

TOXALERT

Newsletter of the Maryland Poison Center, UMAB School of Pharmacy

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**Saving
lives**

**Saving
dollars**

Digoxin Intoxication and the Use of Digoxin-Specific Fab Antibody Fragments

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Digoxin is widely used in the treatment of supraventricular tachyarrhythmias and congestive heart failure. However, there is a narrow margin between therapeutic and toxic doses. In the past, the treatment of digoxin toxicity was largely supportive and aimed at inhibiting the absorption of the drug or counteracting its cardiac effects. In massive overdoses, standard supportive therapy has limited effectiveness often resulting in fatal outcomes. The need for effective treatment for severely toxic patients led to the development of digoxin-specific Fab antibody fragments.

There are many reasons why patients develop digoxin toxicity. Pediatric poisonings are usually the result of accidental ingestions, or errors in the calculation or administration of therapeutic doses. Intentional overdoses in adolescents and adults often result in acute toxicity. Patients who are taking digoxin chronically may become toxic from several disease and drug interactions (hypokalemia, hyperkalemia, hypercalcemia, hypomagnesemia, impaired renal function, and concomitant use of diuretics, glucocorticoids, quinidine, amiodarone and verapamil).

The incidence of toxicity due to digoxin is difficult to quantify due to the fact that although as many as 35% of digitalized patients are said to develop toxicity, many go unreported. In 1996, there were 2,862 cases of cardiac glycoside overdoses reported to the American Association of Poison Control Centers. Unintentional exposures were reported in 2,306 of the cases. In 97 cases,

major toxic effects developed, and there were 16 documented fatalities.

Digoxin exerts its inotropic effects by inhibiting the activity of the enzyme Na^+/K^+ ATPase, resulting in a gradual accumulation of intracellular Na^+ and a loss of intracellular K^+ . The increase in intracellular Na^+ causes myocardial Ca^{++} to increase resulting in an increase in the force of muscle contraction and a decrease in conduction through the AV node. Digoxin's toxic manifestations are an extension of its pharmacologic effect. Inhibition of the Na^+/K^+ pump results in an increase in extracellular K^+ and acute overdoses are characterized by hyperkalemia. Chronic intoxications are often associated with hypokalemia. Symptoms such as anorexia and vomiting are more commonly seen in acute overdoses than chronic. Central nervous system symptoms (more often seen with chronic intoxication) are lethargy, toxic psychosis, hallucinations, delirium, weakness and visual disturbances (photophobia, aberrations of color perception and blurred vision). Cardiovascular signs and symptoms are inevitable in severe intoxications and may precede non-cardiac symptoms. Conduction blocks are more likely to occur in acute overdoses (bradycardia, varying degrees of AV block) while disturbances of impulse formation are more common in chronic overdoses. Intracellular hypokalemia reduces the threshold for ectopic pacemakers leading to AV junctional tachycardia, premature ventricular contractions, ventricular tachycardia or ventricular fibrillation.

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Digoxin Intoxication (continued)

Approximately 70% of digoxin is absorbed from tablets and 80% from elixir. Peak digoxin levels occur in 2-3 hours but may be delayed in overdoses. Digoxin has a large volume of distribution: 5-8 l/kg in adults, 10 l/kg in neonates, 16 l/kg in infants. The volume of distribution may be lower in obese patients and patients with renal failure. Excretion is by renal tubular secretion with 57-80% of a dose excreted unchanged within 6-12 hours. The elimination $T_{1/2}$ of digoxin in therapeutic doses is 36-51 hours and is shortened in overdoses to as low as 15 hours. Therapeutic digoxin concentrations range from 0.5-2.0 ng/ml. In overdoses, the distribution phase may be prolonged, therefore serum digoxin levels may not be meaningful until at least 6 hours post ingestion. Acute toxicity is usually seen above 10 ng/ml. Patients have survived 48 ng/ml but deaths have been reported with levels as low as 3.5 ng/ml. In chronic intoxications, there is an overlap between toxic and nontoxic levels, with many patients developing serious symptoms at lower digoxin levels.

