CURRENT SURVEY

Digitalis intoxication

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Introduction

Cardiac glycoside has probably been the most valuable drug available for our medical practice from the time digitalis was introduced by a British physician, William Withering in 1785.¹ It is well documented that cardiac glycoside is an essential drug in the management of congestive heart failure regardless of underlying heart disease and various supraventricular tachyarrhythmias, particularly atrial fibrillation with rapid ventricular response.²

It is unfortunate that there has been increasing incidence of digitalis toxicity in recent years because of the frequent usage of potent purified cardiac glycosides in conjunction with the potent diuretics which predispose to the development of hypokalaemia. The incidence of digitalis intoxication in general hospitals has been estimated to be approximately 20%.^{2, 3} Digitalis intoxication is often unavoidable because the margin between therapeutic and toxic doses is relatively narrow. This narrow margin becomes further reduced in elderly and seriously ill patients with various modifying factors such as hypokalaemia, myxoedema, hypoxia, pulmonary disease etc. It has been shown that the therapeutic dose is approximately 60% of the toxic dose.^{2, 4}

Although cardiac glycoside is an indispensable drug in the treatment of heart failure and various supraventricular tachyarrhythmias, the drug is no longer beneficial to the patient who develops toxic manifestations of digitalis.² The toxic manifestations are an essential feature of overdosage with the cardiac glycosides. It is common experience that digitalis intoxication may develop with a relatively small dose, which is either therapeutic or inadequate for other patients. This is especially true when there are various modifying factors; such as electrolyte imbalance, advanced age, myxoedema and advancement of underlying heart disease.⁵ Consequently, digitalis requirement varies from patient to patient

and within the same patient from time to time. Use of the standard dosage for digitalization without adjusting to the individual response is a common cause for digitalis toxicity. It is not uncommon to reach digitalis intoxication without achieving the desired therapeutic effect especially in patients with intractable congestive heart failure. In retrospect, otherwise inadequately explained death in patients with refractory congestive heart failure can often be attributed to digitalis intoxication. It should be pointed out that digitalis toxicity does not produce pathognomonic change in the heart at necropsy.

Although digitalis is certainly one of the oldest drugs and the most commonly used drugs, it is not possible for physicians to determine precisely the optimal therapeutic dosage of the drug.² The determination of serum digoxin or digitoxin value is widely utilized at many institutions in the United States of America as well as many European countries in order to assess the therapeutic and toxic doses of digitalis. However, its clinical implication is still not ideal because of a significant overlap between the therapeutic and toxic doses. Nevertheless, markedly increased serum digitalis level certainly indicates digitalis toxicity whereas a very low level usually indicates under-digitalization.⁶⁻⁹ Serum digitalis determination is extremely valuable when dealing with patients who suffer from intractable congestive heart failure and/or complex cardiac arrhythmias when little or no information regarding previous digitalization is available. Details of serum digitalis level determination will be discussed later in this paper.

The most common manifestations of digitalis intoxication are gastrointestinal disturbances, various cardiac arrhythmias, aggravation of pre-existing congestive heart failure or the development of new congestive heart failure, neurological disturbances and visual disturbances.² Common, uncommon and

TABLE 1. Manifestations of digitalis intoxication (Reproduced from Edward K. Chung, *Digitalis Intoxication*, Excerpta Medica, Amsterdam, 1969)

Symptoms	Frequency	Various manifestations
G-I symptoms	Common Uncommon	Anorexia, nausea, vomiting Diarrhoea, abdominal pain, constipation
Cardiac manifestations	Alteration of cardiac contractile forces Cardiac arrhythmias	Development of CHF or aggravation of pre-existing CHF Atrial, A-V nodal, and ventricular arrhythmias and A-V block
Neurologic disturbances	Common Uncommon	Headache, fatigue, insomnia, malaise, confusion, depression, vertigo Neuralgias (especially trigeminal), convulsions, paresthesiae, delirium, psychosis
Visual	Common Uncommon Rare	Colour vision (usually green or yellow) with coloured halos Blurring, shimmering vision Scotomata, micropsia, macropsia, amblyopias (temporary or permanent)
Rare manifestations	Rare	Allergic manifestations (urticaria, eosinophilia), idiosyncrasy, thrombocytopenia, gastro-intestinal haemorrhage and necrosis

G-I, Gastro-intestinal; CHF, congestive heart failure.

rare manifestations of digitalis intoxication are summarized in Table 1.

Gastro-intestinal symptoms

Anorexia is often the earliest sign of digitalis toxicity and it is usually followed by nausea and vomiting within 2 to 3 days if digitalization is continued.² Nausea and vomiting are considered to be central rather than gastric in origin, although direct gastric irritation may be partially responsible, particularly when a large initial dose of digitalis leaf is given. It is still uncertain whether digitalis-induced vomiting results from a direct stimulation of a vomiting centre in the medulla or reflexly from the heart. The central origin of vomiting is supported clearly by the fact that vomiting can be induced even after intravenous or intramuscular injections of digitalis.¹⁰ However, it is, at times, difficult to evaluate the occurrence of nausea and vomiting since these manifestations may be due to underlying heart failure itself and/or digitalis toxicity. In general, digitalis intoxication should be suspected when these gastro-intestinal symptoms reappear after a certain period of improvement. Digitalis toxicity is, needless to say, certain when other manifestations such as visual disturbances or cardiac arrhythmias co-exist. In addition, digitalis toxicity should also be strongly suspected when gastro-intestinal symptoms appear associated with a worsening of heart failure after a period of improvement. On rare occasions, certain patients may develop nausea and vomiting resulting from hypersensitivity to a small amount of a particular preparation of glycoside. In this circumstance, another preparation of cardiac glycoside may be tried.

Diarrhoea is a rather uncommon manifestation of digitalis toxicity and constipation or abdominal pain has been reported.² Gastro-intestinal symptoms are often not clearly evident in elderly patients, being probably masked by the severity of the congestive heart failure and cerebral insufficiency. It is well documented that most of the purified glycosides produce nausea and vomiting much less frequently than digitalis leaf. Thus, digitalis-induced arrhythmias are frequently the earliest manifestation of digitalis toxicity from these preparations.¹¹⁻¹⁴ When nausea and vomiting develop, and the possibilities of over- or under-digitalization are almost equal, digitalis should be discontinued immediately and these patients should be re-evaluated.

