Current Clinical Experience with Staphylokinase in Arterial Thrombosis

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Although thrombolytic therapy has markedly reduced mortality following acute myocardial infarction (MI) [1] and is gaining increasing acceptance for the treatment of various other thromboembolic disorders (including deep venous thrombosis, pulmonary embolism, and peripheral arterial occlusive disease) [2,3], the optimal thrombolytic strategy has yet to be determined [4]. Indeed, failed, suboptimal, or delayed thrombus dissolution and reocclusion frequently prevent appreciable tissue preservation [5]. Because of an inherent bleeding risk, the therapeutic window of thrombolytics is relatively small and may further be narrowed by the conjunctive use of powerful antiplatelet and anticoagulant drugs. These general shortcomings and other disadvantages particular to certain agents [including the high cost for recombinant tissue plasminogen activator (rtPA), acute hypotension, and allergic reactions with streptokinase and derivatives, and the lack of fibrin selectivity with streptokinase and urokinase] inspire the search for newer and better fibrinolytic agents [6]. In this perspective, new light has been shed on a (pro)fibrinolytic agent discovered in 1908 [7] — staphylokinase (Sak).

Staphylokinase is a 136 amino acid protein, with a unique structure, secreted by certain strains of Staphylococcus aureus. Two functionally identical natural allelic variants, SakSTAR and Sak42D, have been produced in Escherichia coli and have been purified and characterized for clinical use [8]. Preclinical evaluation revealed attractive features [9,10], including high thrombolytic potency, also toward platelet-rich and retracted thrombi; fibrin specificity in human plasma in the absence of a systemic lytic state and plasminogen steal; and reduced antigenicity and allergenicity relative to streptokinase in dogs [11] and baboons [12]. The present article summarizes the results obtained thus far in patients with MI and peripheral arterial occlusion (PAO) who have been treated with Sak.

Acute Myocardial Infarction

A total of 128 patients ≤75 years of age who presented within 6 hours of experiencing signs and symptoms of transmural MI and who had no contraindications to thrombolytic therapy were studied after giving informed consent, provided that angiographic evaluation within the prespecified time window was feasible. Conjunctive therapy consisted of aspirin PO and heparin IV beginning at study entry. In the first pilot reperfusion study, 10 patients with angiographically confirmed infarct-related artery occlusion (TIMI flow grade 0) were treated with 10 mg IV Sak, given as a 1 mg bolus followed by infusion of 9 mg over 30 minutes [8,13,14]. Angiography was repeated every 10 minutes up to 40 minutes. All but one of the occluded coronary arteries were recanalized (TIMI flow grade 3 in eight patients and TIMI flow grade 2 in one patient) within 40 minutes. The mean (±SEM) time delay to reperfusion in recanalized arteries, 20 ± 4.0 minutes, compared favorably with the ≥45 minute delays reported for rtPA and streptokinase [15]. Plasma levels of fibrinogen, plasminogen, and α2-antiplasmin did not decrease. Staphylokinase antigen disappeared from the plasma with a mean initial half-life of 6.3 minutes [13]. Thus, Sak proved to be able to induce rapid and sustained restoration of normal coronary artery flow at a dose that did not induce a systemic lytic state.

Subsequently, a multicenter randomized trial (STAR trial) compared the effects of Sak with the present standard regimen, accelerated and weight-adjusted rtPA, on early coronary artery patency in 100 patients with acute MI [16]. Patients randomized to IV Sak were given 10 mg over 30 minutes, as in the pilot trial, in the first half of the study, and, following a prospectively planned interim analysis, 20 mg
over 30 minutes in the second study, always with an initial 10% bolus. The primary study endpoint, TIMI perfusion grade 3 at 90 minutes, was reached in 58% of patients treated with rtPA (n = 52) and in 62% of patients treated with Sak (n = 48) in 50% after 10 mg Sak (n = 25) and in 74% after 20 mg Sak (n = 23). Although 20 mg Sak produced the greatest recanalization benefit, the differences in 90 minute coronary artery patency between groups (rtPA, 10 and 20 mg Sak) were not statistically significant, probably because of the small numbers of patients. Again, Sak proved to be highly fibrin specific, preserving plasma fibrinogen, plasminogen, and a2-antiplasmin levels after infusions of 10 mg, 20 mg, and 40 mg Sak in five additional MI patients, whereas rtPA caused a very significant drop in fibrinogen (mean decrease vs. pretreatment was 30% at 90 minutes) and of plasminogen and a2-antiplasmin (mean decrease of 60% at 90 minutes). The frequencies of hemorrhagic, thrombotic, electrical, mechanical, or allergic complications and of nonpharmacological reperfusion procedures following Sak and rtPA were comparable. However, all five in-hospital deaths, all caused by early cardiogenic shock, appeared in the cohort randomized to rtPA, resulting in an unexpected, and possibly coincidental, borderline significant mortality difference in favor of Sak (0.25 < p < 0.05).

