CLINICAL CHEMISTRY OF ANTI - ARRHYTHMIC DRUGS

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The pharmacological objective of treatment of cardiac arrhythmias is to choose the right drug and achieve a well - tolerated therapeutic concentration swiftly. The therapeutic concentration of the drug needs to be maintained as long as it is needed without toxic side effects of drug interaction. Unfortunately, most antiarrhythmic drugs have a narrow band width in the toxic - therapeutic range. Proper knowledge of the pharmacokinetics of drug concentration and elimination is very necessary. This review will cover some of the more commonly used drugs.

Digoxin

Digoxin is one of the most widely used for supraventricular tachycardias and for congestive cardiac failure. It acts by inhibiting sodium - potassium ATPase, causing accumulation of intracellular sodium. This is followed by a sodium calcium exchange which increases myocardial inotropy.

The average dose of digoxin is 0.25mg/day, with a preceding dose of 0.5mg, in adults. In children, the dose is 5-15ug/ kg per day. The intravenous dose is 1mg/24 hrs given in divided doses. In the presence of renal impairment, the dose is halved or given every other day. To avoid accumulation, some cardiologists omit the daily dose once a week.

Oral doses are well absorbed. The availability ranges from 55-80% and the time to peak levels is 1-2 hours after oral dosing, Blood samples should be collected for serum digoxin levels after a 12-hour interval. Drugs like metoclopramide which increase intestinal motility will decrease its absorption. Following a peak at 2 hours, digoxin is redistributed from the plasma into the muscular and extracellular reaching equilibrium in about 8 hours. The half-life is 30-50 hours in adults and 15-50 hours in children.

Digoxin is excreted unchanged via renal glomerular filtration. Less than 20% is cleared by the liver. Creatinine clearance values are proportional to digoxin clearance rates.

The therapeutic range for digoxin is 0.5 to 2.0 ng/ml. Levels above 2.0ng/ml could produce toxic effects; withdrawal of the drug is recommended at this level especially when the serum potassium level is below normal. Elderly patients are more liable to toxic effects (1). In addition to low potassium, low levels of magnesium may cause cardiac conduction disturbances, arrhythmias, nausea, anorexia and hazy vision with red-green spots. Rarely, colour blindness may be a toxic manifestation.

If large doses of digoxin have been taken, binding agents such as charcoal or cholestyramine are useful, whereas hemodialysis is not. The best antidote is Digibind[®] (2).

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Quinidine and verapamil can raise serum digoxin levels by altering the volume of distribution (3,4). This results in toxicity. Diuretics which cause potassium loss also cause toxicity (5).

Quinidine

Quinidine is an alkaloid from the cinchona bark and an isomer of quinine. It blocks membrane conductance of sodium and calcium and slows conduction velocity. The drug is used for atrial as well as ventricular arrhythmias. The recommended dose is 200 - 400 mg four times a day. Slow - release formulations (gluconate salt) can be given twice a day. It is also given intravenously in the dose of 10 - 20 mg/min, by slow drip.

Quinidine prolongs the QT interval in the ECG. Daily measurements at this interval are mandatory. Oral doses of quinidine are readily absorbed. The bio - availability is 80 - 90%. The volume of distribution ranges from 1 - 4 l/kg. The half-life is 4 - 12 hours (avg. 7 hrs) and 80 - 90% of the drug is bound to serum proteins. Twenty percent is excreted unchanged in the urine, but less may be excreted when the binding to α_1 acid glycoprotein in the plasma is increased. Quinidine is metabolized by hydroxylation in the liver. The major metabolite is 3 - hydroxyquinidine which has some 20% anti-arrhythmic activity of the parent drug.

The therapeutic range for quinidine is 2 - 5 $\mu\text{g} / \text{ml}$. If these levels are exceeded nausea, vomiting, diarrhoea and sudden cardiac arrest can occur. Confusion, coma, seizures and sometimes respiratory arrest show up as toxic effects. Quinidine itself can cause rapid ventricular conduction in atrial fibrillation - hence

co-prescription with digoxin is mandatory. It can also precipitate ventricular tachycardia.

Hemodialysis is of little value for toxicity. Gastric lavage is recommended along with pace maker therapy for slow heart rhythm. Quinidine raises serum digoxin levels (4) and so do anti - convulsants which induce hepatic microsomal enzymes. Cimetidine, amiodarone and verapamil can increase quinidine levels in the serum.

Quinidine is assayed by spectrofluorometry, HPLC or by non - isotopic immunoassay (FPIA, EMIT).

Procainamide

This drug is used in place of quinidine since it has the same therapeutic profile. It is given in the form of capsules 250 to 500 mg four times a day; smaller doses are given to patients with liver dysfunction. Procainamide is well absorbed orally. The bio - availability is 95%, peak levels being quickly obtained in 1 - 2 hours. It is metabolized in the liver to an active substance N-acetylprocainamide (NAPA). Some 20% of patients are slow acetylators. About 15% of the drug is bound to plasma protein. The average half-life in blood is 2-4 hours, and for NAPA 6 - 8 hours except in slow acetylators when it is longer. The drug and the metabolite are cleared by the kidney : lower doses are therefore necessary in renal failure.

