without classical physical signs.⁴ We believe that endophthalmitis has not been reported in man or animals. Only one earlier human case has shown joint disease. Deafness and vestibular disturbances seem to be the commonest permanent sequelae. Young pigs are probably infected via the nasopharynx,⁵ but most human cases have been associated with wound infection. Our patient did not handle pig meat in his work, and the route of infection is uncertain in this case.

Str suis, type II, infection in man is clearly derived from pigs. The organism may be carried by adult pigs, and we assume that it is present in carcasses reaching pork-processing factories. Nevertheless, it appears that there is a low risk of human disease from occupational exposure.

We are grateful to Dr S D Elliott, Department of Pathology, University of Cambridge, and to Dr W R Maxted, Cross Infection Reference Laboratory, Colindale, for identifying *Str suis*, type II, and to Dr L Beilin for permission to report this case.

¹ Windsor, R S, and Elliott, S D, *Journal of Hygiene*, 1975, **75**, 69.

² Kloppenburg, M, Mulder, N H, and Houwerzijl, J, *Lancet*, 1975, **2**, 1218.

³ Zanen, H C, and Engel, H B W, *Lancet*, 1975, **1**, 1286.

⁴ Hickling, P, and Cormack, F C V, *British Medical Journal*, 1976, **4**, 1299.

⁵ Elliott, S D, Alexander, T J L, and Thomas, J H, *Journal of Hygiene*, 1966, **64**, 213.

(Accepted 25 March 1977)

Department of Regius Professor of Medicine, Radcliffe Infirmary, Oxford

M J B AGASS, MRCP, senior house officer
C P WILLOUGHBY, MRCP, registrar

University of Oxford

A J BRON, FRCS, Margaret Ogilvie's reader in ophthalmology

Regional Public Health Laboratory, Radcliffe Infirmary, Oxford

C J MITCHELL, MRCPATH, senior bacteriologist
R T MAYON-WHITE, MRCP, epidemiologist

Oral digitalisation: choice of dose

Ideally the oral loading dose of digoxin should be titrated against response, but this is difficult in practice. In atrial fibrillation account must be taken of the delay in chronotropic response, the mean time to maximum effect being six hours.¹ Rapid ventricular rates do not always respond to digoxin even at doses large enough to cause toxicity.² When digoxin is used for its inotropic effect evaluation may be confounded by response to other interventions such as bed rest, oxygen, sedation, diuretics, or reduction of arterial tension. Since response is difficult to measure, the alternative is to regulate the loading dose according to the concentrations achieved. Redfors³ found that the optimal predose serum digoxin concentration in patients with atrial fibrillation receiving maintenance therapy was 1.3 nmol/l (1.0 ng/ml), while a valuable inotropic effect has been shown at this concentration after an episode of heart failure.⁴ We make recommendations on the choice of dose based on studies in patients and healthy subjects.

Subjects, methods and results

Twenty-one consenting patients weighing 47 to 90 kg (mean $\pm$ 1 SD, 65 $\pm$ 11 kg), aged 44 to 84 years (64 $\pm$ 12 years), and with creatinine clearances 11 to 92 ml/min (56 $\pm$ 23 ml/min) were given loading doses of 1 mg of digoxin (four 0.25 mg Lanoxin tablets) as part of their treatment for heart failure or atrial fibrillation. Four developed gastrointestinal symptoms within 30 minutes. In the 19 who did not vomit, venous blood samples for digoxin assay were collected at 1, 2, 4, 6, and 24 hours after the dose. The concentrations had a stronger correlation with creatinine clearance than with either age or weight (table). Use of lean body mass, estimated from skeletal dimensions, instead of weight failed to improve the correlation. Electrocardiograms taken at each sampling time showed no evidence of cardiotoxicity.

Correlation between serum digoxin concentrations after 1 mg by mouth and patient characteristics in 19 patients

Characteristic	Significance of correlation with serum digoxin concentration		
	4 h*	6 h	24 h
Creatinine clearance	<0.01	<0.001*	<0.05
Age	NS	<0.05	<0.05
Weight	<0.05	<0.05	NS

*Time after dose. At 1 and 2 h there was no significant (NS) correlation between concentration achieved and characteristics.

