REFERENCES

KATO, R., CHIESARA, E. & VASSANELLI, P. (1964). Further studies on the inhibition and stimulation of microsomal drug metabolising enzymes of rat liver by various compounds. *Biochem. Pharmac.*, **13**, 69–83.

O'MALLEY, K., CROOKS, J., DUKE, E. & STEVENSON, I. H. (1971). Effect of age and sex on human drug metabolism. *Br. med. J.*, **3**, 607–609.

SHAND, D. G. & OATES, J. A. (1971). Metabolism of propranolol by rat liver microsomes and its inhibition by phenothiazine and tricyclic antidepressant drugs. *Biochem. Pharmac.*, **20**, 1720–1723.

VESSEL, E. S., PASSANANTI, G. T. & GREEN, F. (1970). Impairment of drug metabolism in man by allopurinol and nortriptyline. *New Engl. J. Med.*, **283**, 1484–1488.

## Digoxin dosage in patients with impaired kidney function

L. DETTLI, E. E. OHNHAUS* and P. SPRING (introduced by W. H. AELLIG)

*Department of Experimental Therapeutics, Biological and Medical Research Division, Sandoz Ltd., and Department of Clinical Pharmacology, Bürgerspital Basel, Switzerland*

Based on the so-called 'intact nephron hypothesis' (Bricker, Morrin & Kime, 1960) a linear relationship between the endogenous creatinine clearance ($V_{Cr}$) and the overall elimination rate constant ($k_e$) of many drugs can be demonstrated: $k_e = k_m + a \cdot V_{Cr}$.

In order to find the appropriate individual dose schedule of digoxin for patients with impaired kidney function, we tested this hypothesis.

Thirty-one patients with different degrees of kidney impairment (endogenous creatinine clearance ranged from 0 to 100 ml/min) were given 0·25–0·5 mg tritium labelled digoxin intravenously. The volume of distribution, the 'overall' ($k_e$), the renal ($k_r$) and extrarenal ($k_m$) rate constant for elimination of digoxin were determined from measurements in the plasma and in the urine. At the same time endogenous creatinine clearance ($V_{Cr}$) was estimated.

According to the equation $k_e = k_m + a \cdot V_{Cr}$ a linear correlation between the elimination constant and the endogenous creatinine clearance was found using the method of 'the least squares of errors'. For digoxin the following equation was calculated: $k_e = 0{\cdot}00593 + 0{\cdot}00013 \cdot V_{Cr}$; $r = 0{\cdot}91$; $S_{y/x} = \pm 0{\cdot}0019$; $P < 0{\cdot}001$. The $k_e$ obtained from the different measurements ranged from 0·004 $h^{-1}$ in the anurics to 0·0196 $h^{-1}$ in normals or from 173·3 h to 35·4 h half-life respectively. The rate constant in the urine was not significantly different from the constant obtained in the plasma.

Based on this quantitative relationship between digoxin elimination and a simple clinical routine test of kidney function the individual dose schedule for patients with kidney impairment can be calculated. For practical clinical purposes, a 'bedside method' described by Dettli, Spring & Habersang (1970) is also suitable for determining the dose of digoxin.

REFERENCES

BRICKER, N. S., MORRIN, P. A. F. & KIME, S. W. (1960). The pathologic physiology of chronic Bright's disease. *Am. J. Med.*, **28**, 77–98.

DETTLI, L., SPRING, P. & HABERSANG, R. (1970). Drug dosage in patients with impaired renal function. *Postgrad. med. J.*, **46**, 32–35.

## Plasma digoxin concentrations in children in heart failure

D. J. COLTART, J. E. CREE* and M. R. HOWARD (introduced by D. A. CHAMBERLAIN)

*Department of Clinical Cardiology, Hammersmith Hospital and St. Bartholomew's Hospital, London, and Department of Paediatrics, Royal Alexandra Hospital, Brighton*

Digoxin dose schedules used in paediatric units in England vary widely. We have

compared those used by the Hospital for Sick Children, Great Ormond Street, Birmingham Children's Hospital, and the Brompton Hospital. All three schedules agree fairly closely on doses for children over 2 years, but under this age there are many discrepancies. It is generally accepted that the younger the child, the greater his tolerance to digoxin, except in the neonatal period when intoxication to many drugs is common because of inadequate renal function and poorly developed enzyme systems.

At any age, there is only a small margin between the effective dose and toxicity of digoxin. With the introduction of radioimmunoassay for plasma digoxin concentrations, it should be possible to assess the safe therapeutic dose for children. Using this method, adult therapeutic concentrations have been shown by Chamberlain, White, Howard & Smith (1970) to lie between 0·5 ng and 3 ng/ml plasma (mean 1·6 ng).

Plasma digoxin concentrations have been measured in more than thirty children, aged 1 week to 10 years, from the Royal Alexandra Hospital, Brighton, and the Hammersmith Hospital. They were all well digitalized for control of heart failure due to a variety of congenital heart disorders. The Brompton Hospital dosage schedule used was:

| | |
|---|---|
| Under 4 weeks | 0·01 mg (digoxin/kg body wt)/day |
| 4 weeks–2 years | 0·02 „ ( „ „ „ „) „ |
| Over 2 years | 0·01 „ ( „ „ „ „) „ |

Plasma digoxin concentrations 6–8 h after an oral maintenance dose, were measured by radioimmunoassay. In most cases, results fell between 1 and 2 ng/ml plasma (average 1·4 ng), agreeing well with therapeutic adult plasma concentrations. No toxic symptoms were noted and heart rate and signs of failure were well controlled.

The Brompton Hospital dosage (after Nadas, 1966) has, therefore, proved satisfactory and safe in our series of children.

REFERENCES

CHAMBERLAIN, D. A., WHITE, R. J., HOWARD, M. R. & SMITH, T. W. (1970). Plasma digoxin concentrations in patients with atrial fibrillation. *Br. med. J.*, **3**, 429.
NADAS, A. S. (1966). *Paediatric Cardiology*, 2nd ed., p. 783. London: W. B. Sanders & Co.

## Action of prostaglandins $A_2$, $B_1$, $E_2$ and $F_{2\alpha}$ on superficial hand veins of man

J. G. COLLIER, S. M. M. KARIM, B. ROBINSON* and K. SOMERS

*Medical Unit, St. George's Hospital, London SW*1, *and Departments of Pharmacology and Medicine, Makerere University, Kampala, Uganda*

The action of prostaglandins (PGs) on superficial hand veins was studied using a modified version of the technique previously described (Nachev, Collier & Robinson, 1971). The distensibility of the vein at a standard congesting pressure was measured by means of a light weight lever, one end of which rested on the skin over the summit of the vein, while the other moved over a millimetre scale. The lever was arranged so that vertical movement of the vein was magnified 2·5 times. Prostaglandins in saline solution were infused into the vein at 0·25 ml/min and the response to each dose was measured at the 6th, 11th and 15th min of infusion. The action of each prostaglandin was investigated both in resting veins, and in veins preconstricted