Guidelines for Therapeutic Drug Monitoring of Cardiovascular Drugs Clinical Use of Blood Drug Concentration Monitoring (JCS 2015) —Digest Version—

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I. Outline of the Guidelines

1. Scope of the Guidelines

The principle of pharmacotherapy is maximizing the therapeutic effect while minimizing adverse reactions. Therapeutic drug monitoring (TDM) is a strategy to individualize drug treatment through monitoring various factors that affect the efficacy and adverse effects of drugs. Antiarrhythmic drugs have long been investigated for their pharmacokinetic behaviors in the body and efficacy, and are used in the clinical setting on the basis of TDM findings. However, blood concentrations of antiarrhythmic drugs should be interpreted according to not only expertise in pharmacokinetics, pharmacodynamics, and drug interactions, but also patient adherence to medication. The National Health Insurance in Japan covers the clinical use of blood drug concentration monitoring for many antiarrhythmic drugs and digoxin, but many practitioners do not use it well because the role and definition of TDM have not been established fully. Accordingly, the Japanese Circulation Society (JCS) and the Japanese Society of Therapeutic Drug Monitoring (JSTDM) decided to jointly create the Guidelines for Therapeutic Drug Monitoring of Cardiovascular Drugs in order to ensure safe and effective pharmacotherapy for the treatment of cardiovascular diseases using appropriate TDM of blood drug concentrations.

Recently, TDM is increasingly being expected to play a role as a safety index especially in the pharmacotherapy of cardiovascular diseases. The present guidelines are prepared for physicians who prescribe drugs for the treatment of cardiovascular diseases, and pharmacists, nurses, and clinical laboratory technologists who work with them.

The present guidelines describe how to conduct TDM appropriately (e.g., appropriate timing of blood sampling as the elapsed time from the last dose and that from the initiation of treatment) in the clinical setting and interpret blood drug concentrations, as well as limitations of TDM. Cardiovascular drugs described in the present guidelines are those of which TDM is commercially available and covered by the National Health Insurance in Japan.

2. Remarks for the Use of the Guidelines

The present guidelines reflect the National Health Insurance in Japan at the time of writing. Reactions to a drug are not defined only by pharmacokinetics of the drug. Pharmacotherapy should be assessed comprehensively based on the patient’s clinical characteristics, pathological conditions, and underlying diseases, among other factors. If a physician uses TDM or interprets its findings in a way inconsistent with the present guidelines considering the circumstances unique to the patient, the physician’s discretion should be prioritized over the guidelines. The present guidelines do not provide any basis for any legal action.

3. Selection of Clinical Questions and Grades of Recommendations

The practice guidelines were prepared according to the procedures proposed by the Medical Information Network Distribution Service (MINDS). Guideline Writing Groups of the JCS and the JSTDM specified Clinical Questions (CQs) on cardiovascular drugs. For each CQ, relevant literature published from 1960 to 2013 were searched and identified via queries of the MEDLINE, EMBASE, and JAMAS, and were used as evidence. The JCS Guideline Writing Group specified questions on the use of TDM where evidence is limited to list them as How To Use (HTU) questions, and the JSTDM Guideline Writing Group prepared answers to HTU questions with a certain level of consensus.

Answers to CQs are indicated with their respective levels of evidence and grades of recommendations.

- Levels of Evidence

Level I: Systematic review or meta-analysis of randomized controlled trials
Level II: One or more randomized controlled trials
Level III: Non-randomized controlled trials
Level IVa: Cohort study
Level IVb: Case-control study or cross-sectional study
Level V: Case reports or case series
Level VI: Expert committee’s or expert’s opinions not based on patient data

- Grades of Recommendations

Grade A: Strongly recommended and supported by strong evidence
Grade B: Recommended with moderately strong supporting evidence
Grade C1: Recommended despite no strong supporting evidence
Grade C2: Not recommended because of the absence of strong supporting evidence.
Grade D: Not recommended as evidence indicates that the treatment is ineffective or even harmful.

4. External Review

Four members each of the JCS and the JSTDM joined as external reviewers to review draft guidelines.
5. Future Plans

The Japanese version of the present guidelines will be published by the JCS as a printed material, and will also become available on the websites of the JCS and the JSTDM. A digest of the guidelines will be prepared in Japanese and in English, and the English version will be published in an English journal of the JCS. The guidelines will also become available on the MINDS website.

6. Conflict of Interest

During the preparation of the present guidelines, guideline

II. Therapeutic Drug Monitoring (TDM)

1. History of TDM

Drugs that show substantial inter-individual variability in response, and those with a narrow therapeutic range, i.e., a small difference between toxic and therapeutic doses, cannot be used at a fixed dose. In order to ensure safer and more effective treatment with these drugs, healthcare professionals needed quantitative methods to quantitatively assess the pharmacokinetics of such drugs and predict drug response in individual patients. As this approach was expected to help physicians create optimal drug treatment strategies for individual patients, researchers started to promote a concept of clinical therapeutic drug monitoring (TDM) in the 1970s. The original meaning of therapeutic drug monitoring (TDM) is to administer drugs in an optimal way for each patient through monitoring various factors that affect drug efficacy and adverse drug reactions (ADRs). As physicians have used blood drug concentrations to ensure optimal drug therapy, TDM is often considered an approach to optimize pharmacotherapy by monitoring drug concentrations in blood.

In Japan, TDM based on drug concentrations in blood was introduced in the early 1970s, and TDM has been widely used in the clinical setting since the 1970s and 1980s. As the importance of TDM in medical treatment is fully accepted, TDM for various types of drugs is now covered by the National Health Insurance under a category of “specific therapeutic drug monitoring fees.” With the advancement in molecular biology, the roles of various proteins and genes have been clarified, which has enabled detailed analysis of the pharmacokinetics of drugs. Nowadays physicians are able to design an optimal treatment strategy for each patient with TDM considering detailed information of these proteins and genes. The era of tailor-made drug therapies has come.

2. Pharmacokinetics Knowledge Essential to TDM

TDM and basic principles of pharmacokinetics (PK) can be used to evaluate or predict the effect of a drug in reference to concentration (C) of the drug in the vicinity of target molecules located in the target organ or tissues. This method is particularly useful for patients whose pathological condition affects PK of a drug of interest. When a drug is given, the drug concentration (C) in the blood reaches its peak level, and then decreases as a function of time and systemic clearance (CL; expressed with a unit of L/hr or other units) of the drug. When the drug is given as a single intravenous injection, it reaches its peak concentration in the blood \( (C_{\text{max}}) \) almost immediately. When the drug is given as a single intravenous dose to achieve the target drug concentration as the Cmax, the required dose may be calculated as the product of the volume of distribution \( (V_d) \) of the drug and the target concentration \( (C) \) (i.e., \( DL=C\times V_d \)). This dose may be used as the first dose (i.e., loading dose, \( D_l \)) for continuous infusion or repeated intravenous injections. When the drug is infused continuously to maintain a stable therapeutic plasma drug concentration, the required dose, i.e., the maintenance dose \( (D_m) \), is calculated as the product of the C and CL \( (D_m=C\times CL) \).

When the drug is administered with repeated intravenous injections at \( D_m \) with an interval \( \tau \) (tau), \( D_m \) is calculated as the product of average plasma drug concentration during the dosing interval \( (C_{av}) \) and CL \( (D_m= \tau C_{av}\times CL) \) (Figure 1).

The time required for a drug to reach drug concentration that is half of any original concentrations is defined as half-life \( (t_1/2) \). A drug having a short \( t_1/2 \) needs to be administered with a shorter dosing interval than that having a longer \( t_1/2 \) in order to maintain therapeutic drug concentrations throughout the dosing interval, because plasma drug concentrations decline rapidly and reach those that no longer elicit clinically appreciable drug effects.

When a drug is administered orally, the fraction of the dose absorbed from the gastrointestinal tract and the first-pass metabolism in the liver (i.e., first-pass effect) should be considered. The proportion of the administered dose
that reaches the systemic circulation following oral administration is defined as the oral bioavailability (F) of the drug. The loading dose for the initiation of oral therapy is calculated with a formula of $C \times V_d/F$. Similarly, the maintenance dose ($D_m$ for a given $\tau$, $D_m/\tau$) is calculated with a formula of $C_{av} \times CL/F$ (Figure 1). Only free, unbound drug molecules in the blood stream can reach the site of action and exert their effects. As plasma or blood drug concentration data for TDM are available, in most cases, as total concentrations of the drug, prescribers should be careful in interpreting plasma drug concentration data reported for TDM particularly when the data are obtained from patients with hypoproteinemia or those who are given drugs that may compete at the plasma protein binding sites of the drug of concern. Because the unbound fraction (fu) of a drug subject to TDM may be increased by drug interactions at the binding sites in those patients, unbound drug concentrations associated with total drug concentrations may be higher than those in patients with normal plasma drug protein binding.

When a patient with renal dysfunction receives a drug that is excreted mainly by the kidneys (i.e., a drug with a percentage of drug recovered unchanged in the urine [$Ae\%$] >70%), the dose of the drug should be reduced according to the patient’s glomerular filtration rate (GFR).

In patients with fulminant acute hepatitis or decompensated liver cirrhosis (Class C in the Child-Pugh classification of liver function), the maintenance dose of a drug that is eliminated by the liver (i.e., $Ae\% < 10\%$) should be reduced. In cirrhotic patients with significant portosystemic shunting, the area under the concentration-time curve (AUC) after an oral administration of a drug that undergoes a substantial first-pass effect may increase substantially as compared those with normal liver function.

When the maintenance dose for a pediatric patient is extrapolated from that for adults, body surface area (BSA) rather than body weight would be a better reference index. As drug-metabolizing enzymes and renal function are not fully developed in neonates and infants under 2 years of age, TDM is useful to individualize their pharmacotherapy.

Pregnant women may undergo pharmacotherapy only when the expected benefit outweighs the potential risk to the fetus. Pregnant women at weeks 3 to 9 of gestation are absolutely susceptible to the teratogenic effects of any chemical agents. Pregnant women have a 1.5-fold increase in GFR as well as an about 1.5-fold increase in the activity of drug-metabolizing enzymes, including cytochrome P450(CYP)3A, as compared with those of non-pregnant counterparts.

In elderly patients, the age-related decrease in drug clearance and change in pharmacodynamics (susceptibility to drug effects) should be considered to ensure appropriate pharmacotherapy.

A standard textbook should be referred to for detailed descriptions of clinical pharmacokinetics.
3. Assays to Determine Drug Concentrations in Blood

Table 1 summarizes commonly used assays to determine drug concentrations in blood. Assays to determine drug concentrations in blood are classified largely into immunoassays, separation analyses, and other methods. Immunoassays use antibodies to detect the presence of the target molecule. Immunoassays are widely used as simple and rapid analytical methods, and many immunoassay kits are commercially available. Recently, general-purpose automated clinical analyzers are often used to determine drug concentrations in blood. Blood concentrations of cardiovascular drugs are typically determined with enzyme multiplied immunoassay techniques (EMIT) and affinity column mediated immunoassays (ACMIA). However, physicians should be aware that substances in the body, metabolites of the target drug, and other drugs used concomitantly with the target drug may affect the results of these assays or interact with detection antibodies. As assays for antiarrhythmic drugs are often commercially unavailable even for drugs of which TDM is covered by the NHI, separation analyses should be used for these drugs. High performance liquid chromatography (HPLC), a separation analysis, is highly specific and is used to determine blood concentrations of many drugs, but it needs complex procedures including pretreatment. Liquid chromatography-mass analysis (LC/MS/MS) is a technique combining HPLC and mass spectrometry (MS) to ensure a high degree of analytical accuracy. Many commercial laboratories use HPLC and LC/MS/MS.

