Myocardial and Skeletal Muscle Concentrations of Digoxin in Patients on Long-term Therapy

JOHN COLTART, MICHAEL HOWARD, DOUGLAS CHAMBERLAIN

British Medical Journal, 1972, 2, 318–319

Summary

The digoxin content was measured in samples of left ventricular papillary muscle, skeletal muscle, and plasma obtained during mitral valve replacement from eight patients on maintenance treatment with the drug. The content in papillary muscle ranged from 15·5 to 132 ng/g (mean 77·7) and in skeletal muscle from 7·5 to 23 ng/g (mean 11·3). The ratio of myocardial digoxin concentration to plasma concentration varied between patients from 39:1 to 155:1. No simple relationship exists between plasma levels of digoxin and its concentration in the heart muscle, but total myocardial concentration may not accurately reflect therapeutic activity.

Introduction

Knowledge of the clinical pharmacology of the cardiac glycosides has expanded greatly since the recent introduction of assays capable of measuring therapeutic concentrations in plasma (Lowenstein and Corill, 1966; Lukas and Peterson, 1966; Smith *et al.*, 1969). Although some overlap exists between the therapeutic and toxic ranges of plasma levels of digoxin and other glycosides, such measurements have proved of value both in selecting optimal dose requirements and in the diagnosis of toxicity (Smith *et al.*, 1969; Chamberlain *et al.*, 1970; Beller *et al.*, 1971).

The therapeutic activity of digitalis is likely to depend on the concentration at the active sites in the tissue rather than on plasma concentration. It is therefore reasonable to assume that plasma levels of digoxin must bear some relation to the quantity of glycoside within the myocardium, or within some fraction of the myocardium, for otherwise the assays would not be of clinical value. The present study was designed to examine this relation in patients on long-term maintenance therapy with digoxin. In addition, skeletal muscle concentrations were compared with those in myocardium and plasma.

Patients and Methods

Samples were obtained from eight patients undergoing mitral valve replacement. Their ages ranged from 41 to 60 (mean 54) years; they had been treated with digoxin for a minimum of seven years. All had normal serum electrolyte and blood urea concentrations at the time of surgery. Venous blood was taken into heparin tubes after induction of anaesthesia but before intravenous infusions had been set up or cardiopulmonary bypass initiated. The plasma digoxin concentration in these samples was determined by radioimmunoassay as previously described (Chamberlain *et al.*, 1970).

The mitral valve and subvalvar apparatus was excised in the usual manner, and samples of the left ventricular papillary muscle together with samples of latissimus dorsi (to represent skeletal muscle) were obtained at this time, about 20 minutes after the start of cardiopulmonary bypass. The biopsy tissue was dried and all excess fatty tissue was removed. It was stored at −4°C to await assay.

Digoxin was eluted from a known weight of tissue by homogenization at room temperature for 30 minutes with 4 ml of chloroform (analar grade), the supernatant was removed, and a further 5 ml of chloroform was added to the homogenized tissue and stirred magnetically for 30 minutes. This last procedure was repeated at least twice. The residual homogenate was preserved for further extractions if subsequent analysis showed that the third supernatant solution contained digoxin. The chloroform supernatants were evaporated to dryness and the residues redissolved in 6 ml of barbitone buffer. Aliquots of each were pooled, the digoxin concentration was measured by radioimmunoassay, and the total digoxin content of the original muscle was calculated.

Results

The plasma digoxin concentration for the eight patients at the time of surgery ranged from 0·4 to 3·3 ng/ml (mean 1·2 ± S.D. 0·8). The concentrations in papillary muscle ranged from 15·5 to 132 ng/g (mean 77·7 ± 43·3), with a ratio compared with plasma levels in the individual patients ranging from 39:1 to 155:1 (mean 68 ± 38).

The concentrations in skeletal muscle were markedly lower than in myocardium in seven of the eight patients, and ranged from 7·5 to 23 ng/g (mean 11·3 ± 4·9) with a ratio ranging from 3:1 to 58:1 (mean 15·9 ± 18·4). A poor correlation was found between myocardial and skeletal concentrations.

The individual results are detailed in the Table, and the ranges are shown diagrammatically in the Chart.

