TOXICITY—A FREQUENT COMPLICATION OF DIGITALIS THERAPY

MERVYN S. GOTSMAN, M.D., M.R.C.P., M.R.C.P.G., D.T.M. & H. AND VELVA SCHRIRE, M.Sc., PH.D., M.D., F.R.C.P.E., F.R.C.P., F.A.C.C.; *Cardiac Clinic, Department of Medicine, Groote Schuur Hospital, and the CSIR Cardiovascular-Pulmonary Research Group, Department of Medicine, University of Cape Town*

Individual intolerance of digitalis is often encountered and recent reports have confirmed the clinical impression that the disorder occurs commonly and with increasing frequency particularly with the more widespread use of diuretics.[1-12] Although the symptoms of digitalis toxicity are well known, arrhythmias frequently occur and these may be fatal if incorrectly treated.

This paper is a brief analysis of the incidence of digitalis toxicity seen at Groote Schuur Hospital, Cape Town, during the 6-month period January - June 1965, to emphasize how frequently this condition occurs in South Africa and to incriminate some of the predisposing factors.

CLINICAL MATERIAL

Information was obtained from a retrospective study of the electrocardiographic records of the Cardiac Clinic. During this period the tracings of 4,800 patients were analysed, of whom 700 were receiving digitalis preparations when the ECG was recorded—an incidence of 15%. Sixty-one of these patients had a long PR interval only, a sign of adequate digitalis therapy, but not necessarily that of toxicity. Fifty-eight patients had a clinical history of digitalis toxicity with a suggestive ECG (long PR interval, marked ST segment depression or frequent ventricular premature systoles), or an arrhythmia due to digitalis therapy. Of these 58 patients complete clinical records were available in 45.

A very small, but very important group of patients were excluded from the analysis: these were patients who were admitted to hospital with digitalis toxicity, who died shortly after admission and whose ECG tracings were not sent for analysis. The true incidence of deaths from toxicity may therefore be higher than our report indicates.

RESULTS

Toxicity was common and occurred in 8% of patients who were receiving digitalis preparations. The age, sex and racial incidence of patients receiving digitalis are shown in Table I

TABLE I. SEX AND AGE OF PATIENTS WITH TOXICITY COMPARED TO ALL PATIENTS RECEIVING DIGITALIS

Type of patient	*Age*	*White*		*Coloured*		*Bantu*	
		M	*F*	*M*	*F*	*M*	*F*
Receiving digitalis	0–19	1	3	8	13	8	4
Toxicity		0	0	0	0	1	0
Receiving digitalis	20–29	3	5	11	21	4	5
Toxicity		0	1	0	0	0	1
Receiving digitalis	30–39	12	15	6	15	5	3
Toxicity		0	2	0	1	1	0
Receiving digitalis	40–49	19	19	20	26	9	5
Toxicity		2	0	1	4	1	0
Receiving digitalis	50–59	36	42	38	38	12	3
Toxicity		0	1	3	5	2	1
Receiving digitalis	60–69	59	38	23	30	0	1
Toxicity		4	4	2	3	0	0
Receiving digitalis	70–79	39	56	17	24	3	1
Toxicity		2	6	4	5	1	0

and are compared with the patients with toxicity. The incidence of toxicity was much higher in non-Whites and in patients older than 70 years.

The nature of the heart disease in the 700 patients, compared with the patients with toxicity, are shown in Table II. The criteria for classification have been presented elsewhere.[13-16] Toxicity was equally common in each of the aetiological groups but was more common in the patients with pulmonary heart disease. The basis for diagnosing toxicity is given in Table III, and the incidence of arrhythmia is analysed. All the common arrhythmias occurred; 24 were dangerous ectopic rhythms.