4. Methods of Pharmacokinetic Analysis

In order to simulate changes over time in blood concentrations of a drug in a patient, pharmacokinetic parameters, such as the clearance, volume of distribution, and absorption rate constant of the drug, of the patient are required. It should be known that pharmacokinetic parameters described in package inserts for ethical drugs and published literature are average values obtained from study subjects. For example, clearance differs substantially by age, body size, or renal/hepatic function, which leads to individual differences in drug concentrations in blood (Figure 2). Accordingly, in order to predict drug concentrations in blood in a patient, pharmacokinetic parameters of the patient have to be calculated. When the results of a population pharmacokinetics (PPK) analysis are available for the target drug, pharmacokinetic parameters for the patient may be calculated using PPK parameters and the blood concentration of the drug in the patient at one or more time points. Pharmacokinetic parameters in the patient may be calculated using the Bayes analysis, and may be used to simulate the pharmacokinetics of the drug in the patient. However, the Bayes analysis cannot always calculate the patient’s individual pharmacokinetic parameters accurately. The accuracy in estimating the patient’s pharmacokinetic parameters depends on when blood samples are obtained. A blood sample obtained at the time of the trough concentration of the drug can accurately estimate the clearance value in the patient. However, a blood sample obtained when the drug concentration is reaching its peak may not lead to accurate estimation of the clearance because the drug concentration at such time point is influenced by the volume of distribution. The Bayes analysis can be used to estimate pharmacokinetic parameters that can explain the drug concentrations in the patient, but the estimated parameters should be used only to predict drug concentrations in the patient and design the patient’s dosage regimen.

5. Coverage With the National Health Insurance in Japan

For almost all drugs described in the present guidelines, analysis of blood concentrations is covered by the National Health Insurance (NHI) in Japan under a category of “specific therapeutic drug monitoring fees”. The criteria
for the coverage are as follows: (MHLW Ordinance No. 76 issued in 2012, and Notification No. 0305-1 of the Medical Economics Division, the Health Insurance Bureau, MHLW dated March 5, 2012).

- When a drug concentration measurement is conducted one or more times a month to ensure accurate management of the treatment with the drug, the physician may claim reimbursement for the fee for only one measurement per month. The NHI price for specific therapeutic drug monitoring is 470 points. (In the first month of the claim for specific therapeutic drug monitoring, an additional NHI price of 280 points will be added.)
- The specific therapeutic drug monitoring fees include fees for the determination of blood concentration of the relevant drug, those for sampling blood for the determination, and management of the dosage regimen according to the analytical results.
- When determinations and scheduled treatment management that are covered under the “specific therapeutic drug monitoring fees” are conducted for a patient more than once in a month, the fees for only one session are covered by the NHI. The claim for the fee should be made when the first session is conducted.
- Drug concentrations in blood and outline of treatment strategies should be described in the medical record.
- The specific therapeutic drug monitoring fees may be applied for patients who use antiarrhythmic drugs regularly, and inpatients who use aminoglycoside antibiotics for at least a few days.
- Patients with heart disease who are receiving digitalis preparations
- Patients with arrhythmia who are receiving antiarrhythmic drugs regularly.
- Antiarrhythmic drugs that may be claimed under a category of specific therapeutic drug monitoring fees are procainamide, N-acetylprocainamide, disopyramide, quinidine, aprindine, lidocaine, pilscainide hydrochloride, propafenone, mexiletine, flecainide, cibenzoline succinate, pirmenol, amiodarone, sotalol hydrochloride, and bepridil hydrochloride.
- For inpatients who receive antimicrobial agents such as aminoglycosides and glycopeptides for at least a few days, the fees for one session per month of determination of blood concentrations and dose adjustment based on the results are covered by the NHI.
- Glycopeptides to be covered under the specific therapeutic drug monitoring fees are vancomycin and teicoplanin.

1. Antiarrhythmic Drugs

**CQ1** Is blood drug concentration monitoring effective for patients with arrhythmia receiving antiarrhythmic drugs?

**Answer:** Confirming the range of blood drug concentrations appropriate for each patient helps physicians prescribe the drug at an optimal dose and thereby avoid adverse drug reactions (ADRs). Blood drug concentration monitoring is especially beneficial in confirming the patient’s adherence to medication, reconsidering the dose when the current treatment is ineffective (diagnosing undertreatment), avoiding the occurrence of drug concentration-dependent ADRs, confirming and managing pharmacokinetic drug interactions, and assessing treatment efficacy when the patient’s condition changes or when a new pharmaceutical form of a regularly used drug is used.

Level of evidence: V
Grade of recommendation: C1

**Commentary:**
Blood drug concentration monitoring of antiarrhythmic drugs is beneficial in ensuring the safety of antiarrhythmic therapy. However, it is unclear whether blood drug concentration monitoring of antiarrhythmic drugs may improve the clinical outcome of patients with arrhythmia.

Drug effects are affected by a variety of factors such as age, gender, genetic differences, environmental factors, meals, life styles, underlying diseases, and drug interactions (Figure 3). Blood concentrations of renally excreted drugs, i.e., drugs extensively excreted unchanged in the urine, are prone to be affected easily by changes in renal function. Drugs excreted by the kidneys include pilscainide, sotalol, digoxin, and cibenzoline. On the other hand, blood concentrations of drugs eliminated by hepatic metabolism are affected by individual differences in the activity of drug-metabolizing enzymes. All drugs are metabolized in different ways. When different drugs are used concomitantly, a drug may reduce or enhance the activity of a particular drug-metabolizing enzyme, which are correspondingly referred to enzyme inhibition or induction, resulting in drug interactions (Table 2).
CQ2 Does blood drug concentration monitoring of antiarrhythmic drugs help reduce ADRs in patients with arrhythmia who are receiving antiarrhythmic drugs?

Answer:
It is unclear whether the occurrence of ADRs, including those by proarrhythmic effects of antiarrhythmic drugs, may be reduced by blood drug concentration monitoring of antiarrhythmic drugs. However, it is useful in terms of safety as ADRs occur more commonly when blood concentrations of antiarrhythmic drugs exceed their therapeutic ranges.

Level of evidence: IVb
Grade of recommendation: C1

Commentary:
Drug concentration-dependent ADRs may be prevented by blood drug concentration monitoring. It has been reported that the incidence of digitalis intoxication decreases by selecting the dose of digoxin based on blood digoxin concentrations. As class I antiarrhythmic drugs and amiodarone cause ADRs more commonly at higher concentrations in blood, monitoring drug concentrations helps prevent ADRs.

CQ3 Can we shorten the time to achieve an optimal dosage regimen by blood drug concentration monitoring of antiarrhythmic drugs in patients with arrhythmia?

Answer:
Adjusting the dose of an antiarrhythmic drug based on blood concentrations of the drug may help maintain the drug concentrations within the therapeutic range, but the effects of antiarrhythmic drugs cannot be evaluated based only on their blood concentrations. It is thus unclear whether blood drug concentration monitoring can shorten the time to achieve an optimal dosage regimen.

Level of evidence: VI
Grade of recommendation: C2

Commentary:
The effects of antiarrhythmic drugs cannot be predicted based only on their blood concentrations. The dosage regimen of antiarrhythmic drugs should be determined comprehensively according to the patient’s signs and symptoms, Electrocardiogram (ECG) findings, and results of exercise testing, among other findings indicating the response of the drugs. The dose should not be set only to achieve the therapeutic range.

HTU1 When should blood samples be taken to monitor blood concentrations of antiarrhythmic drugs?

HTU2 Is it possible to predict the peak and trough concentrations of a drug on the basis of the timing of blood sampling and the blood drug concentration?

Answer:
In general, blood samples should be obtained after the drug concentration reached a steady state. For the purpose of confirming the efficacy and ADRs of a drug, a blood sample should be obtained at trough (just before the next administration). For drugs that cause ADRs when the drug concentration reaches a peak, a blood sample may also be obtained around the time of peak concentration.

When the population pharmacokinetic (PPK) analysis can be used to simulate the pharmacokinetic profile of a drug in a patient, the concentration-time curve in the patient may be estimated using blood concentration data at a single time point, but its accuracy is limited.

Commentary:
A steady state is defined as an equilibrium between the amount of drug administered and the amount of drug eliminated per day, which results in stable drug concentrations. The time to reach a steady state depends on the length of half-life.

As described in the section “II.4. Methods of Pharmacokinetic Analysis” (Page 586), the trough drug concentration is prone to be affected by the clearance of the drug. As clearance is an important pharmacokinetic parameter used to determine a dosage regimen to achieve an optimal steady-state drug concentration, trough blood samples should be obtained to ensure more accurate estimation.

The section “II.4. Methods of Pharmacokinetic Analysis” also describes that the data from a trough blood sample can be used to estimate the peak drug concentration or vice versa when PPK parameters and concentration data at a single time point are available. However, it should be known that the accuracy of estimating the drug concentration at a time point different from the sampling time point (e.g., estimating peak drug concentration using data obtained from a trough sample) is not high.

HTU3 When should drug concentrations be monitored?
Answer:
The purpose of determining drug concentrations in blood is to determine the optimal dose, dosing interval, and method of administration to maximize the efficacy and prevent ADRs in individual patients. Determination of drug concentrations in blood is considered effective and meaningful in the following cases:

1) Situations where the selected dose should be determined as appropriate or not:
   a. when treatment at an apparently adequate dose is not effective (diagnosing undertreatment)
   b. when it is difficult to specify the cause of symptoms to be drug intoxication, ADRs, or disease condition

2) Situations where poor adherence to treatment is suspected

3) Situations where drug poisoning and/or ADRs are suspected:
   a. when the cause of drug poisoning symptoms due to overdosing must be specified in a patient receiving multiple drugs
   b. when it is difficult to specify the cause of symptoms to be drug intoxication, ADRs, or disease condition

4) Situations where blood drug concentrations fluctuate substantially despite no changes in dosage regimen:
   a. when biological or disease-related changes in pharmacokinetics are suspected
   b. when drug interactions are suspected

5) When the pharmaceutical form or dosage regimen of a drug is changed

1.1 Class I Antiarrhythmic Drugs

HTU4 Please summarize the toxic (ADRs) concentration range of each class I antiarrhythmic drug.

Answer:
As the blood concentration range that causes drug-related toxicity (ADRs) differs substantially by the type of ADR of concern, it is difficult to summarize it.

Commentary:
Several clinical reports have described the blood concentration range at which class I antiarrhythmic drugs caused toxicity or ADRs, but the blood concentration range differs by type of toxicity signs/symptoms or ADRs. The level of evidence is not high in some of these reports. As electrolyte levels and genetic factors may affect the occurrence of abnormal ECG findings and/or proarrhythmic effects of these drugs, the blood drug concentration is not a single factor that determines the occurrence of these effects. However, the occurrence of extracardiac ADRs to antiarrhythmic drugs is considered to be related to drug concentrations in tissues, and some studies have investigated the relationship between the occurrence of extracardiac ADRs and blood drug concentrations. For example, the incidence of hypoglycemia (fasting blood glucose level of <70 mg/mL) due to cibenzoline is low when its trough serum concentration is ≤400 ng/mL.

HTU5 What are typical drug concentration-dependent ADRs to antiarrhythmic drugs?

Answer:
As ADRs develop more commonly at higher blood drug concentrations, but the occurrence of abnormal ECG findings as well as a proarrhythmic effect and negative inotropic effect of antiarrhythmic drugs cannot be predicted only with blood drug concentrations. Extracardiac ADRs are relatively related to blood drug concentrations.

