SHORT REPORTS

Plasma exchange in non-haemophiliac patients with inhibitors to factor VIIIc

Treatment of patients with inhibitors to factor VIII clotting activity (VIIIc) remains an unsolved clinical problem. Recent reports^{1,2} suggest that plasma exchange (or plasmapheresis) contributes to the management of haemophiliacs with inhibitors. This report describes how plasmapheresis helped achieve control in two non-haemophiliac patients with acquired inhibitors to factor VIIIc.

Case reports

Case 1—A 72-year-old man suddenly developed spontaneous bruising, a large ileopsoas haematoma, and femoral nerve palsy. Investigations revealed a prolonged kaolin cephalin clotting time (KCCT) of 93 seconds (control 37 s), a plasma factor VIIIc concentration of 0.02 U/ml, and the presence of an inhibitor to factor VIII at a concentration of 13 U/ml. This "in-house" inhibitor titre was calculated by adding standardised human factor VIII concentrate to plasma until neutralisation occurred, the neutralisation point being that concentration of factor VIII concentrate which clotted the patient's plasma in the same time as an inhibitor-free control plasma.³ Initial treatment with human factor VIII concentrates produced little clinical benefit and minimal rise in factor VIIIc. Porcine factor VIIIc (Hyate C; Speywood Laboratories) produced an excellent rise in factor VIIIc. Its further use was precluded, however, by a severe anaphylactic reaction with bronchospasm, pulmonary crepitations, and peripheral circulatory collapse which required extensive resuscitative measures. After 10 days' factor VIII replacement treatment, without clinical improvement and with continuing spontaneous bruising, the inhibitor concentration had risen to over 50 U/ml with the KCCT at 178 s (control 40 s). Intensive plasmapheresis was started to reduce the quantity of circulating antibody; this was combined with immunosuppressive treatment (azathioprine and prednisolone) to inhibit antibody production. Eight 3-litre plasma exchanges over 10 days using an IBM 2997 cell separator and replacement with equal quantities of fresh frozen plasma and human albumin fraction 43 g/litre (Immuno Ltd) produced rapid clinical improvement in the femoral nerve palsy. No further fresh bleeding developed. Laboratory tests reflected this improvement, the KCCT shortening to 68 s (control 38 s), the plasma factor VIIIc concentration rising to 0.05 U/ml, and inhibitor concentration falling to 8 U/ml. Immunosuppressive treatment was gradually reduced. Two months later the inhibitor titre was 1 U/ml with a factor VIIIc assay of 0.34 U/ml.

Case 2—A 28-year-old woman underwent an apparently uneventful caesarean section for fetal distress, but within one week she developed a large wound haematoma. Surgical exploration showed no bleeding vessels, but profuse bleeding continued with the development of a massive anterior abdominal wall haematoma. Transfusion of 14 units of blood was required before the patient was fit to be transferred. Investigation showed an inhibitor to factor VIIIc of 2.5 U/ml, a KCCT of 75 s (control 37 s), and plasma factor VIIIc concentration of 0.04 U/ml. Immunosuppressive drugs were withheld because of the risk of wound dehiscence. Infusions of high doses of human factor VIII concentrates raised the plasma concentration of factor VIIIc but produced no clinical improvement and were associated with a rise in the inhibitor concentration to over 50 U/ml. After two weeks intrarenal and retroperitoneal bleeding had produced a potentially fatal clinical deterioration. Intensive plasmapheresis and immunosuppressive treatment with azathioprine and prednisolone were therefore started. Two plasma exchanges of 1.5 litres and four of 3.0 litres, using human albumin fraction (Immuno Ltd) as the only replacement fluid, were performed during eight days. This resulted in pronounced clinical improvement with no further fresh bleeding. Laboratory tests now showed a KCCT of 53 s (control 40 s), plasma factor VIIIc concentration of 0.23 U/ml, and inhibitor concentration of 1 U/ml. Two months later, with immunosuppressive drugs withdrawn, coagulation results were virtually identical, the abdominal haematoma almost resolved, and the abdominal scar soundly healed.