Visual and neurological manifestations^{2, 15, 17}

Green or yellow colour vision with coloured halos has been considered to be a pathognomonic feature of digitalis toxicity for many years. Other visual disturbances may include scotoma, blurring, shimmering vision, and less commonly, micropsia, macropsia, and temporary or permanent amblyopias. These visual manifestations may easily be unrecognized unless the physician inquires specifically for them.

Cardiac glycosides may produce various neurological symptoms including headache, fatigue, lassitude, insomnia, malaise, depression, confusion, delirium, and vertigo, and less commonly convulsions, neuralgias, especially trigeminal nerve, and paresthesiae, when toxicity develops. A tendency to psychosis in elderly individuals has been observed and in this case, the term 'digitalis delirium' has been used. Visual and neurological manifestations

usually develop later than gastro-intestinal symptoms or cardiac arrhythmias and most of the above-mentioned symptoms are less specific for digitalis toxicity than gastro-intestinal manifestations or arrhythmias, except for the colour vision. Furthermore, neurological symptoms are often difficult to evaluate in elderly individuals because these manifestations may be due to many other conditions, such as cerebrovascular accidents and chronic brain syndrome.

Rare manifestations

Allergic manifestations such as urticaria and eosinophilia, and idiosyncrasy are not true manifestations of digitalis intoxication.^{18, 19} Similarly, unilateral or bilateral gynaecomastia which develops during digitalis therapy does not seem to be a manifestation of digitalis toxicity although some investigators considered it as such.^{14, 15, 20} This author has seen several patients who have been doing very well without any other toxic manifestations after the development of gynaecomastia in spite of continued digitalis therapy. Therefore, gynaecomastia due to an oestrogen-like activity of digitalis is most likely not a toxic manifestation. Furthermore, digitalis-induced gynaecomastia seems to be duration-dependent rather than dosage-dependent because the gynaecomastia usually develops in patients receiving cardiac glycosides over more than 2 years.

A rare occurrence of digitoxin-induced thrombocytopenia was reported and it was considered to be a specific sensitivity reaction to digitoxin bound to the gamma-globulin fraction of the serum.²¹

Cardiac manifestations

There are two major cardiac manifestations induced by digitalis. These include alteration in contractility and digitalis-induced arrhythmias which often occur simultaneously

(1) Alteration of contractility

A worsening of pre-existing congestive heart failure or the development of new heart failure during digitalization is a not uncommon manifestation of digitalis toxicity.^{2, 18} As a result, intractable or refractory congestive heart failure is frequently due to digitalis intoxication and this may be much more common than is recognized. A worsening of congestive heart failure was the first manifestation of digitalis intoxication in 7.5% of 148 patients studied by Von Capeller and his associates.¹⁴ Various digitalis-induced arrhythmias, especially rapid ones, often aggravate pre-existing congestive heart failure but digitalis seems to effect myocardial function independently of electrophysiological effects. How-

ever, in many instances, it is not absolutely certain whether aggravation of congestive heart failure is due to some direct effect on the myocardium, electrolyte imbalance, digitalis-induced arrhythmias, or a combination of these. Regardless of the fundamental mechanism involved, all patients with intractable congestive heart failure should be carefully re-evaluated for possible digitalis toxicity.

(2) Digitalis-induced cardiac arrhythmias

Although cardiac glycoside is often essential in the treatment of most supraventricular tachyarrhythmias, the drug may produce almost every known type of cardiac arrhythmia via an alteration of impulse formation, conduction or both.² Recognition of digitalis-induced arrhythmias is extremely important because this may be not only the earliest but also the only sign of digitalis intoxication without any other clinical manifestation. This is observed more in recent years since the use of purified glycosides has become popular. Furthermore, hypokalaemia induced by frequent use of potent diuretics predisposes to the development of digitalis-induced cardiac arrhythmias.⁵

It has been estimated that various cardiac arrhythmias may occur in 80–90% of the patients with digitalis intoxication.² Various combinations of different cardiac arrhythmias are commonly observed in patients with advanced digitalis toxicity. It is not uncommon to observe that cardiac arrhythmias may change from one type to another in the same electrocardiographic tracing.

It should be emphasized that the classical digitalis effect (S-T, T-wave changes) in the electrocardiogram during digitalis therapy is completely independent of digitalis toxicity. This is observed because digitalis effect in the electrocardiogram may be absent in about two-thirds of the cases with digitalis toxicity.² Furthermore, striking S-T, T-wave changes are frequently observed in the absence of any evidence of digitalis toxicity. By the same token, other electrocardiographic findings such as a shortening of the Q-T interval, increased amplitude of the U waves, and peaking of the terminal portion of the T-waves, during digitalis therapy, do not indicate digitalis toxicity.

Ventricular bigeminy or trigeminy is probably the most common digitalis-induced cardiac arrhythmia. The next common one is A-V nodal (junctional) arrhythmias especially in the presence of pre-existing atrial fibrillation. It is important and interesting to note that the incidence of atrial fibrillation induced by digitalis was reported to be very high until 1959 but its incidence has suddenly declined since then (Table 2).^{2, 3, 11, 12, 14, 22–28} Instead of atrial fibrillation, an incidence of A-V nodal (junctional) arrhythmias in digitalis intoxication has in-

creased markedly since 1959 (Table 2).^{2,3,11,12,14,22-28} When we analyse this marked discrepancy, it is quite obvious that A-V nodal (junctional) arrhythmias in the presence of pre-existing atrial fibrillation had been misinterpreted as a simple atrial fibrillation until 1959. At present, it is generally agreed that digitalis-induced atrial fibrillation is extremely rare, whereas digitalis-induced non-paroxysmal A-V nodal tachycardia or A-V nodal escape rhythm is very common in our practice.²

