ANAESTHETIC PROBLEMS ASSOCIATED WITH THE TREATMENT OF CARDIOVASCULAR DISEASE: I. DIGITALIS TOXICITY

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ABSTRACT

Digitalis intoxication is still a common clinical problem affecting a fifth to a quarter of all digitalized patients. In the surgical patients there are many factors – including fluid, electrolyte and acid-base disturbances, hypoxaemia, abnormal renal function and drug interactions – that can enhance the sensitivity of the heart to digitalis. Unfortunately, the cardiac as well as other systemic signs of digitalis toxicity are non-specific and the difference between therapeutic and toxic serum concentrations is ill-defined. Clinical acumen together with a knowledge of the preparation being used, its pharmacokinetics, factors that can enhance the sensitivity of the heart, and the serum concentration is still necessary in the diagnosis of toxicity.

Whether to proceed with anaesthesia and operation in the toxic patient depends on the urgency of surgery. Elective surgery should be postponed until toxicity subsides. In an emergency, the urgency of the operation precludes any delay, and cardio-toxicity should be treated aggressively before, during and after operation.

Treatment of digitalis toxicity should include the withdrawal of the cardiac glycoside and the elimination of all factors enhancing the toxic effects of digitalis. When the arrhythmia is causing haemodynamic instability or when there is ventricular irritability, treatment with anti-arrhythmic agents is indicated. Potassium chloride, lidocaine and diphenylhydantoin are the drugs of choice in the treatment of tachyarrhythmias and ventricular premature beats. Atropine can be used to counteract the vagal effect of digitalis in bradycardia and heart block. If atropine is ineffective, the placement of a temporary artificial pacemaker may be necessary. When congestive heart failure is a complication, the use of a vasodilator to decrease ventricular preload and afterload will improve the mechanical efficiency of the heart, increase cardiac output and relieve pulmonary congestion.

KEY WORDS: ANAESTHESIA, cardiovascular disease; HEART, digitalis toxicity; TOXICITY, digitalis.

THE CARDIOTONIC EFFECT of cardiac glycosides has been known to man since the Romans.¹ They are not only the most useful drugs in the treatment of congestive heart failure, but also some of the most toxic agents in the pharmacopoeia. Despite the purity of modern preparations and vigorous standards of bioavailability, digitalis* toxicity remains a common problem affecting a fifth to a quarter of all treated patients.^{2,3}

While the digitalized patients pose no new anaesthetic problems, the toxic patients behave

differently. During operation and in the post-operative period there are many factors – including fluid, electrolyte and acid-base disturbances, hypoxaemia, abnormal renal function and drug interactions – that can accentuate this life-threatening complication. In the following discussion the pharmacology of digitalis, factors enhancing its toxic action and the anaesthetic implication of digitalis toxicity are reviewed.

THE MOLECULAR BASIS OF THE INOTROPIC AND CARDIOTOXIC EFFECTS OF DIGITALIS

It is now realized that digitalis has inotropic effects on both normal and failing hearts. Its inotropic effects increase linearly as a function of dose and cardiotoxicity occurs at a higher dose range without affecting contractility. There is considerable overlap between therapeutic and cardiotoxic serum concentrations.⁴ The inotropic and toxic actions of digitalis are mediated

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*In this review, "digitalis" is used synonymously to represent all cardiac glycosides.

FIGURE 1 The sodium-potassium coupled and the sodium-calcium coupled transport system of myocardial cell membrane. (Please refer to text for details.)

through the inhibition of the transmembranous active transport of sodium and potassium.⁵ The toxic action is merely a more advanced stage of the same process.

In the resting cardiac cell, there is a resting membrane potential of approximately -90 mV and a transmembranous ionic concentration difference, with a high intracellular potassium and a high extracellular sodium concentration.⁶ This ionic concentration difference is maintained by the selective permeability of the membrane and by an ATP dependent membrane transport system⁷⁻⁹ known as the sodium-potassium pump (Figure 1); sodium ions are actively returned to the extracellular fluid in exchange for potassium ions. Sodium is also coupled to calcium in another membrane transport system in which sodium efflux is linked to calcium influx.¹⁰ This sodium-calcium transport system is relatively inactive when the intracellular sodium concentration is low.

