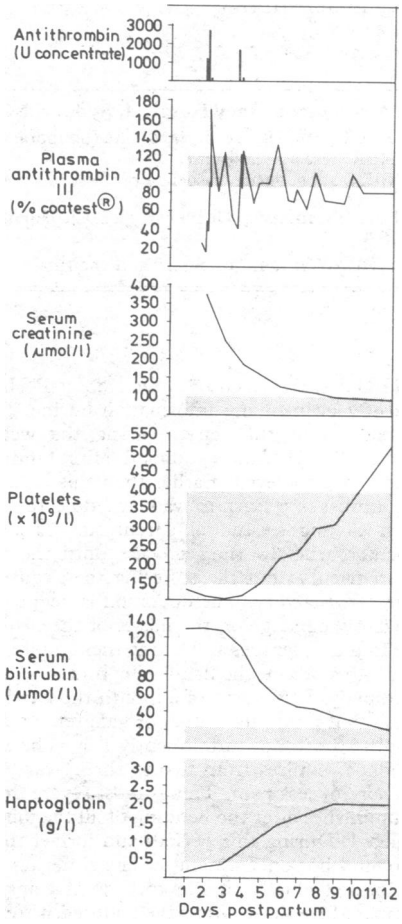
Postpartum haemolytic-uraemic syndrome successfully treated with antithrombin III

Since first described in 1966 the acute postpartum haemolytic-uraemic syndrome (HUS) has been reported in over 40 cases by various authors.[1] In view of the poor prognosis despite treatment with dialysis, immunosuppression and heparin, streptokinase, dipyridamol, acetylsalicylic acid, or corticosteroids, alone or combined, we report a case in which treatment with a concentrate of antithrombin III (AT-III) appeared to cure the haemolytic anaemia and the thrombocytopenia rapidly, normalise kidney function within a few days, and prevent irreversible kidney damage.

Case report

A 34-year-old primipara was admitted to hospital in the eighth month of pregnancy because of a slightly raised blood pressure (150/100 mm Hg) and proteinuria (1·5–4 g/24 h). Thirty hours before delivery her serum creatinine was 277 μmol/l (3·1 mg/100 ml). Four days after admission labour began spontaneously and was completed in 70 minutes without complications.



Course of postpartum haemolytic-uraemic syndrome during treatment with antithrombin III concentrate. Shaded areas represent normal range.

Next day the patient became dyspnoeic with generalised pain, slight icterus, and macroscopic haematuria. Blood pressure and temperature were normal. Radiographs of lungs and an electrocardiogram were normal. Serum creatinine and bilirubin concentrations rose, moderate thrombocytopenia developed (phase contrast microscopy), and haptoglobin (immundiffusion method) decreased (figure). Reticulocytes increased to 5·7% and haemoglobin concentration fell in 48 hours from 11·1 mmol/l (12 g/dl) to 8·2 mmol/l (8·9 g/dl). Coombs test was negative. Catheterisation 24 hours after delivery produced 1000 ml urine.

The plasma AT-III concentration (Antithrombin Coatest) was very low (figure). Therefore 26 hours after delivery treatment was begun with a concentrated solution of AT-III prepared from a purified preparation of human AT-III (Kabi, Stockholm). First 1200 units of AT-III were given as an intravenous bolus (one unit was equivalent to the amount of AT-III/ml normal human plasma). One hour later 2750 units were infused over a period of three hours, followed by a third infusion of 250 units (figure). The AT-III concentrations were unstable. A fall on the third day required an additional infusion of 1650 units over four hours followed by a bolus injection of 150 units, and the concentration stabilised at a slightly subnormal level. During and after the AT-III infusions serum creatinine and bilirubin concentrations fell while haptoglobin and platelets soon returned to normal (figure), as did the patient's clinical condition. Kidney biopsy on the 10th day showed normal morphology. Five months later kidney function was normal and haemoglobin and AT-III concentrations were in the lower range of normal.

