Streptokinase . . . never again

See page 1245 for the article to which this Editorial refers

Streptokinase, a bacterial protein, is still the most frequently used plasminogen activator worldwide. Because of its bacterial origin, immune responses are expected which may lead not only to anaphylaxis but also to a reduced efficacy for clot lysis on repeat administration. Furthermore, previous infections with streptococci may already have induced antibodies to streptokinase which may be the cause of allergic reactions and reduced clinical efficacy. It is recommended not to use streptokinase between 3 days and 1 or even 4 years after a first administration[1].

The immunogenicity of streptokinase has usually been evaluated by measuring inhibition of streptokinase-induced in-vitro fibrinolysis by patient plasma containing streptokinase antibodies.

In this issue Squire and colleagues have tested not only humoral but also cellular responses to streptokinase up to 7·5 years following its first administration in a large population[2]. Compared to a control group of patients who had a myocardial infarction not treated with thrombolytic therapy, patients who received streptokinase had elevated neutralizing anti-streptokinase antibodies and anti-streptokinase IgG titres at all time points up to 7·5 years after treatment. In contrast, the cellular immune response to streptokinase, as assessed by in-vitro proliferation of peripheral blood mononuclear cells, was detectable only from 6 days up to 6 weeks after treatment. Although interesting, this test does not seem to provide useful information regarding late allergic reactions.

The clinical consequences of the findings by Squire et al. are important: there is no time limit beyond which administration of streptokinase is likely to be effective and safe. Thus no patient should ever receive a second treatment with streptokinase. In this regard it is of concern that in many patients who need repeat thrombolytic treatment because of a new infarction the thrombolytic agent given the first time is unknown. In the light of the findings by Squire et al. it is strongly recommended not to give streptokinase in these patients, but a non-immunogenic agent instead.

With regard to the efficacy of streptokinase in patients who had previous streptococcal infections, a bedside efficacy test may become very useful in the future to select patients who are likely to respond to streptokinase and those who are better treated with a non-immunogenic agent[3]. Such in-vitro testing of streptokinase lytic activity has been found to nicely predict an ECG response to a standard dose of streptokinase and will be tested in a large patient population in the near future.

Finally it should be mentioned that the immunoreactivity of a bacterial protein can be reduced by protein engineering. Staphylokinase, a plasminogen activator produced by some strains of Staphylococcus aureus also induces high titres of neutralizing specific IgG antibodies in all patients treated[4]. Staphylokinase variants with markedly reduced antibody induction but intact potency for clot lysis have been made and recently successfully given to patients with acute myocardial infarction[5]. It is very unlikely, however, that new variants of streptokinase with reduced immunogenicity will ever be generated since this agent has already been on the market for more than 30 years at a low price and because many non-immunogenic agents are or will become available in the near future. Thus the use of streptokinase should be restricted to patients who have not received this agent before and (preferably) who, in addition, do not have in-vitro evidence of neutralizing antibodies because of previous streptococcal infections.

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References