Avoiding drug problems

The safety of drugs for supraventricular tachycardia

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To minimize drug problems in the treatment of supraventricular tachycardias, it is important to understand the spectrum of adverse events and to identify patients at high risk for these problems. Adverse cardiac and non-cardiac effects are associated, to varying degrees, with currently available antiarrhythmics. Cardiac adverse events include the development of rhythm disturbances or exacerbation of heart failure. Serious rhythm disturbances, such as ventricular tachycardia or torsades des pointes, may result in syncope or death. In a meta-analysis of six randomized trials of quinidine vs placebo for atrial fibrillation, 1.8% of quinidine-treated patients died as opposed to 0.3% of placebo-treated patients. This increase in mortality was also noted in patients enrolled in the Stroke Prevention in Atrial Fibrillation Trial who were treated with type I antiarrhythmics. This increase in mortality was confined primarily to patients with a history of congestive heart failure. In a randomized trial of propafenone and sotalol for the treatment of atrial fibrillation, two out of 50 patients receiving sotalol died suddenly, one of whom had hypokalaemia-associated torsades des pointes. No patient receiving propafenone died during this trial. In a meta-analysis of propafenone's effect in treating supraventricular tachyarrhythmias in over 3100 adult patients, overall mortality was extremely low at 0.3%.

Structural heart disease may increase the risk of antiarrhythmic agents. During inpatient drug trials in patients treated for atrial fibrillation at Brigham and Women's Hospital, adverse cardiac events, primarily bradyarrhythmias, occurred in up to 15% of the patients. Older age and prior myocardial infarction were associated with an increased risk of adverse events.

Adverse drug problems may be minimized by careful attention to electrolytes, medications, concomitant medical illnesses, and underlying conduction disease. Careful monitoring of patients during initiation of therapy, especially those patients with ischaemic heart disease, congestive heart failure, and who are older, may minimize drug-related problems.

Key Words: Supraventricular tachycardia, adverse events, drug problem.

Introduction

Patients with supraventricular arrhythmias may experience symptoms such as dyspnoea, chest pain, palpitation, lightheadedness and even syncope. Because of these symptoms, pharmacological agents are often prescribed to suppress episodes of supraventricular arrhythmias as well as to decrease the frequency and duration of episodes. These pharmacological agents, however, are associated with side effects which may limit efficacy. Just as the appropriate treatment of patients with coronary artery disease should include risk factor modification, the pharmacological treatment of patients with supraventricular tachycardia should include an assessment of the risk of adverse cardiac and non-cardiac events as well as an assessment of potential efficacy. The goal of antiarrhythmic therapy for supraventricular arrhythmias should be to maximize drug effectiveness while minimizing risk associated with a given agent (Fig. 1). To help achieve this goal, it is important to identify the patients at risk for drug-related side effects and to modify that risk whenever possible.

Adverse drug effects may be divided into two classes, those that are non-cardiac effects and those that are cardiac effects. Non-cardiac adverse effects are generally specific to each individual agent. Non-cardiac adverse effects are important because they may lead to drug non-compliance and ultimately to inefficacy. Non-cardiac adverse effects of quinidine, a type IA agent, include a variety of gastrointestinal side effects, most notably diarrhoea and abdominal discomfort. Any patient exposed to quinidine may be at risk, and the incidence of this side effect may be on the order of 20–40%. Procainemide, another type IA antiarrhythmic
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Figure 1  Effectiveness of antiarrhythmic drug therapy in terms of efficacy and risk.

agent, may be associated with the development of drug-induced lupus erythematosus. This side effect occurs relatively frequently with an incidence of up to 12% in some series. The patients most at risk, however, are those who are slow acetylators. Prospective screening of patients for different patterns of metabolism is not usually performed. As a result, prospective identification of patients at risk is not available. The third commonly available type IA agent, disopyramide, is associated with the development of anti-cholinergic side effects. While symptoms such as dry mouth may be troublesome to all patients, urinary retention is much more problematical in elderly men. By recognizing the higher likelihood of urinary retention in elderly men and avoiding the prescription of this agent in that population, the absolute rate of this side effect should be decreased.

