

# Digoxin in the Critically Ill Patient

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## ABSTRACT

**Objective:** To review the pharmacodynamic and pharmacokinetic properties of digoxin in health and disease and the potential use and toxic effects of digoxin in the critically ill patient.

**Data sources:** A review of studies reported from 1966 to 1998 and identified through a MEDLINE search of the literature on digoxin and the use of digoxin in critical illness.

**Summary of review:** Digoxin inhibits the sarcolemmal NaK-ATPase in many tissues with the effects on myocardial contractile and conducting tissue, neural tissue and smooth muscle providing the major physiological effects in health and disease. Currently the major indications for its clinical use include systolic heart failure, where, in addition to angiotensin conversion enzyme inhibitors and diuretics, it reduces the incidence of pulmonary oedema, and in the management of patients with supraventricular tachycardia, where it reduces the ventricular rate.

In the critically ill patient, digoxin is used infrequently as there are other agents that have a superior inotropic effect, a greater ability to control and reverse supraventricular tachyarrhythmias, have a larger therapeutic window and are easier to regulate. As the myocardial depression associated with septic shock is manifest by ventricular dilation and reduction in ejection fraction, it would seem that digoxin may be of some therapeutic benefit in this disorder, particularly as early experimental and clinical studies have reported an improvement in the myocardial dysfunction associated with sepsis with the use of intravenous digoxin (750 - 1000 µg/70 kg). However, large prospective randomised controlled trials are lacking.

**Conclusions:** Digoxin is a therapeutic agent with unique effects. It should be considered in all patients with systolic heart failure, supraventricular tachycardia, and, in association with other treatment, as a single dose of 750 -1000 µg/70 kg in patients not treated previously with digoxin who have septic shock. It should be avoided in patients with critical coronary artery disease and ischaemic or hypertrophic diastolic failure (**Critical Care and Resuscitation 1999; 1: 252-264**)

**Key Words:** Cardiac glycosides, digoxin, heart failure, supraventricular tachycardia, septic shock

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An endogenous plasma digoxin-like substance (digoxin-like immunoreactive factor or DLIF), causing false-positive digoxin immunoassay measurements, and suggested to be an adrenal cortical ouabain-like compound,<sup>1</sup> has been reported during the third trimester of pregnancy,<sup>2</sup> in premature infants,<sup>3,4</sup> in patients with renal failure,<sup>5</sup> hepatic disease,<sup>6,7</sup> acromegaly<sup>3</sup> and in low renin volume-expanded hypertension.<sup>3,8</sup> As critically ill patients commonly have renal and hepatic failure, they often have increased levels of DLIF, which appear to be related more to the degree of hepatic dysfunction rather than the degree of renal failure or the severity of illness.<sup>9</sup> Currently, the purpose of DLIF is not known, although it

may have a role in improving cardiac output or increasing vascular smooth muscle tone during acute illness.<sup>3,10</sup>

While the cardiac glycosides have unique effects, they are used infrequently in the critically ill patient, as there are other agents available that have a superior inotropic effect, a greater ability to control (and reverse) supraventricular tachyarrhythmias, have a larger therapeutic window and are easier to regulate. Nevertheless, with a greater understanding of their pharmacokinetics and pharmacodynamics in health and disease, they may be used with benefit in many acutely ill patients.

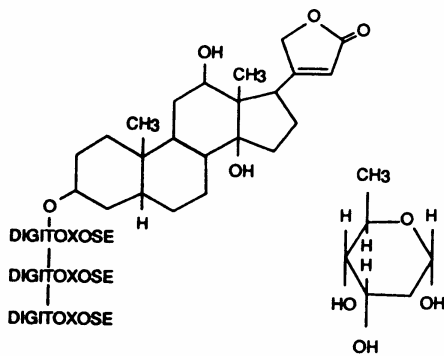
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The most widely used intravenous cardiac glycoside is digoxin, and as all other cardiac glycosides have no major therapeutic advantages compared with this agent, the properties and therapeutic benefits and pitfalls of digoxin in the critically ill patient will be reviewed.

**DIGOXIN**

Digoxin is obtained from leaves of the plant *Digitalis lanata* and is one of a family of cardiac glycosides all of whom share a steroid nucleus and an unsaturated lactone ring attached to the C-17 position (wherein the pharmacological activity resides), combined with one to four molecules of sugar attached to the C-3 position (Figure 1). The sugar modifies the lipid and water solubilities, and thus absorption, duration, and excretion properties of the drug.



**Figure 1.** Structure of digoxin (left) and the digitose sugar, three of which are attached at the C-3 position on the steroid nucleus.

