Infirmery and St Mary's Hospital, Manchester, for consideration for haemodialysis. Her haemoglobin concentration was 8.8 g/dl, blood urea concentration 30 mmol/l (180.7 mg/100 ml), blood creatinine concentration 740 μ mol/l (8.4 mg/100 ml), creatinine clearance 5 ml/min, serum albumin concentration 27 g/l; proteinuria 3 g/day, plasma calcium concentration 1.5 mmol/l (6 mg/100 ml), plasma phosphate concentration 1.8 mmol/l (5.6 mg/100 ml), serum alkaline phosphatase activity 65 IU/l, and plasma urate concentration 0.6 mmol/l (10.1 mg/100 ml). Her blood pressure was 150/100 mm Hg, rising to 170/110 mm Hg. She was treated with methyldopa 1.5 g/day and a diet containing 50 g protein, 50 mmol (mEq) sodium, and 10.5 MJ (2500 kcal). Results of ultrasound scanning and radiography confirmed fetal gestation of 28 weeks. Urinary oestriol excretions were 15 and 24 μ mol/day (4.3 and 6.9 mg/day; normal value over 40 μ mol/day (11.5 mg/day)).

One week later the blood urea concentration was 33 mmol/l (198.8 mg/100 ml), creatinine concentration 800 μ mol/l (9.0 mg/100 ml), and creatinine clearance 3 ml/min. She entered spontaneous labour and delivered a 1600 g boy. The placenta (350 g) was macroscopically normal. The infant suffered respiratory distress syndrome, complicated by a pneumothorax requiring ventilation. His blood urea concentration on delivery was 29.4 mmol/l (177.1 mg/100 ml), falling to normal in three days. One month later he was discharged well and weighing 2000 g.

After delivery the patient's blood pressure rose, requiring methyldopa 500 mg three times daily, hydralazine 25 mg three times daily, and atenolol 100 mg daily. When she was discharged three weeks after delivery her creatinine clearance was only 3 ml/min. Renal function continued to deteriorate, and she was awaiting dialysis. Intravenous pyelography seven weeks after delivery showed small smooth kidneys. Investigation detected no underlying systemic disorder. Renal biopsy was not performed.

Comment

The reasons for poor fetal survival during pregnancy complicated by chronic renal failure are not understood. When serum urea concentration exceeds 7.5 mmol/l (45.2 mg/100 ml) and serum

creatinine concentration 275 μ mol/l (3.1 mg/100 ml), normal gestation is rare and conception not recommended, but these concentrations are symptomless and not troublesome in non-pregnant women.¹ Reciprocal creatinine concentrations showed a linear decline before and after birth (figure), though we do not know the rate of decline before pregnancy. Strauch and Hayslett suggested that pregnancy does not alter the course of the underlying renal disease.⁴

The ease of control of blood pressure was probably important in determining our patient's successful outcome. Felding⁵ showed that in mild renal failure poorly controlled maternal blood pressure increased prenatal mortality from 8% to 31% and prematurity from 12% to 37%. The degree of parity was also important. Mackay concluded that adaptation to pregnancy was less well tolerated in the first than in subsequent pregnancies.² Our patient received transfusions three times during pregnancy and also immediately after delivery (figure). We decided to keep haemoglobin concentrations above 8 g/dl, which was a compromise to meet fetal requirements without reducing maternal renal function.

Pregnancy in patients receiving haemodialysis or with renal transplants is now acceptable. In chronic, severe renal failure not requiring dialysis, however, there is insufficient knowledge and experience. The fear of causing deterioration in maternal condition with no guarantee of a viable infant results in extreme caution when advising on conception and easy acceptance of therapeutic abortion.

This case indicates that with joint care of an obstetrician and nephrologist successful pregnancy is possible when the creatinine clearance is below 10 ml/min on booking, provided that the patient is a multigravida and does not have severe hypertension.

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Haemoglobin concentrations, creatinine clearances, serum urea concentrations, and reciprocal of serum creatinine concentrations in patient with severe chronic renal failure before and after delivery.

Conversion: SI to traditional units—Serum urea: 1 mmol/l $\approx$ 6 mg/100 ml. Serum creatinine: 1 μ mol/l $\approx$ 0.01 mg/100 ml.

Ionised calcium in rheumatoid arthritis: effect of non-steroidal anti-inflammatory drugs

Many patients with rheumatoid arthritis have disordered calcium homeostasis, and some workers have suggested that a hyperparathyroid-like state may exist in rheumatoid arthritis.^{1 2} After correction for low albumin concentrations, hypercalcaemia was present in up to 46% of patients,² although parathyroid hormone concentrations were not raised.¹ Hypocalcaemia may also occur in rheumatoid patients with advanced bone disease, even allowing for low serum albumin concentrations.³ Diseases associated with deranged calcium metabolism are best assessed by measuring the physiologically important ionised fraction of serum calcium because extrapolating from "corrected" calcium values is unreliable.⁴ We decided to re-examine calcium balance in rheumatoid arthritis by measuring serum ionised calcium concentrations. The effects of non-steroidal anti-inflammatory drugs were also studied.

Patients, methods, and results

Serum ionised calcium, total serum calcium, total protein, albumin and phosphate concentrations and alkaline phosphatase activity were estimated in

50 patients with rheumatoid arthritis and 50 controls matched for age and sex. Samples for measuring ionised calcium were collected in evacuated containers, allowed to clot at room temperature for 30 minutes, and centrifuged. Serum ionised calcium was estimated on an Orion SS-20 ionised calcium analyser, which incorporates a microcomputer-controlled ion-selective flow-through electrode. All samples were measured in duplicate. Reproducibility was good, between-batch variation being 1.7%. Patients had taken their usual drugs on the morning of the test, between two and five hours before estimation. The results prompted a study of 26 healthy volunteers (17 men, nine women; mean age 27 years); serum ionised calcium concentration was estimated every 90 minutes on control days (no drug treatment) and after ibuprofen 600 mg at 9 am. All subjects remained mobile and were instructed to follow similar degrees of activity for both days.