The role of calcium ions in excitation-contraction coupling is summarized in Figure 2. In the myocardial cell, there are interdigitating actin and myosin filaments. In the resting state, interaction between actin and myosin is inhibited by a troponin-tropomyosin complex.¹¹ With the development of depolarization and a change in the permeability of the cell membrane, the intracellular calcium ion concentration increases as a result of the influx of calcium ions from the extracellular fluid and the release of bound calcium from the sarcoplasmic pool. Calcium binding of the troponin-tropomyosin complex releases its inhibition on actin-myosin interaction. Cross-bridges form across the filaments and contraction occurs. Furthermore, a myosin-ATPase is stimulated. ATP is hydrolyzed to ADP, releasing the energy necessary for contraction.

Digitalis inhibits the ATP dependent sodium-potassium pump^{12,13} and leads to a net loss of potassium and a net gain of sodium in the intracellular compartment. This increase in intracellular sodium ionic concentration stimulates

FIGURE 2 The role of calcium ions in the excitation-contraction coupling of cardiac muscle. T-T = troponin-tropomyosin complex. (Please refer to text for details.)

the sodium-calcium transport system. Consequently, calcium uptake and turnover is enhanced,¹⁴⁻¹⁶ the efficiency of excitation-contraction coupling improves and myocardial contractility increases.

Cardiotoxicity of digitalis is the result of a more advanced stage of inhibition of the sodium-potassium membrane transport and an excessive loss of intracellular potassium. At this stage the configuration of the action potential is affected. Disorders of impulse formation and impulse conduction ensue.

The action potential of a typical automatic or conducting cardiac cell can be described in 5 phases⁶ (solid line in Figure 3): phase 0 is the phase of depolarization while 1, 2 and 3 are phases of repolarization and phase 4 is the resting period during which there is a slow rate of depolarization (pre-potential or diastolic depolarization). The pre-potential is the result of a small net movement of sodium into the cell (a sodium leak). When the pre-potential reaches a threshold value (threshold potential) phase 0 begins. The

FIGURE 3 The action potential of an automatic or conducting cardiac cell. Solid line = normal cell. Broken line = digitalized cell. (Please refer to text for details).

sequence of depolarization (sodium influx) and repolarization (potassium efflux) is repeated.

With digitalization, the configuration of the action potential is changed⁵ (broken line in Figure 3): the resting potential is less negative than normal and approaches the threshold potential, the rate of phase 4 depolarization or sodium leak is increased¹⁷ and there is an accompanying increase in automaticity and enhanced activity of secondary pacemaker tissues (ectopic activities). With toxic doses, ventricular excitability (responsiveness to electrical stimulus) is depressed. At the same time, the rate of phase 0 depolarization is slowed; the velocity of impulse conduction depressed.¹⁸⁻²¹ With the exception of A-V nodal tissue, digitalis also shortens the duration of the action potential, mostly by shortening the effective refractory period.^{22,23} This combination of increased automaticity, depressed impulse conduction and shortened effective refractory period predisposes to the development of re-entrant arrhythmias.⁵

Digitalis also has a vagomimetic effect on the S-A and A-V nodes.²⁰ A toxic concentration will suppress the pacemaker activity of the sinus node and depress A-V nodal conduction. These vagal effects can be reversed by the administration of atropine.

THE CLINICAL MANIFESTATIONS OF DIGITALIS INTOXICATION

Digitalis intoxication affects many systems.^{1,24,25} These systemic manifestations are non-specific, but their presence should suggest the possibility of cardiotoxicity.

Gastro-intestinal Signs

Gastro-intestinal complaints are among the early indications of digitalis intoxication. Anorexia, nausea and vomiting are the commonest. They arise from the effect of digitalis on the chemoreceptor trigger zone of the medulla and are not direct effects on the gastro-intestinal tract. Other symptoms include diarrhoea and abdominal discomfort.

Neurological Signs

Early neurological symptoms include general malaise, easy fatigability and headache. Paraesthesia and neuralgia are also common. More severe central nervous system intoxication will result in confusion, delirium and convulsions. Psychiatric manifestations ranging from anxiety and depression to frank psychosis may also be present.

Ophthalmic Signs

The typical yellow vision, though commonly quoted in standard medical textbooks, is relatively rare.²⁶ Other visual disturbances include photophobia, halos around objects, light flashes, scotomata and blurring of vision.