Commentary:
ADRs to antiarrhythmic drugs are classified roughly into cardiac effects and extracardiac effects. Cardiac ADRs include abnormal ECG findings, proarrhythmic effects, and negative inotropic effects, and are not necessarily related to drug concentrations in blood. As electrolyte levels and genetic mutations also affect the occurrence of cardiac ADRs, the risk of cardiac ADRs cannot be predicted only with blood concentrations of antiarrhythmic drugs. On the other hand, the occurrence of extracardiac ADRs is relatively more related to blood drug concentrations. Studies have investigated the relationship between the occurrence of extracardiac ADRs to antiarrhythmic drugs such as aprindine, cibenzoline, and disopyramide and blood drug concentration. For example, the incidence of central nervous ADRs to aprindine increased in relation to serum aprindine concentration: The incidence was very low at 0.75–1 μg/mL, and few ADRs developed at <0.75 μg/mL.

HTU6 What are the clinical implications of the active metabolites of drugs subject to TDM?

Answer:
Drugs mainly eliminated via metabolism may produce pharmacologically active metabolites. In these drugs, the parent drug and its active metabolites contribute to their therapeutic and adverse effects. Cautions should be exercised for drugs of which active metabolites are eliminated mainly via the kidneys (e.g., NAPA for procainamide), because blood concentrations of their active metabolites may be elevated to an extent that drug efficacy and ADRs are largely attributable to the active metabolite, rather than the parent drug.

Commentary:
Procainamide is a classic antiarrhythmic drug. Approximately 20% of procainamide administered to humans is metabolized into N-acetylprocainamide (NAPA) by N-acetyltransferase (NAT). NAPA has antiarrhythmic effects. As NAT has genetic polymorphisms, the activity of NAT differs between individuals. As NAPA is eliminated mainly via the kidneys, NAPA concentrations may increase to a level higher than procainamide concentrations in plasma in patients with high NAT activity and renal dysfunction. Determination of NAPA concentrations in plasma would benefit patients who have ADRs despite low plasma procainamide concentrations. The therapeutic range of procainamide is considered 4 to 10 μg/mL, and that of NAPA, 7 to 15 μg/mL. There was an opinion that the therapeutic range should be considered to be 5 to 30 μg/mL as the sum of procainamide and NAPA concentrations. In addition, an active metabolite of propafenone, 5-OH-propafenone, exerts an antiarrhythmic effect that is almost identical to that of the parent drug, but its beta-blocking effect is weaker than that of propafenone. It remains unclear whether plasma 5-OH-propafenone concentrations are to be monitored with propafenone in the routine TDM.
1.2 Class II Antiarrhythmic Drugs

CQ4 Is blood drug concentration monitoring beneficial for patients receiving beta-blockers for the treatment of arrhythmia?

Answer: It is difficult to predict the antiarrhythmic effect of beta-blockers based on blood drug concentrations. ECG monitoring is useful in the evaluation of the antiarrhythmic effect of beta-blockers. There is no evidence indicating that blood drug concentration monitoring is superior to ECG monitoring.

Level of evidence: VI
Grade of recommendation: C2

Commentary:
Sympathetic stimulation of cardiac conduction system cells and cardiac myocytes is mediated mainly through beta-1 receptors, and appears most clearly as an increase in heart rate. In patients with sinus node dysfunction (excluding those complicated with conduction disturbance), the presence or absence of increased automaticity of the lower conduction system or ordinary cardiac muscle such as increased frequency of junctional or ventricular rhythms is a useful indicator.

The antiarrhythmic effect of beta-blockers is dose-dependent. However, some patients may respond well to low doses of beta-blockers, while others may experience ADRs without any beneficial effects. There is no accumulated evidence to indicate the clinical benefits of blood drug monitoring as a predictor of efficacy of beta-blockers in the treatment of arrhythmia.

Drug monitoring assays are commercially available only for propranolol. Propranolol is lipid-soluble, has a high protein binding rate, and is eliminated rapidly through hepatic metabolism by CYP1A2 and CYP2D6. Its bioavailability is as low as about 30%.12,13 Propranolol is comprised of two enantiomers that have a complex metabolism and differ substantially in pharmacokinetic profiles.14,15 As propranolol is a non-selective beta-blocker that inhibits not only beta-1 receptors on cardiac myocytes but also beta-2 receptors on vascular and bronchial smooth muscle cells, it may cause ADRs related to peripheral vasoconstriction (e.g., blood flow disorder in patients with arteriosclerosis obliterans) or exacerbation of bronchial asthma (e.g., bronchospasm). Bisoprolol, one of the most widely used beta 1-selective blockers, has a bioavailability of about 80%. As blood bisoprolol concentration is dose-related, it is not meaningful to determine blood bisoprolol concentrations as an index of efficacy.

No convincing evidence has been obtained for the significance of blood drug concentration monitoring as a measure to prevent ADRs to bisoprolol. Bradycardia may be detected by ECG or pulse monitoring, and cardiac inhibition may be detected by the appearance of symptoms of heart failure, chest X-ray, plasma brain natriuretic peptide (BNP) levels, or echocardiography. The dose of landiolol, a beta-blocker with a short half-life, may be appropriately adjusted according to clinical variables such as heart rate and blood pressure.

1.3 Class III Antiarrhythmic Drugs

CQ5 Is blood drug concentration monitoring beneficial for patients receiving amiodarone for the treatment of arrhythmia?

Answer: Blood amiodarone concentrations is not useful in predicting its antiarrhythmic effect, but is helpful in assessing the efficacy and safety of treatment when the pharmaceutical form or dosage of a drug is changed, and adherence to medication. Within the same patient, there may be a correlation between the antiarrhythmic effect and blood concentration of amiodarone.

Level of evidence: V
Grade of recommendation: C1

Commentary:
There are no data indicating a correlation between the antiarrhythmic effect and blood concentration of amiodarone. According to a report from the United States in the 1980s, amiodarone should be present at a concentration of at least 1 to 2 μg/mL in blood to exert its pharmacological action.16 However, the use of low-dose oral preparations of amiodarone has increased over time in Europe and the United States, and physicians are targeting lower concentrations to treat patients. When new signs, symptoms, or abnormal laboratory findings develop at the occurrence or recurrence of arrhythmia, when a dosage regimen or pharmaceutical form is changed (e.g., from intravenous drug to oral drug or vice versa, or from a brand-name drug to its generic version or vice versa), or when the patient’s adherence to treatment is needed to be confirmed, data on blood drug concentrations will help design an optimal treatment plan.

CQ6 Does blood drug concentration monitoring help decrease the incidence of extracardiac ADRs in patients receiving amiodarone for the treatment of arrhythmia?

Answer: It is unclear whether blood drug concentration monitoring can help decrease the incidence of extracardiac ADRs to amiodarone. However, TDM may be useful in predicting the risk of drug concentration-dependent ADRs (those in the nervous system, gastrointestinal system, or lungs) or prevent the occurrence of them.

Level of evidence: V
Grade of recommendation: C1

Commentary:
It has been reported that neurological or gastrointestinal ADRs to amiodarone often develop at blood drug concentrations of ≥2.5 to 4 μg/mL.17–19 Pulmonary toxicity of amiodarone has been suggested to be associated with long-term treatment at high doses or high blood amiodarone concentrations.18 A study in Japanese patients has reported that the risk of pulmonary toxicity is high in patients with a plasma desethylamiodarone concentration of ≥0.6 μg/mL.19

HTU7 When should blood samples for blood drug concentration monitoring of amiodarone be obtained?
Answer:
In the early phase of oral amiodarone therapy, it is desirable to obtain a trough sample for blood drug concentration monitoring. However, for outpatients who receive the drug for a long period of time, blood samples may be obtained at any time points.

Commentary:
In the early phase of oral amiodarone therapy, blood amiodarone concentration changes over time after administration. A trough blood sample should be obtained. In patients receiving amiodarone for a long period of time, blood amiodarone concentration does not vary substantially after administration. Blood samples from such patients may be obtained at any time in relation to administration.

HTU8 Is blood drug concentration monitoring necessary for patients who receive amiodarone by continuous intravenous infusion?

Answer:
Blood drug concentration monitoring is not necessarily required for patients who receive amiodarone by continuous intravenous infusion. However, when intravenous amiodarone is replaced by oral amiodarone, blood amiodarone concentrations may be monitored for some patients.

Commentary:
When a drug is administered intravenously, the drug is directly distributed into the systemic circulation, and the blood drug concentration is related to the dose administered. Immediately after the initiation of continuous intravenous infusion, amiodarone in the circulating blood is distributed into extravascular tissues especially fat tissues. It takes about 12 hours to stabilize blood amiodarone concentrations. Intravenous amiodarone therapy is used in acute-phase treatment, and the dose should be adjusted according to the effects observed. When the intravenous amiodarone therapy is switched to an oral amiodarone therapy, blood amiodarone concentrations may be changed due to the decrease in bioavailability or changes in dose. In order maintain the antiarrhythmic effect of amiodarone, blood concentration monitoring may help adjust the oral dose to maintain the drug concentration within the therapeutic range for the patient.

HTU9 Is the measurement of blood desethylamiodarone concentration useful as an index of efficacy and safety of amiodarone?

Answer:
As desethylamiodarone is an active metabolite of amiodarone, the measurement of blood desethylamiodarone concentration may be useful as an index of efficacy and safety of amiodarone therapy as in the case of that of amiodarone.

Commentary:
Desethylamiodarone, an active metabolite of amiodarone, has a pharmacological action similar to that of amiodarone and a half-life slightly longer than that of amiodarone. As desethylamiodarone may affect the clinical efficacy of amiodarone therapy, pharmacokinetic analysis of desethylamiodarone may help assess the efficacy of amiodarone therapy. Experimental findings have indicated that desethylamiodarone is more pulmonary toxic than amiodarone. A study has also reported a relationship between the occurrence of pulmonary toxicity and blood desethylamiodarone concentration.

CQ7 Is TDM effective in ensuring optimal antiarrhythmic treatment with sotalol?

Answer:
It is considered difficult to estimate the antiarrhythmic effect of sotalol based on blood drug concentrations. As sotalol has beta-blocking action and potassium channel-blocking action, ECG-based heart rate can be used as an indicator of efficacy, and QT interval as an indicator of the risk of ADRs. No evidence has indicated that TDM is more useful than these indicators.

Level of evidence: VI
Grade of recommendation: C2

Commentary:
Sotalol acts as a beta-blocker and a class III antiarrhythmic drug (potassium channel blocker). Sotalol exerts its potassium channel-blocking effect in relation to dose and blood drug concentration, while it exerts its beta-blocking effect even at low doses or low drug concentrations in blood. There is little evidence indicating that the efficacy of sotalol can be expected with blood sotalol concentrations. Many clinicians think that the effective dose differs substantially among patients in the clinical setting (see “III.1.2 Class II Antiarrhythmic Drugs”, page 590).

ECG monitoring is useful because the efficacy of sotalol as a beta-blocking drug can be assessed based on heart rate (see “III.1.2 Class II Antiarrhythmic Drugs”), and the efficacy as a class III antiarrhythmic drug based on QT interval. Only a small number of reports have described the relationship between blood sotalol concentration and its antiarrhythmic effect. In a study of 17 patients with chronic stable ventricular premature complexes, an antiarrhythmic response to sotalol (70 to 100% reduction in VPCs) was observed at a wide range of plasma concentrations (0.34 to 3.44 μg/mL), and significant QTc prolongation was observed at ≥2.55 μg/mL. However, the therapeutic dose range for the treatment of ventricular tachycardia or fibrillation, or atrial fibrillation (not covered by NHI in Japan) has not been established.