TABLE II. ANALYSIS OF THE NATURE OF HEART DISEASE

	Toxicity	*No. of patients receiving digitalis*
Rheumatic heart disease	12	187
Hypertension	16	182
Ischaemia or infarction	10	139
Pulmonary heart disease	10	53
Myocardial disease	3	18
Pericardial disease	1	14
Endocrine lesions	0	7
Syphilitic heart disease	0	4
Anaemia	0	4
Complete heart block	1	2
Collagen disease	0	1
Congenital heart disease	1	5
Not specified	4	84
Total	58	700

TABLE III. DOMINANT RHYTHM DISTURBANCE IN PATIENTS WITH DIGITALIS TOXICITY

	No. of patients
Clinical signs	
With long PR and VPS	4
With severe ST segment sag	2
APS with nodal escape and ST sag	2
VPS with severe ST sag	5
Multifocal VPS or coupling	11
PAT with block	12
Paroxysmal ventricular tachycardia	1
Severe bradycardia	5
2nd-degree heart block	5
Nodal rhythm	5
Nodal tachycardia	6

VPS=Ventricular premature systoles
APS=Atrial premature systoles
PAT=Paroxysmal atrial tachycardia

Two-thirds of the patients developed toxicity as outpatients or under the care of their general practitioner. In half of these the symptoms or arrhythmia was severe and required admission to hospital. It is also of interest to observe that one-third of the patients developed toxicity while under careful supervision in hospital. Table IV shows the type of heart disease present in the patients who developed toxicity in hospital. Once again, it was more common in patients with pulmonary heart disease.

TABLE IV. CLINICAL DIAGNOSIS OF PATIENTS IN WHOM DIGITALIS TOXICITY OCCURRED IN HOSPITAL

	No. of patients
Cor pulmonale	7
Rheumatic heart disease	3
Ischaemia or infarction	2
Hypertension	2
Myocardial disease	1
Pericarditis	1
Congenital heart disease	1
Not specified	3

A more detailed analysis was possible in the 45 toxic patients whose complete clinical records were available. Four of the 45 patients (9%) died from their underlying cardiac condition with a digitalis-induced arrhythmia. Ten of the patients had severe heart failure and 5 had coexistent renal disease, while 10 had a sudden diuresis before the toxic signs occurred. Thirty-four patients received digitalis folia and only 11 received digoxin. Details of digitalis schedules are given in Table V. Only 7 received greater than normal recommended doses of digitalis preparation. Information about simultaneous diuretic therapy at the onset of toxicity is shown in Tables VI and VII. More than half received benzothiadiazine preparations and one-third were treated simultaneously with 2 diuretic preparations. Only 14 patients received oral potassium supplements (in commercially available preparations combined with the diuretic or as a potassium bicarbonate and acid tartrates mixture). The serum potassium concentration was measured in 18 patients and was low in only 1. None of these factors was related to the type of arrhythmia.

TABLE V. DIGITALIS THERAPY IN 45 PATIENTS WITH COMPLETE CLINICAL INFORMATION

	No. of patients
During initial digitalization	3
Maintenance digitalis folia	
65 mg. daily	2
65 mg. *b.d.*	25
65 mg. *t.d.s.*	3
Maintenance digoxin	
0·25 mg. *b.d.*	8
0·25 mg. *t.d.s.*	4

TABLE VI. DIURETIC THERAPY

	No. of patients
No diuretics	10
One diuretic	31
Two or more diuretics	14

TABLE VII. TYPE OF DIURETIC

	No. of patients
Benzothiadiazine derivatives	30
Mersalyl	15
Furosemide	3
Triampterene	1

The patients were treated by discontinuing digitalis in the first place. Additional potassium was given in 15 and pronethalol in 2. The 4 patients who died all had serious underlying heart disease and died from the effects of an acute arrhythmia on a severely damaged heart.

DISCUSSION

Digitalis toxicity was frequent, occurring in 8% of a population of patients who were receiving digitalis preparations. This is not surprising since full digitalization is achieved when 40% of the lethal dose has been administered and toxic symptoms appear at 60% of the lethal dose.[2] Fortunately our incidence of toxicity is lower than 20% for a similar hospital population.[17]

The unusually high incidence in older patients over 70 years has already been reported by Dall[10] and Dubnow and Burchell.[11] Although older patients may be more susceptible to the drug than younger patients,[2,3,7,9] this may be related as much to the severity of the underlying disorder as the age of the patient. Older patients often have long-standing and more advanced heart disease and require intensive treatment to manage resistant heart failure. They are more disabled, accustomed to unpleasant symptoms and therefore do not complain of prodromal effects. With more advanced myocardial diseases the margin between therapeutic and toxic dose is reduced.[9,18]

The increased incidence in the non-White population can be explained in the same way. As a group they suffer from more advanced heart disease.[13,15]

The clinical features and iatrogenic arrhythmias were insidious in onset, occurring in the outpatient on long-term maintenance therapy or in the inpatient under careful supervision in hospital. Few symptoms were observed and the arrhythmia was often the first sign of toxicity. Von Capeller *et al.*[3] and Soffer[7] suggested that with purified glycosides arrhythmias may precede gastro-intestinal symptoms, but three-quarters of our patients received digitalis folia.