Propafenone, a type IC agent, is associated with gastrointestinal side effects such as constipation. The incidence of constipation is estimated at 4–10%. While all patients are at risk for the development of this non-cardiac adverse effect, addressing the need to take stool softeners or laxatives with patients prospectively may markedly improve drug compliance. If these preventative measures are taken, only a small proportion of patients who develop constipation will ultimately discontinue use of the agent for this reason. The other type IC agents, flecainide and encainide, are associated with similar adverse side effects to propafenone. Headaches and other neurological non-cardiac adverse effects associated with type IC agents may be diminished by decreasing the dose or altering the dosing frequency in patients receiving these agents.

Sotalol, a type III agent with β-adrenergic blocking capabilities, is associated with many of the same non-cardiac adverse effects as more traditional β-blockers. An example of a sotalol-related side effect is fatigue. All patients taking sotalol are at risk for this side effect and the incidence of fatigue may be in the order of 10%. Non-cardiac adverse effects may occur in many patients receiving amiodarone. As an example, nearly all patients receiving amiodarone develop corneal deposits, a side effect that is uncommonly associated with adverse long-term sequelae. Abnormal thyroid function which develops with long-term amiodarone use may be successfully monitored by thyroid tests and treated appropriately.

The non-cardiac side effects discussed above are merely examples of potential adverse effects associated with antiarrhythmic therapy for supraventricular arrhythmias. It should be stressed that in most cases it is difficult to identify prospectively the patient at risk for developing these non-cardiac side effects. Since it is difficult to identify the risk, it is difficult to modify it. These non-cardiac adverse effects should be monitored to help improve the compliance rate. The presence or absence of non-cardiac adverse effects should be assessed at each patient visit. If significant adverse effects are being experienced by the patient, a decision should be made about changing therapy or altering the current dosing regimen.

Cardiac adverse effects

Several cardiac adverse effects are associated with antiarrhythmic therapy. These cardiac adverse effects may be divided into non-fatal and fatal events (Fig. 2). Non-fatal events may be further subdivided into rhythm disturbances including bradyarrhythmias and tachyarrhythmias, the development or exacerbation of congestive heart failure, hypotension, or the development of interventricular conduction abnormalities. Identifying the patients at risk for the development of non-fatal and fatal cardiac adverse effects may ultimately lead to an improvement in drug safety. The development of drug-related arrhythmias, congestive heart failure and hypotension and/or syncope are important to recognize because they increase patient morbidity, may lead to fatal events, and potentially alter the use of medical resources.

The use of quinidine for the treatment of atrial fibrillation is well documented in the medical literature. In an analysis examining the effectiveness and safety of quinidine for the treatment of atrial fibrillation, it was found that 1·8% of quinidine-treated patients died as opposed to 0·3% of placebo-treated patients[3]. While

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some of this increased mortality may have been related to drug-related torsades des points, patients who died were also likely to have coexisting medical conditions such as cancer or end-stage liver disease that may have contributed to the higher mortality\(^1\). In addition, patients with electrolyte abnormalities are prone to the development of proarhythmic effects. Whether or not severe coexisting medical conditions increase the likelihood of fatal events in patients treated with quinidine as opposed to those treated with placebo is difficult to determine from these studies. However, this finding highlights the importance of assessing the potential benefits of antiarhythmic therapy in patients with severe chronic underlying medical conditions.

Bedell and others recently examined the characteristics of cardiac arrests in a series of hospitalized patients\(^2\). In 203 patients experiencing cardiac arrest, 14% of arrests were felt to be iatrogenic\(^2\). The mechanism of the arrest was torsade des points in six patients. Three of these patients were receiving antiarhythmic therapy for the treatment of atrial fibrillation and three patients received therapy for the treatment of post-myocardial infarction ectopy. This group included patients who were treated with procainamide or quinidine. Of note, drug levels drawn prior to the event were elevated in some situations but not in all cases. In addition, the QT interval corrected for the RR interval obtained prior to cardiac arrest was generally prolonged\(^2\). It is clearly important to monitor the QT interval in patients who are being initiated on and chronically treated with suppressive pharmacological antiarhythmic therapy. In patients with underlying conduction system disease, repolarization abnormalities may only be apparent at slow heart rates or after offset pauses.