Dermatological Signs

Skin reactions are rare and are not necessarily a manifestation of true toxicity. Gynaecomastia has been reported in male patients and in post-menopausal female patients.²⁴

Cardiac Signs

Other systemic complaints do not always precede cardiac complications. Arrhythmia is the first evidence of digitalis toxicity in one third of all patients.²⁴ Although no particular arrhythmia is pathognomonic of digitalis toxicity, ventricular extrasystole, particularly bigemini, and various degrees of heart blocks are more common than others.²⁷ Other arrhythmias include sinus, atrial, junctional and ventricular tachycardias, sinus bradycardia, sino-atrial arrest and block, atrial and ventricular fibrillations. More than one type of arrhythmia can coexist in the same patient. Depression of the S-T segment and inversion of the T-wave seen in the digitalized patient are nonspecific changes and do not indicate toxicity.

Precipitation of congestive heart failure or worsening of existing heart failure is a common and a very deceptive complication of digitalis toxicity.²⁴ Misinterpretation can be fatal. Toxicity should be suspected if heart failure is intractable despite digitalis.

FACTORS ENHANCING THE CARDIOTOXIC EFFECTS OF DIGITALIS

Many factors increase the sensitivity of the heart to the arrhythmogenic effect of digitalis. They are partly responsible for the overlap of the therapeutic and toxic serum concentrations. Many of these factors are correctable.

Electrolyte Disturbances

The most common electrolyte disturbance enhancing digitalis toxicity is hypokalaemia.^{28,29} The depletion of intracellular potassium and an abnormal ratio between the intracellular and extracellular concentrations of potassium are determining factors.³⁰ The use of diuretics is a common cause. Furthermore, the myocardial uptake of digitalis is increased by hypokalaemia,^{31,32} while binding to the sodium-potassium pump is inhibited by hyperkalaemia.¹² Therefore, enhancement of digitalis toxicity can still be seen when serum potassium is at the lower limits of normal and hyperkalaemia endows some protection. In the surgical population, gastrointestinal pathology is often accompanied by loss of fluid and electrolytes and rapid correction of fluid depletion and acid-base abnormalities is accompanied by re-distribution of potassium. These patients are vulnerable to digitalis intoxication. Similarly, in the patient with chronic renal failure, digitalis cardiotoxicity can evolve during dialysis when the serum potassium is returned to lower values.

A high serum calcium concentration (7.5 mmol/l or more) will increase the sensitivity of the heart to digitalis.³³ Hypercalcaemia should be suspected in surgical patients with metastatic breast or bronchogenic carcinomas, hyperparathyroidism, hyperthyroidism, milk alkali syndrome and Paget's disease of bone. Hypomagnesaemia, also a complication of diuretic therapy,³⁴ will increase the arrhythmogenic effects of digitalis.^{28,35} Blood pH per se has no effect but acute metabolic alkalosis, accompanied by a shift in extracellular potassium, enhances the sensitivity of the heart to digitalis while acidosis offers some protection.³⁶

Respiratory Disease and Hypoxaemia

Patients with chronic obstructive lung disease or respiratory insufficiency and patients with acute hypoxaemia are very sensitive to digitalis.^{37,38} Since ventilation-perfusion abnormalities are always complications of anaesthesia, the development of hypoxaemia and hypercar-

bia, which enhanced digitalis toxicity, is a real possibility in the anaesthetized patient.

Neuro-endocrine Factors

Beta-adrenergic stimulation of the heart increases digitalis-induced arrhythmias.³⁹ Whether depletion of myocardial catecholamine with reserpine offers any protection is not settled.^{40,41} The thyroid function of the patient influences the sensitivity of the heart by an unknown mechanism⁴² – the hypothyroid patient is sensitive and the hyperthyroid patient resistant.^{43,44}

Physiological Status

Age is an important consideration when prescribing digitalis. Children have a remarkable tolerance and geriatric patients are very sensitive.^{45,46} It is often said that digoxin, 0.25 mg/day, is excessive in many patients over the age of 65 years. Since digitalis is also bound to skeletal muscle, its requirement is reduced in patients with loss of muscle mass. This may be one of the reasons of the increased sensitivity in the aged.