Almost all types of cardiac arrhythmia may be induced by digitalis but some do not seem to be related to cardiac glycosides. The term non-digitalis-induced cardiac arrhythmias may be used in later instances. Non-digitalis-induced cardiac arrhythmias may include Mobitz type-II A-V block, parasyctole, bilateral bundle branch block of varying degree, sinus tachycardia and paroxysmal A-V nodal tachycardia.^{29, 30}

(i) *Disturbances of sinus impulse formation and conduction.* Digitalis may induce sinus bradycardia as a minor toxic effect but it may lead to more serious arrhythmias such as sinus arrest and sinoatrial (S-A) block when digitalization continues. A sudden reduction of the heart rate below 50/min should raise the possibility of digitalis intoxication in all adult patients during digitalization (Fig. 1). A slow pulse rate below 100/min in infancy has the same clinical significance. Sinoatrial block with or without Wenckebach phenomenon is not uncommon in digitalis intoxication, especially in children (Fig. 2).^{18, 31} Digitalis may be the most common cause of S-A block. Sinus tachycardia does not seem to be induced by digitalis. However, it should be noted that some patients with congestive heart failure may have persisting sinus tachycardia even after full digitalization. This is observed when the congestive heart failure is associated with other diseases such as

TABLE 2. Incidences of digitalis-induced cardiac arrhythmias^{2, 11, 12, 14, 22-25, 28}

	Rhythm									
	Herrmann (1944)	Flaxman (1948)	Crouch (1956)	Shrager (1957)	Von Capeller (1959)	Rodensky (1961)	Dreifus (1963)	Dubnow (1965)	Chung (1968)	Total
No. of patients	44	30	80	40	141	88	161	62	180	
AF	10	10	19	3	27	—	—	—	3	72 (10.0%)
A-V NT	—	—	—	—	8	8	74	—	44	134 (18.5%)
A-V NER	—	—	—	5	8	—	—	17	39	69 (9.5%)
A-V diss	—	—	9	1	—	25	—	17	75	127 (17.5%)

AF, Atrial fibrillation; A-V NT, A-V nodal tachycardia; A-V NER, A-V nodal escape rhythm; A-V diss, A-V dissociation

FIG. 1. Leads II-a, b, c, and d are continuous. Arrows indicate sinus P waves. This tracing shows marked sinus bradycardia (rate, 45/min) with A-V nodal (junctional) escape rhythm (rate, 52/min) producing incomplete A-V dissociation. Note frequent ventricular captured beats (marked CB).

chronic pulmonary diseases, hyperthyroidism, obesity and anaemia.

(ii) *Atrial arrhythmias.* It is well documented that various atrial tachyarrhythmias may be produced by digitalis although digitalis is often the drug of choice in their treatment. Atrial tachycardia is the commonest and is frequently associated with varying

degree A-V block² (Fig. 3). In this circumstance, the term 'PAT with block' has been used.²⁵ The importance of PAT with block induced by digitalis was emphasized because the arrhythmia was often found in serious underlying heart disease with a high mortality.^{22, 32} Although the frequent occurrence of digitalis-induced PAT with block is emphasized

FIG. 2. This tracing reveals sinus rhythm with intermittent 3 : 1 and 4 : 1 S-A block. Note that there are occasional A-V nodal escape beats (marked N). (The numbers represent hundredths of a second.) (Reproduced from Edward K. Chung, *Principles of Cardiac Arrhythmias*, Williams & Wilkins Co., Baltimore, 1971.)

FIG. 3. Arrows indicate P waves. The rhythm is atrial tachycardia (atrial rate, 200/min) with 2 : 1 A-V block. Left atrial and ventricular hypertrophy are evident. (Reproduced from Edward K. Chung, *Digitalis Intoxication*, Excerpta Medica, Amsterdam, 1969.)

repeatedly, its average incidence is only about 10% of the total digitalis-induced cardiac arrhythmias.^{2, 3, 11, 12, 14, 22-28}

This author² found twelve instances of atrial tachycardia with A-V block (Fig. 3) and three instances without A-V block among 180 cases with digitalis intoxication. A case of an unusual double atrial tachycardia induced by digitalis was reported previously.³³ A few cases of double supraventricular tachycardia consisting of simultaneous atrial tachycardia and A-V nodal tachycardia resulting in A-V dissociation has been reported.²

It has been said that carotid sinus stimulation frequently terminates PAT with block not due to digitalis toxicity and is ineffective when digitalis is the etiologic factor. However, I would like to emphasize the danger of applying carotid sinus stimulation to patients with suspected digitalis intoxication. It has been shown that some patients expired from ventricular fibrillation during or after carotid sinus stimulation. All of them had been critically ill and had received cardiac glycosides.³⁴⁻³⁷ Based on these observations, carotid sinus stimulation should be avoided as much as possible on patients who are taking even small amounts of digitalis.

As far as the fundamental mechanism responsible for the production of atrial tachycardia is concerned, the refractory period of the atrial musculature is markedly shortened by an indirect vagal stimulation action of digitalis. Thus, increased conductivity within the atrial muscle can produce various atrial tachyarrhythmias. A combination of

the depressive effect on the A-V conduction and the shortening effect on the atrial refractory period results in atrial tachycardia with varying degree A-V block.²

Atrial fibrillation or flutter may be produced by digitalis though very rarely. The exact reason why digitalis-induced atrial fibrillation or flutter is so rare, in comparison with atrial tachycardia, is uncertain. Although atrial premature contractions are not as common as ventricular ones, if the former occur, the ectopic P waves are frequently not conducted to the ventricles (non-conducted or blocked atrial premature contractions) in spite of relatively long coupling intervals² (Fig. 4). The combination of impaired A-V conduction and the increased excitability in the atria results in frequent non-conducted atrial premature contractions.

(iii) *A-V nodal (junctional) arrhythmias.* As mentioned previously in this paper, various A-V nodal (junctional) arrhythmias in digitalis toxicity are probably as common as ventricular premature contractions.² Digitalis induces various A-V nodal (junctional) arrhythmias, either due to passive impulse formation resulting in A-V nodal escape rhythm, or enhancement of A-V nodal impulse formation resulting in non-paroxysmal A-V nodal (junctional) tachycardia.

