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Cardiac glycosides are a class of compounds derived from the foxglove plant. These substances were first identified by William Withering as having therapeutic benefits in 1785. Initially used to treat dropsy (an old term for edema), it was later found that digitalis is most effective against heart failure-induced edema. Digitalis compounds exert their effects on the cardiovascular system through several mechanisms, including an increase in vagal efferent activity to the heart. This parasympathomimetic action reduces sinoatrial firing rate (decreasing heart rate) and slows conduction velocity of electrical impulses through the atrioventricular node. The long half-life of digoxin distinguishes it from other cardiovascular acting drugs, requiring several days of constant dosing to reach steady-state plasma levels. When initiating treatment, a special dosing regimen is used to rapidly increase digoxin plasma levels, a process termed "digitalization." Digoxin is eliminated by the kidneys and has a narrow therapeutic safety window. Therapeutic plasma concentrations range from 0.5-1.5 ng/ml, with small increases above this level potentially leading to significant adverse side effects. Plasma concentrations above 2.0 ng/ml can lead to digitalis toxicity, which may manifest as life-threatening arrhythmias. If toxicity occurs, it may take several days for plasma concentrations to fall to safe levels due to digoxin's long half-life. An immune Fab (Digibind) is available to rapidly reduce plasma digoxin levels in cases of toxicity. Many commonly used drugs interact with digoxin, including Class IA antiarrhythmic quinidine and calcium-channel blockers. Diuretics can indirectly interact with digoxin by reducing plasma potassium levels, leading to increased digoxin binding to the Na+/K+-ATPase and enhanced therapeutic and toxic effects. Hypercalcemia also increases susceptibility to digoxin-induced arrhythmias. Digoxin has been historically used in the treatment of chronic heart failure due to its cardiotonic effect. While newer treatments are available, clinical studies have shown that digoxin improves cardiac output and ejection fraction when used with diuretics and vasodilators. However, it is essential to maintain therapeutic plasma levels within the recommended range to avoid toxicity. Digoxin works by reducing pulmonary congestion and edema, while having a minimal impact on heart rate. As an inotropy-increasing drug, its effects are consistent with its mechanism of action. Although digoxin causes vasoconstriction directly, it leads to decreased systemic vascular resistance in heart failure patients due to enhanced cardiac output and subsequent withdrawal of compensatory mechanisms. This results in vasodilation. Atrial fibrillation and flutter can cause rapid ventricular rates that impair filling time and reduce output. Chronic tachycardia can further lead to heart failure. Digoxin, while not a primary rate-control agent, can be used to decrease ventricular rates when driven by high atrial rates or atrial fibrillation. Its beneficial effect is primarily due to parasympathomimetic activation of vagal efferent nerves, which reduces atrioventricular node conduction and blocks some impulses. The major side effect of digoxin is cardiac arrhythmia, particularly atrial tachycardias and atrioventricular block. It's contraindicated in hypokalemic patients or those with atrioventricular block or Wolff-Parkinson-White syndrome. Impaired renal function leads to increased plasma levels due to decreased elimination. Lean elderly patients are more susceptible to toxicity due to reduced renal function and muscle mass, which increases digoxin binding. A 2018 analysis found that digoxin significantly increased all-cause mortality in atrial fibrillation patients. This challenges the practice of using digoxin for lowering ventricular rate in these patients.

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