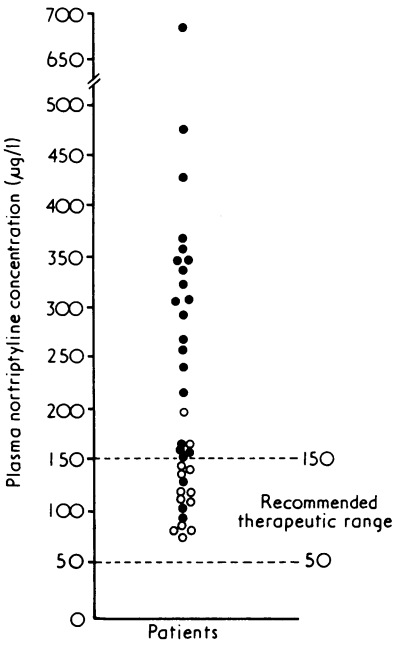
because of concomitant treatment with antidepressants or drugs known to change plasma levels. Three were on monoamine oxidase inhibitors and two on phenothiazines and their levels of nortriptyline and responses to the drug did not seem to differ from those of the other patients. Five of the 36 patients were also taking lithium and 24 were receiving benzodiazepines, mainly nitrazepam. Plasma nortriptyline levels were measured after two or more weeks. Recovery, defined as a pronounced persistent improvement in depressive symptoms observed three to six weeks after starting treatment, was assessed globally at Preston Hall Hospital by the treating psychiatrist, who did not know the plasma levels, and at the Maudsley-Bethlem Hospital by assessing the case papers, which had usually been written before the plasma levels were known, though blindness might not always have been maintained. Plasma levels were measured using a method similar to that of Kragh-Sørensen *et al.*[5] Interlaboratory reproducibility studies were performed.



Relation between plasma nortriptyline levels and clinical response. ● = Non-responders. O Responders.

The mean daily dose (101·2 mg) adjusted for body weight produced a higher dose for women (1·81 mg/kg) than for men (1·53 mg/kg), and men seemed to respond better. There was a ninefold variation in individual plasma nortriptyline concentrations from 77 μg/l to 684 μg/l. Patients with levels within the range 50-150 μg/l responded significantly better than those with higher levels (χ^2 17·9; DF = 1; P<0·0001; see figure). Only two of the 22 patients with levels above 150 μg/l responded, while 11 of the 14 with levels of 50-150 μg/l did so. The mean daily dose of the responders (1·39 mg/kg) was significantly (P<0·01) lower than that of the non-responders (1·86 mg/kg).

Comment

It is surprising that on an average daily dose of 100 mg 61% of our patients produced plasma nortriptyline levels above 150 μg/l, while Kragh-Sørensen *et al*[3] found that only 43% of 30 patients on a dose of 150 mg daily developed such levels. His patients were a little younger than ours, but we failed to show a correlation with age. The British health system, whereby patients are referred to hospital-based psychiatrists by general practitioners who have already attempted treatment, may preselect non-responders with high levels. The correct dose for this study's population would have been 60 mg/day—much lower than that commonly used. Although in any group of psychiatric patients some spontaneous or non-drug-related remissions may be expected, the group of patients with high plasma levels consisted overwhelmingly of those who did not recover. This confirms the view[5] that plasma nortriptyline levels above about 150 μg/l inhibit recovery.

Most patients with high drug levels showed no clinical signs of their high concentrations, though two developed confusional states. High plasma nortriptyline concentrations can be produced by moderate doses, and only the laboratory can detect the presence of these high levels. We therefore recommend the routine measurement of plasma nortriptyline levels in patients taking the drug.

We thank Dr Felix Post for his help; S Dawling, M Tashin, D Montgomery for technical help; and the medical and nursing staff of both hospitals.

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(*Accepted 29 April 1977*)

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Meningitis and endophthalmitis caused by Streptococcus suis type II (group R)

Streptococcus suis, type II, is now recognised to be an important cause of meningitis, septicaemia, and purulent arthritis in young pigs.[1] Human infections are rare, but have been reported in Holland and Denmark[2 3] and the first British case has been recently described.[4] In the case reported here the patient presented with severe bilateral endophthalmitis as well as other reported manifestations of *Str suis infection*.

Case report

A 46-year-old maintenance engineer at a pork-pie factory presented with a three-day history of malaise, fever, right-sided deafness, tinnitus, frontal headache, and discharging eyes. He also complained of swelling of both wrists and pain in both elbows. He was febrile, drowsy, and deaf (more in the right ear). He had a severe bilateral endophthalmitis and secondary glaucoma with left purulent conjunctivitis. His throat was inflamed with areas of superficial ulceration. No skin wounds were found. Both wrists were tender and swollen, but no fluid could be aspirated from them; his elbows were normal apart from slight redness. He had no neck stiffness and Kernig's sign was negative. Cerebrospinal fluid (CSF) examination disclosed a pleomorphic cell count (polymorphonuclear leucocytes 331/mm^3, lymphocytes 29/mm^3, and protein 0·8 g/l). Gram-positive cocci in pairs and short chains were seen in the CSF and in aqueous fluid aspirated from the anterior chamber of the left eye. Cultures of these fluids and blood grew a β-haemolytic streptococcus, which gave a weak reaction with Lancefield Group-D antiserum (both after acid extraction and autoclaving) but was not resistant to bile. The organism was not isolated from the throat swab. The isolate was examined by the Streptococcus Reference Laboratory, Colindale, and by Dr S D Elliott, Cambridge, and was identified as *Str suis*, Type II. The minimum inhibitory concentration of penicillin and of ampicillin was 0·03 mg/l.

The meningitis and septicaemia were treated with benzylpenicillin, 20 000 units intrathecally immediately and 4 million units intravenously every four hours for two days, followed by amoxycillin, 0·5 g 6-hourly. The endophthalmitis and glaucoma responded to acetazolamide, 250 mg, and prednisolone, 10 mg every six hours—together with local eyedrops of atropine, bacitracin, and Maxidex. Benzylpenicillin, 0·5 megaunits, was given subconjunctivally followed by ampicillin, 100 mg, and betamethasone, 4 mg, on alternate days. Systemic antibiotic therapy was continued for a total of six weeks. The patient recovered but was left with high tone deafness, unsteadiness of gait, and impairment of vision in the left eye.

Discussion

Previous case reports of *Str suis*, type II, in man have described septicaemia and meningitis, and in one case meningitis was present

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 carcases 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.

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(*Accepted 25 March 1977*)

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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. Redfors[3] 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 ±1 SD, 65 ± 11 kg), aged 44 to 84 years (64 ± 12 years), and with creatinine clearances 11 to 92 ml/min (56 ± 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 $C_6 = 3{\cdot}87 - 0{\cdot}03Ccr$, C_6(nmol/l) being the concentration 6 h after dose of 1 mg in patient with creatinine clearance Ccr (ml/min). For example, when Ccr = 63 ml/min, $C_6 = 3{\cdot}87 - 0{\cdot}03(63)$ 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 $C_x = C_o D_x / D_o$, where $C_o$nmol/l is the concentration measured after a previous dose of $D_o$mg. Comparison of the predicted and measured concentration at each sampling time showed that the best prediction was for six hours after the dose ($n = 10$, $r = 0{\cdot}92$, $P < 0{\cdot}001$). 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 patients[2] receiving digoxin was 63 ± 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.

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(*Accepted 25 March 1977*)

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