In my previous study,² sixty-nine of 180 patients had atrial fibrillation as the underlying rhythm, and all of them had either A-V nodal (junctional) escape rhythm (Fig. 5) or non-paroxysmal A-V nodal (junctional) tachycardia (Fig. 6), as a manifestation

FIG. 4. Leads V₁-a and b are continuous. Arrows indicate ectopic P waves which are not conducted to the ventricles (non-conducted atrial premature contractions). Some of the post-ectopic pauses are followed by A-V nodal escape beats (marked N). In addition, first degree A-V block is present (P-R interval, 0.23 sec). It is interesting to note that some sinus waves (marked X) following ectopic P waves are P-bizarre. This is termed 'aberrant atrial conduction (Chung's phenomenon)'. (Reproduced from Edward K. Chung, *Digitalis Intoxication*, Excerpta Medica, Amsterdam, 1969.)

FIG. 5. Atrial fibrillation with complete A-V block producing A-V nodal (junctional) escape rhythm (rate, 52/min).

FIG. 6. Atrial fibrillation with non-paroxysmal A-V nodal (junctional) tachycardia (rate, 71/min) producing complete A-V dissociation.

FIG. 7. This tracing shows atrial flutter (rate, 350/min) with independent non-paroxysmal A-V nodal (junctional) tachycardia (rate, 100/min) producing complete A-V dissociation. Arrows indicate atrial flutter waves. Note a ventricular premature contraction in lead V₁ (marked V). (Reproduced from Edward K. Chung, *Principles of Cardiac Arrhythmias*, Williams & Wilkins Co., Baltimore, 1971.)

of digitalis toxicity. Similarly, A-V nodal (junctional) tachycardia may be induced by digitalis in the presence of atrial flutter (Fig. 7) or even an artificial pacemaker-induced ventricular rhythm.

In advanced digitalis intoxication, exit block of varying degree may develop around the A-V nodal (junctional) pacemaker; so that the ventricular cycle may become slower and/or irregular (Fig. 8). When the exit block is of the Wenckebach type, the ventricular cycle may show regular irregularity (Fig. 9). Ventricular tachycardia may be closely simulated when A-V nodal (junctional) tachycardia has aberrant ventricular conduction especially in the presence of pre-existing atrial fibrillation (Fig. 10). On rare

occasions, double A-V nodal (junctional) rhythm or tachycardia may be produced by digitalis and this is a rare form of A-V dissociation (Fig. 11). In a previous study of double A-V nodal rhythm,³⁸ four out of five cases had unequivocal digitalis toxicity, so that the presence of this rare arrhythmia is almost a pathognomonic sign of digitalis intoxication.

(iv) *A-V conduction disturbances.* Digitalis may produce various degrees of A-V block resulting from both the direct and indirect actions of the drug. These actions are, needless to say, essential in the management of various supraventricular tachyarrhythmias especially atrial fibrillation. The degree of A-V block in digitalis intoxication depends largely

FIG. 8. Atrial fibrillation and A-V nodal tachycardia (rate, 76/min) with intermittent 2 : 1 exit block producing incomplete A-V dissociation. Note two ventricular premature contractions (indicated by arrows). (Reproduced from Edward K. Chung, *Digitalis Intoxication*, Excerpta Medica, Amsterdam, 1969.)

FIG. 9. A-V nodal (junctional) escape rhythm (rate, 57/min) with Wenckebach exit block and reciprocal beats occurring every third beat (numbers represent hundredths of a second).

FIG. 10. Leads II-a, b and c are continuous. The rhythm is atrial fibrillation and intermittent A-V nodal tachycardia (ventricular rate, 83/min) with aberrant ventricular conduction producing incomplete A-V dissociation. Note occasional ventricular fusion beats (marked F B). The QRS complexes indicated by X are normally conducted. (Reproduced from Edward K. Chung, *Digitalis Intoxication*, Excerpta Medica, Amsterdam, 1969.)

FIG. 11. This tracing shows double atrioventricular nodal rhythm associated with electrical alternans. Group A atrioventricular nodal pacemaker produces non-paroxysmal atrioventricular nodal tachycardia with a rate of 118/min and group B atrioventricular nodal pacemaker produces atrioventricular nodal escape rhythm with a rate of 43/min.

upon the dosage of the drug, underlying heart disease, pre-existing A-V conduction disturbances, and the possible presence of electrolyte imbalance.

Although first degree A-V block is one of the earliest manifestations of digitalis toxicity², some investigators fail to include it as a toxic manifestation of the drug. Thus, the true incidence of first degree A-V block is probably much higher than the reported incidence (12%).^{2, 3, 11, 12, 14, 22-28} However, there is no doubt that the further administration of digitalis frequently leads to higher degree A-V block and other digitalis-induced arrhythmias. In addition, digitalis-induced second or higher degree

A-V block is often followed by first degree A-V block when digitalis is stopped (Fig. 12). Therefore, first degree A-V block during digitalization should definitely be considered to be a manifestation of digitalis toxicity.

The average incidence of second degree A-V block by different series is estimated to be 11%.^{2, 3, 11, 12, 14, 22-28} Among second degree A-V block, Wenckebach (Mobitz type-I) A-V block is more common than 2 : 1 A-V block (Fig. 12). On the other hand, Mobitz type-II A-V block has not been reported as a manifestation of digitalis toxicity.² It is common to observe that Wenckebach

FIG. 12. Leads II-a and b are continuous. Arrows indicate P waves. This patient initially had a combination of 3 : 2 Wenckebach A-V block and 2 : 1 A-V block (leads II-a and b). Within 12 hr following a discontinuation of digitalis, second degree A-V block became first degree A-V block (lead II-c), and subsequently (several hours later), A-V conduction further improved (lead II-d).

FIG. 13. Atrial fibrillation with A-V nodal escape rhythm (marked N) due to complete A-V block and ventricular bigeminy (marked V).