A few persistent occlusions in some of the first patients randomized to Sak were attributed to suboptimal heparinization, as evidenced by near-normal activated thromboplastin times, as was the one reocclusion in the pilot study [13]. These observations supported the anticipation that optimized and persistent clot dissolution with fibrin-specific agents requires adequate conjunctive antithrombin therapy and inspired a protocol amendment, doubling the heparin bolus from 5000 U to 10,000 U for the remainder of the study. Thus, Sak produced early, stable, and complete patency of the infarct-related vessel at least as frequently as accelerated rtPA, especially at a dose of 20 mg, without apparent excess acute toxicity, and was significantly more fibrin specific.

In a continuing effort to refine thrombolytic therapy for MI in general, and Sak-based thrombolytic strategies in particular, we investigated the feasibility of using bolus Sak administration, analogous to (double) bolus rtPA, which yielded encouraging recanalization rates in at least one nonrandomized clinical trial [17]. The gradual shortening of IV infusion times of (at least relatively) fibrin-specific thrombolytic agents is based on the premise that fibrin specificity ensures persistent fibrinolysis at the clot surface, even after clearance of the thromboytic substance from the circulation and on the anticipation, which was confirmed in animal models, that bolus infusions may benefit not only the ease of administration, but also the speed and frequency of clot lysis, and possibly also its safety [18].

The first patient presenting with a large anterior MI and treated with a double bolus of two times 20 mg Sak, given 15 minutes apart, however, developed a disabling intracerebral hemorrhage. Therefore, a phased, angiographically controlled pilot study of bolus Sak infusion for coronary thrombolysis was undertaken in 12 patients with evolving transmural MI, who were given 20 mg Sak over 5 minutes at study entry [19]. If angiography at 60 minutes showed TIMI perfusion grade 0, 1, or 2, a second bolus of 10 mg Sak over 5 minutes was given. TIMI 3 flow was thus obtained in 7 patients (58%) at 60 minutes and, after addition of the second Sak bolus in the 5 others, and in a total of 10 patients (83%) at 90 minutes, again without any fibrinogen degradation. This encouraging pilot-scale experience with bolus Sak administration inspired a second multicenter randomized trial in patients with evolving MI that is presently comparing accelerated rtPA with double boluses of 15 mg Sak given 30 minutes apart.

From these studies it is concluded that IV Sak, when combined with heparin and aspirin, is a potent, rapidly acting, and completely fibrin-specific thrombolytic agent in MI patients. Its fibrin specificity, safety, and efficacy in coronary thrombolysis appear to compare well with these of the present gold standard, accelerated rtPA. More studies are needed to establish the optimal dose and mode of Sak administration. Initial studies on bolus Sak administration have yielded encouraging results. The relative benefit of Sak versus plasminogen activators in current clinical (or experimental) use in terms of reduction of MI-associated mortality and morbidity awaits larger comparative clinical trials.

**Peripheral Arterial Occlusion**

Thirty patients (37-86 years of age) with limb ischemia or incapacitating claudication of <120 days duration and with angiographically documented thromboembolic peripheral arterial occlusion (PAO), mostly due to in situ thrombosis of native femoropopliteal arteries, were treated in a pilot study [20]. Intraarterial, catheter-directed Sak was given as a bolus of 1 mg, followed by a continuous infusion of 0.5 mg/hr in 20 patients, and as a bolus of 2 mg, followed by an infusion of 1 mg/hr in 10 patients, together with heparin. After 7.0 ± 0.7 mg Sak was infused over 8.7 ± 1.0 hours, recanalization was complete in 25 patients (83%), partial in 2, and absent in 3. Poor prognostic signs (including poor distal runoff, long duration, and distal localization of occlusion) characterized the three PAOs without macroscopic clot lysis. The majority of patients underwent complementary surgical or endovascular procedures, mainly percutaneous transluminal angioplasty, to treat culprit lesions and to promote long-term vessel patency. Major amputations were limited to two patients in whom thrombolysis failed. Three patients developed a reocclusion within 1 month, and two major hemorrhagic complications oc-