Plasma, Myocardial, and Skeletal Muscle Digoxin Concentrations and Ratios

Case No.	Concentration			Ratio	
	Plasma Digoxin (ng/ml)	Myocardial (ng/g)	Skeletal Muscle (ng/g)	Plasma/ Myocardial	Plasma/ Skeletal
1 ..	0·6	31	9	52:1	15:1
2 ..	2·5	125	10	50:1	4:1
3 ..	1·0	54	7·5	54:1	7·5:1
4 ..	0·4	62	10	155:1	25:1
5 ..	1·2	103	12	86:1	10:1
6 ..	3·3	132	11	40:1	3:1
7 ..	1·5	99	8	66:1	5:1
8 ..	0·4	15·5	23	39:1	58:1
Mean .. (± S.D.)	1·2 (0·8)	77·7 (43·3)	11·3 (4·9)	67·7 (38·3)	15·9 (18·4)

Discussion

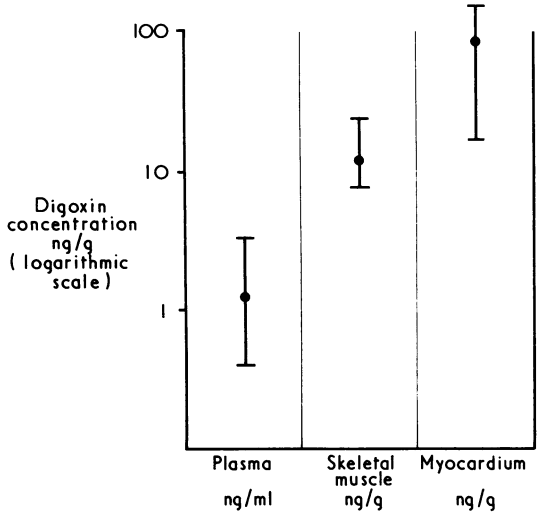
Our experiments underlined the great disparity between the digoxin carried in the plasma and the much greater quantity which is bound to tissue. The myocardial and skeletal muscle digoxin concentrations, and also the ratios between muscle and plasma levels, were greater than those found by Doherty *et al.* (1967) after administration of tritiated digoxin to patients with terminal illnesses who were within a few days of death. However,

St. Bartholomew's Hospital, London E.C.1

D. J. COLTART, M.B., B.S., M.R.C.P., Research Assistant (Present address: Department of Cardiology, Hospital For Sick Children, Great Ormond Street, London W.C.1)

M. R. HOWARD, Research Technician and Medical Student

D. A. CHAMBERLAIN, M.D., M.R.C.P., Consultant Cardiologist (Present address: Royal Sussex County Hospital, Brighton)



Mean and range of the plasma, skeletal, and myocardial muscle digoxin concentrations.

their studies were necessarily short-term, and may not represent tissue levels attained in patients on maintenance digoxin therapy.

In our own experiments it was not possible to take the blood and tissue samples simultaneously because of the need to obtain plasma before the concentration fell precipitously as a result of dilution from infusions and cardiopulmonary bypass (Coltart *et al.*, 1971). While equilibration between tissue and plasma occurs relatively quickly under experimental conditions (Okita, 1969), muscle concentrations would be affected to a comparatively small extent by any leaching of digoxin into the plasma during the time between induction of anaesthesia and biopsy, and any minor inaccuracy due to the delay in obtaining the muscle sample would tend to lower rather than increase the ratio. We cannot exclude the possibility that our measurements of muscle concentration may have been falsely low for a second reason—namely, incomplete extraction. Any inaccuracy from this cause, however, must also have been small because we used a technique of sequential extraction, and we confirmed that digoxin could not be detected in the final micro-homogenized residue. We noted that a single process sufficed for skeletal muscle in which the concentration of digoxin tended to be lower.

Although the concentration of digoxin was much less in skeletal muscle than in myocardium, the total quantity bound in this way is considerable, for skeletal muscle may comprise up to 43% of body weight (Grant, 1958). Experiments with tritiated digoxin (Doherty *et al.*, 1961) have shown that the kidney and liver also form important tissue stores of the drug. These results serve to emphasize the fact that only a small proportion of the body store of digoxin is in the plasma. Consequently, although digoxin has a molecular weight of 781 and is dialysable, an insignificant proportion can be lost to a digitalized patient during haemodialysis; similarly the exchange of blood which may occur between an extracorporeal circulation and the patient during cardiopulmonary bypass results in only a small overall loss of the glycoside (Coltart *et al.*, 1971).

