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The Effect Of Digitalis On The Heart- An Update

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Abstract:

Digitalis is a genus of about 20 species of herbaceous perennials, shrubsand biennials commonly called foxgloves. The term digitalis is also used for drug preparations that contain cardiac glycosides, particularly the one called Digoxin, extracted from various plants of this genus. Cardiac glycosides cause arteriolar and venous constriction in a variety of mammalian species including human beings, and that this vasoconstriction involves the coronary vascular bed as well. A variety of investigations on cardiac muscle in vitro and in vivo have shown that cardiac glycosides improve the contractility of failing mammalian myocardium. It has been shown that digitalis stimulates the contractility of the non-failing heart also. Digitalis contains substances that stimulate heart muscle. The drug has been used for over two centuries to treat heart failure, a condition caused by inability of the injured heart to pump blood adequately. Other drugs that are used for heart failure include diuretics, angiotensinconverting enzyme inhibitors, and beta-blockers. The review of clinical trials have found that digitalis can help to relieve symptoms of heart failure and thus helps to reducehospitalization.

Keywords: Cardiac glycosides, Digitalis, Heart, Digitalis toxicity.

INTRODUCTION:

THE ORIGINAL DESCRIPTION by Withering of the use ofdigitalis for “dropsy” was published in 1785.[1] Even allowingfor the fact that Withering’s observations were uncontrolled,the dramatic diuresis and relief of dyspnoea with the use offoxglove in patients with “dropsy” left him in little doubtabout its efficacy. According to Withering, digitalis was believed to slow heart rate in patients with irregular pulse and result in diuresis. Two hundred years later, digoxin was regarded as one ofthe cornerstones of therapy for heart failure,[2] but controversypersisted about its efficacy, particularly in patients insinus rhythm. More recently, the advent of neurohormonalantagonists (angiotensin-converting enzyme [ACE] inhibitors and spironolactone) that both produceimprovements in survival and reduce symptoms has relegateddigoxin down the list of therapeutic options for heartfailure. Questions have been raised about the incrementalbenefit of adding digoxin to these newer agents, and thereare concerns about the hazards of using digoxin in patientswith heart failure. Two studies in the 1980s reported thatdigoxin use was associated with increased mortality insurvivors of myocardial infarction.[3,4] In addition, otherdrugs with positive inotropic properties were found toincrease mortality in patients with heart failure.[5]

CARDIAC GLYCOSIDES :

Cardiac glycosides comprise a large family of naturally derived compounds, the core structure of which contain a steroid nucleus with a five-membered lactone ring (cardenolides) or a six-membered lactone ring (bufadienolides) and sugar moieties [6]. A few widely recognized examples of cardiac glycosides are digoxin, digitoxin, ouabain, and oleandrin. The cardeno-lides digitoxin and digoxin, two well-known cardiac glycosides, are inhibitors of the plasma membrane Na+ /K+ -ATPase that are clinically used for the treatment of heart failure[7]. Epidemiologic evidence suggests that breast cancer patients who were treated with digitalis have a significantly lower mortality rate, and their cancer cells had more benign characteristics than those from patients not treated with digitalis [8,9]. Interestingly, the concentrations of cardiac glycosides used for cancer treatment are extremely close to those found in the plasma of cardiac patients treated with the same drugs, suggesting that the anticancer effects of these drugs are exerted at non-toxic concentrations [10].

THERAPEUTICAL APPLICATIONS OF CARDIAC GLYCOSIDES :

The principal indication is permanent/persistent atrial fibrillation with a fast ventricular rate. The target should be a resting ventricular rate of approximately 90/minute. It should be considered as monotherapy primarily for sedentary patients. Beta-blockers or rate-limiting calcium-channel blockers are more effective for monotherapy in patients likely to undergo exertion.[11][12]Digoxin is ineffective in converting recent-onset atrial fibrillation to sinus rhythm.[11] It is contraindicated in pre-excited atrial fibrillation.[11] Digoxin is most commonly used in this situation in children with congenital heart disease. It is given intravenously in the acute situation to slow the heart rate. National Institute for Health and Clinical Excellence (NICE) guidance suggests that digoxin should be used as first-line in patients with atrial fibrillation who also have co-existingheart failure. In all other cases where heart failure is due to left ventricular dysfunction it should be reserved for patients in whom the condition has worsened despite the use of angiotensin-converting enzyme (ACE) inhibitors, beta-blockers and diuretic therapy.

DIGITALIS:

Digitalis is a genus of about 20 species of herbaceous perennials, shrubs, and biennials commonly called foxgloves.It's scientific name is Digitalis purpurea L. Digitalis species thrive in acidic soils, in partial sunlight to deep shade, in a range of habitats, including open woods, woodland clearings, moorland and heath margins, sea-cliffs, rocky mountain slopes and hedge banks.[13][14] It is commonly found on sites where the ground has been disturbed, such as recently cleared woodland, or where the vegetation has been burnt.[15]

USES OF DIGITALIS:

Digitalis is used for Irregular heart rhythms (atrial fibrillation). Taking foxglove by mouth may improve irregular heart rhythms such as atrial fibrillation or flutter.

It also helps in treating Congestive heart failure (CHF). Taking foxglove by mouth may improve CHF and CHF-related swelling.