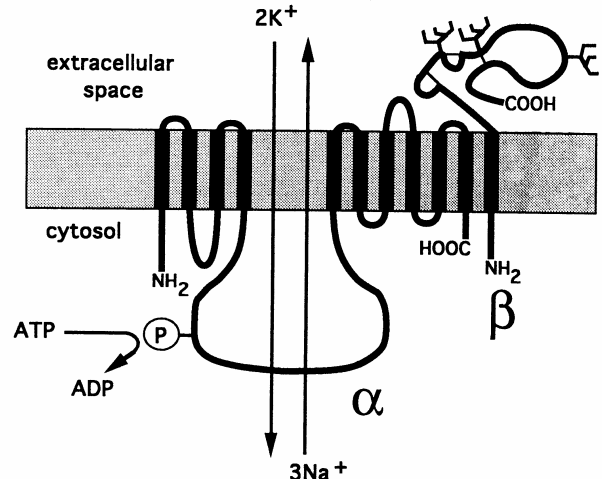
**Pharmacodynamics**

Digoxin binds selectively to the  $\alpha$ -subunit of NaK-ATPase (Figure 2) and its effects arise from its differential binding to, and inactivation of, the multiple distinct  $\alpha$  subunit NaK-ATPase isoforms throughout the various body tissues.<sup>11</sup> For example:

*Myocardial muscle*

Digoxin binds reversibly to the extracellular side of the myocardial membrane bound  $\alpha$  subunit of NaK-ATPase and inhibits the NaK pump.<sup>12</sup> As the positive inotropic effect of digoxin is directly proportional to the degree of inhibition of the myocardial NaK-ATPase, it is thought that the subsequent increase in intracellular  $\text{Na}^+$  activates a  $\text{Na}^+/\text{Ca}^{2+}$  exchanger, increasing the intracellular  $\text{Ca}^{2+}$  concentration which in turn increases myocardial contractility.<sup>13-16</sup> These effects are sustained for weeks to months during the period of administration (with a greater efficiency and less oxygen wasting compared with  $\beta$ -adrenergic agonists or phosphodiesterase inhibitors) and without evidence of desensitization or tachyphylaxis.<sup>17</sup>

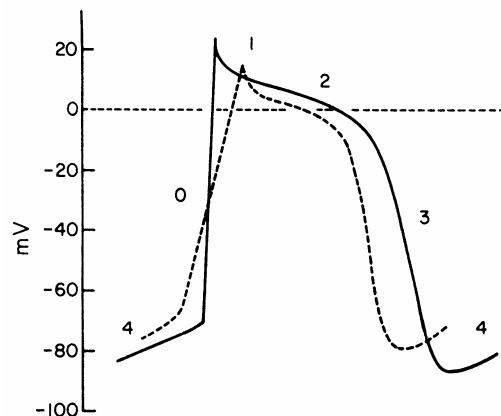
However, cardiac glycosides do not induce a positive lusitropic effect,<sup>18</sup> (contrasting with sympatho-mimetic agents and phosphodiesterase inhibitors) and in animal studies appear to impair myocardial diastolic function.<sup>19</sup>



**Figure 2.** A model illustrating the structure of NaK-ATPase (Modified from Fambrough DM, et al, Am J Physiol 1994;266:C579-C589)

*Myocardial conducting tissue*

By inhibiting conducting tissue NaK-ATPase, digoxin alters the action potential by, a) prolonging phase 3 and shortening phase 2 (i.e. shortens the  $\text{QT}_c$  interval), b) increasing the slope of phase 4 (i.e. enhances the automaticity of atrial, junctional and ventricular tissue),<sup>20</sup> and c) slows phase 0 (i.e. reduces the conduction velocity). These effects are illustrated in figure 3.



**Figure 3.** Action potential of myocardial cell (solid line) and its change under the influence of digoxin (broken line).

Digoxin also increases the refractory period of the atrio-ventricular (AV) junction directly as well as indirectly by increasing the vagal tone. The increase in

vagal tone is due to a digoxin-induced central vagomimetic effect, sensitizing of the AV junctional tissue to vagal stimulation and sensitizing of the vascular baroreceptors.<sup>21-23</sup>

The sensitizing of the vascular baroreceptors occurs at doses less than that necessary to achieve an inotropic effect and is thought to be one of digoxin's more important therapeutic effects as it (unlike sympathomimetic agents and phosphodiesterase inhibitors) reduces the characteristic elevated plasma neuroendocrine activity found in patients with chronic heart failure (e.g. elevated plasma noradrenaline, aldosterone, renin and vasopressin levels which are thought to be responsible for most of the long term deleterious effects of chronic heart failure).<sup>24,25</sup> A reduction in plasma neuroendocrine activity is not observed when digoxin is administered to normal subjects.<sup>26,27</sup>

*ECG effects:* digoxin shortens the QT<sub>c</sub> interval and depresses the T end of the ST segment greater than the J-point end, appearing like a reverse 'tick'. This effect is observed in the leads with the tallest R wave and is not indicative of toxicity unless it appears in all ECG leads. In normal hearts, the terminal portion of the T wave rises above the baseline, an effect which may not occur in the presence of cardiac disease.

