogenicity

Arrhythmia	Patients
Sinus bradycardia	56 (87.5%)
S-A block and A-V rhythm	26 (40.6%)
Advanced A-V block	31 (48.4%)
Complete A-V block	29 (45.3%)
Slow atrial fibrillation*	11 (17.2%)
Polymorphous ventricular tachycardia	1
Ventricular fibrillation	1

*Ventricular rate <50/min.
S-A = sino-atrial, A-V = atrioventricular

ACE = angiotensin-converting enzymes

overall number of drugs used, as already demonstrated by other investigators [7].

Most of the events in 91% of the patients were bradyarrhythmias secondary to therapy with anti-arrhythmic agents of classes 2, 3 and 4 according to Williams's classification. The most commonly used drugs were beta-adrenergic blockers, calcium antagonists, amiodarone or a combination of these drugs. No patient was admitted with a serious adverse event secondary to a class 1 anti-arrhythmic agent. The main reason for this finding is the widespread use of beta-blockers and calcium antagonists among cardiac patients. However, the use of class 1 anti-arrhythmic agents has declined over the last few years due to the growing awareness of the high incidence of pro-arrhythmic events as well as the adverse outcome of patients treated by class 1 agents, as demonstrated in the Cardiac Arrhythmia Suppression Trial (CAST) [8]. Interestingly, only one patient was admitted with a proven diagnosis of digitoxicity. This may be partly explained by the decrease in the number of patients treated with digitalis, and partly by the routine periodic check of digoxin blood levels in the community. Data from the literature support our observation. Recently, Williamson et al. [9] showed a reduction in the frequency of digoxin toxicity in current clinical practice in a study performed in five general hospitals.

ACE inhibitors alone or in combination with diuretics or spironolactone were commonly used drugs among our patients. The use of this class of drugs has increased in recent years, especially in patients with advanced heart failure and hypertension, as was the case in most of the patients in our study. Most of the iatrogenic problems attributed to these agents were due to electrolyte imbalance, mainly hyperkalemia. It should be emphasized that about a quarter of the patients suffered from renal failure as well, which contributed to the development of the iatrogenic event. This finding bears an important clinical implication, since most of the adverse effects could have been prevented in patients treated with ACE inhibitors if renal function and electrolytes were checked more frequently. Darchy et al. [10] recently reported that ACE inhibitors were the leading class of cardiovascular drugs involved in iatrogenic disease among patients admitted to a medical-surgical intensive care unit. Furthermore, cardiovascular drugs accounted for 31% of drug-induced iatrogenicity in their study group.

Nitrates and diuretics were the most frequently used drugs in our patients – 77% and 70% respectively. Although these drugs were not directly responsible for the iatrogenic problem, we believe that these agents could have contributed to the event and we therefore recorded and report them in our study.

The 64% rate of preventable iatrogenic events in our study is higher than the 51% reported by Darchy's group [10]. The difference could be explained by the fact that our patients constitute a highly selective cardiac population with only drug-induced events. As already mentioned, our iatrogenicity criteria were quite strict in that we included only definite or probable adverse drug reactions. This fact also explains the relatively low rate of major cardiac iatrogenic problems – 2.5% as compared to Darchy's 11% all-cause iatrogenicity in a general and less selective group of patients [10].

In cardiac events, it is often difficult to differentiate between the natural course of the underlying disease and iatrogenicity. Therefore, we believe that for the sake of specificity, some iatrogenic events were excluded. We did not include in our study complications of interventional cardiovascular procedures since most of them were non-cardiac. A limitation of our study is that it deals with a selective small population; nonetheless, it describes the tip of the large iceberg of iatrogenic illness.

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