Changes in pharmacokinetics in the elderly and therapeutic drug monitoring of antiarrhythmic drugs

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Abstract

Advanced-age is associated with significant changes in physiological functions, absorption, distribution, metabolism and elimination of drugs. Antiarrhythmic drugs are traditionally classified into four groups, according to Vaughan Williams's classification. The renal and hepatic elimination of many antiarrhythmic drug classes are reduced in the elderly, predisposing this population to serious adverse drug effects. Therapeutic drug monitoring has been a useful clinical tool in the safe use of class I drugs and amiodarone, in the younger population. Given the changes in pharmacokinetics of antiarrhythmic drugs and increased risk of adverse effects in older patients, therapeutic drug monitoring may be of particular importance for dosage adjustment and optimization of individual antiarrhythmic therapy in the elderly. [Life Science Journal. 2007; 4(2): 1 – 7] (ISSN: 1097 – 8135).

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1 Introduction

Care for older patients has become a worldwide issue of all healthcare sectors because the population is rapidly aging. By 2020 the people aged 65 years and older will constitute nearly 17% of the US population and 26% of the population in Japan[1]. Around the world, the proportion of the population aged 80 years and above will range between 3.7% – 7.5%[1] . Physiological changes in the elderly often alter the pharmacokinetics and pharmacodynamics, and cardiovascular function[2]. These changes can have significant impact on the medications that we use to treat cardiovascular disorders in the elderly.

Antiarrhythmic drugs are a large group of chemically disparate compounds; most of these compounds have been at times used to treat cardiac arrhythmias. They are traditionally divided, according to Vaughan William's classification, into Class I to Class IV. The clinical use of some antiarrhythmic drugs, such as the Class I antiarrhythmic agents, has declined in the last decade, whereas others, such as Class II and III agents, have become the mainstay of treatment or prevention of tachycardias.

Therapeutic drug monitoring (TDM) refers to the individualization of drug dosage by maintaining plasma or serum drug concentrations within a target range (therapeutic range). This involves the measurement and interpretation of plasma or serum concentrations of drugs in patients. One of the prime reasons for TDM services is that individual patients may respond differently to the same therapeutic dose regimen, because of the interpatient variability in drug absorption, distribution, elimination or changing pathophysiological conditions. By adjusting doses to maintain plasma drug concentrations within a target range, variability in the pharmacokinetic phase of drug action is greatly reduced. Today, TDM services have been established in the department of clinical pharmacology in many hospitals to assess the patient's responses to the recommended dose regimen, with a view to maximizing the therapeutic effects and minimizing the adverse effects.

Most antiarrhythmic drugs are associated with highly variable plasma concentrations at a given dose. They also show a direct concentration-effect relationship, which fulfils the formal requirements for rational use of TDM.

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Therapeutic ranges for antiarrhythmic drugs are, in general, not very well defined, since the reported effective drug concentrations are often based on small studies or studies not designed to establish a therapeutic range, with varying dosage regimens and unstandardized sampling procedures. Class I agents have well-defined therapeutic range and dose-dependent toxicity. However, the value of TDM for other drug classes remains uncertain.

In this article, the changes in drug pharmacokinetics in the elderly, and the basic principles and clinical applications of TDM in each of the major antiarrhythmic drug classes were discussed.

2 Pharmacokinetic Characteristics in the Elderly

There is a sevenfold increase in drug toxicities as one ages from 20 to 79 years (from 3% at 20 – 29 years to 21% at 70 – 79 years). Part of this increase may well be due to multiple medication-drug interactions. However, a significant part of this increase in drug toxicities is due to incomplete understanding of changes in the absorption, distribution, metabolism and elimination processes of drug disposition with aging.

2.1 Absorption

There is a reduced gastrointestinal blood flow and motility[2], and a reduced gastric pH[3]. Although these physiological changes can alter drug absorption, there has been little evidence to suggest that this is of major consequence. Reduced absorption in the elderly has been observed for some compounds which are actively absorbed (e.g. galactose, calcium, thiamine, and iron)[4]. The absorption of most oral antiarrhythmic drugs, which is mainly by passive processes, is not affected to a significant extent.