Renal Function

Digoxin, the most popular member of the group, is almost entirely excreted unchanged by the kidney. Elimination is by glomerular filtration and tubular secretion.⁴⁷ Renal excretion is closely related to the renal clearance of creatinine.⁴⁸ Hence, impaired renal function is the most important cause of digoxin intoxication. In severe renal failure, this can occur even in the presence of hyperkalaemia and hypermagnesaemia. However, digoxin is still a popular choice in patients with renal failure because of the predictability of its pharmacokinetics.⁴⁹ Its plasma half-life is prolonged from a normal of 36 hours to three and a half to five days in advanced renal failure. The maintenance dose should be reduced to a quarter to a half of normal accordingly.⁴⁸

Hepatic Function

Digitoxin, the second most popular member of the group, is broken down by the liver to inactive metabolites which are then excreted by the kidney. The plasma half-life is five to seven days. Its hepatic metabolism is enhanced by all agents that induce the proliferation of hepatic microsomal enzymes.^{50,51} If enzyme inducing agents given to these patients concurrently are stopped, digitoxin requirement will be reduced and toxicity may develop. If liver function is impaired or if

hepatic blood flow is reduced, the maintenance dose should be decreased.

Type and Severity of Heart Disease

It is paradoxical that the more severe the heart disease, the more sensitive the heart is to digitalis intoxication.⁴ Cardiotoxicity is more common in patients who need digitalis most. Patients with ischaemic heart disease, particularly after an acute myocardial infarction, are especially sensitive.

Digoxin-Quinidine Interaction

It has been reported that when digoxin and quinidine are given concurrently, the total body clearance, renal clearance and volume of distribution of digoxin are all reduced, while its half-life remains unchanged.⁵² These changes in the pharmacokinetics of digoxin are reflected in higher plasma concentrations.⁵³ Although the clinical significance of these findings has not been fully assessed, it is suggested that the dose of digoxin be reduced when quinidine is administered.

Anaesthetic Agents

The effects of anaesthetic agents vary. Halothane,^{54,55} enflurane,⁵⁶ ketamine, droperidol, Innovar⁵⁷ and d-tubocurarine⁵⁸ increase the tolerance of the heart to digitalis-induced arrhythmias while sodium thiopentone⁵⁵ and fentanyl⁵⁷ have no effect. On the other hand, succinylcholine,⁵⁸ neostigmine⁵⁹ and diazepam⁶⁰ induced ventricular arrhythmias have been reported in digitalized subjects. Clinical reports of interactions between anaesthetic agents and digitalis are anecdotal in nature. Most of the quoted findings were obtained from animal experiments. These findings do not necessarily imply that these anaesthetic agents are contraindicated in the digitalized patient.

ANAESTHETIC IMPLICATIONS

All cardiac glycosides have a low therapeutic ratio and many factors can enhance their toxic action in the surgical patient. The seriousness of digitalis cardiotoxicity demands a careful pre-operative assessment of all digitalized patients.

The Use of Serum Concentration Assay

Due to the non-specificity of the systemic and cardiac toxic manifestations of digitalis, attempts have been made to improve the diagnosis of tox-

icity by the assay of serum concentration. Radio-immunoassay of digoxin⁶¹ or digitoxin⁶² serum concentration is now a well established technique.

The therapeutic concentration of digoxin⁶³ is between 0.5 to 2.5 ng/ml. In the range of 2.0 to 3.0 ng/ml the therapeutic and toxic concentrations overlap. The absolute serum concentration of digoxin may vary from laboratory to laboratory. Spurious high levels may be reported in the presence of haemolysis and hyperbilirubinaemia⁶⁴ and if the specimen is drawn less than four hours after an intravenous dose or eight hours after an oral dose.⁶³ On the contrary, spuriously low levels may be reported if the patient has hypoalbuminaemia, uraemia, or if he has been exposed to iodine-125 within the last twenty-four hours.⁶⁴

The therapeutic serum concentration of digitoxin is approximately 10 times that of digoxin.⁴ The range of overlap between non-toxic and toxic concentrations tends to be even greater than that of digoxin. The antibodies used are immunospecific for each cardiac glycoside. Failure to identify the proper cardiac glycoside to be assayed will lead to improper interpretation and potentially fatal mistakes.⁶⁵