Comment

Although about 75% of non-haemophiliac patients with inhibitors respond to immunosuppressive drugs, the response is often slow and variable.⁴ Treatment is difficult to assess, but reports have shown the value of plasmapheresis in haemophiliacs with inhibitors.^{1,2} Plasmapheresis appears rapidly effective and has advantages over other treatments. Circulating antibody concentrations are rapidly lowered, and the risk of hepatitis from albumin products is negligible. Anamnestic reactions associated with factor VIII concentrates are avoided or minimal if fresh frozen plasma is given as replacement

fluid. "Activated" prothrombin complexes have been advocated⁵ but are expensive and potentially thrombogenic.

These two cases indicate that extensive plasmapheresis with immunosuppression should be considered early in the treatment of non-haemophiliacs with inhibitors. Plasmapheresis to remove circulating factor VIII inhibitor antibody may in such cases be a life-saving measure.

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¹ Wensley RT, Stevens RF, Burn AM, Delamore IW. Plasma exchange and human factor VIII concentrate in managing haemophilia A with factor VIII inhibitors. *Br Med J* 1980;**281**:1388-9.

² Colcroft R, Tamagrim G, Dormandy KM. Serial plasmapheresis in a haemophiliac with antibodies to Factor VIII. *J Clin Pathol* 1977;**30**:763-5.

³ Tse D, Fekete L, Shanbrom E. A simple procedure for accurate quantitation of Factor VIII inhibitors. *Thrombosis et Diathesis Haemorrhagica (Stuttgart)* 1970;**23**:19-25.

⁴ Shapiro SS, Hultin M. Acquired inhibitors to the blood coagulation factors. *Semin Thromb Hemostas* 1975;**1**:336-85.

⁵ Kurczynski EM, Penner JA. Activated prothrombin concentrate for patients with factor VIII inhibitors. *N Engl J Med* 1974;**291**:164-7.

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Diagnosis of bladder neck incompetence without use of capital equipment

In cases where symptoms suggest genuine stress urinary incontinence but where stress leakage cannot be shown during examination, alternative diagnostic information is sought. Failure of the primary mechanism of continence at the bladder neck must precede any stress leakage and there is a small range of urethral measurements and tests aimed at identifying failure, or likely failure of this mechanism. These fall into two groups: those which infer that the bladder neck is likely to open during stress, such as the urethral pressure profile test and coughing pressure transmission tests¹; and those in which actual penetration of fluid into the urethra can be seen or detected, such as cine-radiography² and the fluid-bridge test.³

We describe a development of the fluid bridge test which provides clear and useful information on urethral incompetence without the use of capital equipment.

Method

The new test, which we call the fluid bridge (flow) test, requires only a simple plastic catheter, preferably with calibration marks added. To perform the test the catheter is passed until the eye is in the bladder and urine flows freely through it (fig (a)). It is then eased out very slowly until the flow of urine ceases, thus locating the bladder neck (fig (b)). Next it is moved a chosen distance (usually 0.5 cm) down the urethra—calibration marks are helpful at this point (fig (c)). The patient is asked to cough. If the cough causes urine to flow through the catheter (fig (d)) then the bladder neck is shown to open to the chosen point, and the test is said to be positive. If no drops emerge the test is negative. If the test is positive it can be repeated at distal points to see how far the urethra opens during cough.

While the patient is coughing the catheter needs to be kept in position. This can be achieved with a sticking plaster applied to the medial aspect of the thigh, but we use a special clip⁴ set in a rubber ring pessary held between the patient's thighs, which saves time. If there is doubt as to the position of

the catheter, however, it can be relocated at any time by repeating the procedure described above.

The figure shows a side-opening catheter, but the results we obtained with a catheter having a single hole at the tip appear to be the same.

Four stages of fluid bridge (flow) test: (a) catheter is passed up into bladder, (b) bladder neck is located, (c) test position is selected, (d) bladder neck opens during cough.

Comment

We used this method on more than 50 patients and found the results indistinguishable from those of the fluid bridge (pressure) test. The test is reproducible, though the distance from the bladder neck at which the result is positive may vary slightly with the strength of the cough.

