RECENT ADVANCES IN CARDIOVASCULAR MEDICINES
THROMBOLYTICS

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INTRODUCTION

Thrombolytic therapy represents a major advance in reducing mortality following myocardial infarction. Pharmacists must be aware of the principles and problems of thrombolysis and the large studies conducted in hospital and now in the community.

HEMOSTASIS

When a small vessel is cut and damaged the injury initiates a series of events that leads to the formation of a clot. The initial event is constriction of the vessel, followed by the formation of a platelet plug. The platelets adhere to exposed collagen and liberate serotonin and adenosine diphosphate (ADP); this attracts other platelets etc. This is formed into a definitive clot by fibrin, which involves a cascade of reactions (Fig.1). Potential clotting inside vessels and the breaking down of clots so formed are controlled by a number of limiting reactions;

(1) Formation from activated factor X of an antithrombin (antithrombin III) and the removal of some activated clotting factors from the circulation by the liver;

(2) Thromboxane A2 which promotes platelet aggregation and hence clotting, is in dynamic equilibrium with the simultaneous formation of prostacyclin which inhibits aggregation; and

(3) The fibrinolytic system that limits clotting.

The active component of the fibrinolytic system is plasmin which lyses fibrin and fibrinogen with the formation of degradation products which in turn inhibit thrombin.

Plasmin is formed from the inactive plasminogen by the action of thrombin in the presence of plasminogen activators and activator inhibitors (PAI-1). The lysis of fibrin by plasmin is held in check by alpha 2 antiplasmin.

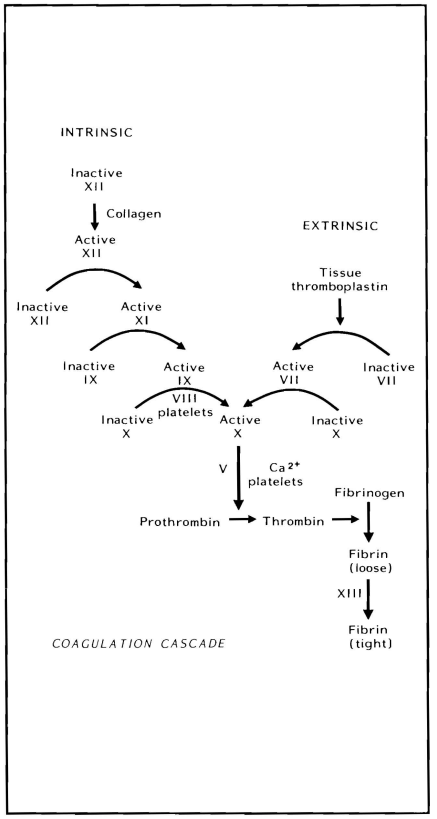

Figure 1 *Schematic diagram of the coagulation cascade (adapted from Guyen 1951).*

DRUGS WHICH INHIBIT CLOTTING AND/OR BREAKDOWN THROMBII

Heparin is a potent anti-coagulant, normally found in the body, which acts by preventing the activation of factor IX and by activating a platelet factor that inhibits the action of thrombin. It also increases the negativity of blood vessel walls and helps prevent thrombus formation (due to its structure). Also included in this group of parenteral anticoagulants are epoprostenol (prostacyclin antiplatelet activity) and ancrod, an enzymatic principle derived from the venom of the Malaysian pit-viper.

With regards to warfarin before release from the liver into the blood stream, the Vitamin K-dependent coagulation factors (prothrombin, VII, IX and X) are converted to a functional group by the addition of an extra carboxyl/group to a glutamic acid residue. In the presence of warfarin, the coagulation factors are released from the liver in their unconverted form and hence inhibit coagulation. Other oral anticoagulants include phenindione and protamine sulphate. Although this latter compound is normally used to counteract heparin overdose, when in excess, it has an anticoagulant effect.

The platelet-aggregation inhibiting effects of aspirin result from its ability to acetylate and irreversibly inhibit platelet cyclooxygenase, thereby reducing the formation of thromboxone A2. Its effects on the synthesis of prostacyclin is less marked at low doses (1). Also in this group is dipyridamole.

