Plasma Digoxin Concentration in Children with Heart Failure

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British Medical Journal, 1973, 1, 443-444

Summary

A dosage schedule for digoxin medication is presented which has proved effective and safe in children of different ages with heart failure due to a variety of cardiac conditions. The plasma digoxin concentrations during maintenance therapy, using this schedule, agree closely with previously reported therapeutic adult plasma concentrations, though the results do not exclude the efficiency and safety of higher doses. A twice-daily dosage regimen is suggested.

Introduction

Several different digoxin dose schedules for children, based on empirically derived formulae, have been recommended, and aim at achieving a therapeutic effect while avoiding intoxication. Some of these schedules are calculated according to the infant's age, others according to the exact body weight (Nadas, 1966), while others increase in a stepwise fashion for weight range changes (Taylor, 1971). At all ages only a small margin exists between the effective digitalizing dose and toxicity. Electrocardiographic changes in children are not easy to interpret and are unreliable as an index of overdosage. Moreover, in the infant many of the usual symptoms of toxicity, such as nausea and headache, cannot be evaluated. In order to help determine a safe and effective dose we have measured plasma digoxin concentrations in neonates, infants, and children whose heart failure has been well controlled.

Patients and Methods

Altogether, 43 children whose ages ranged from 1 week to 10 years were initially digitalized with Lanoxin paediatric elixir* using the following oral dose schedule, dividing the total 24-hour dose into three equal doses: under 4 weeks of age, 0.05 mg digoxin/kg body weight in 24 hr; 4 weeks-2 years, 0.08 mg digoxin/kg body weight in 24 hr; over 2 years, 0.05 mg digoxin/kg body weight in 24 hr. Maintenance dosage was continued as follows: under 4 weeks, 0.01 mg digoxin/kg body weight/day; 4 weeks-2 years, 0.02 mg digoxin/kg body weight/day; over 2 years, 0.01 mg digoxin/kg body weight/day.

In 33 of the 43 cases the drug was given in divided doses every 12 hours. Digitalization was undertaken for heart failure due to a wide spectrum of cardiac disease, including transposition of the

great vessels, pulmonary atresia, ventricular septal defect, truncus arteriosus, hypoplastic left ventricle, patent ductus arteriosus, atrial septal defect, and paroxysmal supraventricular tachycardia. All patients were considered to have normal, or near normal, renal function as judged by the fasting blood urea concentration; all had a normal serum potassium concentration, and there were no rhythm disturbances to suggest digoxin excess.

After at least five days' constant maintenance therapy, venous blood samples were collected for radioimmunoassay of digoxin (Smith *et al.*, 1969) six to eight hours after an oral dose.

In a further 10 cases the daily maintenance dose was given as a single daily dose.

Results

The plasma digoxin concentrations obtained in the various age groups are shown in fig. 1. These are compared with plasma levels in 31 adults whose atrial fibrillation was controlled by 0.5 mg digoxin* daily (Chamberlain *et al.*, 1970).

FIG. 1—Plasma digoxin concentrations in 33 children compared with results previously obtained in 31 adults. Horizontal bars represent mean values.

A close correlation between the plasma levels for the differing age groups was observed. The mean levels were: birth to 4 weeks, 1.5 ng/ml; 4 weeks to 2 years, 1.6 ng/ml; over 2 years, 1.3 ng/ml; adults, 1.5 ng/ml.

No toxic symptoms were noted on this regimen, and heart rate and failure were well controlled.

Five cases not included in the series because they had been given half the dose for their age group 1 month-2 years, had low plasma digoxin levels of 0.9, 0.8, 0.8, 0.7, and 0.6 ng/ml six hours after a dose.

The 10 cases given the daily maintenance dose as a single dose had digoxin levels measured eight hours and again 24 hours after a dose. In seven of these cases the plasma level had fallen

* This digoxin preparation was not subject to the variation in potency which has recently affected digoxin tablets.

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* This study was performed with Lanoxin before a change in the manufacturing process reduced its bioavailability at the end of 1969. The Lanoxin used was equivalent to the Lanoxin produced since May 1972.

FIG. 2—Fall in digoxin concentrations in 10 children after a single daily dose. Shaded area represents therapeutic adult range. Arrows indicate mean values.

below the optimum adult range of 1-2 ng at the end of the 24-hour period (fig. 2).

Discussion

Measurement of plasma digoxin concentrations has proved valuable in determining the therapeutic dose of the drug in adults, and provides a means of studying its pharmacology (Smith *et al.*, 1969; Chamberlain *et al.*, 1970; Beller *et al.*, 1971).

The rationale behind recommendations for digoxin dosages in infants and children has never been clarified. Levine (1962) attempted to determine clinically the maximum safe digitalizing dose for infants and children, and arrived at a dosage similar to the recommended schedule in this study.

Infants in the first month of life receiving half the daily dose given to older infants produce similar plasma concentrations. This may be because of reduced renal clearance in the neonatal period. The doses for all age groups are substantially higher on a mg per kg body weight basis than those for adults; our data show that identical plasma concentrations are produced by infants receiving a maintenance dose of 0.02 mg/kg body weight and adults receiving 0.007 mg/kg body weight. This difference persists when doses are calculated on body surface area, although

it is less pronounced. It is thought that children are more tolerant to digitalis glycosides, but not infrequently intoxication has occurred from over-medication. We have not attempted to show if larger doses cause toxicity, and it may be that the infant's myocardium will tolerate higher plasma levels than those produced by our dose schedules. Failure to secure adequate clinical control of cardiac failure in an infant may suggest a need to increase the digoxin dosage, but it is our impression that an increase in dosage above that of our schedule does not lead to an enhanced therapeutic effect. This impression is supported by recent studies (Levy *et al.*, 1972) showing that a maximal inotropic effect occurs after a single small dose.

By measuring plasma digoxin levels after a single daily dose we have shown that in seven cases out of 10 the therapeutic adult range of 1-2 ng is not maintained 24 hours after the dose. It is, therefore, desirable to follow the usual practice of twice daily dosage.

The paediatric dose schedule presented here produces plasma digoxin levels comparable to those in adults with normal renal function receiving 0.5 mg daily to control atrial fibrillation. Our clinical observations also support our belief that this dosage regimen is effective and safe.

We thank Dr. D. A. Chamberlain for his help in the preparation of this paper. We are grateful to Dr. T. P. Mann, Dr. F. W. Nash, and Dr. G. W. Hatcher, of the Royal Alexandra Hospital, Brighton, and Professor J. F. Goodwin, of the Postgraduate Medical School, London, for permission to study patients under their care.

Dr. J. E. Cree was financed by the Royal Alexandra Hospital Research Fund, and Dr. D. J. Coltart is the Mary Scharlieb Research Scholar of the University of London.

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Rubella Epidemic in a Maternity Unit

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British Medical Journal, 1973, 1, 444-446

Summary

Four cases of rubella, the last confirmed by laboratory tests, occurred among the nurses of a large obstetric unit. Immediate measures were taken to prevent the spread of the infection to pregnant patients and staff, and none was in fact infected.

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Persons susceptible to rubella and who become infected may pose a real danger to women in early stages of gestation during the incubation period. We recommend that the immune status of medical and nursing personnel working in obstetric departments should be ascertained serologically, and that rubella vaccine should be offered to those who are susceptible.

Introduction

About 20% of women of childbearing age in southern England are susceptible to rubella (Public Health Laboratory Service Working Party, 1970; Beazley *et al.*, 1971). Studies on immunity to rubella have been made on women in closed