The commonest rhythm effects associated with a therapeutic plasma digoxin level are sinus arrhythmia, sinus bradycardia and first degree AV block, whereas the commonest effects associated with digoxin toxicity are 1) bigeminal rhythm, due to alternate ventricular extrasystoles (which only occurs in a diseased heart), 2) paroxysmal atrial tachycardia with irregular second-degree block, 3) atrial and ventricular extrasystoles, and 4) second-degree 'Wenckebach' AV block (Mobitz II second-degree block is not a sign of digoxin toxicity). Digoxin toxicity rarely if ever causes atrial flutter, parasystole or third degree AV block, although third degree AV block occurs with massive digoxin overdosage.<sup>28</sup>

#### *Neural tissue*

Inhibition of neural NaK-ATPase reduces the cerebrospinal fluid (CSF) formation by up to 78% (i.e. decreases CSF production from 500 ml/day to 100 ml/day).<sup>29</sup> Digoxin toxicity may also be associated with visual disturbances, neuralgias, agitation, delirium, and encephalopathy (Table 1).

#### *Smooth muscle*

In health, the inhibition of vascular smooth muscle NaK-ATPase and subsequent increase in calcium influx cause arterial and venous constriction, although some of the vasoconstrictive effects of digoxin are thought to be

also due to an inhibition of sympathetic neuronal re-uptake (and therefore inactivation) of noradrenaline.<sup>30</sup> Intravenous digoxin has also been shown to cause vasoconstriction in normal and atherosclerotic epicardial coronary arteries<sup>31</sup> (an effect which is reversed by glyceryl trinitrate but not phentolamine<sup>31,32</sup>).

However, in patients with heart failure, the increase in vascular baroreceptor sensitivity along with the increase in myocardial contractility leads to a reduction in sympathetic tone and indirectly causes vasodilation which often overrides the direct vasoconstrictive effect.<sup>21</sup>

#### *Other effects*

Cardiac glycosides, unlike sympathomimetic agents and phosphodiesterase inhibitors, reduce the basal metabolic rate by reducing the oxidation rate of fats.<sup>33</sup> The oxidation rates of carbohydrates and protein are not altered.<sup>13</sup>

Cardiac glycosides have also been found to have an immunomodulatory effect, inducing production of IL-1, IL-6, and TNF- $\alpha$  in peripheral blood mononuclear cells (PBMC) from healthy individuals, and suppressing the production of IL-6 and TNF- $\alpha$  in PBMC stimulated by endotoxin.<sup>34</sup> Cardiac glycosides have also been associated with a reduction in the incidence of breast cancer<sup>35</sup> (serving perhaps as an oestrogen receptor modulator).<sup>36</sup>

### *Pharmacokinetics*

#### *Absorption*

Oral digoxin is 60-75% absorbed (up to 40% of an oral digoxin dose may be inactivated by the enteric bacterium *Eubacterium lentum*<sup>37</sup>), reaching a peak plasma concentration in 2 h and exhibiting a maximum biological effect in 4 h.<sup>38</sup> Intravenous digoxin has its maximum biological effect after 2 h.<sup>38</sup> The plateau plasma level occurs 2-4 h after the intravenous dose and 5-6 h after the oral dose. The absorption of an intramuscular injection of digoxin is unreliable and therefore not recommended.<sup>38</sup> If a loading dose is not given then a steady state plasma level is reached after 4-5 half-lives of the drug (i.e. after 7 days).

#### *Distribution*

About 25% of plasma digoxin is bound to plasma proteins.<sup>39</sup> At equilibrium, the concentration in cardiac tissue varies from 40 to 150 (mean of 68) times that of the plasma concentration. The skeletal muscle concentration is 16 times that of the plasma concentration (ranging from 3 to 60 times that of plasma concentration, or 25% that of cardiac muscle).<sup>40,41</sup>

**Table 1. Common and uncommon side effects of digoxin**

	<i>Not uncommon</i>	<i>Uncommon</i>
<b>Cardiac</b>		
Tachycardias		
<i>Supraventricular</i>	Ectopic beats Supraventricular tachycardia with 2:1 block	Atrial fibrillation
<i>Ventricular</i>	Ectopic beats (bigeminy) Ventricular tachycardia (bidirectional)	Ventricular fibrillation
Bradycardias	Sinus bradycardia Sinus arrhythmia First degree AV block Wenckebach	Third degree AV block
<b>Noncardiac</b>		
Gastrointestinal	Salivation, anorexia Nausea, vomiting	Diarrhoea Abdominal discomfort/pain
Visual	Haloed surrounding dark objects Red/green colour blindness	Scotomata Cortical blindness Photophobia Micropsia, macropsia Ambyopia, diplopia Shimmering, blurring
Neurological	Depression, fatigue Drowsiness Difficulty in walking or raising arms Neuralgias of arms or legs (e.g. wandering leg syndrome) Nightmares, agitation Headaches, insomnia	Encephalopathy Vertigo Seizures Delirium Muscle cramps Trigeminal neuralgia
Allergic		Eosinophilia Thrombocytopenia Gynaecomastia
Endocrine		