^{*} $r = 0.74$, and corresponding regression equation was $C_6 = 3.87 - 0.03 C_{cr}$, C_6 (nmol/l) being the concentration 6 h after dose of 1 mg in patient with creatinine clearance C_{cr} (ml/min). For example, when $C_{cr} = 63$ ml/min, $C_6 = 3.87 - 0.03(63)$ nmol/l—that is, 1.98 nmol/l. Assuming proportionality between dose and 6-h concentration, dose calculated to achieve 6-h concentration of 1.3 nmol/l would be given by 1 mg (1.3/1.98)—that is, 0.66 mg. (Nearest dose in multiples of 0.125 mg is 0.625 mg.)

Five healthy persons (weight 58 to 75 kg, age 28 to 40 years, creatinine clearance 76 to 101 ml/min) received single doses of 0.5, 0.75, and 1.0 mg in random order at fortnightly intervals. No ill effects occurred. Blood samples were collected as above.

If the serum digoxin concentration in a subject is proportional to dose the concentration, C_x nmol/l, achieved by a single dose of D_x mg will be given by $C_x = C_0 D_x / D_0$, where C_0 nmol/l is the concentration measured after a previous dose of D_0 mg. Comparison of the predicted and measured concentration at each sampling time showed that the best prediction was for six hours after the dose ($n = 10$, $r = 0.92$, $P < 0.001$). Since the slope of the corresponding regression line did not differ significantly from 1, nor did the intercept from zero, the assumption of proportionality between dose and the six-hour concentration was justified.

Comment

Although the dose of 1 mg achieved an average concentration of 1.3 nmol/l at 24 hours, it produced gastrointestinal symptoms in 19% of cases. This early emetic effect should be avoided by giving a smaller dose, but this would necessitate shortening the interval to the first maintenance dose. In normal subjects proportionality between dose administered and serum concentration occurred at six hours. If the relationship holds in patients this would be an ideal time to give the first maintenance dose.

Patients with severe renal insufficiency require reduced loading doses.⁵ This study shows that in patients with a wide range of renal function creatinine clearance remains the best predictor of dose requirements. Since the mean creatinine clearance of a much larger group of general medical patients² receiving digoxin was 63 $\pm$ 20 ml/min 0.625 mg is suggested as a standard dose (for calculation see table), with reduction to 0.5 mg at clearances of 50 ml/min and to 0.375 mg at 30 ml/min. The data from healthy subjects indicate that the loading dose for patients with good renal function may be calculated in a similar manner. We must emphasise that as the recommendations are based on population means adjustment of subsequent doses according to individual variation in sensitivity and tolerance may be necessary.

SMD was supported by a research grant from the North West Regional Health Authority, EMR by an MRC grant to Professor G E Mawer.

¹ Gold, H, et al, *Journal of Pharmacology and Experimental Therapeutics*, 1953, **109**, 45.

² Dobbs, S M, et al, *British Journal of Clinical Pharmacology*, 1977, **4**, 327.

³ Redfors, A, *British Heart Journal*, 1972, **34**, 383.

⁴ Dobbs, S M, et al, *British Medical Journal*, 1977, **1**, 749.

⁵ Reuning, R H, et al, *Journal Clinical Pharmacology*, 1973, **13**, 1, 27.

(Accepted 25 March 1977)

Department of Pharmacology, Materia Medica, and Therapeutics, University of Manchester, Manchester M13 9PT

SYLVIA M DOBBS, MSc, MB, lecturer (now lecturer in clinical pharmacology, Department of Pharmacology and Therapeutics, The Middlesex Hospital Medical School, London W1P 7PN)

JANET PARKES, technician

ELAINE M RODGERS, MRC technician

Department of Medicine, Tameside General Hospital, Ashton-under-Lyne, Lancs

W I KENYON, MB, FRCP, consultant physician