2.2 Distribution

Drug distribution in the elderly differs from that of young adults or pediatric population. Great changes in body composition occur as people age. Body fat increases from 15% to 30% and lean body weight decreases in proportion to total body weight[5]. This gives lower volume of distribution values for drugs which stay in the central compartment, while lipid soluble drugs would have somewhat larger apparent volume of distribution. The apparent volume of distribution for lipid soluble drugs, such as diazepam and chlordiazepoxide, is larger in the elderly.

Although total plasma protein concentrations remain relatively constant, albumin concentrations are lower in the aged[6]. Levels of plasma protein determine the volume of distribution and extent of distribution into tissues of highly protein-bound drugs. The reduction of plasma protein leads to a higher free fraction of highly protein-bound drugs and therefore, a greater proportion of pharmacologically active drug. For example, the fraction of unbound phenytoin increases 25% to 40% in the aged, however, this would also lead to increased clearance. Drug interactions based on protein binding can be more pronounced in the elderly because they tend to be taking multiple drugs.

Cardiac output in the elderly is reduced, thus distribution to the kidneys and liver are expected to be reduced. For high extraction drugs this could alter the overall elimination of the drug.

2.3 Metabolism

Physiological changes in drug metabolism have also been observed in the elderly. The liver is the major organ involved in drug metabolism; liver blood flow and liver mass tend to decrease with age. It appears that for drugs which undergo Phase I metabolism (oxidations or reductions), metabolism reduces with increasing age. Examples of this reduced liver metabolism are quinidine, lignocaine, phenytoin and propranolol[2]. For other drugs which undergo Phase II metabolism (conjugations), the metabolism does not appear to change greatly with age.

2.4 Renal excretion

Renal excretion of medications is generally reduced in the elderly. With increasing age the glomerular filtration process is reduced by a reduction in kidney size (20%), reduction in the number of nephrons (35%), reduction in the number of functioning glomeruli (30%), and a decrease in renal blood flow (40% – 50%)[7,8]. Serum creatinine is also decreased with age because of the reduced muscle mass. Antiarrhythmic drugs which are mainly renally excreted and for which dosage adjustments should be made in elderly patients include digoxin and quinidine[9,10].

The changes in pharmacokinetics in the elderly have significant implications to drug dose recommendations. However, the effects of age on drug disposition depend on the particular drug in question and the characteristics of the population being studied. When evaluating elderly patients to make dosage recommendations, it is important to distinguish between long-term-care patients who are not considered to be active, and the older patients living independently in the community. Some of the changes ascribed to the elderly may be due to immobility of the patient or an underlying disease or diseases. Also because of

changing body composition between males and females, it is often important to distinguish between these gender groups as well.

3 Therapeutic Range of Antiarrhythmic Drugs

Not all therapeutic agents require TDM when it comes to adjustment of therapeutic regimens. The characteristics of drugs which TDM provides additional value in dosage optimization are summarized in Table 1.

Table 1. Characteristics of drugs that require therapeutic monitoring

Drugs with a good relationship between plasma concentration and clinical effects.
Drugs with a narrow therapeutic-toxic range, such as digoxin.
Drugs for which there is no easily measured clinical response and/or failure of response is "all or nothing" (e.g. antiarrhythmic drugs or anticonvulsants).
Drugs for which the pharmacological response is difficult to quantify.
Drugs for which plasma concentration has prognostic significance in over dosage.
Drugs for which the expected or desired therapeutic effect is not observed (may be absorption or compliance problem).
A patient has altered and/or variable renal state and the drug is eliminated mostly as unchanged drug in urine.

