Therapeutic Drug Monitoring of Antiarrhythmic Agents

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Summary

Therapeutic drug monitoring has come of age in clinical medicine and, in particular, its use with antiarrhythmic agents has flourished. The classic indications for the use of therapeutic drug monitoring are commonly encountered with antiarrhythmic drug use. Most of the currently available antiarrhythmics have a narrow therapeutic index, necessitating careful dose titration. The effectiveness of these agents in clinical use is frequently difficult to determine as a result of marked variability in arrhythmia frequency or infrequent events. Thus, therapeutic drug monitoring seems appropriate for adjusting therapy in arrhythmia prophylaxis or in the prevention of sudden death. Most antiarrhythmic agents appear to have generally accepted therapeutic ranges, a prerequisite for therapeutic drug monitoring. The historical determination of the therapeutic range for each of the antiarrhythmics will be discussed in addition to the numerous factors affecting the definition of this range for any drug, including type of arrhythmia, aetiology of underlying cardiac disease, the concept of true individual dose ranging, adequate control periods, the definition of true drug efficacy and the quantitation of arrhythmia frequency (including 24-hour ECG recording with computer-assisted analysis and the invasive technology of programmable ventricular stimulation), and the roles of protein binding, drug interactions and active metabolites.

In addition to these considerations, therapeutic drug monitoring is particularly useful in this drug class because of marked interindividual variability in pharmacokinetic parameters including absorption, clearance and volume of distribution, resulting in variable dose-concentration relationships. This information can be useful in distinguishing between true therapeutic failures and inadequate plasma concentrations.

The therapeutic concentration range of quinidine appears to be 1 to 5μg/ml utilising newer, more specific assay techniques, but the accepted range is very dependent on the type of assay. There is wide interindividual variability in the optimal drug concentration with toxicity occurring from 3μg/ml.

The effective concentration range for procainamide is 4 to 10μg/ml, with early toxicity commencing at 8 to 10μg/ml and progressively increasing with further increments in plasma concentration. However, some patients may respond to higher concentrations without experiencing toxicity. The therapeutic concentration range for N-acetylprocainamide is not clearly defined, but appears to be greater than 10μg/ml with toxicity occurring over a wide range of concentrations (10 to 40μg/ml). As yet, there is no satisfactory method to deal with combined procainamide and N-acetylprocainamide concentrations.
Clinical studies have not carefully defined the effective concentration range of disopyramide, but it appears to be 2.5 to 6.0μg/ml with toxicity occurring throughout the therapeutic range. Interpretation of therapeutic drug monitoring on disopyramide is made difficult by the presence of concentration-dependent protein binding.

Lignocaine is effective in the concentration range from 1.5 to 5.5μg/ml with toxicity common at concentrations higher than 5.0μg/ml. Protein binding is probably of greater importance than initially presumed, particularly in patients with acute myocardial infarction who develop enhanced protein binding of this drug. Some patients whose arrhythmia appears refractory at usual concentrations, may respond if the therapeutic range is exceeded.

Mexiletine has a very low therapeutic index. Although its therapeutic range has not been carefully defined, effective concentrations appear to vary from 0.5 to 2.0μg/ml. Toxicity can span this entire range, with marked interindividual variability.

There are few studies that have carefully studied the therapeutic concentration range of phenytoin as an antiarrhythmic agent. Within this context, the therapeutic concentration range appears to be from 10 to 20μg/ml; from the neurology literature toxicity occurs when concentrations exceed 20μg/ml.

Few studies have defined the effective antiarrhythmic concentration range of propranolol. Its efficacy appears to be related to its β-blocking properties and accordingly the effective concentration should exceed 20ng/ml. There is evidence that some patients may respond to higher doses and concentrations than are usually necessary to achieve adequate β-blockade. Toxicity does not appear to be related to excessive plasma concentrations, but rather tends to occur early in therapy at low concentrations.

In conclusion, therapeutic drug monitoring appears to be of benefit in antiarrhythmic therapy. However, its proper use depends on an intimate understanding of the concepts of effective and toxic ranges, as well as the pharmacokinetic parameters of each agent.

Our ability to both measure drug concentrations and interpret their meaning is now very sophisticated, and over the past decade has been increasingly applied to the therapeutic monitoring of circulating drug concentrations. The rationale for therapeutic drug monitoring rests firmly on the principle that the effects of a drug (both good and bad) are a predictable function of its concentration at the site of action, which in turn is reflected by drug concentration in the circulation. The appropriateness of therapeutic drug monitoring depends on the drug or drug group in question. It is always best to measure a drug’s effect directly, and whenever this is possible the role of therapeutic drug monitoring is relegated to one of assessing compliance. In some cases, however, therapeutic drug monitoring can be of great value as an aid to individualising drug therapy. This review discusses the major requirements that make therapeutic drug monitoring appropriate (table I). These general principles and potential problems are illustrated with reference to the antiarrhythmic drugs, before reviewing therapeutic drug monitoring of individual antiarrhythmic agents, which have been selected on the basis of their widespread use and/or general availability.

1. General Requirements for Rational Therapeutic Drug Monitoring

1.1 Narrow Therapeutic Index

Therapeutic drug monitoring becomes an extremely useful tool when a drug has a narrow therapeutic index in relation to its pharmacokinetic variability. It is not at all uncommon with anti-