No superiority of TDM over ECG monitoring has been demonstrated in terms of clinical assessment of patients receiving sotalol for the treatment of arrhythmia. Sotalol is a racemic mixture of d- and l-sotalol, and these isomers differ in their pharmacological effects and pharmacokinetic profiles. The benefit of TDM of d-sotalol, a pure potassium channel-blocking agent, should be assessed in the future.
of sotalol, but blood samples obtained in the elimination phase may provide useful data when the interval between dosing and sampling is considered.

### 1.4 Class IV Antiarrhythmic Drugs (Bepridil)

**CQ8** Is blood drug concentration monitoring effective for patients with arrhythmia receiving bepridil?

**Answer:**
Increased blood bepridil concentrations are associated with increased risk of polymorphic ventricular tachycardia (torsades de pointes) with QT prolongation. Blood bepridil concentration is not useful in predicting its antiarrhythmic effect, but is useful in assessing whether the changed dose is effective or not and whether the patient takes the drug as directed (adherence to medication). Within the same patient, there may be a correlation between the antiarrhythmic effect and blood concentration of bepridil.

**Level of evidence:** V
**Grade of recommendation:** C1

**Commentary:**
Bepridil undergoes a complex metabolism, has a bioavailability of about 60%, and is metabolized in the liver by CYP2D6 and CYP3A4 with a half-life after repeated doses of about 80 hours. Bepridil increases the risk of polymorphic ventricular tachycardia (torsades de pointes), and a relationship between increased bepridil concentration and QT prolongation has been documented. The therapeutic range of bepridil is 250 to 800 ng/mL, and the risk of QT prolongation increases at plasma bepridil concentrations of >800 ng/mL. The clearance of bepridil is low in low-body-weight individuals and elderly individuals. Monitoring blood bepridil concentrations is significant in order to assess the safety of treatment.

**HTU11** When should blood samples be taken to perform blood drug concentration monitoring of bepridil?

**Answer:**
Basically, blood samples should be obtained at steady state. It takes about 3 weeks to reach steady-state concentrations, a trough blood sample should be taken at 3 weeks after the initiation of bepridil therapy. However, as bepridil has a nonlinear pharmacokinetic profile, it may take a longer time to reach steady-state concentrations in some patients. Blood bepridil concentrations should be determined even before the steady state is attained when the drug is administered to high-risk patients or when ADRs to bepridil are suspected.

**Commentary:**
Only a small amount of unchanged bepridil is excreted via the kidney. Bepridil is eliminated from the body mainly by hepatic metabolism by CYP2D6 and CYP3A4. Metabolism of bepridil differs substantially among individuals. Bepridil is metabolized slowly, and saturation of CYP2D6 occurs during the process of metabolism, which produces a nonlinear pharmacokinetic profile. As bepridil has an extremely large volume of distribution, and it takes a long period of time for bepridil to diffuse from blood into tissues, careful consideration should be taken to determine when blood samples should be taken. When bepridil is administered repeatedly, it takes 3 weeks to reach steady-state concentrations, but it may take more time in some cases. Blood bepridil concentrations should therefore be evaluated at more than one time point in patients receiving the drug for a long period of time. Blood samples should be taken immediately before the next dose when the drug concentration is at trough, but blood samples may be obtained at other time points. The target therapeutic range is 250 to 800 ng/mL. Blood bepridil concentrations should be determined for patients with a high risk of ADRs and those suspected to have ADRs, even when the steady state has not been achieved. In such cases, blood samples may be obtained at any time points.

### 1.5 Inotropic Drugs (Digoxin)

**CQ9** Is blood drug concentration monitoring effective for patients with arrhythmia receiving digoxin?

**Answer:**
Blood drug concentration monitoring is useful as it may decrease the occurrence of digitalis intoxication. Data on the time of dosing and that of blood sampling are important to interpret blood digoxin concentrations appropriately. Blood samples should be taken at an appropriate timing.

**Level of evidence:** IVb
**Grade of recommendation:** B

**Commentary:**
Digitalis intoxication is a common problem in digoxin therapy (Table 3). It has been reported that high blood digoxin concentrations are a risk factor for digitalis intoxication. Reports have indicated that the occurrence of digitalis intoxication during digoxin therapy can be decreased by adjusting the dose based on digoxin concentrations. Since digoxin has a high renal excretion rate, blood digoxin concentrations increase as renal dysfunction. When the effect of treatment is insufficient, data on blood digoxin concentrations may provide useful information on whether the dose should be increased or not, and whether the patient is taking the drug as directed (adherence to medication).

Blood samples for TDM should be taken at an appropriate timing. When blood samples are taken at an inappropriate condition such as conducting TDM without a clear purpose, and obtaining a blood sample before reaching a steady state, or within 6 hours after dosing, no TDM assessment can be conducted even if blood concentrations are outside the therapeutic range.

**CQ10** Is blood drug concentration monitoring effective for patients with heart failure receiving digoxin?

**Answer:**
Blood drug concentration monitoring is useful as it may decrease the occurrence of ADRs to digoxin. Data on the time of dosing and that of blood sampling are important to interpret blood digoxin concentrations appropriately. Blood samples should be taken at an appropriate timing.

**Level of evidence:** IVb
**Grade of recommendation:** B
Commentary:
Digoxin causes ADRs in relation to its serum concentration. It has been reported that serum digoxin concentrations may be used as a predictor of digitalis intoxication. In a post-hoc analysis of the randomized, double-blinded, placebo-controlled Digitalis Investigation Group (DIG) trial that was conducted before beta-blocker therapy for heart failure was established in patients with chronic heart failure who had a left ventricular ejection fraction (LVEF) of ≤45% and were in sinus rhythm, an association of serum digoxin concentration and all-cause mortality rate was shown in men. Lower serum digoxin concentrations (0.5 to 0.8 ng/mL) were significantly associated with decreased all-cause mortality rates, and higher concentrations (≥1.2 ng/mL) were significantly associated with increased all-cause mortality rates as compared with patients receiving placebo. As digoxin is currently used to alleviate symptoms and reduce hospitalization due to heart failure rather than to improve their life expectancy, serum digoxin concentration should be maintained low in order to avoid ADRs as much as possible. TDM of blood digoxin concentration is considered useful to ensure the safety of treatment.

**HTU12** When should blood samples be taken to monitor blood concentrations of digoxin?

**Answer:**
A trough blood sample at 12 to 24 hours after dosing should be obtained from the patient at steady state. When it is difficult to obtain a trough blood sample, it is preferable to obtain a blood sample in the elimination phase, that is at ≥6 hours after dosing cannot be interpreted fully, and can only help assess the risk of drug concentration-related ADRs and the patient’s adherence to treatment.

**Commentary:**
It takes a long period of time to achieve equilibrium between blood and tissue digoxin concentrations. When administered orally, digoxin is not fully distributed in the heart until 6 to 8 hours after the last dose, and digoxin concentrations in blood do not represent those in myocardium during early hours after dosing. Accordingly, a blood sample should be taken immediately before the next dose to determine a trough concentration. If it difficult to obtain a trough blood sample in the clinical setting, a blood sample should be taken 6 to 8 hours after the last dose (Figure 4). For the timing in terms of the number of days after the initiation of digoxin therapy or the modification of digoxin dose, a blood sample for TDM should be obtained at least 7 days after the initiation or dose modification in patients with intact renal function when blood digoxin concentrations have achieved steady state. For patients with renal dysfunction, a blood sample for TDM should be obtained after at least four half-lives (Figure 5). When drug concentration-related ADRs or excessive effects of digoxin are suspected, a blood sample should be taken without delay to determine digoxin concentration.

**HTU13** How frequently should blood samples be taken when blood drug concentration monitoring is conducted during long-term digoxin therapy?

**Answer:**
No clear recommendations have been proposed on the frequency or interval of blood drug concentration monitoring for patients, especially ambulatory patients, who are receiving digoxin for a long period of time. Blood samples may be taken at any time when a change in efficacy, ADRs, or drug interactions are suspected, or when the patient’s condition has changed. It is not necessary to determine digoxin concentrations in patients who respond well to treatment, have a stable condition, and have no change in their treatment regimens. However, annual drug concentration monitoring may be acceptable.

**Commentary:**
Blood drug concentration monitoring for patients receiving digoxin is known to reduce the risk of ADRs to digoxin, but there is no evidence indicating that routine digoxin concentration monitoring helps increase the efficacy of...
digoxin therapy and reduces the risk of ADRs.

As different patients undergo TDM for different purposes, the frequency of blood sampling should be determined individually. Serum digoxin concentrations should be determined whenever necessary, such as when ECG changes occur during long-term treatment with digoxin, when ADRs are suspected, or when a change in the patient’s condition may affect the pharmacokinetics or efficacy of digoxin.

As age-related changes in physiological functions may occur even in patients who respond to digoxin, have a stable condition, and may not change their treatment regimens, annual blood drug concentration monitoring is acceptable.

**HTU14** What is the target blood concentration of digoxin?

**Answer:** Minimum effective concentrations should be targeted. Considering the safety and efficacy of digoxin therapy, it is appropriate to target (from 0.5 to) 1.5 ng/mL. For patients with heart failure due to systolic dysfunction, it is preferable to target ≤0.9 ng/mL.

**Commentary:** It has been reported that the therapeutic range of digoxin is 0.5 to 2.0 ng/mL,\(^1\,^2\) based on the findings that the risk of ADRs (digitalis intoxication) increases at serum concentrations of ≥2.0 ng/mL.\(^1\,^4\) A study in Japanese patients has indicated that the risk of gastrointestinal ADRs increases at digoxin concentrations of ≥1.5 ng/mL,\(^7\) while another study reported extracardiac ADRs did not develop at digoxin concentrations of <1.4 ng/mL.\(^9\) The purpose of blood concentration monitoring of digoxin is the prevention of ADRs, especially extracardiac ADRs, and digoxin should be administered at minimum effective concentrations. Based on the published studies, it is considered appropriate to target a blood digoxin concentration of (0.5 to) 1.5 ng/mL.\(^5\,^9\)

In a post-hoc analysis of the DIG trial in patients with chronic heart failure and systolic dysfunction (LVEF ≤45%), the crude all-cause mortality rate was lower in male patients with lower serum digoxin concentrations (0.5 to 0.8 ng/mL) and higher in those with higher serum digoxin concentrations (≥1.2 ng/mL) than in those receiving placebo.\(^4\) An analysis of women with heart failure in the DIG trial demonstrated that lower serum digoxin concentrations (0.5 to 0.9 ng/mL) should be targeted to ensure the efficacy and safety of treatment.\(^6\) It is thus preferable to maintain serum digoxin concentrations at ≤0.9 ng/mL when this drug is administered to patients with chronic heart failure due to systolic dysfunction.

**HTU15** Can we use digoxin concentrations during blood drug concentration monitoring of methyldigoxin?

**Answer:** Methyldigoxin, a substance that cross-reacts with digoxin immunoassays, is determined as digoxin in immunoassays. As digoxin concentrations determined with immunoassays represent the sum of concentrations of methyldigoxin and its metabolite digoxin, the results of digoxin immunoassays may be used in TDM of methyldigoxin in the clinical setting. When methyldigoxin is switched to digoxin or vice versa, TDM should be conducted to confirm that the
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Serum digoxin concentration is within the target range.

**Commentary:**
Serum digoxin concentrations are often determined with enzyme immunoassays (EIA) that show cross-reactions between digoxin and methyldigoxin. The sum of concentrations of digoxin and methyldigoxin are determined as a digoxin concentration. HPLC or other appropriate assays should be used to determine accurate methyldigoxin concentrations. However, considering the absence of substantial differences between methyldigoxin and digoxin in terms of molecular weight and antibody crossreactivity, the sum of methyldigoxin and digoxin concentrations determined with EIA may be used instead of methyldigoxin concentrations in the clinical setting.