As the skeletal muscle is 40% of the total body weight, the major body depot resides in skeletal muscle. Following exercise, skeletal muscle binding of digoxin increases, with the plasma digoxin concentration decreasing by 20%, and remaining significantly lower than the baseline level for approximately 20 minutes.<sup>42</sup>

Plasma levels are performed by a radioimmunoassay 6 h after the last dose to allow for tissue equilibrium.<sup>43</sup> Therapeutic plasma levels are stated to be between 0.6 and 2 µg/L, although larger doses may be desirable in the individual patient in whom clinical toxicity is not present and for whom a greater effect from digoxin is required. Signs or symptoms of toxicity occur in 13% of patients at plasma levels from 1.5-2 µg/L and there is usually some manifestation of toxicity in all patients at blood levels greater than 3.0 µg/L.

Measurements of plasma levels are usually performed, if toxicity is suspected (i.e. overdose, drug interaction, changing renal status), to detect a reduction in bioavailability or poor patient compliance (up to 50% of patients take their digoxin incorrectly<sup>44</sup>), or to differentiate toxic symptoms and signs from other disorders (e.g. septic shock, pancreatitis, hypovolaemia, aminophylline toxicity).<sup>45</sup>

#### *Excretion*

Approximately 33% of the total body digoxin is excreted daily (90% via urine, 10% via stool), 93% is excreted unchanged.<sup>38</sup> With normal renal function, digoxin has a half-life of 36 h. This increases up to 5 days in anephric patients.<sup>46</sup>

**Indications**

The two main indications for digoxin are to improve myocardial contractility in patients who have systolic heart failure, and to reduce the ventricular rate in patients who have a rapid supraventricular tachycardia. Digoxin is contraindicated in atrial fibrillation associated with WPW syndrome or where positive inotropic agents are not indicated (e.g. hypertrophic cardiomyopathies or diastolic heart failure).

**Heart failure**

While the effectiveness of digoxin in patients with chronic heart failure with sinus rhythm, has been questioned,<sup>47</sup> recent studies have shown that digoxin has a prolonged beneficial effect by reducing symptoms of fatigue and dyspnoea and signs of cardiomegaly and peripheral and pulmonary oedema, in these patients.<sup>48-54</sup> The responsiveness of the myocardium to cardiac glycosides in patients with terminal heart failure is preserved, even when a reduction in responsiveness to beta-adrenergic agonists and phosphodiesterase inhibitors is present,<sup>55</sup> and is additive to the effect of ACE inhibitors.<sup>56</sup> While patients with heart failure who are in sinus rhythm and are treated with ACE inhibitors and diuretics have worse heart failure if digoxin is not added to therapy,<sup>54</sup> or if digoxin is withdrawn from therapy,<sup>56</sup> digoxin does not alter mortality (although it is the only positive inotropic agent which has not been shown to increase mortality<sup>57</sup>) when added to therapy.<sup>54</sup>

Patients with dilated failing hearts and impaired systolic function, have subjective and objective improvement after receiving digoxin, whereas patients with elevated filling pressures due to reduced ventricular compliance, but with preserved systolic function at rest, are not appropriate candidates for digoxin therapy unless supraventricular tachycardia is a concomitant problem.<sup>51</sup> The therapeutic endpoint is assessed by the correction of symptoms and signs of heart failure, improvement in exercise tolerance (i.e. change in functional class) and ECG observation of digoxin effect. Currently, it is believed that digoxin is indicated to reduce symptoms of systolic heart failure unresponsive to ACE inhibitors and diuretics.<sup>57</sup>

**Supraventricular tachycardias**

Treatment of supraventricular tachycardias involves the correction of any underlying causes or precipitating factors and the control of the rapid ventricular response (to a resting heart rate of < 110 to increase coronary perfusion, reduce cardiac work and reduce left atrial pressure) by either restoration of sinus rhythm and prevention of recurrence of the supraventricular tachycardia, or slowing ventricular rate with AV blocking drugs, and (in the case of atrial fibrillation)

prevention of thromboembolic complications. Digoxin is used largely to slow the ventricular rate.

**Atrial fibrillation.** Ideally, the digoxin dosage is adjusted so that the ventricular rate is 60-70 per minute at rest and less than 120 per minute with moderate exercise. It is important to realise that rapid atrial fibrillation will not be able to be reduced to below 110-120 per minute in patients with conditions that would normally produce sinus tachycardia (e.g. fever, hypoxia, hypercapnia, pneumonia, thyrotoxicosis or shock from sepsis, pancreatitis, hypovolaemia, pulmonary embolism, or cardiac tamponade).