A-V block and 2 : 1 A-V block co-exist in the same electrocardiographic tracing (Fig. 12).

High degree (advanced) or complete A-V block is very common in digitalis intoxication, when the underlying rhythm is atrial fibrillation (Fig. 5). In my previous study², digitalis-induced high degree or complete A-V block in the presence of atrial fibrillation was encountered in thirty-five among 180 cases. It has been said that digitalis intoxication is the second most common cause of complete A-V block.

(v) *Ventricular arrhythmias*. Ventricular premature contractions are the most common and often the earliest manifestation of digitalis toxicity in the adult population. The incidence has been reported to be approximately 50% of all digitalis-induced arrhythmias.^{2, 3, 11, 12, 14, 22-28} It has been known for many years that ventricular bigeminy is a hallmark of digitalis-induced arrhythmia. Digitalis intoxication is 100% certain when ventricular bigeminy co-exists with non-paroxysmal A-V nodal (junctional) tachycardia or A-V block, especially in the presence of atrial fibrillation (Fig. 13).

In children and normal adults, supraventricular

arrhythmias and A-V conduction disturbances are a more common occurrence than ventricular premature contractions. Thus, it can be stated that ventricular bigeminy or trigeminy induced by digitalis frequently occurs in the presence of a diseased myocardium particularly in the aged. Ventricular premature contractions may originate from a single focus or multiple foci. Multifocal ventricular premature contractions are more pathognomonic for digitalis intoxication than unifocal ones.

When ventricular premature contractions become frequent, particularly multifocal or bidirectional ones, ventricular tachycardia may develop producing unidirectional or bidirectional tachycardia or even ventricular fibrillation. The average incidence of ventricular tachycardia has been estimated to be 10% of all digitalis-induced arrhythmias.^{2, 3, 11, 12, 14, 22-28} If ventricular tachycardia persists, there is always the possibility of the development of ventricular fibrillation and sudden death. The mortality of patients with digitalis-induced ventricular tachycardia is extremely high (68-100%).^{2, 22}

Bidirectional ventricular tachycardia (Fig. 14) is

FIG. 14. Leads II-a and b, and leads V₁-a and b are continuous in each given lead. Arrows indicate atrial activities (rate, 200/min.) which represent atrial tachycardia. Some areas where atrial activities are not discernible probably represent intermittent exit block from atrial ectopic focus. In addition, there is bidirectional ventricular tachycardia with a rate of 150/min. Atrial and ventricular activities are independent so that complete A-V dissociation exists. (Reproduced from Edward K. Chung, *Digitalis Intoxication*, Excerpta Medica, Amsterdam, 1969.)

considered to be a more pathognomonic feature of digitalis toxicity than is unidirectional. This tachycardia is more common in advanced heart disease and frequently the basic atrial mechanism is atrial fibrillation, flutter or tachycardia² (Fig. 14).

Except for idioventricular rhythm, the mechanism of ventricular tachycardia or fibrillation is most likely similar to that responsible for the production of ventricular premature contractions. Enhancement of automaticity is probably responsible for the majority of digitalis-induced ventricular arrhythmias.²

Determination of serum digitalis level by radioimmunoassay methods

In the past 10 years, various methods have been developed to determine serum cardiac glycosides to assess an optimal therapeutic dosage and to diagnose digitalis toxicity with accuracy.^{6-9, 39-51}

In early 1950, Okita *et al.*⁴⁷ and later Doherty⁴² developed methods for accurate quantitation of ¹⁴C or tritium-labelled digitoxin and digoxin in the nanogram (10⁻⁹ g)/ml range which is well below the sensitivity of conventional physiochemical techniques. In 1964, a double isotope dilution derivative assay method was introduced by Lukas & Peterson.⁴⁸ By this method, accurate therapeutic blood levels of unlabelled digitoxin could be determined but the technique involved proved to be too complicated and time-consuming which apparently prevented

widespread clinical application. In 1965, Lowenstein^{46, 47} developed the red cell ⁸⁶Rb (rubidium) uptake assay method in which the therapeutic plasma concentration of digitoxin as well as of digoxin were determined. Subsequently, various investigators^{41, 51} have utilized this method with different modifications. In 1968, Burnett & Conklin⁴⁰ introduced a Na-K ATPase inhibition assay method for the determination of plasma digitoxin level and subsequently in 1969, Jelliffe⁴⁵ was able to measure the serum digoxin level by enzymatic isotopic displacement of ³H digoxin from Na-K ATPase.

The radioimmunoassay method most commonly used at present was first employed, by Oliver *et al.*,⁵⁰ for the determination of serum digitoxin level. Later, Smith *et al.*⁶⁻⁹ developed a radioimmunoassay method in measuring serum digoxin level.

Clinical implications of serum cardiac glycoside levels are based upon the fact that there is reasonably close correlation between blood and tissue contents of digitalis so that the blood levels reflect total body and myocardial concentrations. This important information was obtained by Doherty *et al.*⁴⁴ who observed a relatively constant ratio between blood and myocardial levels of digoxin in animals as well as humans.

At present, it is generally agreed that patients with unequivocal digitalis intoxication have significantly higher serum or plasma levels of digoxin or digitoxin

than nontoxic patients.^{6, 9, 39, 42-44, 46, 47-50} Nevertheless, substantial overlap between toxic and nontoxic serum or plasma cardiac glycosides levels can not be avoided.^{6-9, 42-44, 46, 47, 50} This is particularly true when dealing with problem patients who suffer from intractable congestive heart failure and/or various complex arrhythmias. As repeatedly emphasized, the dosage of digitalis not only varies from patient to patient but also it may vary from time to time even on the same patient.² Similarly, toxic and nontoxic serum or plasma digitalis levels may be different from patient to patient depending largely upon various modifying factors including electrolyte imbalance, thyroid diseases, renal diseases, acute or chronic lung disease, and particularly the nature and severity of underlying heart disease.