The wide range of overlap between therapeutic and toxic levels has cast doubts on the usefulness of serum concentration alone in the diagnosis of digitalis toxicity in recent years.^{66,67} It certainly should not be used as a routine diagnostic test, but is indicated in the following situations:⁶⁸

- (1) When digitalization is contemplated in a patient whose drug history is unobtainable.
- (2) To determine whether a patient is receiving digoxin or digitoxin.
- (3) In the patient who shows unexpected sensitivity or resistance to digitalis.
- (4) In the patient who has developed clinical signs suggestive of digitalis toxicity. Here, it is useful in differentiating between arrhythmias due to digitalis toxicity or intrinsic heart disease.

Otherwise, the diagnosis of digitalis toxicity must still be based on clinical acumen in which the history of medication, the type and dose of digitalis preparation employed, factors affecting pharmacokinetics, factors known to affect the sensitivity of the heart, and the systemic and electrocardiographic evidence of toxicity are considered together with the serum concentration. Only the disappearance of symptoms and signs of toxicity following the withdrawal of digitalis is an absolute proof of intoxication.

Whether to proceed with anaesthesia in the toxic patient depends entirely on the urgency of surgery. Elective operations should be postponed until cardiotoxicity subsides; even the mildly toxic patient can behave unpredictably during operation and in the postoperative period. To proceed without waiting for digitalis toxicity to subside is to court disaster. When surgery is urgent, this urgency outweighs all other risks. Cardiotoxicity should be treated aggressively without delay. When it is under control, anaesthesia and operation can proceed. A little time well spent in the preoperative preparation of the patient will save endless anxiety afterwards.

No single anaesthetic agent is contraindicated in the digitoxic patient, but agents known to induce arrhythmias in digitalized patients should be given with caution. During the operation special attention should be paid to the monitoring of cardiac rhythm and circulatory dynamics; fluid, electrolyte and acid-base balance and normal renal function should be maintained.

THE MANAGEMENT OF DIGITALIS TOXICITY

The treatment of cardiotoxicity can be graded according to its severity and urgency. When the arrhythmia is relatively benign and in the absence of ventricular irritability, haemodynamic disturbance and urgency, the following measures are usually adequate:

- (1) Withhold digitalis and diuretics.
- (2) Correct hypokalaemia. Give potassium salt, 4 to 8 g/day, in divided doses.
- (3) Identify and eliminate all other correctable factors that enhance digitalis toxicity.

Generally speaking, toxicity will subside in two to three days and the dosage of digitalis, diuretic and potassium supplement can be adjusted.

In the more urgent situation and when cardiotoxicity is severe, aggressive treatment is necessary. Naturally, digitalis and diuretics should be withdrawn, and factors enhancing toxicity eliminated. The pharmacological treatment of digitalis induced arrhythmias varies according to the nature of the disturbance of rhythm.^{26,69,70}

The Treatment of Tachyarrhythmias and Extrasystoles

Supraventricular and ventricular tachyarrhythmias and ventricular premature contractions associated with digitalis toxicity can be controlled with a number of anti-arrhythmic agents:

Potassium Salts

Hypokalaemia must be corrected. In the presence of ventricular extrasystoles, potassium should be administered even when the serum potassium concentration is in the lower range of normal. This is an attempt to replace potassium depletion and to reverse the electro-physiological process of digitalis cardiotoxicity. Potassium chloride, 20 to 40 mmol, diluted to 100 ml in five per cent dextrose solution, can be given intravenously over one to two hours under constant electrocardiographic monitoring. Further supplements can be given according to serum potassium level. However, potassium itself, like digitalis, will prolong A-V nodal conduction. It is contraindicated in the presence of second or third degree heart block. It is also contraindicated in the presence of renal failure.

Lidocaine (Xylocaine®)

Lidocaine is the drug of choice in the treatment of digitalis-induced ventricular irritability.^{71,72} In therapeutic concentrations it reduces the enhanced automaticity of subsidiary pacemakers without affecting myocardial contractility and A-V nodal conduction. However, it is not very useful in the treatment of supraventricular arrhythmias. The recommended dose is 1 mg/kg given as a bolus followed by 2 to 4 mg/min in a continuous intravenous infusion of appropriate dilution (e.g., 1 g in 500 ml of five per cent dextrose solution giving 2 mg/ml).