The arrhythmias were frequent in patients receiving diuretics, particularly if they needed more than one drug. Potassium supplements were neglected in many patients and it is possible that the potassium present in the commercially available combined preparations or combined potassium bicarbonate and potassium acid tartrate tablets (1 G *t.d.s.*) were inadequate to counteract the potassium-losing effect of cardiac failure and prolonged diuretic therapy. Toxicity is related to a low intracellular concentration of potassium in patients with heart failure, as a result of long-term diuretic therapy and following a sudden diuresis whether this is produced by mersalyl or a benzothiadiazine derivative.[6,8,19-21] The serum potassium concentration was low in only one patient, but intracellular potassium depletion was probably present in all, as a result of prolonged therapy or from long-standing cardiac failure.[22] Dubnow and Burchell[11] also noted that in their patients with digitalis toxicity very few had low serum levels of potassium. Ebert, Jude and Gaertner[23] have shown that when severe haemodynamic lesions are corrected, post-operative hypokalaemia is evidence of potassium influx into depleted cells.

It is of interest to observe the high incidence of toxicity in patients with pulmonary heart disease. These patients may have received more intensive digitalis or diuretic therapy or the toxicity may have been conditioned by respiratory acidosis and its treatment. Personal clinical studies after cardio-pulmonary bypass suggest that intracellular acidosis produces hypokalaemia, sensitizing the heart to small doses of digitalis. Baum *et al.*[24] showed that arterial oxygen unsaturation was correlated with digitalis sensitivity and that correction of the hypoxia improved the therapeutic response to digitalis and reduced the chance of toxicity. The treatment of chronic pulmonary heart disease therefore consists of improving hypercapnia, hypoxia and acidosis supplemented by the judicious use of digitalis.

In patients with coexisting renal disease, detoxication and excretion of digitalis is impaired and these patients require smaller dosage schedules.[25]

All the known digitalis-induced arrhythmias were seen: ventricular premature systoles, bigeminal rhythm (coupling), paroxysmal atrial tachycardia with atrioventricular block,[4-6] nodal rhythm and tachycardia,[26-28] ventricular tachycardia, atrioventricular dissociation[29] and heart block. The type of arrhythmia could not be related to the kind of underlying heart disease or to previous management.

Treatment was usually effective and consisted of stopping digitalis and administering additional potassium orally or intravenously.[4,5] Calcium chelation was not used in this series but has been useful in the past.[30,31] Pronethalol was given to only 2 patients in the series.[32,33]

Only 4 patients died. This was probably an underestimate of the true incidence since occasionally the ECGs of patients who died shortly after admission to hospital were not sent for reporting. Toxicity was only fatal in patients with serious underlying heart disease. The incidence is much lower than other reported series.[8,9]

Toxicity therefore appears to be common in patients receiving digitalis, particularly if they are elderly or non-White. It is more common in patients with serious heart disease and those with pulmonary heart disease. It is conditioned by intensive diuretic therapy with inadequate potassium supplements and is common in patients with co-existent renal disease. All patients receiving digitalis are at risk and require careful supervision and reassessment since the incidence of toxicity is high. In patients at risk, the recommended 'standard' dose of digoxin or digitalis folia may be excessive and smaller doses are often needed.

SUMMARY

Seven hundred of our 4,800 patients who had electrocardiographic recordings made during a 6-month period received digitalis. Sixty-one of these had a long PR interval and 58 had clinical and ECG evidence of toxicity.

Toxicity was more common in elderly and non-White patients and in patients with pulmonary heart disease. It was frequently seen in patients receiving diuretics, often without adequate potassium supplements. It was also seen if there was coexistent renal disease or following a sudden diuresis. One-third of the episodes occurred in hospital with the patients under careful medical supervision. Four patients with severe heart failure and a digitalis-induced arrhythmia died.