According to a prospective study of 931 consecutive patients with digitalis intoxication by Beller *et al.*,³⁹ serum concentrations of digoxin and digitoxin by radioimmunoassay methods in toxic patients were 2.3 ± 1.6 ng/ml and 34 ± 18 ng/ml, respectively. On the other hand, serum digoxin and digitoxin levels in nontoxic patients were 1.0 ± 0.5 ng/ml and 20 ± 11 ng/ml, respectively in the same study, significant overlap between toxic and nontoxic groups being observed.

In general, serum digoxin levels of 2.0 ng/ml or below, and serum digitoxin levels of 20 ng/ml or below are considered to be nontoxic although toxic patients may have serum levels below these values.^{6-9, 39} Very low (digoxin levels below 0.4 ng/ml or digitoxin levels below 10 ng/ml) serum cardiac glycosides concentrations usually indicate underdigitalization.³⁹ These low values are, as a rule, not observed among toxic patients.

Clinical usefulness of serum digoxin or digitoxin levels by radioimmunoassay methods is still far from ideal primarily because of the considerable overlap described. However, these methods are extremely valuable when the values of serum cardiac glycoside levels are interpreted in conjunction with the total clinical picture and electrocardiographic findings. Serum digitalis level determination is very useful when there is little or no information available as to previous digitalization. By knowing the serum digitalis level in a given patient an additional digitalis dosage may then be determined much more accurately. On the other hand, the serum digitalis level may indicate digitalis intoxication. In addition, serum digitalis levels are valuable when dealing with patients who have various modifying factors, where daily regulation of digitalis dosage is indicated. Another role of serum digitalis level determination is to assess under-digitalization which may be difficult or even impossible to ascertain clinically and/or electrocardiographically, especially in the presence of sinus rhythm.

In the near future, the most important role of the determination of serum digoxin or digitoxin levels by radioimmunoassay methods will be in establishing the optimal dose of digoxin or digitoxin in a given patient. Hopefully, these methods will enable many physicians to prescribe cardiac glycosides more effectively, so that digitalis intoxication can be minimized or even prevented.

Determination of saliva electrolytes

Recently, it has been shown that the electrolyte levels in the saliva have a close relationship with digitalis intoxication. Wotman *et al.*⁵² demonstrated that patients with digitalis intoxication have a disproportionately high concentration of potassium as well as calcium. This test also shows some overlapping between toxic and nontoxic groups although mean values of saliva potassium and calcium were significantly higher in the group with digitalis toxicity.⁵² Further clinical evaluation will be needed to assess the value of the saliva test.

In conclusion, it should be re-emphasized that the evaluation of the total clinical picture in each individual patient during digitalis therapy is essential rather than reliance upon the result of any single laboratory test.

Management of digitalis intoxication

Unfortunately, there is no known drug which has an antagonistic action to digitalis. Different agents have been tried in the treatment of digitalis intoxication with varied success. Among many agents, diphenylhydantoin (Dilantin, Epanutin) and potassium have proved to be the most effective in terminating various digitalis-induced tachyarrhythmias.²

The most important treatment of digitalis toxicity is, needless to say, the immediate withdrawal of the drug rather than reducing dosage.² Most patients with mild digitalis intoxication such as sinus bradycardia, first degree A-V block and occasional ventricular premature contractions can recover from digitalis toxicity by merely discontinuing the drug for several days. Generally, in patients with digitalis toxicity, emotional and physical activities should be restricted, and all factors which may aggravate the toxicity should be prevented and corrected. Any patient with advanced digitalis intoxication, particularly serious cardiac arrhythmias, should be treated in a cardiac care unit or a room with similar facilities. Various agents can be given orally, intramuscularly or intravenously depending upon the clinical situation. The usual dosages of different agents in the treatment of digitalis intoxication are summarized in Table 3.

(1) Potassium^{2, 53}

Potassium is probably one of the most effective agents in abolishing various atrial as well as ven-

TABLE 3. Treatment of digitalis intoxication (Reproduced from Edward K. Chung, *Digitalis Intoxication*, Excerpta Medica Amsterdam, 1969)

Drugs and other therapies	Mild toxicity	Severe toxicity	Contra-indications
Potassium	1-2 g KCl every 4 hr	Immediate withdrawal of digitalis! 40-60 mEq/l KCl in 500 ml 5% d/w i.v. infusion (1-3 hr period) under ECG monitor and periodic serum K ⁺ determination	Hyperkalaemia, uremia, second and third degree A-V block, S-A block
Dilantin, Epanutin (diphenylhydantoin)	100-200 mg by mouth t.i.d. or q.i.d.	125-250 mg i.v. injection (2-3 min period) under ECG monitor. Same dosage may be repeated every 5-10 min	Second and third degree A-V block, S-A block, marked sinus bradycardia
Xylocaine (lidocaine, lignocaine)		1 mg/kg body wt i.v. injection every 20 min (max. doses, 750 mg)	Same as Dilantin
Inderal (propranolol)	10-30 mg t.i.d. or q.i.d. before meals and at bed time	1-3 mg slow i.v. injection (not exceed 1 mg/min) under ECG monitor. Second dose may be repeated after 2 min. Additional medication should not be given less than 4 hr	Bronchial asthma, allergic rhinitis, marked sinus bradycardia, S-A block, second and third degree A-V block, cardiogenic shock, heart failure, pulmonary hypertension
Pronestyl (procaine amide)	0.5-0.75 g every 4-6 hr by mouth	50-100 mg every 2-4 min slow i.v. injection or 1 g in 200 ml 5% d/w i.v. drip (30-60 min period) under ECG monitor (max. doses, 2.0 g)	Same as Dilantin
Quinidine		0.6 g in 200 ml 5% d/w i.v. drip (30-60-min period) under ECG monitor	Same as Dilantin
Magnesium sulphate	Slow (1 ml/min) i.v. infusion (20 ml of 20% solution) under continuous ECG monitoring		
Sodium EDTA	Not recommended for clinical use		
DC countershock	Not recommended unless tried as a last resort after all available measures have been exhausted		
Artificial pacemaker	Temporary installation of an endocardial catheter pacemaker is indicated for third degree A-V block and occasionally for second degree A-V block or S-A block		

d/w, Dextrose in water; i.v., intravenous.