Digoxin levels of 2.5 µg/L or more may be required to control the resting ventricular response in up to 40% of patients with atrial fibrillation<sup>58</sup> and in one study of 12 patients even high levels of digoxin were unable to control the heart rate with moderate exercise.<sup>59</sup> Spontaneous reversion to sinus rhythm is common in patients with atrial fibrillation of recent onset and the likelihood of reversion is not affected by the acute administration of digoxin.<sup>60</sup>

**Atrial flutter.** While digoxin has been used in atrial flutter to increase the AV block and reduce the ventricular rate, cardioversion<sup>61</sup> and/or class Ia, III or IV antiarrhythmic drugs (e.g. amiodarone, verapamil, dofetilide or procainamide) are often preferred.

**Paroxysmal atrial tachycardia.** Digoxin has been used to increase the vagal tone and improve the success of vagal stimulation reversion of paroxysmal atrial tachycardia.

**Septic shock**

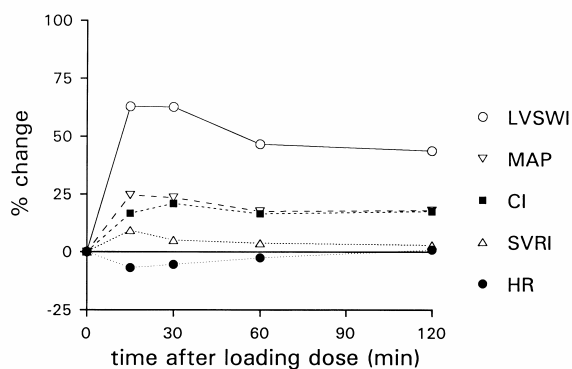
Myocardial depression associated with septic shock is manifest by ventricular dilation and reduction in the ejection fraction (a reduction in ventricular compliance may also occur<sup>62</sup>), and is completely reversible<sup>63,64</sup> 7-10 days after the episode of septic shock has resolved.<sup>63,64</sup> It is not caused by a reduction in coronary perfusion<sup>65</sup> and is believed to be caused by endogenous circulating myocardial toxic factors (e.g. TNF-α)<sup>66,67</sup> rather than a metabolic derangement (i.e. changes in pH, nutrient and oxygen availability),<sup>68,69</sup> although, downregulation or dysfunction of beta-adrenergic receptors may also be responsible for some of the haemodynamic effects.<sup>70,71</sup> Vasodilation associated with septic shock is caused by TNF-α activation of inducible nitric oxide synthase.

While some believe that supernormal haemodynamic values are required to reduce mortality associated with critical illness (e.g.  $\dot{V}O_2 > 600 \text{ ml} \cdot \text{min}^{-1} \cdot \text{m}^{-2}$ , in association with a cardiac index  $> 4.5 \text{ L} \cdot \text{min}^{-1} \cdot \text{m}^{-2}$  and a  $\dot{V}O_2 > 170 \text{ ml} \cdot \text{min}^{-1} \cdot \text{m}^{-2}$ );<sup>72,73</sup> recent large prospective randomised, controlled clinical studies have demonstrated improved,<sup>74</sup> unchanged,<sup>75</sup> and decreased,<sup>76</sup> survivals when volume expansion and inotropic agents were used

in an attempt to achieve these therapeutic goals. In the largest controlled study of critically ill patients, intravascular volume expansion, inotropic agents, and vasodilator agents were used to increase the cardiac index (in one group) to greater than  $4.5 \text{ L}\cdot\text{min}^{-1}\cdot\text{m}^{-2}$ , or the mixed venous oxygen saturation to 70% or greater (in another group); both therapeutic interventions were not associated with a reduction in mortality.<sup>75</sup>

Significantly, in an animal model of septic shock, appropriate antibiotics and cardiovascular support have a synergistic effect in reducing the mortality, although the effect of cardiovascular support is due largely to the intravenous fluid administered rather than the inotropic agent.<sup>77</sup> In this regard, while digoxin  $750\text{-}1000 \mu\text{g}/70 \text{ kg}$  as an intravenous bolus, has been reported to improve significantly the myocardial dysfunction associated with sepsis,<sup>78-83</sup> and in clinical practice it will allow reduction in the amount of sympathomimetic infusion necessary to reach a desired perfusion pressure, there have been no studies reviewing its effect on mortality.

The combined positive inotropic and vasoconstrictive effects of digoxin results in a significant improvement in haemodynamic parameters in patients with septic shock in sinus rhythm even when catecholamine infusions are being used. Data from four patients in septic shock on a mean dose of adrenaline of  $0.22 \mu\text{g}/\text{kg}/\text{min}$  and noradrenaline of  $0.16 \mu\text{g}/\text{kg}/\text{min}$  who were given intravenous digoxin  $12 \mu\text{g}/\text{kg}$ , are shown in figure 4.



