

Neutralising antibodies after streptokinase treatment for myocardial infarction: a persisting puzzle

K McGrath, C Hogan, D Hunt, C O'Malley, N Green, R Dauer, A Dalli

Abstract

Objective—To determine the development of titres of streptokinase (SK) neutralising antibodies after a single dose of SK, to establish when titres decrease to levels at which a second dose might be effective.

Design—Analyses of blood samples taken from patients at intervals after SK administration.

Setting—Australian public hospital.

Patients—104 patients with acute myocardial infarction who were treated with SK and 27 controls who were not.

Outcome measure—SK neutralising antibodies were measured once in each of the 27 controls and on 166 occasions in the 104 treated patients.

Results—Titres of SK neutralising antibodies rose after SK administration but returned to control levels by 2 years.

Conclusions—SK might be effective again as a thrombolytic agent as early as 2 years after a single dose. These results are at variance with most previously published data and the reasons for this are not clear. Data evaluating patency rates after standard doses of streptokinase in patients with increased titres of neutralising antibodies are necessary before re-exposure to streptokinase can be recommended.

(Br Heart J 1995;74:122-123)

Keywords: streptokinase; antibodies; myocardial infarction

Streptokinase (SK) improves morbidity and survival in patients with acute myocardial infarction. As a foreign bacterial protein, it provokes the formation of various antibodies,

which may cause allergic phenomena, or neutralising antibodies, which may diminish or abolish the thrombolytic activity of SK. As survivors of myocardial infarction are prone to further coronary thrombosis, they may require repeat treatment with thrombolytic agents. Whether SK will be effective on a second occasion remains uncertain. Alternative thrombolytic agents are expensive and hence it is more cost effective to use repeated doses of SK.

The aim of the study was to determine the natural history of antibody titres after SK administration and to ascertain when re-exposure to SK might be effective.

Patients and methods

A total of 104 patients received a standard dose of 1.5×10^6 U of SK. No patient received steroid treatment or was known to have had previous exposure to SK. Single samples were obtained from 53 patients at 54-84 months after their SK dose. A further 51 patients who had received SK were also tested on one or more occasions between 6 and 33 months after their SK doses. Controls consisted of 27 patients from the coronary care unit who had not received SK. SK neutralisation titres were determined using the method of Hamby and Howell.¹

Results

The control patients had a mean SK neutralising capacity of 0.17×10^6 IU (0.01-3.0). (One patient had a neutralising capacity of 3.0×10^6 IU; we were unable to explain such a high titre (figure).

Titres of neutralising antibody did not differ significantly from those of the controls at 2 years after administration of SK.

Studies of neutralising antibodies at 24 or more months after administration of streptokinase

Reference	Year	Time after treatment (months)	Antibody type	No of patients	Return to pretreatment level at 24 months or more (%)
Fears, <i>et al</i> ²	1992	30	NEUT	67	100
			IgG	67	89
Buchalter, <i>et al</i> ⁶	1992	24	NEUT	8	100
			IgG	8	50
Patel, <i>et al</i> ³	1993	29	NEUT	189	<10
Lee, <i>et al</i> ⁴	1992	36-54	NEUT	57	53
			IgG	57	70
Elliot, <i>et al</i> ⁵	1993	48	NEUT	145	11
					(no controls)
McGrath, <i>et al</i>	1995	24-84	NEUT	131	100

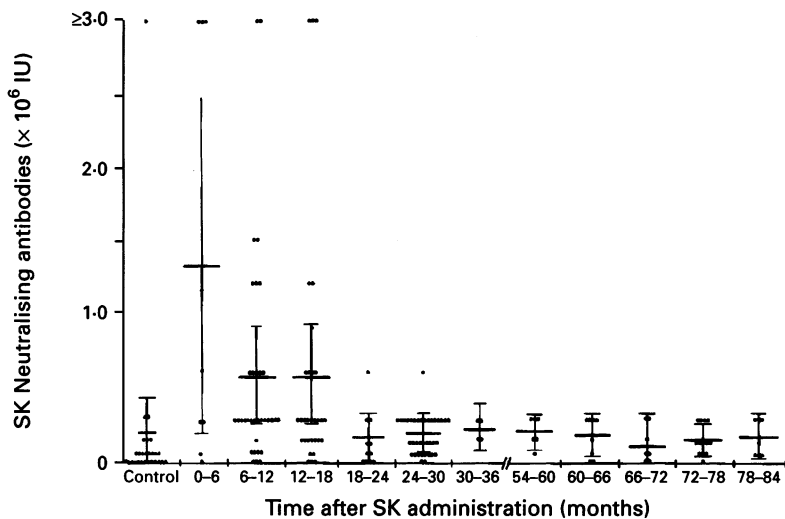
NEUT, neutralising antibodies measured by clot lysis; IgG, antistreptokinase binding immunoglobulin G antibodies.

Department of Diagnostic Haematology, Royal Melbourne Hospital, Parkville, Australia
K McGrath
C Hogan
C O'Malley
R Dauer
A Dalli

Department of Cardiology, Royal Melbourne Hospital, Parkville, Australia
D Hunt
N Green

Correspondence to: Dr K McGrath, Department of Diagnostic Haematology, Royal Melbourne Hospital, Parkville, Victoria 3050, Australia.

Accepted for publication 16 January 1995



Mean (95% confidence intervals) and individual patient levels of streptokinase (SK) antibody neutralising capacity for each interval.

Discussion

Several studies have attempted to clarify the interval after which a second dose of SK can be safely and effectively given.

Four major studies have examined levels of neutralising antibodies 2 or more years after a dose of SK,²⁻⁵ but the results are inconsistent (table). The method in three of the studies²⁻⁴ was similar to ours and in the others was based on release of radioactive degradation products from the clot. Three of these studies³⁻⁵ showed increased levels of neutralising antibody at 54, 27, and 48 months respectively, while the fourth study² demonstrated normal levels in over 90 per cent of patients by 24 months.

Three reports^{2,4,6} have looked at SK binding antibody levels. One study² again showed normal levels in 89 per cent of patients by 18

months, while increased levels persisted to 27 and 57 months in the other studies.^{4,6}

There have been three important studies⁷⁻⁹ of safety or efficacy of repeated doses of SK or anistreplase in patients with known increased antibody levels. Two studies^{7,8} showed good relations between raised antibody levels and hypersensitivity reactions. Of the two studies examining subsequent patency of the infarct related artery, one showed patent arteries despite increased antibody levels,⁸ while the other showed persistently occluded arteries.⁹

Thus not only does the time course of raised antibody titres remain in doubt but so also does the significance of such increases in terms of hypersensitivity reactions and thrombolytic efficacy.

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