tricular tachyarrhythmias in digitalis intoxication. The amount of potassium administration depends upon the severity of the toxicity, degree of suspected potassium deficiency in the myocardium and the response to potassium therapy. Potassium is definitely contra-indicated in the presence of renal failure and hyperkalaemia. Potassium is also relatively contra-indicated in the presence of second degree or complete A-V block unless the serum potassium is proved to be very low. Potassium in the form of potassium chloride may be administered orally in doses of 20-80 mEq/l daily or by a slow intravenous infusion in doses of 40-60 mEq/l over a 2-3-hr period initially. Intravenous administration is preferred because the exact amount received by the patient can be controlled and the drug may be discontinued at any time when indicated. Oral administration is widely used for milder cases with digitalis toxicity when hypokalaemia is suspected or present. During intravenous administration of potassium, con-

tinuous electrocardiographic monitoring is essential in order to prevent or avoid toxic signs of hyperkalaemia or any cardiac arrhythmia. Frequent determinations of serum potassium are also indicated.

(2) Diphenylhydantoin (Dilantin, Epanutin)

The primary indication for Dilantin has been in the treatment of epileptic seizures ever since the drug was introduced 30 years ago. However, this drug has been found to be effective in the management of various cardiac arrhythmias including the digitalis-induced since 1950 when Mosley & Tyler successfully abolished ouabain-induced ventricular tachycardia in an experimental study.⁵⁴ In 1958, the successful clinical use of Dilantin in the treatment of ventricular tachycardia was reported following ineffective therapy with procainamide and quinidine. Subsequently, the use of Dilantin in the treatment of cardiac arrhythmias has become popular in both experimental and clinical studies.

Various clinical investigations^{2, 53, 55, 56} have demonstrated that Dilantin was effective in treating digitalis-induced arrhythmias including paroxysmal atrial tachycardia, A-V nodal (junctional) rhythm, wandering atrial pacemaker, ventricular bigeminy, multifocal ventricular premature contractions, and A-V nodal (junctional) or ventricular tachycardia. Most patients respond within 3 sec to 5 min to intravenous administration. The duration of response varies from 5 min to 4–6 hr. The initial dose intravenously is between 125 and 250 mg for 1–3 min under electrocardiographic monitoring. The same dose may be repeated every 5–10 min until the effect is established. Toxic manifestations or side effects of Dilantin include respiratory arrest, skin reaction (urticaria, purpura), drowsiness, depression, nervousness, arthralgia, gingival hyperplasia, transient eosinophilia and transient hypotension; but these manifestations are usually rare and not serious. After conversion to sinus rhythm or the disappearance of digitalis-induced arrhythmias, oral maintenance doses (300–400 mg) in divided doses are sufficient.

It has been shown recently that Dilantin is of prophylactic value prior to direct current shock in a digitalized patient since the drug is capable of preventing arrhythmias induced by cardioversion. The reason is that Dilantin increases the threshold of the excitability of the heart by counteracting the electrophysiological actions of digitalis. Dilantin is probably the safest and most effective drug in the treatment of all types of digitalis-induced tachyarrhythmias.

(3) Beta-adrenergic blocking agents

Since the introduction of pronethalol in 1962 and propranolol in 1964 by Black and associates,^{57, 58} experimental and clinical investigations have shown that beta-adrenergic blocking agents are capable of abolishing various arrhythmias including those induced by digitalis and those resistant to digitalis. Initially, pronethalol was used but subsequently propranolol (Inderal) was found to be a more potent and a less toxic compound which was effective in the treatment of supraventricular tachycardia, ventricular tachycardia or fibrillation and ventricular premature contractions. Propranolol and pronethalol augment the refractory period at the sinoatrial and A-V junctions and depress the automaticity of the sinus and ectopic myocardial pacemakers.^{59, 60} Stock *et al.* successfully treated seven patients with digitalis-induced rhythms by using intravenous pronethalol.⁶⁰ Subsequently, Stock successfully used propranolol intravenously in eight patients with digitalis-induced arrhythmias (three paroxysmal atrial tachycardia with block and five frequent ventricular premature contractions).⁶⁰

Pronethalol is no longer recommended for clinical

use since the drug was found to be carcinogenic in mice.⁶¹ In addition, the effectiveness of propranolol is approximately ten times that of pronethalol.⁵⁸ Irons *et al.* found that propranolol was particularly effective in treating atrial tachycardia with A-V block and ventricular premature contractions induced by digitalis.⁶² Furthermore, Gianelly and his co-workers⁶³ have proposed that in the presence of normokalaemia, propranolol is the drug of choice for treatment of digitalis-induced arrhythmias. The usual intravenous dose of propranolol is between 1 and 3 mg under continuous electrocardiographic monitoring.⁶² The drug should be administered slowly, and the rate of administration should not exceed 1 mg (1 ml)/min. Sufficient time should be allowed to enable a slow circulation to carry the drug to its site of action. A second dose, if needed, may be repeated after 2 min. Additional medication should be withheld for at least 4 hr. The oral route may be instituted as soon as cardiac arrhythmias are abolished or are markedly improved. Intravenous atropine (0.5–1.0 mg) may be needed if marked bradycardia occurs. In non-urgent situations, the drug may be given orally in doses ranging between 10 and 30 mg three to four times daily before meals and at bedtime.⁶⁴ The same dosage schedule is also recommended for long-term use or for prophylactic purposes.

Propranolol is contra-indicated for patients with bronchial asthma and allergic rhinitis (especially during the pollen season), marked sinus bradycardia, second or third degree A-V block, S-A block, sinus arrest, cardiogenic shock and significant congestive heart failure.^{63, 64} The drug is also contra-indicated when patients are receiving any anaesthetics which produce myocardial depression such as chloroform and ether. Patients receiving adrenergic-augmenting psychotropic drugs (including MAO inhibitors) should also not receive the drug.⁶⁴ Propranolol may be given with caution after the 2-week withdrawal period from such drugs. It should be emphasized that electrocardiographic monitoring is mandatory during the intravenous administration of propranolol. In many cases, particularly those with asthma, practolol is now preferable to propranolol.