Comment

The aetiology of HUS is unknown, but our data suggest that a stage of disseminated intravascular coagulation (DIC) is a factor of pathogenetic significance.[1] Quite possibly thromboplastin escapes from the thromboplastin-rich placenta by uterine contraction during labour. Also in pregnancy sensitivity is increased to stimuli known to induce DIC.[2] Interestingly infusion of AT-III can protect chicken embryos against the injection of thromboplastin.[3] Similarly, heparin is reported to prevent the toxicity of thromboplastin injection in mice. But heparin increases the turnover rate of AT-III,[4] and giving heparin to patients low in plasma AT-III may therefore paradoxically increase an existing risk of thrombosis.[5] Therefore the low plasma AT-III concentration at the onset of the syndrome in our patient seems particularly significant, and we believe her recovery was due to the treatment with AT-III concentrate.

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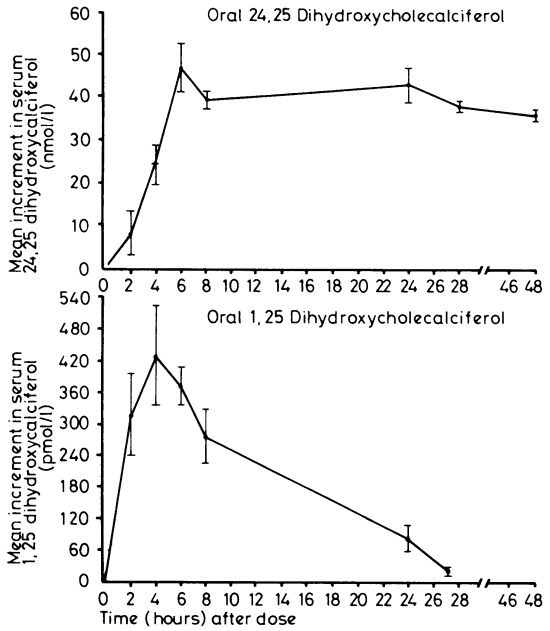
Blood concentrations of dihydroxylated vitamin D metabolites after an oral dose

Dihydroxylated vitamin D metabolites are being used increasingly in clinical medicine. We therefore measured blood concentrations of these compounds in normal subjects after single oral doses of 1,25-dihydroxycholecalciferol (1,25-$(OH)_2D_3$) and 24,25-dihydroxycholecalciferol (24,25-$(OH)_2D_3$).

Subjects, methods, and results

Four normal volunteers (three men, one woman) were given 4 μg 1,25-$(OH)_2D_3$ after an overnight fast. Three normal volunteers (two men, one woman) were given 250 μg 24,25-$(OH)_2D_3$ (in 0·5 ml ethanol) after an overnight fast. Blood was taken at the times indicated (see figure) and the serum stored at −20°C. Serum concentrations of both metabolites were measured in each person by a method[1] which gives a range of 29-168 pmol/l for 1,25-$(OH)_2D_3$ and a range of 2·9-16 nmol/l for 24,25-$(OH)_2D_3$.



Mean (±SEM) serum concentrations of $1,25(OH)_2D_3$ in four subjects after taking 4 μg by mouth and of $24,25\text{-}(OH)_2D_3$ in three subjects after taking 250 μg by mouth.

Peak concentrations of $1,25\text{-}(OH)_2D_3$ were reached after four hours and of $24,25\text{-}(OH)_2D_3$ after six hours (figure). Concentrations of $1,25\text{-}(OH)_2D_3$ had returned to baseline levels 27 hours after administration, whereas $24,25\text{-}(OH)_2D_3$ concentrations were still considerably raised even after 48 hours. In one of the subjects who had received $24,25\text{-}(OH)_2D_3$ observations were continued for 21 days. By day 9 serum concentrations had returned to within the normal range, but pretreatment levels had not been reached by day 21. Serum calcium and serum inorganic phosphate concentrations were not significantly altered by single doses of either metabolite, and serum concentrations of the non-administered dihydroxylated metabolite did not change significantly during the period of observation.