The other uses of digitalis include Asthma, Epilepsy, Tuberculosis, Constipation, Headache, Spasm, Wounds, Burns, Causing vomiting andOther conditions.

MECHANISM OF ACTION:

Digoxin's primary mechanism of action is the ability to inhibit membrane-bound alpha subunits of sodium-potassium ATPase (sodium pump), mainly but not exclusively located in the human myocardium. This inhibition promotes sodium-calcium exchange, which increases the intracellular calcium concentration that is available to the contractile proteins, resulting in an increase in the force of myocardial contraction.[16,17] In the human myocardium, there is no evidence of up-regulation of the sodium pump during chronic digoxin therapy.[18] The inhibition of the sodium pump may also improve baroreceptor sensitivity in HF and may explain some of the neurohormonal effects of digoxin.[19] Digoxin also has important parasympathetic effects, particularly on the atrioventricular node.

HEMODYNAMIC EFFECTS:

In patients with reduced systolic function and abnormal central hemodynamics who are in sinus rhythm, digoxin improves left ventricular ejection fraction (LVEF) and reduces pulmonary capillary wedge pressure while increasing cardiac output both at rest and during exercise. In HF, however, when hemodynamics are normalized first with diuretics and vasodilators, no further improvement in pulmonary capillary wedge pressure or cardiac output is achieved after the acute administration of digoxin.[20,21] The improvement in hemodynamics is sustained during chronic therapy.[22]

ELECTROPHYSIOLOGICAL EFFECTS:

Therapeutic doses of digoxin have a predominantly parasympathomimetic action on atrial myocardium, slowing conduction, and prolonging atrioventricular node refractory period. There are practically no electrophysiological effects on the Purkinje system. Although digoxin intoxication may produce lethal arrhythmias, therapeutic doses do not appear to increase arrhythmias in the absence of ischemia.[23]

PHARMACOKINETICS:

About 70 to 80% of an oral dose of digoxin is absorbed, mainly in the proximal part of the small intestine. The degree of binding to serum albumin is 20 to 30%. Digoxin is extensively distributed in the tissues, as reflected by the large volume of distribution. High concentrations are found in the heart and kidneys, but the skeletal muscles form the largest digoxin storage. The half-life of elimination in healthy persons varies between 26 and 45 hours. The main route of elimination is renal excretion of digoxin, which is closely correlated with the glomerular filtration rate. In addition, some tubular secretion and perhaps tubular reabsorption occurs. Nearly all of the digoxin in the urine is excreted unchanged, with a small part as active metabolites.

DIGITALIS TOXICITY:

Therapeutic effects of cardiac glycosides are observed in the presence of plasma concentrations between 1 and 2 ng/ml (about 2 nmol/L). Toxicity occurs at doses exceeding 3.1 ng/ml; its origin can be either a therapeutic overdose (5% of reported cases) or ingestion of a large quantity. There are extracardiac and cardiac manifestations of digoxin toxicity. In 80% of the toxic episodes observed, anorexia is an early symptom of toxicity that can be hidden by vomiting that is directly related to the plasma concentration of digoxin. High concentrations of digoxin also affect color vision, and between 25 and 67% of patients have neurological problems, mainly headache and dizziness (vertigo). Several other symptoms of digoxin toxicity have been described: significant arterial vasoconstriction, muscular and cutaneous pathologies (caused by hypersensitivity to cardiac glycosides), severe thrombocytopenia that disappears over a period of 7 days after withdrawal of digoxin, and interference with estrogen as a result of structural similarities that it shared with digoxin metabolites. The cardiac manifestations of toxicity caused by digoxin are characterized by 'abnormal' rhythms and alterations in conduction. Atrial systolic tachycardia with atrioventricular blockade immediately evoke the typical digitalis-induced arrhythmias. Ectopic rhythms as a result of re-entry and increases in automatism lead to atrial flutter, atrial fibrillation, ventricular premature beats and ventricular tachycardia. These phenomena are the results of increased excitability of fibers and diminished conduction velocity at the level of the Tawara node. Non paroxysmal junctional tachycardias are frequently observed. Redundant 3- or 4-multiform ventricular extra-systoles also represent a frequent manifestation, but this is a less specific criterion in the presence of previous cardiac impairment. Digoxin toxicity is clearly characterized when ventricular extra-systoles and atrioventricular block are associated symptoms. It is worthy of note that these manifestations are enhanced by pre-existing factors such as age, cardiomyopathies, plasma concentration of digitalis, and hyperkalemia (>6.5 mmol/L). When the toxic effects of digoxin are associated with hypokalemia, the hydroelectrolytic imbalance can be corrected by intravenous perfusion of potassium chloride 40 mmol/L per hour, with electrocardiographic monitoring.

CONCLUSION :

Digoxin has a limited but useful role, either alone or incombination with other agents such as beta-blockers, diltiazemor verapamil, in achieving satisfactory resting ventricularrate control in patients with chronic atrial fibrillation .In patients who lead a predominantly sedentary lifestyle,particularly the elderly, digoxin alone may be the agent ofchoice for chronic atrial fibrillation . Certainly, digoxincarries a potential advantage over the other agents

in that it is very unlikely to precipitate worsening ventricular functionin patients whose ventricular function is either depressed orunknown. Other than this, there is no role for digoxin inpharmacological reversion of atrial fibrillation, and little orno support for the use of digoxin in the management ofother arrhythmias.

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