If the clinical effects of drugs can be readily measured (e.g. antihypertensive drugs-blood pressure, warfarin-INR), it is obviously better to adjust the dose on the basis of patient's response. When this cannot be done, TDM should be performed. Majority of antiarrhythmic drugs fulfil the formal requirements of rational use of TDM, which offers additional values to the clinical efficacy of some of the drugs (e.g. digoxin or lignocaine).

The therapeutic ranges of some antiarrhythmic drugs are shown in Table 2. The therapeutic ranges in Table 2 are in most cases derived from observation of therapeutic and adverse effects in small groups of patients. Therefore, when applied to a wider population of patients, there will be individuals who achieve adequate effects at lower concentrations or experience adverse events within the therapeutic range. For example, the accepted therapeutic range of lignocaine is 2.0 – 6.0 mg/L. Some patients may experience signs of lignocaine intoxication at serum drug concentration below 6.0 mg/L, where some patients may show therapeutic efficacy at drug concentration below 2.0 mg/L. Therefore, one must remember that therapeutic range is more a probability concept and should never be considered as an absolute value.

Table 2. Therapeutic range of antiarrhythmic drugs

Drug	Therapeutic range
Amiodarone (mg/L)	1.0 – 2.5
Digoxin (μg/L)	0.8 – 2.0
Disopyramide (mg/L)	2.0 – 6.0
Lignocaine (mg/L)	2.0 – 6.0
Quinidine (mg/L)	2.0 – 5.0
Flecainide (mg/L)	0.2 – 0.9
Mexilitine (mg/L)	0.8 – 2.0
Propafenone (mg/L)	0.2 – 1.0
Procainamide (mg/L)	6.0 – 14.0
Sotalol (mg/L)	1.0 – 3.2

Note: Modified from references 11 – 14.

4 Technical Considerations of TDM

4.1 Blood sample collection

Usually plasma or serum is used for drug assays. Plasma is obtained from the supernatant of centrifuged whole blood to which heparin has been added. Plasma perfuses all the tissues of the body including the cellular elements in the blood. Changes in the drug concentration in the plasma are considered to reflect changes in tissue drug concentrations.

The correct time of sampling is important for TDM. Drug concentrations vary over the dosing interval, and with the duration of dosing in relation to achieving a steady state. The least variable point in the dosing interval is the pre-dose or trough concentration. In almost all cases, quoted therapeutic ranges of anti-arrhythmic drugs have been established on trough sample measurements[11,12]. For this reason, trough concentration is the recommended sampling time for the majority of drugs. Patient should therefore be asked to omit their morning dose of drug until the blood sample has been taken.

For most antiarrhythmic drugs with short half-lives, samples should be collected pre-dose. However, for drug with long half-lives, such as amiodarone, samples collected at any point in the dose interval can be satisfactory[12].

Taking peak samples for orally administered anti-arrhythmic drugs is not recommended since there is wide interpatient variability in concentrations achieved, and it is impossible to know when the peak occurs. The only indica-

tion for trying to take a peak sample is if the patient experiences toxicities some hours after taking the medication.

With digoxin, an antiarrhythmic drug outside of the Vaughan William's classification, the maximum serum level is reached 1 – 2 hours after an oral dose. The level then falls rapidly for 3 – 5 hours as it is distributed. The serum level then falls with a half-life of 1.5 – 2 days. Due to this delayed distribution, blood sample for digoxin analysis must be taken at least 6 hours after the last oral dose.

Above all, it is important to wait until a drug has been fully distributed in the body (i.e. has reached steady state) before taking samples for concentration measurement. The time for a drug to reach steady state can be calculated by multiplying the elimination half-life by 5. Thus a drug with a half-life of 8 hours should not normally be monitored until at least 2 days after the first dose is taken. However, an earlier sample may be taken if toxicity is suspected.

4.2 Frequency of sampling

A blood sample is often taken after the initial dose was given. If the result is within the therapeutic range, and the patient's symptoms are well controlled, then a further measurement should be made 6 – 8 weeks later[11–14].

