

EDITORIAL

DIGITALIS TOXICITY

The cardiac glycosides are widely used drugs with great potentialities of producing toxic effects, but serious results from overdosage are relatively infrequent judging by reports in the medical literature and from the experience of physicians generally. The increased use of chemically pure glycosides in the place of the traditional preparations such as the standardized leaf products has emphasized the problem of toxicity. The frequent concurrent use of diuretics is an important factor in inducing digitalis toxicity. The use of adrenocortical steroids, when regarded as necessary in a particular patient with congestive cardiac failure who is receiving digitalis, might conceivably induce alteration in the responsiveness of the cardiac muscle to the glycosides. Potassium depletion produced in these two instances would enhance the toxic effects of digitalis. Calcium in excess also increases the toxic effects of digitalis.

The mode of action of digitalis glycosides on the myocardium is not clearly understood. Many factors may be involved. Amongst others it has been known for many years that the systolic effect occurs only in the presence of calcium ions. Calcium ions and digitalis have a synergistic action on the heart. This has been demonstrated not only experimentally, but clinically also deaths have occurred in digitalized patients who received calcium salts intravenously. Digitalis may act by rendering the heart more sensitive to calcium or by mobilizing calcium ions for the activation of the enzyme adenosinetriphosphatase in heart muscle. The concentration of potassium ions is also affected by the glycosides, toxic doses producing a decrease in the potassium content of heart muscle.

The administration of potassium salts experimentally and clinically has been shown to prevent or abolish digitalis-induced arrhythmias. The use of potassium is not without danger and the greatest care is required because of the depressant action of potassium ions on the heart.

Deficiency of calcium produced in animals has been shown to reduce the toxic effects of digitalis. A hypocalcaemic state can be rapidly induced by intravenous injection of the chelating agent ethylenediamine tetra-acetic acid (EDTA). This has been demonstrated to be of some value in the severely digitalized animal, in which irregular auricular and ventricular contractions and fluctuating blood pressure were temporarily restored to normal.¹ By this controlling action time may be gained for the body mechanisms to clear the glycosides and thus save the life of a severely digitalized

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DIGITALIS-VERGIFTIGING

Die hart-glikosiede is alombekende middels wat baie maklik vergiftiging kan veroorsaak, maar ernstige gevolge weens oormatige toediening is betreklik seldsaam, as 'n mens moet oordeel na verslae in die mediese literatuur en die onder-vinding van geneeshere in die algemeen. Die toenemende gebruik van chemies suiwer glikosiede in plaas van die tradisionele preparate soos die standaard bereide blaar-produkte, het die probleem van vergiftiging beklemtoon. Die feit dat diuretika dikwels tegelykertyd gebruik word, is 'n belangrike faktor by die ontstaan van digitalis-vergiftiging. Dit is moontlik dat die gebruik van bynierskors-sterofede, wanneer dit nodig geag word by 'n besondere pasiënt met stuwende hartversaking wat met digitalis behandel word, 'n verandering in die reaksie in die hartspeer op die glikosiede teweeg kan bring. Die kaliumvermindering wat by hierdie twee gevalle veroorsaak word, sal die vergiftigende effekte van digitalis versterk. Ook sal 'n oormaat kalsium die vergiftigende uitwerking van digitalis aanhits.

Daar is nog duisterheid oor die wyse waarop digitalis op die hartspeer inwerk. Baie faktore is moontlik daarby betrokke. Onder andere is dit reeds jare lank bekend dat die sistoliese effek slegs voorkom as kalsium-ione aanwesig is. Die kalsium-ione en digitalis het 'n sinergistiese aksie op die hart. Hierdie feit is reeds proefondervindelik bevestig, en ook in die kliniek het daar sterfgevälle voorgekom onder pasiënte wat met digitalis behandel was en wat kalsiumsoute binnears ontvang het. Moontlik werk digitalis deur die hart gevoeliger te maak vir kalsium, of deur die kalsium-ione te mobiliseer vir die aktiveer van die ensiem adenosientrifosfatase in die hartspeer. Die konsentrasie van kalium-ione word ook geaffekteer deur die glikosiede, aangesien vergiftigende dosisse 'n vermindering van die kaliumgehalte van die hartspeer veroorsaak.