Diphenylhydantoin (Dilantin)

Diphenylhydantoin is another agent which reduces ventricular irritability without affecting contractility. It also suppresses supraventricular arrhythmias induced by digitalis and has the added advantage of enhancing A-V conduction which is slowed by digitalis.⁷¹⁻⁷⁴ It is the drug of choice in the treatment of supraventricular tachyarrhythmias with or without A-V block. The recommended dose is 20 mg/min given through a fast running intravenous infusion. It should be stopped when the arrhythmia is abolished or when undesirable effects appear.⁷⁵ A total dose of 1000 mg should not be exceeded. Its effect is almost immediate. If no response is seen after several minutes, it will probably be ineffective. During its administration, constant electrocardiographic and blood pressure monitoring is mandatory. Shortening of the P-R and Q-T intervals is part of the therapeutic effect. The deterioration of ventricular arrhythmias, the de-

velopment of A-V block and the onset of drowsiness, nystagmus, vertigo, nausea or hypotension are toxic reactions to diphenylhydantoin or its solvent which is 40 per cent propylene glycol and ten per cent ethanol.

Propranolol (Inderal)

The disadvantage of propranolol in the treatment of both ventricular and supraventricular arrhythmias induced by digitalis is the depression of myocardial contractility and a further prolongation of A-V conduction.⁷⁶ Therefore it is contraindicated in the presence of existing heart block or congestive heart failure, unless further supportive measures are instituted. Being less effective than lidocaine or diphenylhydantoin in the treatment of digitalis-induced ventricular tachycardias,⁷¹ it should not be regarded as the drug of first choice. When both lidocaine and diphenylhydantoin are unsuccessful, propranolol may be given intravenously in small increments up to a total dose of 0.1 mg · kg⁻¹.

If A-V block is already present or develops before control is obtained, a transvenous pacemaker should be inserted before initiation of therapy or administration of further increments.

Other Drugs

Procainamide (Pronestyl) is still a popular agent in the treatment of ventricular arrhythmias and some supraventricular arrhythmias, but its usefulness in the treatment of digitalis-induced tachyarrhythmias has largely been superseded by superior agents.⁷⁷ However, other authors still find it useful in the treatment of some toxic arrhythmias, particularly paroxysmal atrial tachycardia with block in the absence of hypokalaemia.²⁶ One hundred milligrams should be given slowly every five minutes until the arrhythmia is controlled. The total dose should not exceed 1000 mg. Since hypotension and excessive widening of the QRS complex or prolongation of the P-R interval are warning signs of myocardial toxicity, patients should be monitored appropriately when procainamide is being administered.

Although bretylium tosylate (Bretylate), a sympatholytic agent, has been used in the treatment of digitalis-induced ventricular arrhythmias,⁷⁸ it cannot be recommended because the initial release of catecholamines caused by this agent may actually aggravate digitalis toxicity.⁷⁹

Cardioversion

Cardioversion is usually contraindicated in digitalis-induced tachyarrhythmias because even more severe and bizarre ventricular arrhythmias have occurred after countershock.⁸⁰ However, direct current (D.C.) countershock is sometimes necessary in tachyarrhythmias resistant to drug therapy. It is a desperate measure and should not be undertaken unless all correctable factors have been eliminated. When it is essential to proceed, low energy level and small graded increments should be employed; start with the lowest energy level possible and certainly not more than 25 joules.⁷⁰ Lidocaine^{69,81} or diphenylhydantoin⁸² should be given immediately before cardioversion to suppress ventricular irritability often seen after cardioversion in the digitalized patient. If propranolol is used instead of lidocaine or diphenylhydantoin, the prophylactic placement of a transvenous pacemaker is advisable.