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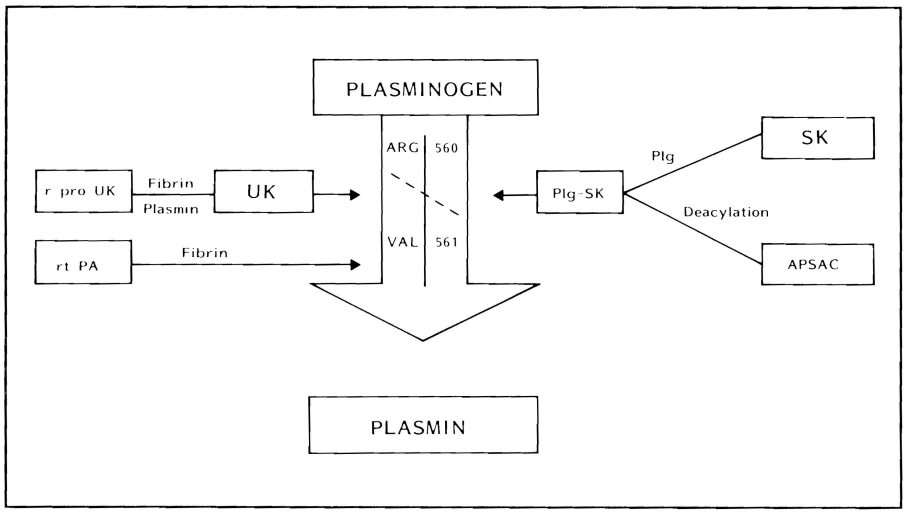

Figure 2 *Activation of plasminogen to plasmin (adapted from Sherry 1988).*

Plasminogen activators (see list below) act by converting the inert pro-enzyme plasminogen, into its proteolytically active form plasmin.

This latter group of drugs is now widely used as thrombolytic therapy following acute myocardial infarction. The rationale is that reperfusion will retard myocardial necrosis, reduce infarct size and possibly maintain ventricular function and hence enhance patient survival. Other uses may include pulmonary embolus, deep vein thrombosis, peripheral arterial thrombosis and local instillation into occluded shunts, e.g. in renal dialysis patients or restoring potency in occluded central venous catheters.

THROMBOLYTIC AGENTS AND THEIR MECHANISMS OFACTION

There are now 6 agents being used or evaluated for the lysis of thrombi following myocardial infarction. These are -

(a) Indirect acting
  (1) Streptokinase (SK).
  (2) Anisoylated plasminogen - streptokinase activator complex (APSAC).
(b) Directly acting
  (3) Urokinase (UK).
  (4) Recombinant single stranded tissue-type plasminogen activator (r t-PA, one chain).
  (5) Recombinant prourokinase (r pro UK or r scu-PK).
  (6) Recombinant double stranded tissue-type plasminogen activator (rt-PA, 2 chain).

The compounds act indirectly/directly to activate plasminogen (2); this involves splitting of the arg560-val561 band in plasminogen, which exposes the serine protease enzyme centre of plasmin (Fig.2). Plasmin is a non-specific proteolytic enzyme which derives its fibrinolytic properties by the binding of plasminogen to fibrin during clotting and also by the binding of endogenous t-PA to fibrin in close proximity to plasminogen following its release locally from endothelial cells. As a result, plasmin formation is facilitated on the fibrin surface and is independent of the various mechanisms governing and regulating plasminogen activation in the systemic circulation (2).

effects. The aim of therapeutic fibrinolysis is the selective activation of plasminogen associated with fibrin, while sparing the plasminogen in the surrounding blood (i.e. fibrin specificity). This occurs with the natural plasminogen activators of blood, t-PA and pro-UK. However if infused at high doses which are necessary for effective thrombolysis in patients with coronary thrombosis, non-specific plasminogen activation takes place(2).

STREPTOKINASE

This is a bacterial protein (from cultures of Group C beta- haemolytic streptococci) that reacts on a one-to-one basis with human plasminogen forming a streptokinase-plasminogen complex which activates the fibrinolytic mechanism. As streptokinase is a foreign protein it is antigenic.

Apsac (Anisoylated derivative of the Lys-plasminogen streptokinase)

This is a complex of human lys-plasminogen and streptokinase in which a para-anisoyl group has been added to the catalytic centre of the enzyme complex (Figure 3).