Dit is proefondervindelik sowel as klinies bewys dat die toediening van kaliumsoute aritmie, veroorsaak deur digitalis, kan voorkom of oorwin. Daar skuil egter gevaar in die gebruik van kalium, en dit moet baie versigtig toegedien word, omdat kalium-ione 'n neerdrukkende of stremmende uitwerking op die hart uitoefen.

Dit is reeds bewys dat 'n kalsiumtekort bewerkstellig by diere die vergiftigende aksie van digitalis verminder. So 'n toestand van bloedkalsiumtekort kan vinnig bewerkstellig word deur aarinspuiting van die chelaatmiddel etieleen-diamien-tetra-asynsuur (EDTA). Hierdie prosedure het waardevol geblyk by diere wat sterk onder die invloed van digitalis was; die onreëlmatige voorkamer- en kamersame-trekkings en wisselende bloeddruk is op hierdie wyse weer tydelik op normaal gebring.¹ Deur so 'n beheeraksie kan die liggaamsmeganismes kans kry om die glikosiede weg te ruim, en die lewe van 'n digitalis-vergiftigde pasiënt kan so

individual. Nice adjustment of the dose is necessary. Too big a dose of the chelating agent injected rapidly sometimes produces depression of the myocardium with a marked fall of blood pressure. The action of the chelating agent may be explained on the basis of its combination with calcium and alteration of the calcium-potassium ratio.

In a clinical study of digitalis toxicity prompt termination of arrhythmias was induced in 3 patients by the intravenous administration of the disodium salt of EDTA, and in 2 others the previous administration of this compound in one patient and of the magnesium salt in the other significantly increased the dose of digitalis glycosides required to produce major arrhythmias.² The circulating serum calcium was not actually lowered but the fraction bound (unionized) to the chelating agent was physiologically not available. Much depends on the dose; large doses can produce hypocalcaemic tetany. The authors administered 600 mg. of the disodium salt of EDTA (in 250 ml. of 5% dextrose in water) intravenously over a period of half an hour, but larger doses may also be given.

Both supraventricular and ventricular arrhythmias induced by digitalis (incidentally also ectopic beats not caused by digitalis) were abolished by the chelating agent. Control of the arrhythmias removed their aggravating effect on the heart failure.

The desirability of an antidote for use in severe intoxication with digitalis is obvious. No satisfactory antagonist has hitherto been available. Potassium salts are not without danger. The use of EDTA would appear to offer the advantages of prompt action and greater safety.

1. Sapeika, N. (1954): Arch. Int. Pharmacodyn., 97, 373.

2. Gubner, R. S. and Kallmann, H. (1957): Amer. J. Med. Sci., 234, 136.

gered word. Die dosis moet egter baie sekuur bereken word. As te veel van die chelaatmiddel vinnig ingespuut word, veroorsaak dit soms stremming van die miokardium en 'n skerp daling in die bloeddruk. Die aksie van die chelaatmiddel kan verduidelik word op die basis van sy verbinding met kalsium en verandering van die kalium-kalsium verhouding.

In 'n kliniese studie van digitalis-vergiftiging was die aritmie by 3 pasiënte dadelik beheer deur binnearse toediening van die dinatrium-sout van EDTA; by 2 ander het die voorafgaande toediening van hierdie verbinding by die een, en van magnesiumsout by die ander, die dosis van digitalis-glikosiede nodig om ernstige aritmie te veroorsaak aansienlik opgeskuif.² Die sirkulerende serum-kalsium was nie werklik verminder nie, maar die fraksie onverbind (ongeïoniseer) met die chelaatmiddel was fisiologies nie te vinde nie. Baie hang van die dosis af—groot dosisse kan tetanie weens hipokalsemie veroorsaak. Die skrywers het 600 mg. van die dinatrium-sout van EDTA (in 250 ml. van 5% dekstroze in water) binnears toegedien oor 'n tydperk van 'n halfuur, maar groter dosisse is ook toelaatbaar. Die chelaatmiddel het beide die supraventrikulêre en die ventrikulêre aritmie wat deur die digitalis veroorsaak was, beheer (en terloops ook ektopiese kloppings wat nie hieraan te wyte was nie). Die beheer van die aritmie het dan ook verhinder dat die onreëlmatighede die hartstoornis vererger.

