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CARDIAC GLYCOSIDES

1.Heart failure

a.Decrease in contractile force --> reduced stroke volume --> lowered cardiac output

b.Compensatory mechanisms (including renal responses and sympathetic reflexes): increased ventricular end diastolic pressure (hence increase in preload by Starling's Law), vasoconstriction (hence greater afterload) and high heart rate (sympathetic activity), Na and water retention (renin-angiotensin-aldosterone system in response to reduced renal blood flow), edema due to increased pressure through capillary walls

c.Digitalis glycosides increase contractile force and stroke volume, causing reduced end diastolic volume and pressure --> improvement in circulation reduces sympathetic activity and hence peripheral resistance

2.Cardiac glycosides

a.History: 1785, English physician, Sir William Whithering, used foxglove leaves as a diuretic for the treatment of edema

b.Chemistry: aglycone (pharmacologically active portion of molecule) + sugar moiety (determines absorption, onset, duration of action, and potency); aglycone = steroid + lactone ring

c.Source of commonly used glycosides: dried leaves of foxglove plants, Digitalis purpurea (digitoxin) and Digitalis lanata (digoxin, digitoxin)

d.Positive inotropic effect of glycosides

i.Increase in rate of tension developed and peak contractile force

ii.Probable mechanism of positive inotropic action: inhibition of Na/K pump --> increased intracellular Na --> reduced Na/Ca exchange --> increased intracellular Ca --> enhanced contractile force

iii.Other theories: displacement of membrane-bound Ca by elevated intracellular Na; interference with the ability of the sarcoplasmic reticulum to bind Ca

e.Electrophysiological action of cardiac glycosides (relevant to cardiotoxicity of digitalis)

i.Digitalis glycosides increase the vagal tone of the heart. They prolong the effective refractory period of the A-V node and decrease the conduction velocity through the A-V node. The latter action results from direct and vagally mediated indirect effects of digitalis. Shortening of atrial AP (indirect effect of digitalis) à conversion of atrial flutter to atrial fibrillation

ii.Negative chronotropic effect in patients with heart failure (due to reflex decrease in sympathetic activity); tachycardia with excessive digitalis concentrations

iii.Arrhythmogenesis in cardiac Purkinje fibers: increase in phase 4 slope and delayed after depolarizations (seen with toxic concentrations of digitalis):

f.Pharmacokinetics (see Table)

	DIGOXIN	**DIGITOXIN**
ABSORPTION (VIA SMALL INTESTINE)	60-80%	90-100%
TI/2	l.6 DAYS	7 DAYS
RENAL EXCRETION	++++	+
HEPATIC METABOLISM	+	++++
PROTEIN BINDING	25-30%	86-94%
THERAPEUTIC LEVELS	0.9-2.2 NG/ML	12-18 NG/ML
TOXIC LEVELS	>3 NG/ML	>35 NG/ML

i.Impairment of a patient's renal and hepatic function will affect half life of digitalis glycosides in the circulation

ii.Digoxin can normally be eliminated rapidly compared to digitoxin, as is desirable if cardiac toxicity develops

iii.Note that therapeutic index can be quite low (~3-10) for both glycosides

iv.Digoxin is most commonly used; there is rarely justification for preferring digitoxin: in patients with renal failure digoxin is not used, since it may build up to toxic levels if not properly eliminated

a.Therapeutic applications: heart failure due to impaired systolic function (i.e. 'low output' cardiac failure) **and** aggravated by the presence of atrial fibrillation. Patients with dilated hearts due to a cause other than loss of systolic function may not benefit from digitalis therapy. (Vasodilators and angiotensin converting enzyme inhibitors may be of greater value.)

b.Cardiotoxicity of Digitalis glycosides (note low margin of safety)

i.Cardiac dysrhythmias (premature ventricular beat, ventricular tachycardia leading to ventricular fibrillation)

ii.Decrease in serum K concentration predisposes to cardiac arrhythmia

iii.Extracardiac: a) CNS effects on alimentary tract (anorexia, nausea vomiting, diarrhea); b) other CNS effects (headache, weakness, dizziness, disturbed vision with yellow halo around white objects, convulsions, and coma)

c.Treatment of digitalis toxicity

i.Discontinue digitalis

ii.Discontinue any concomitant administration of kaliuretic diuretics

iii.Careful administration of intravenous K salts

iv.Cardiac dysrhythmias usually respond to the antiarrhythmic agents lidocaine and phenytoin

v.Infusion of digitalis-specific antibodies (to lower serum concentration of

drug)

d.Drug interactions that may lead to digitalis toxicity

i.Substances that disturb body electrolytes by lowering plasma K levels (e.g., thiazide or loop diuretics)

ii.Substances that change renal clearance may affect serum concentrations of digoxin; quinidine is known to displace cardiac glycosides from their binding sites on plasma proteins, thereby increasing the serum concentration of digitalis

e.Radioimmunoassay for monitoring serum digitalis levels

f.Be aware of definition of "Digitalization" (process of obtaining the optimum safe level of cardiotonic glycosides during the period of treatment)