Antibodies to digitalis were originally developed and used experimentally in animals in the 1960's. Digoxin-specific antibodies are produced by immunizing sheep or rabbits with digoxin that has been coupled as a hapten to an immunogenic protein carrier (serum albumin). After several weeks to months, the serum rich in digoxin-specific antibodies is harvested. The IgG antibody molecule is digested with papain into 2 Fab fragments and 1 Fc fragment. The digoxin-specific Fab fragments are isolated and purified by affinity chromatography. Fab fragments distribute rapidly into tissues, occupy a large volume of distribution, and are rapidly excreted by glomerular filtration with a $T_{1/2}$ of 15-20 hours in the presence of normal renal function.

Digoxin-specific Fab antibody fragments are indicated for treatment of potentially life-threatening digitalis intoxication with severe ventricular arrhythmias, progressive bradycardia, second or third degree heart block not responsive to atropine, and/or hyperkalemia (usually >5.5 mEq/l). Fab fragments are also indicated for digoxin ingestions of >10 mg in an adult, >4 mg in a child or a serum level of >10 ng/ml (6-8 hours post-ingestion). Fab fragments are commercially available as

DIGIBIND[®] (Glaxo Wellcome), each vial containing 38 mg which will bind approximately 0.5 mg digoxin. For chronic intoxications, 6 vials in adults and 1 vial in children are usually adequate to reverse toxicity. Twenty vials (760 mg) are recommended in adults and children who ingest an unknown amount of digoxin acutely. An equimolar dose of Fab fragments can be calculated if the total amount of digoxin ingested acutely is known:

Digoxin body load (mg) = dose ingested x 0.8 (accounts for incomplete absorption)

$$\text{Dose (\# of vials)} = \frac{\text{digoxin body load (mg)}}{0.5 \text{ mg digoxin bound/vial}}$$

If the steady state serum digoxin concentration is known, the dose of Fab fragments can be calculated using the following equations:

$$\text{Adults: Dose (\# vials)} = \frac{\text{serum digoxin conc (ng/ml)} \times \text{weight (kg)}}{100}$$

$$\text{Children: Dose (mg)} = \text{dose (\# of vials from above)} \times 38 \text{ mg/vial}$$

Recurrent toxicity is likely to occur in patients receiving less than the estimated required Fab fragment dose. Onset is usually within 3 days but may be as late as 11 days. The decision to retreat should be made on clinical observations of the patient.

Shortly after the administration of Fab fragments, the amount of free circulating digoxin decreases to near zero but there is a rapid rise in the serum concentration of the Fab-digoxin complex. Standard immunoassays for digoxin measure both free and bound digoxin, thus total serum digoxin measurements may be meaningless following Fab fragment administration. (Techniques that separate free from bound digoxin are useful but not generally available). Renal failure slows the elimination of total digoxin after Fab therapy.

Few adverse reactions to Fab fragments have been observed. Allergic reactions

Fab fragments rapidly distribute into tissues, have a large Vd and are rapidly excreted.

Recurrent toxicity is likely to occur in patients receiving less than the required DIGIBIND dose.

**National
Poison
Prevention
Week is
March 15-
21, 1998.
Call 410-
706-7604
for more in-
formation.**

**“Update:
Poisoning
Emergen-
cies” will
prepare you
to diagnose
and treat
poisoned
patients.**

**Radioactive
meat ????**

Digoxin Intoxication (cont)

appear in <1% of patients. Hypokalemia from reactivation of Na⁺/K⁺ ATPase occurs in less than 10% of patients. Serum potassium levels should be monitored repeatedly during therapy. Congestive heart failure may be precipitated in patients who require digoxin to maintain cardiac output. Similarly, an increase in ventricular rate might be noted in patients being treated with digoxin for atrial fibrillation. Patients who require redigitalization must wait 4-7 days for the digoxin-Fab complex to be eliminated.