Bedell also examined the clinical characteristics of patients suffering cardiac arrest due to digoxin toxicity\(^2\). Digoxin levels drawn prior to the arrest were frequently elevated and several patients had experienced symptoms of digoxin toxicity. The most common associated abnormality in these patients was a recent decline in renal function\(^2\). Since digoxin is excreted renally, those patients with failing renal function may develop digoxin toxicity even while on a stable dose of digoxin. The potential benefits and risks of digoxin were also studied in the recent Digoxin Investigators Group (DIG) Trial orally presented at the 1996 American College of Cardiology meeting. In this multicentre trial, over 7000 patients with congestive heart failure were randomized to digoxin versus placebo for the treatment of heart failure. These patients were also treated with other pharmacological agents including diuretics and angiotensin-converting enzyme inhibitors. At the conclusion of the trial, overall survival was similar in patients receiving digoxin and placebo, suggesting no clear survival benefit or detrimental overall effect. While there was a decrease in hospitalizations for congestive heart failure in the patients treated with digoxin, there was a suggestion of increased arrhythmias, including supraventricular arrhythmias, in those patients exposed to this agent. Final published results of this study are forthcoming.

More recent trials of the contemporary antiarrhythmics propafenone and sotalol in the treatment of supraventricular tachycardias such as atrial fibrillation and flutter have also noted cardiac risks. In a study of 100 patients (50 randomized to sotalol and 50 to propafenone) two patients receiving sotalol died during the follow-up as opposed to no patient receiving propafenone\(^3\). Of the two deaths in patients receiving sotalol, one of them was related to torsades des points in a patient who was hypokalaemic in the setting of diarrhoea. The second patient developed dyspnoea, but the exact aetiology of her death is unclear. Other studies investigating the role of sotalol in the treatment of supraventricular arrhythmias have suggested that a mortality rate in the order of 1–2% may be seen in patients receiving this agent\(^4\). The incidence of torsades des points increases with increasing dosage of sotalol. The development of monomorphic as well as polymorphic ventricular tachycardia may be seen in patients receiving sotalol. Recently, it has been suggested that female gender is a risk factor for the development of torsades des points\(^3\). In a review of the English language literature, 70% (95% confidence interval 64% to 75%) of the 322 cases of torsade occurred in women. This increased incidence in women was still present after examining potential confounders such as coronary artery disease, rheumatic disease, electrolyte disorders, level of QTC at baseline, digoxin usage, bradyarrhythmia, and type of underlying arrhythmia\(^3\). For quinidine, disopyramide, amiodarone, sotalol, and bepridil, female predominance of torsade was noted but this gender difference was not seen with procainamide. The mechanism for this gender difference is incompletely understood.

Propafenone has been used in thousands of patients with a variety of supraventricular arrhythmias including atrioventricular nodal re-entrant tachycardia, atrial flutter and atrial fibrillation, and Wolff–Parkinson–White associated arrhythmias. Propafenone may be administered via either intravenous or oral routes. The most frequent cardiac side effects include bradyarhythmia (approximate incidence 0.8%), ventricular tachycardia (1%), and the development of congestive heart failure (0.1%). The development of congestive heart failure may be more likely in those individuals with a history of cardiac decompensation. Out of over 3000 patients receiving propafenone for the treatment of supraventricular tachycardias and whose outcome has been published in clinical trials, there was an overall mortality of approximately 0.3%. While this incidence is extremely low, it remains greater than no risk at all. In examining the risk factors of the patients who died after receiving propafenone, those patients who had congenital heart disease, cardiomyopathies or coronary artery disease appeared to be at risk as well as those patients with Wolff–Parkinson–White syndrome.

The Stroke Prevention in Atrial Fibrillation study (SPAF) also found increased mortality in patients
who received antiarrhythmic agents for the treatment of atrial fibrillation. This increase in mortality was almost entirely confined to those patients with a history of congestive heart failure. While the overall risk of death in patients receiving antiarrhythmics was 1.8 times greater than in patients not receiving antiarrhythmic agents, this hazard ratio rose to 3.3 in patients with congestive heart failure and dropped to 0.77 in patients without a history of congestive heart failure. In addition to the increased risk of cardiac death there was also an increased risk of arrhythmic death in this population with a hazard ratio of 5.8 in patients with definite congestive heart failure, as opposed to a hazard of 0.83 in patients without a history of congestive heart failure. These results certainly suggest that not only active congestive heart failure but a history of congestive heart failure provides the substrate for the development of adverse outcomes upon receiving antiarrhythmic therapy. Unfortunately, patients with a history of heart failure may be those who are most symptomatic upon developing a supraventricular arrhythmia, thus creating a paradox: those who may benefit greatest from an agent may be most at risk for the development of adverse cardiac effects. When the risk exceeds the benefit in a given patient, the drug should not be administered.