**Figure 4.** The effect of i.v. digoxin  $12 \mu\text{g}/\text{kg}$  over 15 minutes on mean circulatory variables in 4 patients with septic shock in sinus rhythm and on a catecholamine infusion.

#### Other uses.

There have been a number of other clinical disorders for which digoxin has been used. For example:

**Acute myocardial infarction.** While early studies concluded that there was no increase in the incidence of digoxin toxicity and mortality when it was given in the

usual therapeutic doses to patients who have acute myocardial infarction,<sup>84,85</sup> a recent large study concluded that there was an increased mortality with digoxin,<sup>86</sup> which was dose dependent.<sup>87</sup> Furthermore, in the experimental model, digoxin appears to abolish the infarct size-limiting effect of ischaemic preconditioning.<sup>88</sup>

As digoxin administration is an independent and significant predictor of increased total mortality in patients with acute myocardial infarction, it is currently recommended that other agents should be used for supraventricular tachycardia and heart failure associated with acute myocardial infarction.<sup>89</sup>

**Preoperative prophylaxis.** While some believe that there is merit in preoperative prophylactic digoxin, particularly in patients with coronary artery disease,<sup>90</sup> generally it is not recommended because the benefits are minimal and the side-effects may be potentiated by intraoperative procedures.<sup>91,92</sup>

**Portal hypertension.** Digoxin lowers portal pressure and has been suggested in the treatment of acute variceal haemorrhage.<sup>93</sup> However, there have been no studies that have demonstrated any reduction in morbidity or mortality associated with this practice.

**Multiple sclerosis.** Digoxin has been reported to reverse the conduction block in denervated nerve fibers and has been used in an attempt to improve clinical deficits in patients with multiple sclerosis.<sup>94</sup> This has not yet been confirmed by a prospective randomised and controlled trial.

#### Dosage

In a patient who has not received digoxin previously, to achieve a rapid effect, an initial dose of  $10\text{-}20 \mu\text{g}/\text{kg}$  ( $750\text{-}1000 \mu\text{g}/70 \text{ kg}$ ) may be given as an intravenous dose of over 10 minutes, which will produce an effect within 10 minutes with maximal effect after 2 h.<sup>38,46,95</sup> This is followed by a further intravenous dose of  $250\text{-}500 \mu\text{g}/70 \text{ kg}$ , 2-4 h later. The maintenance dose is equal to the daily loss, and in patients with normal renal function is  $3.5\text{-}7 \mu\text{g}\cdot\text{kg}^{-1}\cdot\text{day}^{-1}$  (i.e.  $250\text{-}500 \mu\text{g}/70 \text{ kg}/\text{day}$ ). It is recommended that no greater than  $125 \mu\text{g}/70 \text{ kg}/\text{day}$  be given to patients with chronic renal failure.<sup>96</sup>

Tolerance to high doses of digoxin often occurs in infants and young children and in patients with hyperkalaemia,<sup>45</sup> hypocalcaemia,<sup>97</sup> hypermagnesaemia<sup>45</sup> and hyperthyroidism.<sup>98</sup>

#### Side effects

The diagnosis of digoxin toxicity is a clinical one (Table 1) and is not made on a plasma level alone.<sup>99,100</sup> There is no convincing evidence that depression of myocardial contractility occurs as an isolated manifest-

ation of digoxin toxicity.<sup>101</sup> Cardiac toxicity occurs before noncardiac toxicity in 50% cases,<sup>101,102</sup> and may be predicted by the development or worsening of digoxin toxic arrhythmias following carotid sinus massage.<sup>103</sup> Cardiac toxicity may be exacerbated in patients with:

- renal, cardiac and chronic pulmonary disease (due to a decrease in excretion of digoxin or an increase in myocardial sensitivity to digoxin),<sup>104</sup>
- hypokalaemia (due to an increase in myocardial concentration of digoxin),<sup>43,105</sup>
- hypomagnesaemia (due to an increase in the myocardial concentration of digoxin),<sup>106</sup> which also reduces the ventricular response to digoxin in atrial fibrillation (both the digoxin induced arrhythmias and reduced ventricular effect in atrial fibrillation are reversed with intravenous magnesium sulphate),<sup>107-109</sup>
- alkalosis (due to a decrease in extracellular  $K^+$  concentration and not due to the pH change *per se*),<sup>110</sup>
- hyponatraemia (due to a reduction in activity of the NaK-ATPase),
- hypercalcaemia (due to an increase in myocardial intracellular  $Ca^{2+}$ ), and,
- lithium toxicity (due to an increase in myocardial intracellular  $Ca^{2+}$ ).<sup>111</sup>

Digoxin toxicity is treated by, withdrawing digoxin and restoring body  $K^+$ ,  $Mg^{2+}$  and acid-base balances. The tachyarrhythmias may be treated with intravenous magnesium sulphate,<sup>112-114</sup> potassium chloride, lignocaine or phenytoin. The bradyarrhythmias may be treated with atropine or a temporary pacemaker. Potassium and magnesium are believed to be contraindicated in patients who have AV block.<sup>115</sup>

As the enterohepatic circulation for digoxin is approximately 10%,<sup>38</sup> cholestyramine (4 g three times a day) has been used as a useful adjunct in the treatment of digoxin toxicity.<sup>116</sup> However, haemoperfusion and haemodialysis are of little use, because of low plasma levels and high tissue binding.<sup>116</sup> For severe digoxin toxicity, or poisoning, digoxin-specific antibody fragments may be required (see later).