The dose should be carefully selected when methyldigoxin is replaced with digoxin or vice versa. As these two substances have different bioavailability, and their pharmacokinetic profiles may differ within and among individuals, a fixed factor cannot be used to convert the dose from methyldigoxin to digoxin or vice versa. Blood drug concentrations should be determined when treatment is changed from methyldigoxin to digoxin or vice versa.

**HTU16 Should physicians consider the possible effects of endogenous digoxin-like immunoreactive substances or drugs that have a chemical structure similar to digoxin on blood digoxin concentration monitoring?**

**Answer:**
When determined serum digoxin concentrations are higher than expected, the presence of digoxin-like immunoreactive substances (DLISs) should be considered. The patient should also be assessed for the presence/absence of signs/symptoms of digoxin intoxication, clinical features (renal dysfunction, liver disease, neonates, or pregnancy), and concomitant drug use (drugs that have a clinical structure similar to digoxin).

**Commentary:**
Endogenous DLISs may be detected in neonates, pregnant women, patients with renal dysfunction, or patients with liver disease. Several studies have indicated that endogenous DLISs may increase blood digoxin concentrations determined with enzyme immunoassays. It has been suggested that different signs and symptoms of digitalis intoxication develop at different ranges (thresholds) of blood digoxin concentrations. In addition to blood digoxin concentration, other risk factors such as age-related changes in physical activity and renal dysfunction, underlying heart disease, sinus dysfunction, and atrioventricular conduction disturbance, as well as exacerbating factors such as hypoxemia, hypokalemia, hypomagnesemia, and hypercalcemia may affect the occurrence of digitalis intoxication. The risk of digitalis intoxication cannot be explained only with serum digoxin concentrations. In studies in Japanese patients, the incidence of extracardiac symptoms of digitalis intoxication such as gastrointestinal symptoms increased in patients in whom blood digoxin concentration exceeded 1.5 ng/mL (Figure 6).

**2. Antimicrobial Drugs for the Treatment of Infective Endocarditis**

**CQ11 Does TDM of vancomycin help ensure effective treatment of infective endocarditis?**

**Answer:**
Confirming the range of blood drug concentrations appropriate for each patient helps physicians prescribe the drug at an optimal dose and thereby avoid ADRs. TDM is particularly useful in adjusting the dose for patients who do not respond to vancomycin at the current dose, avoiding drug concentration-related ADRs, and assessing the efficacy of treatment when the patient’s condition changes.

**Level of evidence:** I and III
**Grade of recommendation:** A
Commentary:
It has been reported that a lower vancomycin area under the concentration-time curve from 0 to 24 h (AUC24)/minimum inhibitory concentration (MIC) ratio is associated with higher attributable mortality among patients with methicillin-resistant Staphylococcus aureus (MRSA)-associated complicated bacteremia or infective endocarditis.71 As vegetation may reduce penetration of vancomycin into MRSA,72,73 it is considered that higher trough concentrations should be maintained in the treatment of infective endocarditis.73 The guidelines for the diagnosis and treatment of infective endocarditis published in the United Kingdom,74 and those in the United States75 recommend that trough serum vancomycin concentrations be maintained at 15–20 μg/mL. On the other hand, an initial trough concentration of ≥15 μg/mL is reported as a risk factor for nephrotoxicity.76

CQ12 Does TDM of aminoglycosides help ensure effective treatment of infective endocarditis?

Answer:
Confirming the range of blood drug concentrations appropriate for each patient helps physicians prescribe the drug at an optimal dose and thereby avoid adverse drug reactions (ADRs). TDM is especially useful in avoiding (trough) drug concentration-related renal dysfunction and assessing the efficacy of treatment when the patient’s condition changes.

Level of evidence: II
Grade of recommendation: B

Commentary:
High trough concentrations and a large accumulated dose increase the risk of renal dysfunction due to aminoglycosides, and it has been reported that TDM helps reduce the incidence of ADRs to aminoglycosides.77 In the treatment of gram-positive bacterial infections, serum gentamycin concentration should target a trough concentration of ≤1 μg/mL and a peak concentration (Cpeak) of 3 to 5 μg/mL when the drug is given more than once a day.74

HTU18 When should blood samples be taken to monitor blood concentrations of vancomycin?

Answer:
Typically, a trough sample within 30 minutes before the next dose should be taken. Routine measurement of peak concentrations is not recommended. For patients with intact renal function, blood samples for TDM should be taken on day 3 of treatment or thereafter, and then once a week. More frequent measurement may be necessary when renal function is unstable.

Commentary:
The AUC/MIC ratio is a useful factor of clinical and bacteriological efficacy of vancomycin. However, as there is correlation between trough concentrations and AUC of vancomycin, trough concentrations in the steady state should be determined.75,76 Trough vancomycin concentrations should be determined during twice-daily treatment in patients with intact renal function, and during once-daily treatment in those with renal dysfunction. The dose for the treatment of infective endocarditis should be adjusted to achieve a trough concentration of 15 to 20 μg/mL, which is higher than those for other indications. When renal function is intact, serum vancomycin concentrations reach a steady state in 3 days after the initiation of treatment.79 As the half-life of vancomycin is prolonged in patients with renal dysfunction, 80,81 serum drug concentrations should be determined at later time points. Patients who receive vancomycin for a long period of time should be monitored carefully for renal function and changes in trough drug concentrations.

HTU19 When should blood samples for TDM of aminoglycosides be obtained?

Answer:
Typically, a trough sample within 30 minutes before the next dose should be taken. The peak concentration at 1 hour after the initiation of intravenous administration should also be determined. For patients with intact renal function, blood samples for TDM should be taken on day 2 or 3 of treatment, and then once a week. More frequent measurement may be necessary when renal function is unstable.

Commentary:
The peak concentration/MIC ratios are a useful factor of clinical and bacteriological efficacy of aminoglycosides.82 As there is a relationship between higher trough concentrations and the occurrence of nephrotoxicity,83 two blood samples should be obtained to determine trough and peak concentrations. A trough sample should be obtained within 30 minutes before the next dose. The peak concentration that represents drug concentration in the blood after the drug is distributed into tissues should be determined using a blood sample obtained 1 hour after the initiation of intravenous infusion.84 Blood samples should be obtained in the steady state.84 The first blood sample for TDM of an aminoglycoside drug may be obtained on day 2 of treatment, but it is practical to obtain it on day 3 as renal function is low in many patients.

HTU20 When should blood samples be taken to monitor blood concentrations of teicoplanin?

Answer:
When blood teicoplanin concentration after the loading doses is obtained, a trough sample on day 4 after the initial treatment for 3 days should be obtained regardless of the level of renal function. When a trough teicoplanin concentration on the day after the initial treatment for 2 days is determined to confirm drug concentration in an early phase of treatment, a sample should be obtained at least 18 hours after the last dose. TDM should be conducted once a week thereafter. More frequent measurement may be necessary when renal function is unstable.

Commentary:
As teicoplanin rarely causes drug concentration-related ADRs at the therapeutic range in the clinical setting, TDM of teicoplanin is conducted to confirm the onset of drug effects. For severe or complicated infections such as infective endocarditis and bone and joint infections, clinicians should target a trough teicoplanin level of ≥20 μg/mL.85,86 During the first three days of treatment, teicoplanin should be administered according to the established protocol...
regardless of the level of renal function. On day 4 and thereafter, the dose should be adjusted according the patient’s renal function. Although the standard procedures for TDM of teicoplanin have not been established, many of the previous reports have described the trough concentration on day 4 of treatment. A blood sample should be taken at least 18 hours after the last dosing, when the distribution phase has been completed.84

3. Considerations for Special Patient Populations

3.1 Patients With Renal Dysfunction or on Hemodialysis

HTU21 How should blood drug concentration monitoring of antiarrhythmic drugs be conducted for patients with renal dysfunction or those on hemodialysis?

Answer:
Disopyramide, cibenzoline, procainamide, pilscainide, and sotalol are excreted mainly through the kidneys. Flecainide is also excreted through the kidney. A trough sample should be determined immediately before the next dose in the steady state. It takes a longer time to reach the steady state when renally excreted drugs are administered to this patient population.

Commentary:
When renally excreted drugs are administered to patients with renal dysfunction or those on hemodialysis, the dose should be reduced or the dosing interval should be increased. Among antiarrhythmic drugs, pilscainide, sotalol, cibenzoline, procainamide, and disopyramide are excreted mainly through the kidneys, while flecainide is eliminated through the liver and kidneys.

When renally excreted drugs are administered to patients with renal dysfunction, physicians must consider the effects of the renal function on the pharmacokinetics of these drugs. When these drugs are given to patients on hemodialysis, physicians must also consider drug removal with hemodialysis, and the effect of hemodialysis on alpha-1-acid glycoprotein binding. However, drug concentrations in blood are obtained as the sum of concentrations of free drug molecules and protein-bound drug molecules, and it is difficult to delineate the biological fate of free drug molecules.

In order to confirm the efficacy of these drugs and the risk of ADRs, a trough sample should be obtained at a steady state that is achieved after 4 to 5 half-lives. Physicians should be aware that the half-life of renally excreted drugs prolongs as renal function decreases.

In general, drugs with a low protein binding rate (<80%) and a small volume of distribution (<1 L/kg) are removed by hemodialysis.88 As cibenzoline has a large volume of distribution (5 to 7 L/kg) and is not removed by hemodialysis, physicians should be aware of this fact when an initial administration strategy is planned. Drugs removed by hemodialysis should be administered after a hemodialysis session.

HTU22 How should blood drug concentration monitoring of digoxin be conducted for patients with renal dysfunction or those on hemodialysis?

Answer:
A trough blood sample at 12 to 24 hours after dosing should be obtained at the steady state. When it is difficult to obtain a trough blood sample, it is preferable to obtain a blood sample in the elimination phase, that is at ≥6 hours after dosing. As digoxin is mainly excreted through the kidneys, administration plans should be made according to the patient’s renal function. As it takes 2 to 3 weeks to achieve the steady state level of digoxin in patients with end-stage renal disease or those on hemodialysis, blood samples for TDM should be obtained thereafter.

Commentary:
As digoxin is a renally excreted drug with 70% of the dose excreted unchanged in the urine, the dose for patients with renal dysfunction should be adjusted according to the patient’s renal function. As the half-life of digoxin is prolonged in patients with renal dysfunction, it takes longer time to achieve a steady state. It is appropriate to obtain a blood sample after a week of treatment for patients with renal dysfunction, and after 2 to 3 weeks of treatment for patients with end-stage renal disease or those on hemodialysis.

Digoxin has a large volume of distribution of 4 to 8 L/kg in patients with intact renal function, and is distributed mainly in the skeletal muscle. The volume of distribution of digoxin decreases as renal dysfunction, but is still as large as 4 to 5 L/kg in patients with end-stage renal disease.89 Digoxin cannot be removed efficiently by any type of renal replacement therapy.90,91 Therefore, the initial administration planning and TDM are important. In patients on hemodialysis, a blood sample for TDM should be obtained before a hemodialysis session. Patients who start a session in the morning should be instructed to take digoxin after the session in order to avoid blood sampling during the distribution phase.

Patients with renal dysfunction are prone to be affected by DLIS, and some immunoassays may cause false high values (see HTU16 [page 595]). The effects of P-glycoprotein inhibitors and inducers on the pharmacokinetics of digoxin are similar between patients on hemodialysis and individuals with intact renal function.93

Dose Selection for Patients With Renal Dysfunction

A leading principle in dose selection for patients with renal dysfunction is reducing the dose of “drugs of which unchanged compound or active metabolites are largely excreted in the urine”.