UPDATE:

POISONING EMERGENCIES

Tuesday March 24, 1998

8:00 AM - 4:00 PM

Are you prepared to treat your poisoned patients? This seminar at the University of MD, Baltimore, will present the latest advances in the diagnosis and treatment of common drug and environmental poisoning emergencies. Continuing education units will be provided to prehospital providers, nurses and pharmacists. Call 410-706-7604

Maryland Poison Center Forms Board of Advisors



The Maryland Poison Center would like to introduce the members of its newly formed **Board of Advisors**:

David Booze, Astra Merck, Inc.; *William Byrnes*, O'Connor, Piper & Flynn, *Lamont Corprew*, WJZ-TV; *Susan Gilson*, MD SAFEKIDS Coalition; *Richard Gorman*, Pediatrician; *Lucien Tancil*, Liberty Medical Center; *Winston Wong*, Blue Cross, Blue Shield of Maryland.

Ex Officio members: *Bruce Anderson*, University of MD School of Pharmacy; *Tina Christine*, University of MD, Baltimore; *Erich Daub*, MD Department of Health and Mental Hygiene; *Wendy Klein-Schwartz*, University of MD School of Pharmacy.

TOXNOTES

In December 1997, the FDA approved irradiation of red meat to protect the public from food poisoning. Is it effective and is it harmful?

It is estimated that between 6.5 and 33 million cases of food borne illness occur annually in the U.S. *Escherichia coli* has recently been implicated in outbreaks resulting from poor conditions in ground beef packaging. Irradiation of foods such as grains and poultry has been in use since the 1960's. The process involves exposing the meat to gamma rays produced by Cobalt 60. Gamma rays have very short wave lengths and do not emit subatomic particles. These high-energy waves disrupt cellular function, killing the bacteria. The energy passes through the meat and bacteria, and the only residue is heat. It should be stressed that this won't make the meat radioactive! Over exposure will simply cook the meat, similar to the way a microwave oven works. Irradiation of red meat can minimize the occurrence of food poisoning but cannot improve the quality of meat that is not fresh and cannot prevent contamination from occurring after the process. Sanitary processing, handling and storage are essential. More information on irradiation and food handling can be obtained from the CDC (www.cdc.gov/ncidod/EID) and the FDA (www.fda.gov/fdahomepage.html).

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TOXALERT

TOXICOLOGY GRAND ROUNDS

Jointly sponsored by the
Maryland
Poison Center and the
University of
Maryland
Medical Systems (UMMS)
Division of
Emergency
Medicine

February 11, 1998, 12:00 p.m.

Bradley Library
N5W56, UMMS

March 11, 1998, 12:30 p.m.

Orthopedic Conference room
NGW44, UMMS

April 8, 1998, 12:30 p.m.

Orthopedic Conference room
NGW44, UMMS

May 6, 1998, 7:30 a.m.

Shock Trauma Auditorium
UMMS

June 10, 1998, 12:30 p.m.

Orthopedic Conference room
NGW44, UMMS

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Common Pediatric Household Ingestions

Joe Zorc, M.D.
Department of Pediatrics, Johns Hopkins University

Toxicity of GHB (Gamma Hydroxy Butyrate)

Katherine Prybys, D.O., Assistant Professor
Division of Emergency Medicine, UMMS

Toxicology of Herbal Products

J. Greene Shepherd, PharmD
Clinical Toxicology Fellow, Maryland Poison Center

Snake and Spider Envenomations

Barry Gold, M.D., Assistant Professor of Medicine
University of Maryland & Johns Hopkins University

Toxicology of Diet drugs

Wendy Klein-Schwartz, PharmD, MPH
Coordinator of Research & Educ., Maryland Poison Center
Associate Professor, Univ. of MD School of Pharmacy