#### **Therapeutic interactions with digoxin**

##### *Drugs*

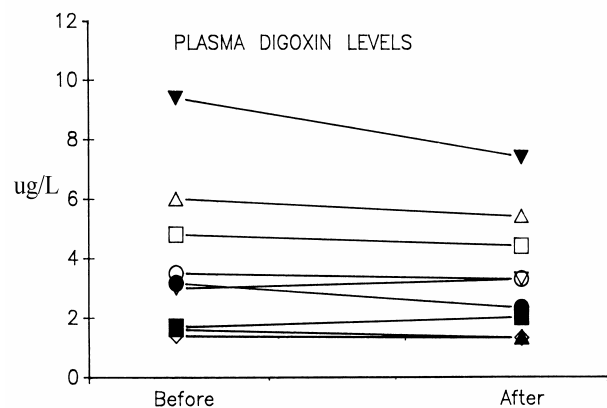
*Quinidine* increases the incidence of digoxin toxicity by decreasing its renal clearance and altering its volume of distribution.<sup>20,45</sup> The plasma level rise occurs immediately on institution of quinidine therapy, achieves a steady state after one week, and is dose related, i.e. the larger the quinidine dose the higher the

plasma digoxin level.<sup>117</sup> The average rise in plasma digoxin is approximately 70%, but varies in patients from 0% to 400%, thus digoxin administration should be halved when quinidine therapy is administered and plasma levels should be measured after 5 to 7 days.<sup>117</sup>

*Verapamil* decreases both renal and nonrenal clearance by 20-40%, thus the dose of digoxin should be reduced.<sup>45</sup> *Diltiazem* reduces the renal clearance of digoxin,<sup>118</sup> although as the effect is small adjustment of the digoxin dose is probably unnecessary. While *nifedipine* has also been reported to increase plasma digoxin levels,<sup>119</sup> other reports have shown no interaction between *nifedipine* and digoxin, in either patients,<sup>120</sup> or normal subjects.<sup>121,122</sup>

*Spirolactone* inhibits renal tubular secretion of digoxin,<sup>45</sup> and *canrenoate* competes with digoxin for myocardial binding sites.<sup>123</sup>

*Amiodarone* was also implicated in acutely increasing digoxin levels by altering the volume of distribution of digoxin in much the same way that *quinidine* did as well as decreasing the renal clearance of digoxin.<sup>20,124</sup> However, in 10 acutely ill patients with atrial fibrillation in whom high dose digoxin failed to control the ventricular rate, a loading dose of *amiodarone* (3.7 - 5.0 mg/kg) had no effect on plasma digoxin levels (figure 5).<sup>125</sup>



**Figure 5.** Plasma digoxin levels before and after 3.7 - 5.0 mg/kg loading dose of *amiodarone*

*Diazepam* increases the plasma level by enhancing protein binding by digoxin.<sup>126</sup> The effect upon enhancement of digoxin toxicity, however, is not clear.

*Rifampicin* reduces plasma digoxin levels due to an increase in its elimination by P-glycoprotein-mediated transport at the intestinal level.<sup>127</sup>

*Tetracycline* and *macrolide* antibiotics may increase plasma digoxin levels due to a decrease in the gastrointestinal inactivation of digoxin by the bacterium

*Eubacterium lentum*.<sup>128</sup> Clarithromycin decreases renal digoxin excretion by inhibiting the renal p-glycoprotein drug efflux pump.<sup>129</sup>

*Acarbose*<sup>130</sup> and cholestyramine reduce the absorption of digoxin.

*Itraconazole* increases plasma levels by reducing renal clearance of digoxin.<sup>131</sup>

**Cardioversion**

While direct current cardioversion for arrhythmias due to digoxin toxicity may be followed by malignant ventricular arrhythmias (e.g. ventricular tachycardia or ventricular fibrillation), cardioversion for non digoxin-toxic arrhythmias in patients who have a plasma digoxin level of less than 2.0 µg/L is not followed by malignant ventricular arrhythmias.<sup>117,132</sup>

**Digoxin poisoning**<sup>133-136</sup>

**Clinical features**

In patients with normal cardiac function who take an overdose of digoxin, hyperkalaemia (due to the profound inhibition of NaK-ATPase), AV block and sino-atrial block are common features, with the peak effect occurring 12 h after ingestion. In patients with cardiac disease, supraventricular and ventricular tachycardias often occur within 1-4 h and may be the major effects. If life-threatening arrhythmias have not occurred within 24 h of the poisoning, then they are unlikely to occur.