The Giusti-Hayton method has been used as a simple method to adjust the dose and/or dosage interval in patients with renal dysfunction (Figure 7).84 For example, when a patient with a creatinine clearance (CCr) of 30 mL/min receives digoxin (percentage of the dose excreted unchanged in the urine [fe]: 0.7) to obtain the effect equivalent to that obtained in patients with intact renal function (CCr: 120 mL/min) receiving digoxin at a dose of 0.125 mg once daily, the patient should receive the drug at a dose of 0.060 mg once daily, when he/she prefers a once-daily regimen. This adjusted dose is the product of the factor G (1 to 0.7×(1 to 30/120) [nearly equal] 0.48) and the dose for those with intact renal function (0.125 mg).

When the dose adjustment is made by changing the dosing interval, the appropriate interval can be calculated as a quotient of the interval for those with intact renal function and the factor G (24 hours/0.48=50 hours). The
patient may receive digoxin at a dose of 0.125 mg every other day.

**HTU23** How should TDM of vancomycin be conducted for patients with renal dysfunction or those on hemodialysis who are complicated with infective endocarditis?

**Answer:**
In patients with renal dysfunction who are not undergoing hemodialysis, a trough concentration during 30 minutes before the next dose should be determined in principle. In patients on hemodialysis, a blood sample should be taken before a hemodialysis session, and an additional dose of vancomycin should be administered after the session. Routine measurement of peak vancomycin concentration is not recommended. As the time to achieve a steady state prolongs as renal function decreases, it takes 2 to 3 weeks to achieve the steady state in patients on hemodialysis. In order to shorten the time to achieve the steady state, an initial loading dose of vancomycin should be given at 15 to 20 mg/kg for patients with renal dysfunction, and at 25 to 30 mg/kg for those with severe renal dysfunction and those on hemodialysis.

**Commentary:**
It has been reported that renal dysfunction may lead to decreased immunity, and that the incidence of infective endocarditis in patients on hemodialysis is 17-fold that in the general population, and that the outcome of infective endocarditis is poor in this patient population. As vancomycin is a renally excreted drug with 90% of the dose excreted unchanged in the urine, the dose should be adjusted according to the patient’s renal function. In the treatment of infective endocarditis, trough vancomycin concentrations should be maintained high at 15 to 20 μg/mL, which may impair the patient’s renal function. As vancomycin should be given for a long period of time in the treatment of infective endocarditis, TDM is necessary to continue the treatment safely and effectively.

As the time to achieve steady state concentrations of vancomycin prolongs as renal function decreases, it takes 2 to 3 weeks to achieve the steady state in patients on hemodialysis. In order to shorten the time to achieve the steady state, an initial loading dose of vancomycin should be given at 15 to 20 mg/kg for patients with renal dysfunction, and at 25 to 30 mg/kg for those with severe renal dysfunction and those on hemodialysis.

In patients with renal dysfunction who are not undergoing hemodialysis, a trough concentration during 30 minutes before the next dose should be determined. In patients on hemodialysis, a blood sample should be taken before a hemodialysis session, and an additional dose of vancomycin should be administered after the session. In order to confirm that vancomycin concentrations are within the optimal range, TDM should be conducted in the first week of treatment. As a rebound in serum vancomycin concentrations occurs after hemodialysis, serum vancomycin concentrations immediately after a hemodialysis session do not reflect the drug concentration within the target tissue.

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**3.2 Cirrhosis**

**HTU24** How should blood drug concentration monitoring of antiarrhythmic drugs be conducted for patients with cirrhosis?

**Answer:**
Cirrhosis delays the elimination of many antiarrhythmic drugs that are metabolized extensively in the liver. As such, when these drugs are administered in patients with cirrhosis, dose reduction with blood concentration monitoring should be considered on the basis of the severity of hepatic dysfunction. Careful consideration for dose reduction is especially essential for patients with severe cirrhosis of Child-Pugh class C.

**Commentary:**
Careful consideration for dose reduction is especially essential for patients with severe cirrhosis of Child-Pugh class C. Blood drug concentration monitoring is essential for patients with severe cirrhosis of Child-Pugh class C. Blood drug concentration monitoring of these drugs is acceptable in patients with cirrhosis.

Blood concentrations of drugs that are eliminated by both hepatic metabolism and renal excretion may increase unexpectedly as the patients with cirrhosis develop renal dysfunction. Blood drug concentration monitoring of these drugs is acceptable for such cases.
### 3.4 Elderly Patients

**HTU26** How should blood drug concentration monitoring of antiarrhythmic drugs be conducted for elderly patients?

**Answer:**

Physiological function declines with age, and reduced renal function (i.e., low glomerular filtration rate) is especially common among elderly patients. Elderly patients with reduced renal function have lower renal clearance and longer half-lives of drugs excreted by the kidneys. In general, TDM using a blood sample obtained at the steady state is recommended. If possible, a trough blood sample or a blood sample during the elimination phase should be obtained. As elderly patients may respond to or have ADRs to antiarrhythmic drugs before achieving steady-state concentrations, TDM at the onset of efficacy or ADRs may also be beneficial. The initial dose should be set carefully.

**Commentary:**

Physiological function in the elderly is lower than in younger people. As glomerular filtration rate and renal blood flow are low in elderly people, systemic clearance of drugs excreted by the kidneys, i.e., drugs with ≥50% of the dose excreted unchanged in the urine, is substantially lower in the elderly than younger people. As elderly patients have low clearance rates and longer half-lives of renally-excreted drugs, it takes a longer time to achieve steady-state concentrations of these drugs (it generally takes 4-5 half-lives). Drug concentrations in blood may also be high. Accordingly, drug concentrations should be determined before steady-state concentrations to confirm whether drug concentrations are within the therapeutic range. When elderly patients are treated with antiarrhythmic drugs that are extensively excreted by the kidneys, the initial dose should be set carefully. A nomogram for digoxin therapy may help the physician determine the initial dose according to the patient’s renal function and age.

Elderly patients tend to have abrupt changes in pathological and physiological conditions, a reduction in total protein in blood, and dehydration, among others, which may affect the drug’s clearance and unbound drug fraction in blood. Blood drug concentration monitoring should therefore be conducted in response to changes in the patient’s condition. The total drug concentration that represents the sum of free and protein-bound drug molecules, rather than the unbound drug fraction, may be used in TDM for these cases. However, physicians should be aware that an increase in free drug concentration due to a change in the unbound drug fraction may lead to a stronger response (or ADRs) even when the total drug concentration is within the therapeutic range.

**HTU27** How should blood drug concentration monitoring of pilsicainide be conducted for elderly patients?

### Table 4. Delayed Clearance of Hepatically-Metabolized Antiarrhythmic Drugs in Patients With Cirrhosis and Dose Adjustment

<table>
<thead>
<tr>
<th>Drug</th>
<th>Major enzymes</th>
<th>Clearance in patients with cirrhosis</th>
<th>Desirable dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Quinidine</td>
<td>CYP3A4</td>
<td>No change(^{103,104}) (The half-life is prolonged)</td>
<td>No recommendations</td>
</tr>
<tr>
<td>Procainamide</td>
<td>N-acetyltransferase</td>
<td>No sufficient data</td>
<td>No recommendations</td>
</tr>
<tr>
<td>Disopyramide</td>
<td>CYP3A4</td>
<td>No sufficient data</td>
<td>No recommendations</td>
</tr>
<tr>
<td>Aprindine</td>
<td>CYP2D6</td>
<td>No data</td>
<td>No recommendations</td>
</tr>
<tr>
<td>Mexiletine</td>
<td>CYP2D6, 1A2</td>
<td>Reduced(^{102})</td>
<td>1/3</td>
</tr>
<tr>
<td>Lidocaine</td>
<td>CYP3A4</td>
<td>Reduced(^{99-101})</td>
<td>1/3–1/2</td>
</tr>
<tr>
<td>Flecainide</td>
<td>CYP2D6, 1A2</td>
<td>Reduced(^{97})</td>
<td>1/3–1/2</td>
</tr>
<tr>
<td>Propafenone</td>
<td>CYP2D6</td>
<td>Reduced(^{98})</td>
<td>1/3–1/2</td>
</tr>
<tr>
<td>Amiodarone</td>
<td>CYP3A4</td>
<td>No data</td>
<td>No recommendations</td>
</tr>
<tr>
<td>Bepridil</td>
<td>CYP2D6</td>
<td>No data</td>
<td>No recommendations</td>
</tr>
</tbody>
</table>

**Reference:** Child-Pugh classification for severity of liver disease\(^{105}\)

<table>
<thead>
<tr>
<th>Score</th>
<th>Hepatic encephalopathy</th>
<th>1</th>
<th>2</th>
<th>3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ascites</td>
<td>Absent</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Serum bilirubin (mg/dL)</td>
<td>&lt;2.0</td>
<td>2.0–3.0</td>
<td>&gt;3.0</td>
<td></td>
</tr>
<tr>
<td>Serum albumin (g/dL)</td>
<td>&gt;3.5</td>
<td>2.8–3.5</td>
<td>&lt;2.8</td>
<td></td>
</tr>
<tr>
<td>Prolonged prothrombin time (sec)</td>
<td>1–4</td>
<td>4–6</td>
<td>&gt;6</td>
<td></td>
</tr>
</tbody>
</table>


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Circulation Journal Vol.81, April 2017
Answer:
A trough blood sample or a blood sample during the elimination phase should be obtained on day 4 or 5 of treatment or thereafter after achieving steady-state concentrations. However, a sample should be taken earlier when the patient shows a strong response or possible ADRs to determine blood concentrations. When the dose is changed, a blood sample should be taken 4 or 5 days after the dose change or thereafter to determine whether drug concentrations are within the therapeutic range. When renal function is stable, changes in drug concentrations in blood depend on the dose.

Commentary:
As pilsicainide is a drug excreted by the kidneys with about 90% of the dose excreted unchanged in the urine, the systemic clearance of the drug is affected substantially by renal function. As renal function is reduced in elderly patients, special care should be taken to develop administration plans for them. As pilsicainide has a short half-life (4 to 5 hours in healthy adults), pilsicainide concentrations in blood achieve the steady state in 2 to 3 days after the initiation of treatment. When pilsicainide is administered to elderly patients, it is important to set the initial dose carefully, and blood drug concentration monitoring during the initial phase of treatment. A nomogram for calculating the initial dose of pilsicainide has been developed on the basis of a population pharmacokinetics analysis, and should be used to set the initial dose for elderly patients (Figure 8).109,110

**HTU28** How should blood drug concentration monitoring of digoxin be conducted for elderly patients?

Answer:
A trough blood sample at 12 to 24 hours after dosing should be obtained from the patient at steady state. When it is difficult to obtain a trough blood sample, it is preferable to obtain a blood sample in the elimination phase, i.e., at ≥6 hours after dosing. As renal function is low in elderly patients, and it takes a longer period of time to achieve steady state drug concentrations, administration plans should be developed according to the patient’s renal function. Drug concentrations in blood tend to be higher in elderly patients with low body weight or low muscle mass.

Commentary:
As elderly people tend to have reduced renal function and receive multiple drugs, and those with a fragile constitution have a reduction in muscle mass, blood concentrations of digoxin, a drug excreted by the kidneys, tends to be higher than in younger patients.111 Although the effects of aging on renal function and muscle mass differ among individuals, digoxin therapy should be planned individually according to the patient’s renal function, and the dose and dosing interval should be adjusted via TDM. Patients should be instructed to visit the clinic when they have nausea, anorexia, diarrhea, confusion, disorientation, visual impairment, and/or severe bradycardia, which suggest digoxin intoxication.