The experiments of Doherty *et al.* (1967) were said to indicate that a relatively constant relation exists between myocardial and serum digoxin concentrations and they have been quoted widely in support of this contention. Analysis of the data on which the claim was based showed that the variation in ratio between patients ranged from 17:1 to 65:1. In this respect the results did not differ from our own, for we also observed about a fourfold variation in ratio between subjects. Some variation would be expected, for a number of factors are known to influence myocardial binding of cardiac glycosides. These include plasma concentrations of potassium, calcium, and magnesium, acid-base balance, oxygen tension, and thyroid function (Surawicz and Mortelmans, 1969). Another important factor which must militate against a constant relation under experimental conditions is the non-homogenous nature of muscle samples. Although we attempted to remove all excess fat, a variable amount of fibrous tissue is present, especially in papillary muscles affected by the rheumatic process.

Our data are therefore consistent with the complex relation which must exist between plasma concentrations and the content of digoxin in the myocardium and other tissues. It must also be stressed that plasma concentrations may provide a more meaningful index of therapeutic activity than total myocardial concentration. The cardiac glycosides are thought to act by inhibiting sodium-potassium activated membrane adenosine triphosphatase, and it has been suggested that only about 10% of the myocardial digoxin is bound to these active sites (Kuschinsky *et al.*, 1967). Furthermore, experiments with red blood cells (Hoffman, 1966) indicate that this enzyme is influenced by digitalis present on the external cell surface rather than by glycoside within the cell. However, a knowledge of total myocardial and other tissue concentrations is of value in so far as it helps to increase our understanding of the pharmacodynamics of the drug.

We gratefully acknowledge the expert technical help of Miss Jill Cooper, the co-operation of the cardiothoracic operating theatre staff, and the consent of the surgeons, Mr. O. S. Tubbs and Mr. I. M. Hill.

D.J.C. is the Mary Scharlieb Research Scholar of the University of London, 1970-2, and the Cooper and Coventson Research Scholar of St. Bartholomew's Hospital 1970-1.

Requests for reprints should be addressed to Dr. D. J. Coltart, 9 Baronsmede, London W.5.

References

Beller, G. A., Smith, T. W., Abelmann, W. H., Haber, E., and Hood, W. B. (1971). *New England Journal of Medicine*, **284**, 989.

Chamberlain, D. A., White, R. J., Howard, M. R., and Smith, T. W. (1970). *British Medical Journal*, **3**, 429.

Coltart, D. J., *et al.* (1971). *British Heart Journal*, **33**, 334.

Doherty, J. E., Perkins, W. H., and Mitchell, G. K. (1961). *Archives of Internal Medicine*, **108**, 531.

Doherty, J. E., Perkins, W. H., and Flanigan, W. J. (1967). *Annals of Internal Medicine*, **66**, 116.

Grant, J. C. B. (1958). *A Method of Anatomy*, 6th edn., p. 7. Baltimore, Williams and Wilken.

Hoffman, J. F. (1966). *American Journal of Medicine*, **41**, 666.

Kuschinsky, K., Lahrtz, H., Lüllmann, H., and Van Zwieten, P. A. (1967). *British Journal of Pharmacology and Chemotherapy*, **30**, 317.

Lowenstein, J. M., and Corill, E. M. (1966). *Journal of Laboratory and Clinical Medicine*, **67**, 1048.

Lukas, D. S., and Peterson, R. E. (1966). *Journal of Clinical Investigation*, **45**, 782.

Okita, G. T. (1969). In *Digitalis*, ed. C. Fisch and B. Surawicz, p. 18. New York, Grune and Stratton.

Smith, T. W., Butler, V. P., and Haber, E. (1969). *New England Journal of Medicine*, **281**, 1212.

Surawicz, B., and Mortelmans, S. (1969). In *Digitalis*, ed. C. Fisch and B. Surawicz, p. 127. New York, Grune and Stratton.