Mechanisms, manifestations, and management of digoxin toxicity

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Abstract

Well known functional structures are implicated in the development of digoxin toxicity in the heart: (Na^+/K^+-) Mg^{2+}-ATPase, the Na^+–Ca^{2+} exchanger, and sarcoplasmic reticulum; there is both direct and indirect involvement of sodium, potassium, and calcium ions. The therapeutic effect of digoxin in doses between 1 and 2 ng/ml involves the alpha 2 isoform of Na^+/K^+-ATPase. Toxic effects occur at doses of digoxin exceeding 3 ng/ml, when the main three Na^+/K^+-ATPase isoforms become – at least partially – inhibited. As a result, calcium overload and an imbalance of K^+ concentration induce arrhythmias and atrial systolic tachycardia with atrioventricular blockade. These types of arrhythmia can be treated effectively by pharmacological approaches involving antidigoxin Fab fragments.
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Introduction

The mechanisms of action of digitalis (digoxin) in the human heart have been studied extensively, including the clinical and molecular basis of both its therapeutic and its toxic effects.

Molecular mechanisms of action of digoxin

Digoxin is a cardiac glycoside that binds to and inhibits sarcolemma-bound (Na^+/K^+-) Mg^{2+}-ATPase*. This ATPase catalyses both an active influx of 2 K^+ ions and an efflux of 3 Na^+ ions against their respective concentration gradients, the energy being provided by the hydrolysis of ATP. The inhibition induced by digoxin leads to an efflux of potassium from the cell and, in proportion to the extent of inhibition of the ATPase, an increase in internal sodium ion concentration ($[Na^+]$) at the inner face of the cardiac membranes. This local accumulation of sodium causes an increase in free calcium concentrations via the Na^+–Ca^{2+} exchanger. This free cellular calcium concentration ($[Ca^{2+}]$) is responsible for the inotropic action of digoxin, secondary to the release of Ca^{2+} from the sarcoplasmic reticulum *Figure 1* [1].

Toxic effects of digoxin (ie, arrhythmias) occur when the cytoplasmic Ca^{2+} increases to concentrations exceeding the storage capacity of the sarcoplasmic reticulum [2,3]. As a consequence of this internal Ca^{2+} overload, several cycles of Ca^{2+} release–reuptake are required to restore the Ca^{2+}equilibrium between sarcoplasmic reticulum and cytoplasm. In addition, high internal concentrations of Ca^{2+} activate a depolarizing (inward) current corresponding to the forward mode of the electrogenic Na^+–Ca^{2+} exchanger (3Na/2Ca)*. This current generates delayed after-depolarizations that give rise to extra-systoles and sustained ventricular arrhythmias in vivo [4]. The increase in internal Na^+ induces two effects on calcium concentrations: the

Main clinical article
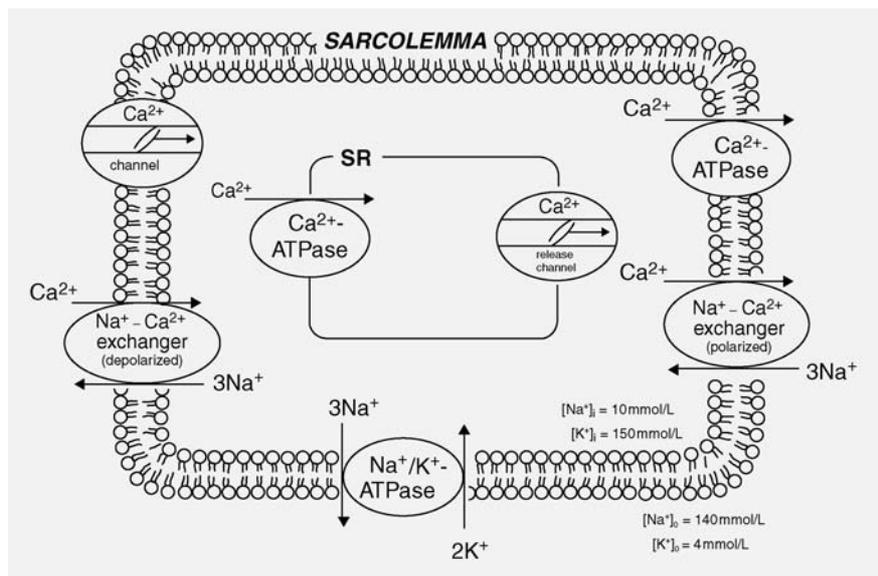*Lionel G. Lelièvre and Philippe Lechat*

Figure 1. Effect of Na$^+$ pump inhibition on cellular Ca^{2+} homeostasis. (From Smith et al [1], with permission.)

Ca^{2+} efflux that normally occurs via the electrogenic Na$^+$–Ca^{2+} exchanger is diminished, and Ca^{2+} influx is promoted via the Na$^+$–Ca^{2+} exchanger in the reverse mode as a result of high internal concentrations of Na$^+$.

The toxicity of digoxin could also be amplified in human heart failure, because the Na$^+$–Ca^{2+} exchanger is upregulated [5].

The pharmacological properties of the three main human cardiac Na$^+$/K$^+$-ATPase isoforms explain the role of hypokalemia in the toxic effects of digoxin. The functional Na$^+$/K$^+$-ATPase is a heterodimer of alpha and beta subunits. The alpha subunit bears the catalytic site and binds digoxin, ATP, Na$^+$, and K$^+$. The three isoforms have the same apparent affinity for digoxin, in the nanomolar range [6]; however, their apparent affinities vary according to the concentration of potassium. In the presence of physiological concentrations, the alpha 1 and alpha 3 isoforms exhibit 3–5-fold lower sensitivities to digoxin; potassium exerts a protective effect. In contrast, the alpha 2 isoform remains highly sensitive to cardiac glycosides. Furthermore, the alpha 2 isoform very rapidly binds and releases digoxin (within a few minutes), whereas the half-times for the dissociation of digoxin from alpha 1 and alpha 3 are 80 and 30 min, respectively. Thus, under physiological conditions, the alpha 2 isoform could be effectively inhibited at low concentrations of digoxin. It has been assumed that, in the presence of high concentrations of digoxin, alpha 1 [7] and alpha 2 isoforms are inhibited and induce toxic effects. Indeed, according to James et al [8], a 50% genetically reduced concentration of the functional alpha 2 isoform in the heart leads to an inotropic effect that mimics that of digitalis. In the case of the alpha 3 isoform, the same genetic approach leads

to cardiac hypocontractility, which mimics the toxic effects of digoxin (reviewed in [9]).

Manifestations of digoxin 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)

Management of digoxin toxicity

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. Hyperkalemia can be corrected only by using digoxin-specific immunoglobulin fragments (Fab)* that remove the drug from the Na^+/K^+ pumps and restore the potassium fluxes into the cells. Such antidigoxin Fab fragments represent a rapid and efficient treatment of this drug-induced toxicity. Prescribed in humans since 1976, this approach is used even in the presence of plasma concentrations of digoxin as high as 100 ng/ml (200 nmol/L). Typically, potassium concentrations are normalized in 1 h, by which time normal behavior is also partially restored; complete neutralization of toxicity occurs in 4 h.

For the treatment of arrhythmias, classical anti-arrhythmic compounds – β-blockers, converting enzyme inhibitors, and vagolytic agents such as atropine – can be used (reviewed in [10]). Intracavitary ventricular stimulation can also be prescribed. ■

* See glossary for definition of these terms.

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