Seven patients with rheumatoid arthritis had ionised calcium values outside normal (1.15-1.30 mmol/l; 4.62-5.2 mg/100 ml). Two patients were hypercalcaemic and five were severely hypocalcaemic. The "uncorrected" total calcium concentration was often the best predictor of a low ionised value. All patients with hypocalcaemia were postmenopausal women taking non-steroidal anti-inflammatory agents in addition to other drugs.

Of the matched controls, only one had a marginally low ionised calcium concentration (1.14 mmol/l; 4.6 mg/100 ml). In the non-matched group of volunteers ionised calcium fell from a mean 9 am value (± 1 SD) of 1.22 ± 0.05 mmol/l (4.9 ± 0.2 mg/100 ml) to 1.20 ± 0.04 mmol/l (4.8 ± 0.17 mg/100 ml) at 3 pm on control days (figure). This pattern was consistent and significant

Mean changes ($\pm$ SEM) in ionised calcium concentration compared with 9 am value.

($t=3.455$, $p<0.01$, paired t test). On days after ibuprofen 600 mg the mean ionised calcium concentration fell from 1.22 ± 0.04 mmol/l (4.9 ± 0.15 mg/100 ml) at 9 am to 1.19 ± 0.04 mmol/l (4.8 ± 0.18 mg/100 ml) at 1.30 pm ($t=6.373$, $p<0.001$). To assess the significance of this variation the mean differences between the fall in ionised calcium on each day were calculated for each time period. The results confirm that a significant fall occurs four and a half hours after ingestion of ibuprofen ($t=3.227$, $p<0.01$).

Comment

Our results differ from those of Kennedy *et al*¹ as hypocalcaemia, assessed by the ionised calcium fraction, was present in five of our 50 patients whereas only two were hypercalcaemic. Nevertheless, these studies varied in the time that elapsed between taking the drug and measuring calcium. Although in both studies blood was taken in the morning, in the series of Kennedy *et al*¹ drugs were not taken after 6 pm the evening before, whereas all our patients took their usual medication between two and five hours before calcium estimation. The effect observed in our second study is probably inherent in treatment with any non-steroidal anti-inflammatory drugs.

The effect of these drugs on calcium metabolism has been studied in animals, and indomethacin in particular exhibits hypocalcaemic, hyperphosphataemic, and parathyroid hormone inhibitory action in rats.⁵ In young healthy adults the drugs can apparently significantly reduce ionised calcium, and five of our subjects became hypocalcaemic. Further studies may show whether this effect is beneficial or detrimental.

In conclusion, hypocalcaemia, as assessed by a low serum ionised calcium concentration, was present in five out of 50 patients with rheumatoid arthritis. Other studies on healthy subjects suggest that these results may be an unreported effect of non-steroidal anti-inflammatory drugs.

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Gonorrhoea presenting as "sterile" pyuria

In men the diagnosis of gonorrhoea depends on the detection of Gram-negative intracellular diplococci in smears and on the culture of *Neisseria gonorrhoeae* from urethral discharge. After inoculation of the specimen the plates are incubated as soon as possible to grow this delicate organism. We describe two recent cases where gonococci were isolated from ordinary mid-stream specimens of urine sent for culture of pathogens causing urinary tract infection more than 24 hours after receipt of the samples. After inoculation of the plates with centrifuged deposit they were left in a carbon dioxide incubator for three days before any recognisable growth was noticed.

Case reports

Two men, aged 17 and 20 years respectively, presented to their family practitioners with a two-to-four day history of dysuria; one had frequency of micturition, but neither had a history of any discharge. The patients were instructed to collect and deliver specimens of mid-stream urine to the laboratory for ordinary culture and sensitivity testing. Microscopy showed over 100×10^6 pus cells/l (100 pus cells/mm³), but no other abnormalities. Specimens were inoculated on to cysteine, lactose, and electrolyte-deficient medium and placed in a carbon dioxide incubator, together with a primary sensitivity plate of direct sensitivity test agar (DST-Oxoid) medium with 5% lysed blood, in a hot room at 37°C. The next day there was no visible growth on the plates. Instead of reincubating the plates, as is the usual practice, Gram stains were done on the centrifuged deposit of urine, which showed typical Gram-negative intracellular diplococci and no other organisms. The family practitioner was then informed and was asked to obtain a swab of urethral discharge, if any, and a smear if the patient had not already received treatment. At the same time an attempt was made to grow the organism by inoculating the centrifuged deposit of urine on to chocolate agar and GC selective medium (Difco) in the presence of carbon dioxide. After 72 hours' incubation, growth was recognisable. The organism in each case was identified as *N gonorrhoeae* by Gram staining, the oxidase test, and sugar fermentation reactions.

Comment

The use of urine sediment culture for diagnosing gonococcal infection in male patients was first described in 1973,¹ when it was stated that the organisms remained viable at room temperature for as long as two hours. Later, successful culture of gonococci was reported from uncentrifuged, first-voided urine in male patients; in our cases, however, gonococci grew only from the centrifuged deposit. The success rate of isolation from specimens of urine more than one day old, however, must be very low. If we had tried to grow anaerobic or fastidious CO₂ dependent organisms, which have been highlighted recently, on media unsuitable for gonococci or from uncentrifuged urine—instead of looking for gonococci—the diagnosis would have been missed. In the absence of discharge (unless gonorrhoea is