**Treatment**

If either hyperkalaemia (i.e. plasma K<sup>+</sup> greater than 5 mmol/L) or life-threatening cardiac arrhythmias occur, or the plasma digoxin concentration is greater than 10 µg/L (e.g. an ingestion of 10 mg or more of digoxin), then digoxin antibodies (i.e. antigen- binding fragments of digoxin antibody - Fab fragments - produced by papain digestion of a specific IgG sheep antibody to digoxin) should be used.<sup>137</sup> Because the antigenic Fc fragment (crystallisable fragment) is absent, antigenicity is reduced. In fact, allergic reactions to digoxin immune Fab fragments have not yet been reported, even in a case of multiple episodes of digoxin overdose where Fab fragments were used on three separate occasions.<sup>138</sup>

Each milligram of digoxin immune Fab binds to 15µg of digoxin (i.e. 66.7 mg of digoxin immune Fab binds to 1 mg of digoxin). The intravenous dose may be calculated by estimating the total body load of digoxin required to be removed, for example:

- total digoxin absorbed (i.e. oral dose in mg x 0.75), which may overestimate the amount as it does not take into account vomiting or treatment by

nasogastric lavage. Table 2 gives the amount of digoxin immune Fab required from the estimated number of 250 µg digoxin tablets ingested.

- plasma level (µg/L) x 5.6 x body wt (kg)/1000; this figure is then multiplied by 66.7. However, this is only accurate if the plasma level is taken 6 h or more after the ingestion.
- if the dose is unknown (as is often the case) then one may empirically give 800-1000 mg (i.e. 20-25 of the 40 mg vials) and if there is no clinical response within 30 minutes a further infusion of digoxin immune Fab may be given.

**Table 2. Dose of digoxin immune Fab fragments per 250 µg digoxin tablet ingested**

Number of 250 µg digoxin tablets ingested	Dose of digoxin immune Fab in mg
25	340
50	680
75	1000
100	1360
150	2000
200	2680

In patients with digoxin poisoning, plasma concentrations of *free* digoxin reduce to undetectable levels within several minutes following the completion of the 15-30 minute infusion of digoxin immune Fab and remain low for about 8-12 h. However, the total bound digoxin rises rapidly (i.e. to 10-20 times the preinfusion value) due to the increase in circulating pharmacologically inactive digoxin-Fab complex. Thus, an initial plasma digoxin level is all that is required because further total digoxin levels will be high and of little clinical use. If plasma levels of *free* digoxin can be performed, then these may allow one to assess and even modify therapy with digoxin immune Fab.<sup>139</sup> Accurate determinations of total plasma digoxin levels can be performed 4-7 days after the digoxin immune Fab infusion.

The elimination half-life of the digoxin-Fab complex ranges from 14 - 20 h. Digoxin immune Fab fragments may be used in patients with renal failure, although the half-life and elimination mechanisms are unknown.

Improvement in signs and symptoms of digoxin toxicity are apparent within 30 minutes after completion of the infusion, and complete reversal of toxicity (including hyperkalaemia and digoxin induced thrombocytopenia) occurs within 2-6 h.

The hyperkalaemia associated with digoxin toxicity is characteristically resistant to conventional treatment<sup>140</sup> and as it resolves rapidly with digoxin immune Fab



fragments, it requires no specific treatment. Furthermore, hypokalaemia often follows the Fab fragment infusion and may require intravenous  $K^+$  supplementation. The patient should be continuously monitored for 24 h in an intensive care unit and 2-4 hourly plasma  $K^+$  estimations should be performed.<sup>141</sup> In a case of digoxin poisoning and refractory ventricular tachycardia, intravenous magnesium sulphate abolished the ventricular tachycardia and reduced the serum potassium from 5.7 to 4.8 mmol/L.<sup>142</sup> The report suggested that the magnesium sulphate blocked the cardiac glycoside-induced egress of potassium from the intracellular to the extracellular compartment (a mechanism which is supported by experimental studies).<sup>143</sup>

Digoxin immune Fab fragments (usually the empirical dose, i.e. 800-1000 mg and repeated after 30 minutes if signs of toxicity return) have also been used to treat cardioactive steroid (i.e. cardiac glycosides and cardiac genins) toxicity associated with toad venom or Chan Su poisoning (due to bufalin, cinobufagin and resibufogenin),<sup>144,145</sup> oleander intoxication (due to oleandrin, nerine, oleandroside and digitoxigenin),<sup>145,146</sup> and red squill poisoning (due to proscillaridin and scilliroside).<sup>147</sup>

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