(4) Procaine amide (Pronestyl) and quinidine^{2, 30}

Procaine amide and quinidine may be effective in abolishing supraventricular and ventricular tachyarrhythmias induced by digitalis. Procaine amide may be used if potassium, Dilantin and/or propranolol are ineffective or contra-indicated. The drug may be given intravenously in a slow drip not exceeding 50–100 mg every 2–4 min, or orally in a dose of 500–750 mg every 4–6 hr. Quinidine has been less widely used because of the frequent occurrence of hypo-

tension during parenteral administration. Its effect is often unpredictable and hazardous. During parenteral administration of either procaine amide or quinidine, electrocardiographic monitoring and frequent blood pressure determinations are indicated. A vasopressor agent should be readily available.

The therapeutic effects of quinidine and procaine amide include a prolongation of the Q-T interval, a widening and notching of the P waves, a flattening or inversion of the T waves and depression of S-T segments. If patients develop toxic manifestations from these drugs, the electrocardiogram will show varying degrees of A-V block, progressive intra-atrial and intra-ventricular block and atrial standstill. In severe cases, ventricular fibrillation or tachycardia may develop. Both procaine amide and quinidine are contra-indicated in the presence of A-V or intra-ventricular block.

(5) *Xylocaine (Lidocaine, lignocaine)*

Southworth *et al.*⁶⁶ in 1950 were the first to demonstrate the anti-arrhythmic action of Xylocaine. Since then, Xylocaine has been widely used primarily for the treatment of ventricular tachyarrhythmias and ventricular premature contractions following acute myocardial infarction. The drug has also been used during and after cardiac surgery and cardiac catheterization. Xylocaine has recently replaced procaine amide in the treatment of certain arrhythmias because the latter has been found to produce marked hypotension and/or impairment of myocardial contractility. Thus, Xylocaine may be used in the treatment of digitalis-induced ventricular tachyarrhythmias or frequent ventricular premature contractions when potassium and/or Dilantin are ineffective or contra-indicated.

Like procaine amide, the antiarrhythmic mechanism of Xylocaine is related to the drug's ability to raise the diastolic threshold of the ventricles to stimulation.⁶⁶ Xylocaine penetrates the tissue more rapidly than procaine or procaine amide but its action is often transient.

Xylocaine may be given in doses of 1–2 mg/kg body weight intravenously over 1–2 min.⁶⁶ The same dose may be repeated at 20-min intervals if needed. A constant intravenous drip is often necessary following a direct intravenous bolus of Xylocaine since the duration of the anti-arrhythmic effect is relatively brief (10–20 min).⁶⁶ Although most adult patients require 75–150 mg of the drug, as much as 750 mg of Xylocaine has been safely used in anaesthetized patients during the first hour of administration.⁶⁷

Side-effects include hypotension, depression of the central nervous system and convulsions.⁶⁶ Xylocaine is contra-indicated in the presence of A-V block, S-A block, intraventricular block and hypotension.

(6) *Chelating agent*^{2, 3, 13, 68}

Sodium EDTA (ethylenediamine tetra-acetic acid) is occasionally of value in the treatment of digitalis-induced ventricular arrhythmias and A-V block. The chief advantage of this drug is its rapid onset of action, while its disadvantages include transient effect, occasional hypotension and renal damage following large doses. Chelating agents may be used when potassium and/or Dilantin are contra-indicated or ineffective.

(7) *Magnesium*^{69–73}

Recent clinical and experimental investigations have shown that hypomagnesaemia predisposes to digitalis intoxication. Therefore, magnesium sulphate should be administered when digitalis toxicity is associated with hypomagnesaemia. The drug may be given by slow (1 ml/min) intravenous infusion (20 ml of 20% solution) under continuous electrocardiographic monitoring.

(8) *Direct current shock*^{2, 34–37, 74}

Cardioversion should not be attempted on patients with suspected or proven digitalis-induced arrhythmias because the procedure frequently induces more serious and irreversible arrhythmias such as ventricular tachycardia or fibrillation. If cardioversion is definitely needed, prophylactic administration of Dilantin or potassium may prevent the occurrence of serious arrhythmias. It is essential to discontinue cardiac glycosides prior to the application of cardioversion. If a short-acting preparation had been given, the procedure should be postponed for at least 24–48 hr while if long-acting preparations had been used, the procedure should be delayed for at least 3–5 days.

In general, when treating the digitalis-induced tachyarrhythmias, cardioversion may be attempted only as a last resort after all available measures have been exhausted.

(9) *Artificial pacemakers*^{2, 13, 30, 75}

The primary indication for artificial pacemaker is in treating A-V block associated with the Adams-Stokes syndrome. Although digitalis intoxication is reported to be the second most common cause of complete A-V block, the Adams-Stokes syndrome as a manifestation of digitalis overdose has been found to be rare, since the ventricular rate in digitalis-induced complete A-V block tends to be faster than that in complete A-V block due to other causes. Therefore, a withdrawal of digitalis alone is often sufficient treatment. However, if the underlying rhythm is atrial fibrillation, the incidence of Adams-Stokes seizures increases. When Adams-Stokes syndrome develops due to digitalis intoxication, a

temporary 'demand' (or 'stand-by') pacemaker is quite suitable because the A-V block induced by digitalis is often transient and intermittent. The use of an artificial pacemaker with a 'fixed-rate' is not recommended because of the danger of provoking a pacemaker-induced parasystolic rhythm which competes with the patient's own basic rhythm or ectopic rhythm resulting in ventricular tachycardia or fibrillation. Permanent pacemaker implantation for the treatment of digitalis-induced A-V block is rarely called for unless other causes of A-V block co-exist.

(10) Lactones

There are two saturated lactones (tetrahydrofurfuryl alcohol and gammabutyrolactone) which have in animals been effective in treating digitalis-induced cardiac arrhythmias.¹³ Further investigation of these compounds is needed in order to establish its value in clinical medicine.

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