### 3.5 Children

**HTU29** When antiarrhythmic drugs are administered to children, can physicians target blood drug concentrations similar to those for adults?

Answer:
Although no reports have described blood drug concentration monitoring of antiarrhythmic drugs in children, it is considered that target blood drug concentrations, i.e., therapeutic range, of these drugs are roughly similar between children and adults.

Commentary:
**Dosage regimens and reference therapeutic ranges of antiarrhythmic drugs for children.**

- **Lidocaine**
  - Indications: Mainly indicated for the treatment of ventricular tachycardia (its effects on atrial muscle is small). Intravenous injection: 1 to 2 mg/kg, administer by slow intravenous injection
  - Continuous infusion: 1 to 3 mg/kg/hr (15 to 50 µg/kg/min)
  - Reference therapeutic range: 1 to 5 µg/mL
  - After metabolized in the liver, 70% of the dose is excreted in the urine. The half-life is ≤2 hours in healthy individuals.

- **Mexiletine**
  - Indications: Mainly indicated for the treatment of ventricular tachycardia (its effects on atrial muscle is small), and long QT syndrome (especially LQT3).
  - Intravenous injection: 2 to 3 mg/kg, administer by slow intravenous injection
  - Continuous infusion: 0.4 to 0.6 mg/kg/hr
  - Oral administration: 5 to 10 µg/kg/day, usually divided into 3 doses
  - Reference therapeutic range: 0.5 to 2 µg/mL
  - After metabolized in the liver, the drug is excreted in the urine. The half-life is 10 hours in healthy individuals.

- **Disopyramide**
  - Indications: Atrial arrhythmia, ventricular arrhythmia, and supraventricular tachycardia
  - Intravenous injection: 1 to 2 mg/kg, inject intravenously over 5 to 20 minutes
  - Oral administration: 5 to 10 mg/kg/day
  - Reference therapeutic range: 2 to 4 µg/mL
  - Part of the dose is metabolized in the liver, the metabolites and free disopyramide are excreted in the urine. Children need higher oral doses per body weight than adults to achieve effective disopyramide concentrations.
- Bepridil  
Indications: Tachyarrhythmias (supraventricular and ventricular)  
Intravenous injection: 1 to 1.5 mg/kg, inject over 10 minutes  
Oral administration: 2 mg/kg/day  
Reference therapeutic range: 0.2 to 0.9 μg/mL  
Most of the dose is excreted unchanged in the urine. The half-life is about 4 hours in adults.

- Flecainide  
Indications: Tachyarrhythmia (paroxysmal atrial fibrillation/flutter, paroxysmal supraventricular tachyarrhythmia, ventricular tachyarrhythmia)  
Intravenous injection: 1 to 2 mg/kg or 100 to 150 mg/m², administer by slow intravenous injection  
Oral administration: 3 to 5 mg/kg/day. The daily dose may be divided into 2 doses for some children <1 year of age and those ≥12 years of age, but usually into 3 doses.  
The use in children has been approved in Japan.  
Reference therapeutic range: 0.2 to 1 μg/mL  
About a third of the dose is metabolized in the liver, and about two thirds of the dose are excreted unchanged into the urine. The half-life of oral flecainide is about 8 hours in children 1 to 12 years of age, and 11 hours in infants under 1 year of age and children ≥12 years of age.  

- Pilsicainide  
Indications: Tachyarrhythmia (supraventricular and ventricular)  
Intravenous injection: 2 to 10 mg/kg/day, divided into 1 or 2 doses. For children ≥2 years of age, initiate the treatment at a dose of 1 to 2 mg/kg, increase the dose up to 6 mg/kg, divided into 2 doses. For children ≥2 years of age, initiate the treatment at 90 to 100 mg/body surface area (m²)/day, divided into 2 doses. The maximum dose is 250 mg/m²/day.  
Reference therapeutic range: 0.5 to 1.0 μg/mL

- Amiodarone  
Indications: Tachyarrhythmia (supraventricular and ventricular)  
Intravenous injection: Initiate the treatment with either the loading dose of 5 mg/kg over 30 minutes or ≤5 bolus doses of 1 mg/kg with ≥5 minute intervals. Maintain the treatment at a dose of 10 mg/kg/day.  
Oral administration: Initiate the treatment at a dose of 10 to 20 mg/kg (divided into 1 or 2 doses) for 1 to 2 weeks, and maintain the treatment at a dose of 5 to 10 mg/kg (divided into 1 or 2 doses).  
Reference therapeutic range: 0.5 to 1.0 μg/mL

- Propranolol  
Indications: Tachyarrhythmia (supraventricular and ventricular)  
Intravenous injection: 0.05 to 0.1 mg/kg, administer by slow intravenous injection  
Oral administration: 1 to 4 mg/kg/day, usually divided into 3 doses  
Reference therapeutic range: 0.05 to 0.1 μg/mL

- Sotalol  
Oral administration: Initiate the treatment at a dose of 1 to 2 mg/kg, increase the dose up to 6 mg/kg, divided into 2 doses. For children ≥2 years of age, initiate the treatment at 90 to 100 mg/body surface area (m²)/day, divided into 2 doses. The maximum dose is 250 mg/m²/day.  
Reference therapeutic range: ≤5 bolus doses by slow intravenous injections with an interval of 6 to 8 hours.)  
Oral administration: Maintenance dose: 0.0075 to 0.01 mg/kg/day for infants and young children, 0.005 to 0.0075 mg/kg/day for school children, divided into 1 or 2 doses. The half-life is 20 hours in infants, and 40 hours in children (36 to 48 hours in adults).  
The therapeutic range: 0.5 to 2.0 mg/mL. As digoxin has a narrow therapeutic range, physicians should observe patients carefully for digitalis intoxication. When rapid digitalization is not necessary, it is safe to start the treatment at the maintenance dose. Patients should also be monitored for hypokalemia.

**HTU31 When glycopeptides or aminoglycosides are administered to children with infective endocarditis, can physicians target blood drug concentrations similar to those for adults?**

**Answer:**  
Children are treated with antimicrobial drugs according to the regimens recommended for adults. The therapeutic ranges of antimicrobial drugs in children may be considered identical to those in adults.

**Commentary:**  
The prognosis of infective endocarditis depends on factors including whether the patient is an infant, has a large vegetation (>20 mm), heart failure, or staphylococcal infection. The risk of ADRs to antimicrobial drugs listed in Tables 5 and 6 is low, and the results are favorable in many cases. Regular TDM sessions should be conducted for children receiving glycopeptides or aminoglycosides to adjust the treatment regimen accordingly.

**Pharmacokinetics of Antimicrobial Drugs in Children and Treatment Planning - Vancomycin**  
Dose: 30 to 40 mg/kg/day, divided into 2 to 4 doses  
The usual dose should be 15 mg/kg every 8 hours for...
Table 5. Antimicrobial Therapy for Infective Endocarditis

<table>
<thead>
<tr>
<th>Causative organism</th>
<th>Antimicrobial agents</th>
<th>Treatment period</th>
</tr>
</thead>
<tbody>
<tr>
<td>Streptococci</td>
<td>1. Penicillin G + gentamicin</td>
<td>Penicillin G: 4 weeks</td>
</tr>
<tr>
<td></td>
<td>2. Ampicillin + gentamicin</td>
<td>Ampicillin: 4 weeks</td>
</tr>
<tr>
<td></td>
<td>3. Ceftriaxone + gentamicin</td>
<td>Ceftriaxone: 4 weeks</td>
</tr>
<tr>
<td></td>
<td>4. Vancomycin + gentamicin</td>
<td>Gentamicin: 2 weeks</td>
</tr>
<tr>
<td>Staphylococcus aureus</td>
<td>1. Cefazolin + gentamicin</td>
<td>Cefazolin: 4–6 weeks</td>
</tr>
<tr>
<td>(methicillin-sensitive)</td>
<td>2. Vancomycin + gentamicin</td>
<td>Gentamicin: 2 weeks</td>
</tr>
<tr>
<td>Staphylococcus aureus</td>
<td>Vancomycin (or teicoplanin) + gentamicin</td>
<td>Vancomycin: 4–6 weeks</td>
</tr>
<tr>
<td>(methicillin-resistant)</td>
<td></td>
<td>Gentamicin: 2 weeks</td>
</tr>
<tr>
<td>Enterococci</td>
<td>1. Ampicillin + gentamicin</td>
<td>Ampicillin: 6 weeks</td>
</tr>
<tr>
<td></td>
<td>2. Vancomycin + gentamicin</td>
<td>Gentamicin: 4–6 weeks</td>
</tr>
<tr>
<td>Gram-negative bacteria (HACEK)</td>
<td>Ceftriaxone + gentamicin</td>
<td>Ceftriaxone: 4 weeks</td>
</tr>
</tbody>
</table>

(Adapted from the Japanese Circulation Society. Guidelines for the prevention and treatment of infective endocarditis (JCS 2008), with modifications.)

Table 6. Antimicrobial Therapy for Infective Endocarditis of Unknown Etiology

<table>
<thead>
<tr>
<th>Causative organisms</th>
<th>Antimicrobial agents</th>
<th>Treatment period</th>
</tr>
</thead>
<tbody>
<tr>
<td>Postoperative cases with a negative blood culture result</td>
<td>Vancomycin + gentamicin</td>
<td>Vancomycin: 6–8 weeks</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Gentamicin: 2 weeks</td>
</tr>
<tr>
<td>Non-postoperative cases with a negative blood culture result</td>
<td>Cefazolin + gentamicin ± penicillin G</td>
<td>Cefazolin: 6–8 weeks</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Gentamicin: 2 weeks</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Penicillin G: 6–8 weeks</td>
</tr>
</tbody>
</table>

• Daily dose for children with normal renal function.
  Penicillin G: 200,000 to 300,000 U/kg/day, divided into 4–6 doses. Gentamicin: 3 mg/kg/day, divided into 3 doses. Vancomycin: 30 to 40 mg/kg/day, divided into 2 to 4 doses. Cefazolin: 100 mg/kg/day, divided into 4 doses. Ceftriaxone: 75 to 100 mg/kg/day, divided into 2 doses. Ampicillin: 200 to 300 mg/kg/day, divided into 4 doses.

(Adapted from the Japanese Circulation Society. Guidelines for the prevention and treatment of infective endocarditis (JCS 2008), with modifications.)

children, 10 to 15 mg/kg every 12 hours for neonates <1 week of age, and 10 to 15 mg/kg every 8 hours for neonates 1 week to 1 month of age. TDM of vancomycin should be conducted on days 3 and 7 of treatment and weekly thereafter to adjust the dosage regimen.\textsuperscript{118–124}

Target drug concentrations in blood: 25 to 40 $\mu$g/mL for peak concentrations, and 10 to 15 $\mu$g for trough concentrations.

Trough vancomycin concentrations ranged from 10 to 15 $\mu$g/mL in children who received the drug at a dose of 60 mg/kg/day for the treatment of meninges. Although no prospective studies were conducted to assess the efficacy and safety of vancomycin in children, these concentrations are considered effective and safe in children.

Further studies should be carried out to confirm the efficacy and safety of vancomycin in children who achieve a trough concentration of 15 to 20 $\mu$g/mL, the target for adults.\textsuperscript{123} Half-life: About 2 hours

As the clearance of vancomycin depends on renal function, the half-life of the drug varies among children in whom renal function develops differently with age. 6 to 10 hours in neonates; 4 hours in children 3 months to 3 years of age; and 2 to 3 hours in children over 3 years of age.

ADR: It has been reported that the risk of auditory ADRs increases when peak concentrations range between 60 and 80 $\mu$g/mL, and that of ADRs related to renal toxicity increases when trough concentrations are $\geq$20 $\mu$g/mL.