More recently, Maisel and colleagues examined the incidence and time course of adverse effects associated with the use of antiarrhythmic agents for atrial fibrillation. Maisel retrospectively analyzed the hospital course of 169 patients undergoing 253 trials of class I and III agents for the treatment of atrial fibrillation. Over half of the population was male (60%) with an average age of 64 years. The choice of antiarrhythmic agent was at the discretion of the primary cardiologist. The distribution of antiarrhythmic agent use was: 65% type IA agents, 19% type IC agents, and 16% representing type III agents. Adverse events occurred in 15% of patients, prospectively defined as bradycardyarrhythmias, QT prolongation, ventricular arrhythmias, conduction abnormalities, development of rapid ventricular response to atrial fibrillation, embolic stroke, exacerbation of heart failure or hypotension. The most common adverse events were bradycardyarrhythmias which were noted with each of the drug groups. The development of bradycardyarrhythmias was associated not only with the need to discontinue atrial ventricular nodal blocking therapy but also the necessity to place a pacemaker in some patients.

Predictors of adverse events in this patient population were analyzed using a multivariate model. The risk of developing adverse events after being treated with antiarrhythmic therapy for supraventricular tachycardia increased with age (odds ratio of 1.03, confidence interval 1 to 1.06) and in those patients with a history of previous myocardial infarction (odds ratio of 1.79, confidence interval of 0.99 to 3.24). There was a non-significant trend for patients with previous heart failure to be at increased risk for side effects or adverse events. Of note, very few patients in this study had a history of prior heart failure. Male gender, coronary artery disease and structural heart disease were not predictors of adverse events. When instituting antiarrhythmic therapy for the treatment of supraventricular tachycardia, one must be concerned about the potential for developing adverse events in those patients who are elderly, those who have had a prior myocardial infarction and those with previous heart failure.

The time distribution of the development of these side effects was examined; it decreased in incidence after the establishment of sinus rhythm. In patients undergoing cardioversion, side effects were common within 8 h of the procedure (26 out of 221 patients). These adverse events consisted of bradyarrhythmias (71%), conduction defects (14%), QT prolongation (11%), and torsade de pointes (4%). This observation emphasizes the importance of monitoring patients carefully in the early post-cardioversion period.

**Summary**

The decision to institute antiarrhythmic therapy in patients with supraventricular tachycardias depends on the frequency, duration, and the extent of symptoms. Often those patients who are most symptomatic are at greatest risk from antiarrhythmic agents. By examining prior trials, it is possible to identify profiles of the patient at risk, including those patients who are older, those with a history of prior myocardial infarction, those with a history of congestive heart failure, those with a history of electrolyte abnormalities or on cardiac medications, those with coexisting medical illnesses and those with underlying conduction diseases.

Risk modification (given below) in patients with supraventricular tachycardia should occur prior to institution of antiarrhythmic therapy.

(1) Electrolyte balance should be restored as well as metabolic orders assessed. Maintaining normal potassium and magnesium levels, assessing for the presence of thyroid disorders and drug interactions form part of the initial evaluation. Occasional problems develop with the concomitant administration of atrioventricular nodal blocking agents and a type I or III antiarrhythmic agent.

(2) Underlying heart disease and heart failure should be identified and treated with attention to the issue of benefits and risks of antiarrhythmic agents. Echocardiography and exercise testing may be helpful in identifying ischaemic substrate, significant valvular pathology and myocardial dysfunction. It is unknown how other pharmacological therapies for heart failure or ischaemic disease influences the risk from these antiarrhythmic agents.

(3) Physicians should consider withdrawal or modification of antiarrhythmic therapy in times of metabolic stress. Patients hospitalized with a variety of medical and surgical disorders may develop supraventricular arrhythmias. Pharmacological therapy should be used carefully in this population, especially in those with renal dysfunction, electrolyte disorders, or hypoxaemia.

(4) Drug therapy should be initiated in hospital in those...
patients at greatest risk for adverse effects. These patients should be carefully monitored during the first 8–24 h following electrocardioversion, a time of greatest risk for the development of adverse events. The optimal duration of time over which patients should be monitored after therapy is unknown, and is likely to vary from patient to patient.

The risk of antiarrhythmic therapy should be less than the risk of the supraventricular arrhythmia to the patient. By examining patient profiles, the clinician has the opportunity to modify the risk for patients needing antiarrhythmic therapy and to select the most appropriate therapy based on both the pharmacological and patient profiles.

References