If the initial sample is above or below the therapeutic range, or the patient still has symptoms, then dose adjustment is necessary and samples should be taken every 5 to 10 half-lives until such times as adequate control is achieved[11–14]. If the second monitoring is still in the therapeutic range and there are no clinical problems, monitoring may be performed at 6 – 12 monthly intervals. More frequent monitoring would only become necessary if a change in hepatic or renal function occurs, or a potential interacting drug is added to the regimen.

4.3 Assay methods

Drug assay methods should have adequate sensitivity, be specific for the drug to be measured and have appropriate accuracy and precision.

Assays are usually under the direction of pathology or clinical chemistry laboratories. A variety of methods are available for measuring drugs but the most widely used assay for commonly monitored drugs is the Abbott TDX system that uses fluorescence polarization immunoassay[15]. Less commonly used are HPLC, or gas chromatography (GC) and these are only performed in specialised laboratories.

Amiodarone and quinidine, if collected in the testing tubes in gel, require immediate centrifugation and separation within 2 hours of collection, and supernatant should be separated immediately on removal from centrifuge, because the rate of drug absorption by gel increases once red blood cells are precipitated from the serum.

5 Interpretation of Drug Concentration

It is critical to know that drug concentrations need to be interpreted in the context of the individual patients without rigid adherence to therapeutic range. To interpret the drug concentration, some basic patient information is required (Table 3).

Table 3. Basic information required for interpretation of drug concentration

Patient: age, weight, sex, height, smoking.
Time of sample in relation to last dose.
Duration of treatment with the current dose.
Other drug therapy.
Clinical: drug requirements, clinical status (renal: serum creatinine; cardiac: cardiac output; liver, etc.).
Reason for request: for example, lack of effect, routine monitoring, suspected toxicity.

There are two important factors that can make interpretation of a result difficult in some cases. First, assays are done using plasma or blood and thus measured total (bound and unbound) drug, whereas it is the unbound drug that interacts with the receptor to produce a therapeutic response. If binding is changed by disease states, such as acute myocardial infarction[16] or atrial fibrillation[17], the interpretation of total plasma or blood drug concentrations must be modified.

Second, active metabolites, which may not be measured, can contribute to the therapeutic response. Examples include procainamide in which N-acetylprocainamide is the active metabolite[18]. For amiodarone, the active metabolite is desethyl-amiodarone, which is responsible for at least half of its effect[19].

The possible considerations for a lower, higher or normal drug concentration are summarized in Table 4.

6 Individual Antiarrhythmic Drugs in the Elderly

6.1 Class I antiarrhythmic drugs

Class I antiarrhythmic drugs are the largest and oldest group, including three subgroups (Table 5). The mechanism of action of these compounds is blockade of the fast

inward sodium current responsible for the upstroke and rapid conduction of the cardiac action potential. Many of these drugs are found to be proarrhythmic[20–22], and as a result, their clinical use, except for lignocaine and flecainide, has declined dramatically in recent years.

Table 4. Interpretation of drug concentration

Concentration lower than anticipated
Poor patient compliance
Error in dosage regimen
Wrong drug product (controlled-release instead of immediate-release)
Poor bioavailability
Rapid elimination
Reduced plasma protein binding
Enlarged volume of distribution
Steady state not reached
Timing of blood sample
Improved renal/hepatic function
Drug interaction due to stimulation of elimination enzyme autoinduction
Changing hepatic blood flow
Concentration higher than anticipated
Poor patient compliance
Error in dosage regimen
Wrong drug product (immediate-release instead of controlled-release)
Rapid bioavailability
Smaller than anticipated volume of distribution
Slow elimination
Increased plasma protein binding
Poor renal/hepatic function
Drug interaction due to inhibition of elimination
Concentration correct but patient does not respond to therapy
Altered receptor sensitivity (e.g. tolerance)
Drug interaction at receptor site

6.2 Beta-blockers

Beta-blockers have been mainly used to control ventricular rate in patients with atrial fibrillation/flutter, and to prevent ventricular arrhythmias. They have been shown to reduce mortality and hospitalizations in both older and younger patients with systolic heart failure[23,24]. Beta-blockers such as atenolol, nadolol and sotalol, which are cleared primarily by renal elimination, are affected by the age-associated changes in renal function[25]. Atenolol and nadolol, which undergo complete renal elimination, may have a prolonged half-life in the elderly whose glomerular filtration and tubular secretion may decline with age[26,27]. Dose adjustment of both agents may be needed in older patients.