- **Teicoplanin**

  Dose: Administer three doses of 10 mg/kg with 12-hour intervals, and infuse at a dose of 10 mg/kg/day thereafter. The dose should be infused over 30 minutes and should be adjusted according to teicoplanin concentrations in blood. Although a trough concentration of $\geq$15 $\mu$g/mL may not be maintained at this standard dose, there is no evidence on high-dose treatment with teicoplanin in children. Further studies are awaited.\textsuperscript{125–132} Neonates should be treated with an initial loading dose of 16 mg/kg followed by a maintenance dose of 8 mg/kg/day. The dose should be infused intravenously over at least 30 minutes. Elimination half-life: As the half-life is 50 hours, TDM should be conducted after 7 days of treatment. Target trough concentrations are $\geq$20 $\mu$g/mL (if possible 25 $\mu$g/mL). Although peak concentrations are not determined commonly, a peak concentration of about 40 $\mu$g/mL should be obtained. The half-life of teicoplanin varies among chil-
dren in whom renal function develops differently with age. ADRs: The incidence of ADRs to teicoplanin is relatively lower than that to vancomycin.

- Aminoglycosides (Gentamicin)

Dose: 3 to 7.5 mg/kg/day, divided into 3 doses.

As the level of accumulation of aminoglycosides correlates with their toxicity and can be predicted from trough drug concentrations, patients receiving aminoglycosides should be monitored for peak and trough concentrations in blood from an early phase of treatment.\[118\] \[133\] \[136\] Target concentrations in blood: Target concentrations are lower than in adults: 3 to 5 μg/mL for peak concentrations and 2 to 3-fold those obtained with more frequent dosage regimens. In adults, the incidence of nephrotoxicity of aminoglycosides is lower in once-daily regimens, and very low trough concentrations. As the level of accumulation of aminoglycosides correlates with their toxicity and can be predicted from trough concentrations over 2 μg/mL, even when peak concentrations are not increased.

Once-daily treatment with aminoglycosides is conducted in adults and some children. Once-daily regimens are associated with peak aminoglycoside concentrations that are 2 to 3-fold those obtained with more frequent dosage regimens, and very low trough concentrations. As the bactericidal effects of aminoglycosides are concentration-dependent, once-daily regimens that can achieve higher concentrations in blood are more effective than more frequent dosage regimens. In adults, the incidence of nephrotoxicity of aminoglycosides is lower in once-daily dosing than in three-times-daily dosing, but clinical experience with once-daily dosing is limited in children.\[137\]

### Table 7. Current Findings on the Use of Antiarrhythmic Drugs During Pregnancy or Breastfeeding (as of 2015)

<table>
<thead>
<tr>
<th>Drugs</th>
<th>Class</th>
<th>Use during pregnancy</th>
<th>Use during breastfeeding</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Briggs</td>
<td>Placental transfer</td>
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<td>Propranolol</td>
<td>II</td>
<td>Limited human data</td>
<td>compatible</td>
</tr>
<tr>
<td>Mexiletine</td>
<td>I</td>
<td>Human data suggest moderate risk</td>
<td>compatible</td>
</tr>
<tr>
<td>Flecainide</td>
<td>I</td>
<td>Human data suggest low risk</td>
<td>compatible</td>
</tr>
<tr>
<td>Cibenzoline succinate</td>
<td>I</td>
<td>No data</td>
<td>No data</td>
</tr>
<tr>
<td>Pimbenol</td>
<td>I</td>
<td>Human data suggest risk in 2nd and 3rd trimesters</td>
<td>compatible</td>
</tr>
<tr>
<td>Amiodarone</td>
<td>III</td>
<td>Human and animal data suggest risk</td>
<td>compatible</td>
</tr>
<tr>
<td>Sotalol</td>
<td>III</td>
<td>Human data suggest risk in 2nd and 3rd trimesters</td>
<td>compatible</td>
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<tr>
<td>Bepridil*</td>
<td>IV</td>
<td>No human data</td>
<td>Animal data suggest low risk</td>
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<td>Digoxin (methyldigoxin)</td>
<td>Inotrop drugs</td>
<td>Compatible</td>
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<td>Digitoxin</td>
<td>Inotrop drugs</td>
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*As bepridil is no longer distributed in the United States as of 2014, the descriptions on this drug is based on the findings available in 2012. Bepridil is available in Japan.

### 3.6 Women During Pregnancy and Breastfeeding

**CQ13** What are indications and precautions for the use of antiarrhythmic drugs in women during pregnancy and breastfeeding?

**Answer:**

Only a limited number of reports have described TDM of antiarrhythmic drugs in women during pregnancy and breastfeeding. Physicians should monitor drug concentrations in blood and observe the patients carefully according to the therapeutic ranges of these drugs in adults. Table 7 summarizes the current findings as of 2015 on the use of...
Table 8. Major Route of Excretion and Pharmacokinetic Parameters of Antiarrhythmic Drugs

<table>
<thead>
<tr>
<th>Generic name</th>
<th>Volume of distribution (L/Kg)</th>
<th>Protein binding rate (%)</th>
<th>Major route of excretion</th>
<th>Percentage of metabolites (%)</th>
<th>CYP enzymes mainly responsible for the metabolism</th>
<th>Percentage of the dose excreted unchanged in the urine (%)</th>
<th>Half-life (hr)</th>
<th>Reference therapeutic range (µg/mL)</th>
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<tr>
<td>Amiodarone**</td>
<td>106</td>
<td>96</td>
<td>Liver</td>
<td>100</td>
<td>3A4, 2C8</td>
<td>&lt;1</td>
<td>14–107 days**</td>
<td>0.5–2(?)</td>
</tr>
<tr>
<td>Nifekalant</td>
<td>0.14</td>
<td>90</td>
<td>Liver</td>
<td>90–90</td>
<td>Conjugation</td>
<td>28–31</td>
<td>1–2</td>
<td>–*</td>
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<tr>
<td>Lidocaine**</td>
<td>1–2</td>
<td>70</td>
<td>Liver</td>
<td>95–95</td>
<td>3A4</td>
<td>&lt;1</td>
<td>1–3</td>
<td>2–5</td>
</tr>
<tr>
<td>Quinidine</td>
<td>3</td>
<td>80–90</td>
<td>Liver</td>
<td>70–90</td>
<td>3A4</td>
<td>20</td>
<td>6–8</td>
<td>2–5</td>
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<tr>
<td>Aprindine**</td>
<td>3</td>
<td>95–98</td>
<td>Liver</td>
<td>100</td>
<td>2D6</td>
<td>&lt;1</td>
<td>1–2 days</td>
<td>0.25–1</td>
</tr>
<tr>
<td>Propafenone**</td>
<td>3.7</td>
<td>75–88</td>
<td>Liver</td>
<td>90–90</td>
<td>2D6</td>
<td>3</td>
<td>3–5</td>
<td>0.05–1(?)</td>
</tr>
<tr>
<td>Bepridil**</td>
<td>8</td>
<td>99</td>
<td>Liver</td>
<td>95–95</td>
<td>2D6</td>
<td>&lt;1</td>
<td>80</td>
<td>0.2–0.8</td>
</tr>
<tr>
<td>Mexiletine</td>
<td>5–12</td>
<td>70</td>
<td>Liver</td>
<td>90–90</td>
<td>2D6, 1A2</td>
<td>6</td>
<td>10</td>
<td>0.5–2.0</td>
</tr>
<tr>
<td>Disopyramide</td>
<td>0.6</td>
<td>20–75</td>
<td>Liver/kidney</td>
<td>40–50</td>
<td>3A4</td>
<td>48</td>
<td>5–9</td>
<td>2–5</td>
</tr>
<tr>
<td>Flecaïnide</td>
<td>7–10</td>
<td>60</td>
<td>Liver/kidney</td>
<td>60</td>
<td>2D6</td>
<td>40</td>
<td>11–15</td>
<td>0.2–1</td>
</tr>
<tr>
<td>Procainamide**</td>
<td>1.7–2.4</td>
<td>15</td>
<td>Liver/kidney</td>
<td>40–50</td>
<td>NAT**</td>
<td>60</td>
<td>2–3</td>
<td>4–10</td>
</tr>
<tr>
<td>Pirmenol</td>
<td>1–1.5</td>
<td>80</td>
<td>Liver/kidney</td>
<td>35</td>
<td>3A4(?)</td>
<td>20–30</td>
<td>7–10</td>
<td>0.4–(?)</td>
</tr>
<tr>
<td>Cibenzoline</td>
<td>7</td>
<td>70</td>
<td>Kidney</td>
<td>35</td>
<td>2D6</td>
<td>55–62</td>
<td>5–6</td>
<td>0.2–0.8</td>
</tr>
<tr>
<td>Pilscainide</td>
<td>1.5</td>
<td>35</td>
<td>Kidney</td>
<td>10</td>
<td>–</td>
<td>75–86</td>
<td>4–5</td>
<td>0.2–0.9</td>
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<tr>
<td>Sotalol</td>
<td>1.2–2.4</td>
<td>10</td>
<td>Kidney</td>
<td>0</td>
<td>–</td>
<td>75</td>
<td>7–11</td>
<td>?*</td>
</tr>
</tbody>
</table>

*1Producing active metabolites; *2non-linear excretion, *3N-acetyltransferase; *4about 13 hours after a single administration; *5Not determined in commercial laboratories; *6Not established in Japanese (adults). All drugs listed above other than nifekalant are covered with the specific therapeutic drug monitoring fees.

4. Pharmacokinetic Profiles of Cardiovascular Drugs

Pharmacokinetic Profiles of Antiarrhythmic Drugs

Table 8 summarizes the route of excretion and pharmacokinetic parameters of antiarrhythmic drugs.

5. Drug Interactions of Cardiovascular Drugs

During treatment with antiarrhythmic drugs, healthcare professionals should carefully observe for the following three types of drug interactions:

1. Interaction With Drugs That Prolong QT Interval

QT interval should be monitored during the use of the following drugs regardless of whether antiarrhythmic drugs are used concomitantly or not: vardenafil, moxifloxacin, toremifene, fingolimod, or others.

2. Pharmacodynamic Drug Interactions

Drugs that affect cardiac function such as beta-blockers should be used carefully [with antiarrhythmic drugs] as this combination may also prolong QT interval through a pharmacodynamic interaction.

3. Pharmacokinetic Drug Interactions

Pharmacokinetic drug interactions may lead to adverse

and information centers’ in order to determine the use of drugs during pregnancy and breastfeeding in a comprehensive manner.


drug reactions due to an increase in drug concentrations in blood or loss of efficacy due to a decrease in drug concentrations in blood. Table 2 (page 588) lists major enzymes that are involved in the metabolism of antiarrhythmic drugs, and Table 9 summarizes drugs that affect blood concentrations of antiarrhythmic drugs in TDM.
reference to the sampling time, to the overlapping range of serum concentration where intoxicated and non-intoxicated patients are located and to atrial fibrillation. Jpn Circ J 1986; 50: 628 – 635.


Appendix 1

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- Wataru Shimizu, Department of Cardiovascular Medicine, Nippon Medical School
- Mitsuru Sugawara, Laboratory of Pharmacokinetics, Faculty of Pharmaceutical Sciences, Hokkaido University
Circulation Journal Vol.81, April 2017

**Appendix 2 Disclosure of Potential Conflicts of Interest (COI): Guidelines for Therapeutic Drug Monitoring of Cardiovascular Drugs**

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(Appendix 2 continued the next page.)
Companies are listed only by name. No relevant COIs were declared by other members or collaborators.
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Member: Kazuyuki Ueno, none
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Collaborator: Sumio Hirata, none
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