The recommended 'standard' dose of digoxin or digitalis folia may be too high, particularly in the groups at risk, and individual patients should receive smaller doses. The incidence of toxicity can be reduced only if clinicians are aware of its high frequency in patients with serious heart disease and reassess patients frequently with toxicity in mind.

We should like to thank Dr. W. Beck for reporting on many of the ECG records, the physicians who supervised the patients, and Dr. J. G. Burger, Medical Superintendent of Groote Schuur Hospital, for permission to publish. Our special thanks are due to the Council for Scientific and Industrial Research and the City Council of Cape Town for their continued financial support.

REFERENCES

1. Herrman, G. R., Dechard, G. M. and McKinley, W. F. (1944): J. Amer. Med. Assoc., **126**, 760.
2. DeGraff, A. C. (1954): Circulation, **9**, 115.
3. Von Capeller, D., Copeland, G. D. and Stern, T. N. (1959): Ann. Intern. Med., **50**, 869.
4. Lown, B., Wyatt, N. F. and Levine, H. D. (1960): Circulation, **21**, 129.
5. Oram, S., Resnekov, L. and Davies, P. (1960): Brit. Med. J., **2**, 1402.
6. Harris, E. A., Julian, D. G. and Oliver, M. F. (1960): *Ibid.*, **2**, 1409.
7. Soffer, A. (1961): Arch. Intern. Med., **107**, 681.
8. Rodensky, P. L. and Wasserman, F. (1961): *Ibid.*, **108**, 171.
9. Schott, A. (1964): Postgrad. Med. J., **40**, 628.
10. Dall, J. L. C. (1965): Lancet, **1**, 194.
11. Dubnow, M. H. and Burchell, H. B. (1965): Ann. Intern. Med., **62**, 956.
12. Sodeman, W. A. (1965): New Engl. J. Med., **273**, 35 and 93.
13. Schrire, V. (1958): Amer. Heart J., **56**, 280.
14. *Idem* (1964): S. Afr. Med. J., **38**, 46.
15. *Idem* (1964): *Ibid.*, **38**, 488.
16. *Idem* (1964): *Ibid.*, **38**, 598.
17. Resnick, N. (1964): Med. Sci., **4**, 31.
18. Lown, B., Marcus, F. and Levine, H. D. (1959): New Engl. J. Med., **260**, 301.
19. Lown, B. and Levine, S. A. (1954): *Ibid.*, **250**, 771, 819 and 866.
20. Lown, B. *in* Dimond, E. G., ed. (1957): *Digitalis*, p. 187. Springfield, Ill.: Charles C. Thomas.
21. McIntosh, H. D. and Morris, J. J. (1965): Progr. Cardiovasc. Dis., **7**, 360.
22. Flear, C. T. G. (1960): 'Studies on congestive cardiac failure', M.D.

thesis, Birmingham University.
23. Ebert, P. A., Jude, J. R. and Gaertner, R. A. (1965): Circulation, **1**, 137.
24. Baum, G. L., Dick, M. M., Blum, A., Kaupe, A. and Carbello, J. (1959): Amer. Heart J., **57**, 460.
25. Luchi, R. J. and Conn, H. L. (1965): Progr. Cardiovasc. Dis., **7**, 336.
26. Pick, A. and Dominguez, P. (1957): Circulation, **16**, 1022.
27. Castellanos, A. (1961): Amer. Heart J., **61**, 733.
28. Castellanos, A. and Lemberg, L. (1963): *Ibid.*, **66**, 605.
29. Jacobs, D. R., Donoso, E. and Friedberg, C. K. (1961): Medicine (Baltimore), **40**, 101.
30. Page, E. and Real, J. D. (1955): Circulat. Res., **3**, 501.
31. Szekely, P. and Wynne, N. A. (1963): Brit. Heart J., **25**, 589.
32. Vaughan Williams, E. M. and Sekiya, A. (1963): Lancet, **1**, 420.
33. Taylor, R. R., Johnston, C. I. and Jose, A. D. (1964): New Engl. J. Med., **271**, 877.