Propranolol and metoprolol are metabolised in the liver. The age-associated decrease in hepatic blood flow is expected to alter clearance of these drugs and as a result, plasma concentrations of propranolol are found to be 3 to 4 times higher in elderly patients compared with younger patients[28].

Table 5. Vaughan William's classification of antiarrhythmic drugs

Class	Actions	Drugs
I	Sodium channel blockade	
IA	prolong repolarization	quinidine, procainamide, disopyramide
IB	shorten repolarization	lidocaine, mexiletine, tocainide, phenytoin
IC	little effect on repolarization	flecainide, encainide, propafenone
II	Beta-adrenergic blockade	propanolol, esmolol
III	Prolong repolarization potassium channel blockade	sotalol, amiodarone
IV	Calcium channel blockade	verapamil, diltiazem

6.3 Amiodarone

Amiodarone is a highly effective antiarrhythmic drug and has been widely used in the management of supraventricular and ventricular arrhythmia. Many previous studies did not specifically assess the effect of amiodarone on elderly patients but current evidence suggests that this antiarrhythmic agent is equally effective in the older patients.

Amiodarone is a lipophilic drug with a long elimination half-life ranging between 35 – 110 days. Therefore, measurement of blood levels should be done until 3 months

after a change in the dosage regime.

Amiodarone is expected to display a larger volume distribution in the elderly due to age-associated increase in body fat. In the elderly, amiodarone has a reduced clearance and prolonged elimination half-life, although this agent is not mainly renally excreted[29].

Older patients appear to be more prone to suffer adverse effects from amiodarone. Advanced age has been demonstrated as a risk factor for amiodarone-induced thyroid disease[30].

6.4 Verapamil, diltiazem

Verapamil and diltiazem are effective in controlling heart rate in patients with atrial fibrillation/flutter. Verapamil is also effective in terminating atrioventricular nodal re-entrant tachycardia. With both agents, there is a reduced total body clearance and increased elimination half-life in older patients[31]. The elderly also show an increased therapeutic response to verapamil and diltiazem[31]. Verapamil appears to lower heart rate and blood pressure to a greater extent in the elderly compared with younger patients[32].

6.5 Digoxin

Digoxin falls out of the traditional Vaughn William's classification but it remains an important drug for ventricular rate control in patients with atrial fibrillation. In the elderly, the decreased total body water, increased total body fat and reduced muscle mass lead to a reduced volume of distribution of digoxin, a water-soluble compound. This leads to an increased risk of toxicity in the older patients.

Digoxin is excreted unchanged through glomerular filtration and tubular secretion in patients with normal renal function[33]. General decline in renal function in the elderly results in accumulation of digoxin and prolongation in elimination half-life[34]. Polypharmacy in older patients increases the risk of drug interaction with digoxin. Quinidine, verapamil, flecainide and amiodarone may interact with digoxin and reduce its renal elimination[35]. This will result in higher plasma concentrations of digoxin for the same dose and assays are required to determine if dose reduction is necessary.

7 Conclusions

Advanced age is associated with significant changes in physiological functions which affect pharmacokinetics of many drugs used to treat or prevent arrhythmia. Renal and hepatic elimination of many antiarrhythmic drug groups are reduced in the elderly, leading to a prolonged elimination half-life and increased risk of adverse effects. Therapeutic drug monitoring may increase the safe use of antiarrhythmic drugs in general, Class I agents, amiodarone and digoxin in particular.

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