In aqueous media, including blood, the anisoyl group is removed by hydrolytic deacylation. The kringles on the complex are the molecular elements which bind to

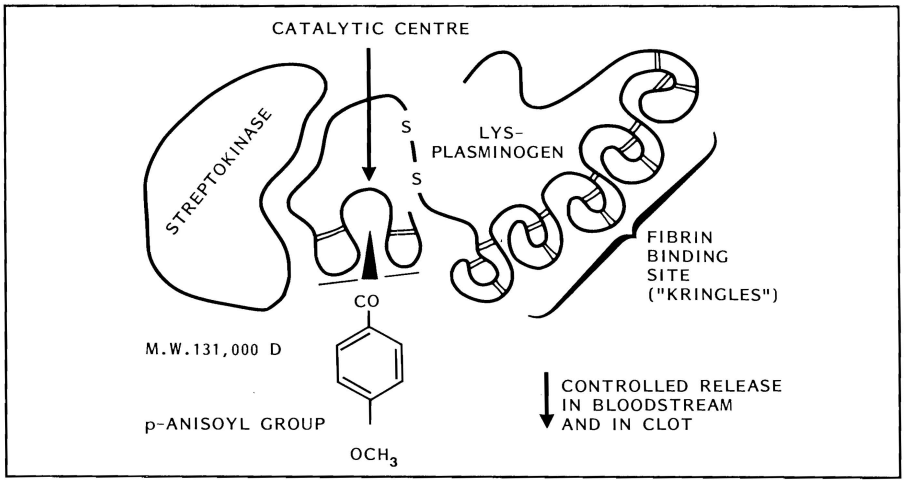

Figure 3 *Schematic representation of the molecular structure of APSAC. (Permission from Beecham).*

The hallmark of physiological fibrinolysis is its specificity, by contrast therapeutic thrombolysis, even by the newer activators, is accompanied by non-specific proteolysis which may have untoward

the fibrin that holds together the thrombus. This binding capacity is increased 170 times by using the lys71 plasminogen rather than the glu-form which circulates in the bloodstream (Figure 4) - (fibrin

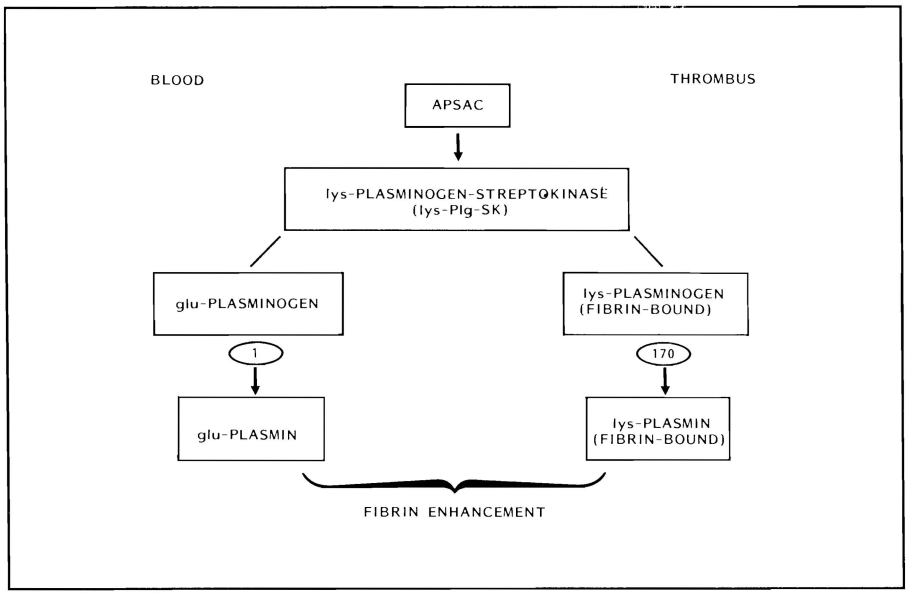

Figure 4 *Catalytic efficiency of APSAC. (Permission from Beecham).*

enhancement factor). The value of the para-anisoyl group is that it protects the catalytic centre of the enzyme and acts as a possible pro- drug for its fibrolytic activity. Advantages of this include a gradual onset on action following a 4-5 min injection and hence possibly avoiding hypotension. It also prolongs APSACs duration of action. Antigenicity occurs with APSAC.