Comment

We believe that these are the first systematic pharmacokinetic studies of unlabelled dihydroxylated vitamin D metabolites in normal man. Our results are consistent with the data of Rosen *et al*,[2] who gave $1,25\text{-}(OH)_2D_3$ by mouth to hypoparathyroid children and found raised serum concentrations four hours later but not 16 hours later. Our peak serum concentration at four hours agrees with data obtained after an oral dose of tritiated $1,25\text{-}(OH)_2D_3$,[3] while the rapid disappearance rate of this metabolite is similar to that reported by Gray *et al*,[4] who gave tritiated material intravenously to healthy adults. In two pseudohypoparathyroid patients receiving $1,25\text{-}(OH)_2D_3$ daily, serum concentrations of the metabolite were not raised 24 hours after the last dose except at times of hypercalcaemia.[5] The distribution volume of $1,25\text{-}(OH)_2D_3$ calculated from the mean peak value was about seven times the plasma volume. We know of no published data on $24,25\text{-}(OH)_2D_3$ concentrations in human serum after an oral dose. The calculated distribution volume was about three times the plasma volume, which is comparable with that reported for 25-hydroxycholecalciferol.[3] The relatively slow disappearance rate of $24,25\text{-}(OH)_2D_3$ also resembles that of 25-hydroxycholecalciferol, which remains raised in human serum for at least 14 days after an oral dose.[3]

Serum concentrations of $1,25\text{-}(OH)_2D_3$ are about 1% of those of $24,25\text{-}(OH)_2D_3$.[1 3] Our study indicates at least one reason for this—the difference in turnover times. This is more than adequate to account for the differences in serum concentrations, even though normal subjects synthetise the two metabolites at about similar rates.[3] The different disappearance rates of the two metabolites may be related to their affinities for vitamin D-binding protein(s) in serum or to different rates of uptake by various tissues.[3] As with glucocorticoids, it is impossible to relate the biological potency of compounds to their disappearance rates from plasma. Moreover, the biological effects of a single dose of $1,25\text{-}(OH)_2D_3$ persist for at least seven days,[3] so our findings do not necessarily indicate a requirement for multiple daily doses. Nevertheless, the rapid disappearance rate of $1,25\text{-}(OH)_2D_3$ indicates that blood concentrations may be used to monitor treatment only if samples are taken at standard times after the last oral dose.

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ONE HUNDRED YEARS AGO Dr Robert P Harris of Philadelphia has recently been giving information on foot-binding to the College of Physicians of that city. Among the wealthy Chinese and those who can afford to have it done, the first binding takes place at the age of from five to seven. Earlier than this it cannot be done, because the child must first learn to walk and do certain acts or kinds of work in which walking is essential. Circumstances sometimes cause the postponement of the dwarfing process until the age of twelve, fourteen, or even twenty; but the suffering then caused is extreme, and the result less satisfactory. The operation is begun by placing the end of a long narrow bandage on the inside of the instep, carrying it around over the four smaller toes and taking them under the foot. After several turns with this object, the bandage is turned so as to compress the foot longitudinally. At the end of a month the bandage is opened, when the skin is often found ulcerated, or gangrenous from pressure, and one or more toes are not unfrequently lost. The shaping of the foot by the bandage requires from two to three years, during which period there is more or less pain. This is most severe in the first year, and gradually diminishes after the bending of all the joints and articulations is completed. During this period, and in fact throughout life, the feet are unbound but once a month. The suffering at first is very severe, and is located chiefly in the toes, joints, ankle-bones, and instep: it is compared by those who have endured it to that produced by the thrusting of sharp needles into the flesh. At night, the girl lies across her bed, putting her legs over the edge of the bedstead, so as to make a pressure under the knees, and thus benumb the parts below them. In this position on her back, swinging her legs backward and forward, she passes many a weary night. Febrile disturbance is said to be an accompaniment of this torturing process. If the feet are firmly bound, and the girl young, they will cease to ache generally in about two years, the parts being then denominated "dead." By this time, the calf of the leg, for want of use, has disappeared, the skin is shrivelled, and the whole extremity below the knee presents an atrophied and shrunken appearance, being little more than skin and bone. The bones eventually become attenuated, and the ankle measurement of a dwarf-footed woman is about the same as that of her wrist. In adult life, the leg frequently becomes rounded and enlarged by adipose deposit, and the muscles regain their form in a measure; but the ankle always remains small. (*British Medical Journal*, 1880.)