The importance of the fluid bridge test has already been established and it appears to be a more sensitive indicator of bladder neck incompetence than other urodynamic tests, with the possible exception of pressure-cine-cystography.^{4,5} This simpler test permits wider use of work already done with more complex apparatus. Because no apparatus is required it should be possible to conduct this test in the outpatient clinic, avoiding referral of some patients to specialised units, saving time and effort.

¹ Asmussen M, Ulmsten U. Simultaneous urethro-cystometry with a new technique. *Scand J Urol Nephrol* 1976;10:7-11.

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³ Brown M, Sutherst J. A test for bladder neck competence: the fluid bridge test. *Urol Int* 1979;34:403-9.

⁴ Sutherst JR, Brown M. Detection of urethral incompetence. Erect studies using the fluid bridge test. *Br J Urol* (in press).

⁵ Sutherst JR, Brown M. Detection of urethral incompetence in women using the fluid bridge test. *Br J Urol* 1980;52:138-42.

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No evidence of transfer of fluoride from plasma to breast milk

Artificially fluoridated drinking water is supplied throughout the world as a mass-prophylactic agent against dental caries. No data are available, however, on the transfer of fluoride from maternal plasma to breast milk. We have therefore compared the fluoride concentrations in the plasma and breast milk of nursing mothers after an oral dose of fluoride.

Subjects, methods, and results

Five mothers aged 27-36 years were given fluoride by mouth on the third postpartum day. A dose of 1.5 mg was given as an aqueous solution of sodium fluoride in the morning after fasting for 10 hours. Blood and breast milk were sampled simultaneously in a non-glass system before and 30, 60, 90, and 120 minutes after the dose. Fluoride concentration in plasma was measured with a fluoride-sensitive electrode,¹ and in milk was determined using a modified microdiffusion technique.² Recovery experiments showed no evidence that fluoride binds to the constituents of breast milk. Hence the figures given for breast milk represent exclusively free fluoride.

The plasma fluoride concentration in all subjects rapidly increased after fluoride intake (figure). The highest plasma concentrations appeared 30 minutes after dosing, when they varied between 3.6 and 4.5 $\mu\text{mol/l}$ (70 and 86 ng/ml). This rapid absorption was in line with our results from oral single-dose studies in man.³ There was no corresponding increase in the fluoride concentrations in the breast milk, the values varying between 0.1 and 0.4 $\mu\text{mol/l}$ (2 and 8 ng/ml).

Plasma (open symbols) and breast milk (closed symbols) fluoride concentrations in five mothers after oral dose of 1.5 mg fluoride as sodium fluoride solution.

Conversion: SI to traditional units—Fluoride: 1 $\mu\text{mol/l} \approx 19 \text{ ng/ml}$.

Comment

These findings show that plasma fluoride is poorly transferred to breast milk and infants thus receive almost no fluoride during breast feeding. This is in contrast to another halogen, bromide, which reportedly accumulates in breast milk.⁴

In this study plasma and milk were sampled for a period of two hours after a single dose had been taken by the mother. The possibility of delayed transfer, not detected during the period of observation, was ruled out by other results from our laboratory, which showed that fluoride concentrations in breast milk remain steady, even when fluoride is given repeatedly and despite considerable variations in the maternal plasma fluoride concentrations.

The reason for the poor transfer of fluoride into the cells of the breast is obscure. Such a phenomenon has not been observed in other mammalian glands—for example, the salivary glands. The concentration in saliva follows that in plasma, and the ratio between salivary and plasma fluoride is around 0.65.³ Fluoride is excluded from certain cultured cells,⁵ but whether the same mechanisms are concerned in the mammary gland remains to be clarified.

Infants fed on milk substitutes receive higher fluoride doses, especially in areas where the drinking water is rich in fluoride. Thus in an area where the fluoride concentration is one part per million the daily fluoride dose in the newborn infant will be about 800-1000 μg when a milk substitute is used, whereas the fluoride dose for breast-fed children in the same area will not exceed 10 $\mu\text{g/day}$. The existence of a physiological plasma-milk barrier against fluoride suggests that the newborn is actively protected from this halogen. Hence the recommendation made in several countries to give breast-fed infants fluoride supplementation should be reconsidered.

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