Use of Cardiac Glycosides

Most physicians believe that they understand and know how to use at least one of the digitalis preparations. The preparation most commonly used is digoxin (lanoxin). For some reason, however, digitalis or cardiac glycoside toxicity (ICD-9-CM code 972.1) keeps on showing up even on problem lists at major teaching hospitals. In fact, "dig. toxicity" is the fourth most common ADR at most hospitals with usually 1-2 incidences per month. If this is a significant problem in hospitals, It is not unreasonable to think that it is at least as large in general medical practice, For this reason it is appropriate to understand the principles involved in the proper and judicious use of these agents so as to establish guidelines to reduce the occurrence of toxicity and to provide guidance for proper dosing.

The two reasons for digitalis toxicity is that either the dosage prescribed is too large or there is an increased sensitivity to the drug. The dosage may be too large because of a dosage error or because of failure to perceive a compromised renal function.

An increased sensitivity to digitalis occurs with advanced age, potassium depletion, calcium excess, thyroid hypo-function, cardiomyopathies and some pulmonary disorders such as cor-pulmonale.

Those at risk for dig. toxicity would then be those receiving or about to receive digoxin (or other preparations) who are elderly (>65 years) and/or have diminished renal function (serum creatinine >2 mg/dl and/or are on concurrent therapy with agents known to interact with digoxin. The latter are drugs such as quinidine or those calcium channel inhibitors affecting digitalis action (especially verapamil). See attached "Digoxin Drug Interactions" sheet.

Other risk factors are the conditions associated with a hypersensitivity to cardiac glycosides which have been listed above. As evidenced by the Adverse Drug Reaction reporting, there remain physicians unfamiliar with the **four basic principles** necessary to use digoxin properly.

The **first** principle is that this agent has a very narrow (low) therapeutic index i.e. the difference between the optimal serum concentration (0.5-2.0 ng/ml) and the toxic range (3.0 ng/ml) is very small. This is complicated by the observation that the usefulness of the serum digitalis concentration as a test for digitalis toxicity is not established (N.E.J.M. 249:867-70, 1976) and also that the clinical manifestations of toxicity occur in most body systems.

In the heart changes in myocardial irritability, rhythmicity, intracardiac conductivity and contractility can lead to almost any dysrrhythmia. It is only slightly helpful that ventricular ectopy and paroxysmal atrial tachycardia with block are the most common, as the spectrum is wide.

It is the extracardiac effects which should command our respect and attention, however, as they are more subtle but equally serious. Of the extracardiac effects nausea and vomiting are well known. Less well appreciated, especially in the elderly, is digitalis induced mental function deterioration or psychotoxicity. This may take the form of depression, lethargy, confusion, emotional instability, clouded sensorium, restlessness or delerium to name a few. It has been repeatedly reaffirmed that changes in mental function in a digitalized elderly patient must be considered drug related unless proven otherwise (J. Clin. Pharm. 19: 747-50, 1979).

The **second** principle is that, for digoxin, you must consider the creatinine clearance (Cl/Cr) which in turn is affected by age when considering your chronic dosage. For males an estimate of Cl/Cr is 98 - .8(age - 20) (Cr)s.

A 70 year old male with a serum creatinine of 1.0 mg would already have a compromised renal excretory process with a Cl/Cr of approximately 58 ml/min. Double the creatinine to 2.0 mg/dl and the Cl/Cr would be approximately 29 ml/min. From the above you may correctly conclude that the elderly or those with compromised renal function should receive a reduced maintenance dose.

The **third** principle is to understand the timing involved from dosage to maximum effect and concentration. Digoxin has a serum half-life of 36-42 hours. For any drug it takes 5 half-lives of continuous dosing to reach 97% of the expected steady-state concentration even if you digitalize with a properly calculated loading dose. In addition, the optimal time to draw a sample for a digoxin concentration is 6-8 hours after the last dose.

Taking these factors into consideration will allow you to draw proper conclusions when comparing serum concentrations you have ordered with the clinical state of your patient. Obviously, a digitalis level assessed before steady state has been attained is of minimal utility unless toxicity is already suspected.

The **fourth** principle is to know the indications for using the drug. Care must be taken in determining the clinical indications for using these potent agents. A commonly accepted indication is for control of the ventricular response in chronic atrial fibrillation. Digitalis blood levels are generally unnecessary as the goal of therapy is a ventricular response of 80-100 bpm at rest. The indications in chronic heart failure, for its inotropic effects are probably more limited than previously thought. Certainly, all patients with left ventricular dysfunction do not benefit symptomatically. Patients most likely to benefit are those with severe left ventricular systolic dysfunction, those with an S3 heard clinically, and those who are clearly limited symptomatically by exertional dyspnea. Patients with primarily diastolic dysfunction or primarily right ventricular dysfunction may not only not benefit but could also see their clinical status deteriorate.

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