The therapeutic range for procainamide is 4 - 10 $\mu\text{g}/\text{ml}$. High doses can cause nausea, anorexia, diarrhoea and the lupus syndrome (6) over a long period. It also causes myocardial depression. Drug interactions occur with ranitidine, cimetidine, trimethoprim, diuretics,

amiodarone and cephalosporin antibiotics.

Procainamide and its derivatives are analyzed by non-isotopic immunoassays or by chromatography techniques.

Lidocaine (Xylocard)

Often it is the first drug to be given intravenously in arrhythmias following myocardial infarction. Usually a bolus of 50 - 75 mg i.v. is given for ventricular tachycardia. This is followed by a maintenance infusion of 1 - 4 mg/min.

The i.v. route produces a two compartment model. The first compartment is central with a volume distribution of 0.5 l/kg. This diffuses into the peripheral compartment rapidly. The initial half - life is only 8 minutes. The clearance is via flow limited hepatic metabolism with a second half - life of 90 - 120 minutes. The drug is protein bound, approximately 70-80% to an α_1 -glycoprotein. It is de - alkylated in the liver to MEGX (monoethylglycinexylidide) which is transformed to GX and then to GX in about 2 hours. GX is also eliminated by the renal route.

The therapeutic range is 1.5 to 5.0 $\mu\text{g} / \text{ml}$. High doses cause dizziness, disorientation, blurred vision and drowsiness. Prolonged toxicity can result in convulsions. Isoniazid, chloramphenicol, cimetidine, glucagon, isoproterenol, propranolol and nor - epinephrine can alter the clearance of lidocaine.

Lidocaine is measured by gas chromatography, HPLC and non-isotopic immunoassay. The oral analogues of lidocaine are mexiletine and tocainide.

Disopyramide

This drug is useful in treating ventricular arrhythmias and, because of its negative inotropy, in hypertrophic subaortic stenosis. The drug is given in doses of 100-200 mg at 6-hourly intervals.

Orally administered doses are well absorbed. The bio availability is roughly 80% and peak levels are reached in 2 - 3 hours. The volume of distribution is 0.8 l/kg. Protein binding can vary from 80% at therapeutic levels to 35% at toxic levels. The half - life of the drug is 6 - 8 hours. The drug is eliminated by the kidney and creatinine clearance is a rough guide to its elimination.

The de-alkylated metabolite has some 25% antiarrhythmic activity of the parent drug. The therapeutic range of the drug is 2 - 5 $\mu\text{g} / \text{ml}$.

Disopyramide is anticholinergic. It causes dryness of the mouth, blurred vision and urinary retention. Drug interactions are known with phenobarbital, phenytoin and rifampicin.

Disopyramide is estimated by gas chromatography, HPLC and non - isotopic immunoassay. For research purposes the (+) and (R) (-) enantiomers may be selectively monitored by HPLC equipped with special chiral separation analytic columns.

Amiodarone

Amiodarone is one of the best and most versatile antiarrhythmic drugs. It is generally given in a loading dose of four 200 mg capsules

followed by 200 mg OD. In elderly patients the maintenance dose can be 100 mg / day. The total i.v. dose in 24 hours is 1 gm, given usually by drip and starting with a bolus of 200 - 300 mg.

Oral doses are poorly absorbed. The bio availability is about 45%. Peak concentrations occur in the plasma after 5-6 hours. However, the drug is very lipophilic and bound to body fat (including fat over the heart) for months. The half - time of elimination is 25 to 60 days. During long treatment the derivative desmethyl-amiodarone accumulates in the plasma and its level may exceed the serum amiodarone levels, as assessed by non - isotopic immunoassay (7).

The effective plasma concentrations of amiodarone is 1.0 to 2.5 µg/ml. Amiodarone therapy is best not combined with any other drug except beta - blocks in small doses. The drug prolongs the QT interval and produces a characteristic humped T wave. Because of its prolonged stay in the body tissues, plasma levels of amiodarone are only a rough guide to therapy.

Amiodarone increases the plasma concentrations of digoxin, warfarin, quinidine, procainamide, phenytoin, diltiazem and flecainide. It can cause bradycardia. It raises the threshold for the pacing stimulus.

There are many more antiarrhythmic drugs introduced recently. One of these is adenosine which is given as a 6 to 9 mg bolus i.v. for supraventricular arrhythmia. The other drugs include ibutilide and dofetilide which act on the potassium channels in the cardiac membrane.

The wise clinician will not dull his palm with many unfledged remedies. He should know his therapeutics well and not play around with many drugs. Antiarrhythmic drugs can be pro-arrhythmic (8). It would be wise to know the pharmacokinetics of a few drugs well and to use them in the right dose with an eye on the therapeutic range. The role of the clinical chemist in this decision making process cannot be underestimated.

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