Dit is duidelik dat 'n teenmiddel vir gebruik by ernstige digitalis-vergiftiging dringend nodig is. Dusver was daar nog geen bevredigende weermiddel nie. Die kaliumsoute is nie heeltemal veilig nie. Skynbaar bied die gebruik van EDTA die voordele van vinnige uitwerking en groter veiligheid aan.

1. Sapeika, N. (1954): Arch. Int. Pharmacodyn., 97, 373.

2. Grubner, R. S. en Kallmann, H. (1957): Amer. J. Med. Sci., 234, 136.

NAUDÉ VERSUS WHITTLE

This action came to trial at Grahamstown in the Supreme Court (Eastern Districts Local Division) in February 1957 and judgment was delivered on 29 April 1957. The judgment was published in this *Journal* on 8 July 1957.

The plaintiff is Dr. W. J. Naudé who is in practice at Franklin and is District Surgeon for the Franklin and Zwartberg areas of the Mount Currie District, and the defendant is a farmer in the Zwartberg area who is a member of the Zwartberg Farmers' Association. Dr. Naudé sued the defendant for damages in respect of the publication by the defendant of a certain statement made at the annual meeting of the Zwartberg Farmers' Association held on 27 October 1955, when over 50 persons were present. The statement was to the effect that when a suicide was committed 'on the night of 13 October 1955 the District Surgeon, Franklin (meaning and referring to the plaintiff), was telephoned at 10.30 p.m. and refused to appear at that hour although the circumstances were explained'. The statement was in fact untrue, for Dr. Naudé was never notified of the suicide during the night on which it occurred or received a request that he should go out to see the body. Dr. Naudé suffered both socially and professionally, and his practice deteriorated sharply after the meeting at which the statement was made.

The learned Judge said: 'It is clear that the statement about plaintiff . . . was a highly misleading one which conveyed implications altogether untrue, implications which defendant Naudé has said he intended to convey. These implications were of a defamatory nature and there has been no attempt on the part of the defendant to show that they were not defamatory. The only serious defence to the resultant claim for damages is that of qualified privilege . . .' In dismissing the case with costs the learned Judge said that he considered the defendant's statement was made on a privileged occasion without malice and in the *bona fide* belief that it was true; and added: 'If, however, I am wrong in finding that the occasion of its publication was privileged, I would after consideration of all the circumstances . . . allow in damages the sum of £800.'

Although Dr. Naudé had morally succeeded in his action, the decision had gone against him on a question of law. He had cleared his good name and reputation but, apart from the damage he had suffered from the defamatory statement, he must have sustained a heavy financial loss from the action.

At that stage the matter was one for grave concern to the medical profession, for in the light of the judgment it appeared that medical practitioners (as well as other members of the

community) would find that the circumstances under which defamatory statements might be made against them with impunity were much wider in scope than they had hitherto supposed.

The judgment, however, has been reversed on appeal. Dr. Naudé's appeal was heard by the Appellate Division on 3 December 1957 and the judgment of Chief Justice Fagan delivered on 9 December is published in the present issue of the *Journal* (p. 80). The fact was not disputed that Dr. Naudé had not been informed of the suicide and had not been asked to go and see the body, and the case turned on the issue of privilege. The Chief Justice towards the end of his judgment said:

'The impression I get is that the respondent worked himself up into such a state of annoyance when he . . . failed to get the immediate response he apparently expected from the telephone service, the police and the District Surgeon that

he did not even try to form a calm and dispassionate judgment but decided to have them all taught a lesson. It seems to me to have been that frame of mind, and not a sense of duty, which led him to put on the message he had received a sinister construction not warranted by its actual content, and then to pass his construction on to the farmers' meeting as if it was the actual wording of the message. That was an abuse of whatever privilege the occasion might have afforded him.

'It follows that the appeal should succeed . . .'

The appeal was allowed and damages awarded to Dr. Naudé in the sum of £800 with costs.

Dr. Naudé is to be congratulated on the result of his action, which is to be regarded as having been fought in vindication of the medical profession as a whole, and not only of himself. It is gratifying to note the support which was afforded to Dr. Naudé by the Transkei Branch of the Medical Association and its East Griqualand and East Pondoland Divisions.