The Use of Urokinase in Declotting of Arteriovenous Shunts


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It has previously been reported from several dialysis centres that local use of fibrinolytic agents is of value in restoring patency of arterial and venous channels after clotting of the arteriovenous shunts used for regular haemodialysis. Such treatment is reserved for cases in which routine declotting procedures have been unsuccessful. Two preparations shown to be effective for this purpose are streptokinase (Anderson et al, 1967; Kjellstrand et al, 1967) and a protease derived from Aspergillus oryzae (Bennhold et al, 1968; Bucht, 1968). Streptokinase has the disadvantage of being antigenic, and its use is sometimes followed by haemorrhagic complications, while the Aspergillus protease can cause tissue damage if extravasation occurs when it is administered. We therefore decided to employ urokinase, an enzyme obtained from human urine and free from antigenic properties. Like streptokinase, it activates plasminogen to form plasmin, the natural fibrinolytic agent of plasma.

METHODS

Routine declotting measures, including aspiration by syringe, with or without catheter, milking of the silastic tubing, instillation of warm heparinised saline and local use of lignocaine, resembled those practised elsewhere.

If these failed, urokinase (Leo Laboratories Ltd.), 5000 Ploug units (equivalent to about 7000 CTA units) dissolved in about 5 ml of warm saline, was introduced into one or both limbs of the shunt and left in situ for about 20 minutes. In some cases we tried to estimate on the basis of preliminary shunt angiograms how much urokinase solution would be needed to reach the site of clotting; the volume of saline in which the powdered urokinase was dissolved was then modified in order to obtain maximal concentration of the enzyme. After the use of urokinase, warm heparinised saline was injected to complete the removal of clot, and the shunt was again connected.
On some occasions, when adequate flow was not restored, streptokinase infusion (Kjellstrand et al, 1967) was subsequently given, premedication with hydrocortisone being used to prevent allergic reactions.

The efficacy of the treatment with urokinase was assessed by improvement in flow-rate through the shunt or in several cases by serial shunt angiograms, using Conray 280 (May & Baker Ltd.) warmed to 37°C as the contrast medium.

RESULTS

Of 73 episodes of shunt clotting in our 14 patients, 36 episodes in 8 patients were treated with urokinase. On 25 of the 36 occasions (69%) immediate success, as judged by relief of obstruction and restoration of satisfactory flow-rate was achieved. Twenty-four hours later, 44% remained satisfactory, but after a week further clotting had occurred in all but 6 cases (17%). After 4 weeks only two of the shunts had remained patent (Table I).

Streptokinase infusion was given after failure of urokinase in 8 instances, with satisfactory results in 4 of these.

Although the long-term success rate appears rather low, somewhat better

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<th>TABLE I. Experience with Urokinase</th>
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<td>Number of patients in Series</td>
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<td>14</td>
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*Figures in brackets refer to one patient (M.B.): see text

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<th>TABLE II. Experience with Urokinase</th>
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<td>Prolongation of Shunt Survival Time</td>
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<td>G.G.</td>
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Figure 1. The venous cannula and adjacent part of the vein are occluded by thrombus; marked improvement is evident after urokinase.

Figure 2. The main venous channel is completely obstructed by clot; after urokinase free flow is shown along both veins.
Figure 3. In this case urokinase failed to dislodge the obstruction at the top of the arterial cannula.

Figure 4. Absence of improvement after urokinase in this case is attributable to the obvious kinking of the vein at the tip of the cannula.
figures (22% success after one week) are obtained if the data relating to one
patient (M.B.) are excluded. This woman had a poor vasculature, and lack
of alternative shunt sites led to repeated attempts to maintain flow in a shunt
which would otherwise have been abandoned much earlier.

From the practical point of view, the value of urokinase treatment is
reflected in prolongation of shunt survival. Five of our patients had worth-
while benefit of this kind from two or more applications of urokinase (Table
II).

Examples of shunt angiograms before and after urokinase are shown in
Figures 1 - 4.

DISCUSSION

Urokinase has been shown to be effective in the management of shunt
clotting after routine declotting procedures have failed. Recurrence of clot-
ting after fibrinolytic treatment has, in our experience, been commonly
associated with infection in the region of the shunt, usually by coagulase-
producing staphylococci. The direct effect of these organisms on blood
coagulation can give rise to repeated clotting even before an inflammatory
reaction is clinically apparent. We therefore feel that recurrent episodes
of clotting in the absence of other predisposing factors constitute an indica-
tion for antibiotic therapy. In one of our cases, mild staphylococcal infection
of the shunt was eradicated by cloxacillin, and repeated use of urokinase ex-
tended the life of this shunt by 88 days.

Another important cause of recurrent shunt clotting is the presence of
mechanical factors such as misalignment of the cannula tip with the vessel
or obstruction by a fold of thickened intima just beyond the cannula (Curtis
et al, 1969). One example of each of these problems was encountered in our
series and in both cases shunt patency was maintained by urokinase for 17
days, but it is clear that in the presence of such mechanical defects long-
term benefit from fibrinolytic therapy can hardly be expected. Before
resorting to repeated doses of fibrinolytic agents, therefore, it is advisable
to ascertain by shunt angiograms whether such factors are responsible for
recurrent clotting episodes.

It is theoretically possible that in some instances complete failure of
attempted declotting by plasminogen activators may be attributable to im-
pairment of the plasmin system, for example by local or systemic depletion
of plasminogen or presence of excess of antiplasmin. We propose to investi-
gate this possibility further, in order to determine whether tests of the
fibrinolytic mechanism may enable fruitless use of urokinase to be avoided.

It is known that in certain circumstances the preparations of urokinase
at present available can exert coagulative effects (McNicol et al, 1963;
Prentice et al, 1969). We have no evidence that such effects resulted in
further shunt clotting in any of our patients, and it may be noted that low concentrations of urokinase are more likely to lead to this problem. Our technique aims to ensure maximal concentration at the site of clot formation, and in this respect prolonged exposure to a concentrated solution appears preferable to slow infusion of a more dilute preparation.

No complications or side-effects from use of urokinase have been noted in this study. For this reason we consider that although urokinase in the dosage we have used may be less effective than high-dosage streptokinase infusion, urokinase is the preparation of first choice when local fibrinolytic treatment is required.

CONCLUSIONS

Urokinase is a safe and effective agent for local use in declotting of shunts after conservative methods have failed. Its efficacy is limited in the presence of active infection or of mechanical obstruction to flow. Early treatment of shunt infections may enable considerable prolongation of shunt life by urokinase.

REFERENCES