Drug-Induced Cardiac Arrhythmias
Incidence, Prevention and Management

J. Colin Doig
Cardiology Department, North Tyneside General Hospital, Rake Lane, North Shields, England

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Summary

Drugs can cause cardiac arrhythmias in a number of clinical situations, and many of the implicated agents are used to treat non-cardiac conditions. These adverse effects are frequently idiosyncratic, but are often mediated via triggered activity causing torsade de pointes. Drugs being used for treatment of cardiac conditions may promote arrhythmias by re-entrant mechanisms or via triggered activity. Many drugs may cause cardiac arrhythmic complications when taken in excessive amounts.

Keys to reducing the incidence of drug-induced cardiac arrhythmias include increased awareness among the medical, pharmaceutical and nursing professions of the potential problems in using certain agents, especially in specific situations. Appropriate monitoring when such treatment is essential and, after diagnosis, prompt withdrawal of the offending agent and treatment for the arrhythmia should be initiated.

The term drug-induced arrhythmogenesis refers to a disorder of cardiac rhythm (tachycardia or bradycardia) induced by a pharmacological agent. This may occur in several ways.

1. As an adverse effect of non-cardiac treatment, either as a dose-dependent cardiac complication or as a result of a mechanistic distortion of normal electrical activity.

2. As a proarrhythmic complication of antiarrhythmic therapy. This includes provocation of a new
cardiac arrhythmia (e.g. ventricular tachycardia in a patient being treated for atrial fibrillation), aggrava­tion of a pre-existing arrhythmia (increased frequency, altered morphology, development of incess­ant arrhythmia), or the occurrence of bradycardia due to an antiarrhythmic drug effect on the sinus node, atrioventricular node, or ventricular conduct­ing tissue.

3. As an effect of deliberate ingestion of excessive amounts of pharmaceutical agents, with resultant dysrhythmic consequences.

This review will not deal with arrhythmias which might result from metabolic consequences of drug treatment, e.g. hypokalaemia from diuretic therapy. Instead, it will concentrate on direct cardiac-mediated complications of therapy. Although semantics dictate that the term ‘arrhythmia’ strictly means an absence of rhythm, while ‘dysrhythmia’ refers to a distortion of cardiac rhythm, in this paper the 2 terms are used interchangeably, with arrhythmia being used in its colloquial and popular sense.

1. Incidence of Drug-Induced Cardiac Arrhythmias

The incidence of sudden cardiac death from all causes in the general population is 0.25% per year. In 30 to 40% of cases, an outcome of sudden death can be predicted because there is pre-existing cardiac disease.[1] Most of these cases occur in patients with ischaemic heart disease.

The incidence of drug-induced death due to arrhythmias is unknown. Furthermore, the incidence of drug-induced arrhythmias is even harder to quantify. One estimate suggests that for a wide variety of agents, an incidence of 3 to 15% may be seen.[2]

1.1 Non-Antiarrhythmic Agents

For the incidence or prevalence of arrhythmias caused by non-antiarrhythmic drugs to be estimated, there must be accurate reporting of cases of unexpected cardiac deaths in patients taking drugs for non-cardiac conditions. However, it is impossible to determine the extent of the problem. In addition, the increasing frequency of drugs available as ‘over-the-counter’ medications without need for a medical prescription exacerbates this difficulty.[3]

1.2 Antiarrhythmic Agents

Proarrhythmic events with antiarrhythmic drugs have been estimated to occur with a frequency of 3 to 15%.[4,5] The proarrhythmic potential of class I antiarrhythmic agents is exacerbated in the presence of significant left ventricular dysfunction.[6] Major studies[7,8] have highlighted the problems of proarrhythmia when ventricular arrhythmias are being treated. However, the true incidence of drug-induced arrhythmogenesis is very difficult to determine, particularly in the antiarrhythmic management of life-threatening ventricular arrhythmias. In such circumstances, is a sudden cardiac death due to the treatment, or the dysrhythmia being treated?

However, proarrhythmias have also occurred during the treatment of atrial fibrillation with quinidine. Here, good clinical effect by the drug on the primary arrhythmia has been observed, but at the cost of a significant increase in total mortality,[9] due to the effect of the drug on the QT interval. Although meta-analyses of the antidysrhythmic effects of drug therapy in atrial fibrillation are controversial[10] there is growing concern about the safety of quinidine.[11]

Not all antidysrhythmic agents are associated with proarrhythmic tendencies. The incidence with amiodarone has been reported at 3% with a less than 1% occurrence of torsade de pointes.[12,13] In most studies investigating amiodarone, there has been a survival benefit in the amiodarone-treated groups.

2. Mechanisms of Arrhythmogenesis

2.1 Re-Entry

Drug-induced ventricular tachycardia related to re-entry primarily involves class I antiarrhythmic drugs. They act as membrane-stabilising agents by blocking sodium channels, resulting in reduced conduction velocity and prolongation of refractory periods. Proarrhythmic effects are due to the relative