The Treatment of Bradyarrhythmias and A-V Block

If time permits and if the patient's state is stable, it is only necessary to withhold digitalis and allow the automatic and conducting tissues of the heart to recover. Potassium should not be administered unless hypokalaemia can be demonstrated. When operation is urgent or when bradycardia is complicated by syncope, hypotension or heart failure, atropine 0.6 to 1.2 mg, should be given intravenously. This will often restore normal sinus rhythm with an acceptable rate and blood pressure. When atropine is unsuccessful, the placement of a transvenous pacemaker^{26,83} is warranted before proceeding with anaesthesia and operation. Administration of catecholamines is contraindicated because they enhance ventricular irritability.³⁹

The Treatment of Concomitant Congestive Heart Failure

Congestive heart failure is often a complication of digitalis toxicity. When this is secondary to an arrhythmia, it will improve when the arrhythmia is controlled. If myocardial disease is severe, withdrawal of digitalis should be accompanied by other means of circulatory support. The use of a peripheral vasodilator [nitroprusside or nitroglycerine] to reduce preload and afterload of the heart will improve its mechanical efficiency, enhance cardiac output and relieve pulmonary congestion.⁸⁴

The Role of Cholestyramine

Twenty-five to 30 per cent of digitoxin undergoes entero-hepatic circulation.⁶⁸ Orally administered cholestyramine⁶⁵ (a steroid binding resin), colestipol and activated charcoal⁶⁸ can bind this portion of the cardiac glycoside and prevent its re-absorption. Its half-life will be shortened and the serum concentration will fall. In contrast to previous findings, digoxin has been also reported to undergo significant entero-hepatic circulation.^{86,87} Cholestyramine 4 g three times a day is a useful adjunct in the treatment of toxicity due to digitoxin and digoxin.

Experimental Treatments of Digitalis Intoxication

Digitalis specific antibody fragments of animal source have been used successfully in the treatment of massive digoxin overdose in attempted suicide.⁸⁸ Purified preparations of these antibodies with low antigenicity are being developed for general clinical use. The reversal of toxicity is rapid in onset because the binding of digitalis to cellular receptors is reversible.

In experimental animals, potassium canrenoate⁸⁹, an aldosterone antagonist, has been shown to abolish the toxic electrophysiological manifestations of ouabain without abolishing its inotropic effect. This compound will be very useful in the treatment of digitalis toxicity if these animal data are found applicable to man.

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RÉSUMÉ

L'intoxication digitalique est un problème fréquent que l'on peut retrouver chez le quart des malades digitalisés. Le malade chirurgical est particulièrement susceptible de se retrouver dans des situations où la sensibilité du myocarde à la digitale est augmentée: perturbations liquidiennes, électrolytiques et acido-basiques, hypoxémie, fonction rénale anormale et interactions médicamenteuses. Malheureusement, les signes cardiaques et systémiques d'intoxication digitalique ne sont pas spécifiques et la limite entre les concentrations sériques thérapeutique et toxique de la digitale sont mal définies. Le flair clinique, la connaissance de la pharmacologie des préparations utilisées et des facteurs qui peuvent modifier la sensibilité myocardique à la digitale, ainsi que la détermination des concentrations sériques de cet agent sont nécessaires pour établir le diagnostic d'intoxication digitalique.

La décision d'anesthésier et d'opérer un malade en intoxication digitalique est basée sur la présence ou l'absence d'urgence. La chirurgie électorale devrait être retardée jusqu'à disparition de l'intoxication. En situation d'urgence, on devrait procéder sans délai à la chirurgie en prenant des mesures thérapeutiques agressives avant, durant et après l'intervention.

Le traitement de l'intoxication digitalique implique l'arrêt d'administration des glycosides cardiaques et l'élimination des facteurs qui augmentent la sensibilité du myocarde à la digitale. Lorsque la présence d'arythmies a des répercussions hémodynamiques ou en cas d'irritabilité ventriculaire, les an-

tiarythmiques sont indiqués. Le chlorure de potassium, la lidocaïne et la diphénylhydantoïne sont les agents de choix dans le traitement des tachyarythmies et extrasystoles ventriculaires. L'atropine peut antagoniser les effets vagues de la digitale en cas de bradycardie ou de blocs auriculo-ventriculaires. Si l'atropine s'avère inefficace, la mise en place d'une électrode temporaire de pacemaker peut se révéler nécessaire. En présence d'insuffisance cardiaque congestive, l'emploi des vasodilatateurs permet d'améliorer l'efficacité mécanique du myocarde, d'augmenter le débit cardiaque et de diminuer la congestion pulmonaire par leurs actions sur la pré-charge et la post-charge.