UROKINASE

This is the first of the naturally occurring and direct plasminogen activators (can stimulate plasmin formation without first forming an activator complex). Currently it is being produced by growing human foetal kidney cells in tissue culture. (It is not antigenic).

rt-PA

Tissue plasminogen activator is released under physiological conditions from various tissue cells. The preparation of this highly clot selective type of activator has utilized recombinant DNA technology. Its preparation has involved the transfer of genetic material from a t-PA producing cell line (originally a melanoma) to a Chinese hamster ovarian cell line. rt-PA is not antigenic.

r-pro-UROKINASE

This is a highly clot selective single chain urokinase, which, like t-PA is released from various tissue cells under physiological conditions. It has been suggested as having a different mechanism of action than t-PA, in that it is thought that pro-urokinase only activates lys-plasminogen (the type bound to fibrin) and not glu-plasminogen (the plasma form) and this is the basis for its clot sensitivity. It is being produced commercially by recombinant DNA technology by transfer of the cyclic DNA from a human tumour source to a non-human cell line. As with urokinase and rt-PA it is not antigenic.

COMPARISONS BETWEEN THROMBOLYTIC AGENTS

Plasminogen activation in the plasma, and the 'fibrin- enhancement' of its effect associated with the thrombus platelets and endothelial cells varies between drugs (Table 1), although as stated earlier at therapeutic thrombolytic doses differentiation disappears. Pharmaceutical and pharmacokinetic differences are shown in Table 2. They indicate that t1/2 plasma elimination half lives range from 90 min for APSAC, with a very short infusion of 5 min compared with a 5 min t1/2 for rt-PA; an infusion of 180 mins is required for its therapeutic effect. The clinical profiles demonstration reperfusion in 65-70% of patients if treated in three hours with re-occlusion occurring in 10-20% of patients (Table 3).

CLINICAL EVALUATION OF THROMBOLYTICS IN ACUTE MYOCARDIAL INFARCTIO(AMI)

The clinical evaluation of thrombolytics in AMI has been marked by a number of major well conducted placebo controlled trials.

STREPTOKINASE

ISIS-2 (Second International Study of Infarct Survival) (3). In this study, 17,187 patients entering 417 hospitals up to 24 hours (median 5 hours) after the onset of acute myocardial infarction were randomised with a placebo control, between -

(1) a 1-hour i.v. infusion of 1.5 million units of streptokinase (SK),
(2) one month of 160 mg/day enteric coated aspirin (ASA),
(3) both active treatments (SK and ASA),
(4) neither.

The results indicated that both SK and ASA alone produced a significant reduction in 5 week vascular mortality.

SK	791/8592 (9.2%) vs placebo 1029/8595 (12.0%) (25% reduction)
ASA	804/8587 (9.4%) vs placebo 1016/8600 (11.8%) (23% reduction)
SK + ASA	343/4292 (8.0%) vs neither 568/4300 (13.2%) (42% reduction)

There was evidence of benefit from each agent even for patients treated late after pain onset. Adverse effects associated with SK were an excess of bleeds requiring transfusion (0.5% vs 0.2%) and of confirmed cerebral haemorrhage (0.1% vs 0.0%) but with fewer other strokes (0.6% vs 0.8%).

Aspirin significantly reduced non-fatal reinfarction (1.0% vs 2.0%) and non-fatal strokes (0.3% vs 0.6%) and was not associated with any significant increase in cerebral haemorrhage or in bleeds requiring transfusion. An excess of non-fatal reinfarction was reported with SK when used alone, but not in combination with ASA. Those given both had significantly fewer reinfarctions (1.8% vs 2.9%) and strokes (0.6% vs. 1.0%). The differences in vascular and all cause mortality produced by SK and ASA remained significant over the 15 month follow-up.

TABLE 1 *Plasminogen activation of thrombolytics*

PLASMINOGEN ACTIVATION OF THROMBOLYTICS

	Sk	APSA	Uk	rt-PA	rpro-Uk
Plasma	4	4	3	2	2
Fibrin	1	1	2	3	4
Platelet	–	–	–	2	–
Endothelial cell	–	–	–	2	–

(1- 4 indicated increasing activity)

TABLE 2 *Pharmaceutic and pharmacokinetic profile of thrombolytics.*

PHARMACEUTIC AND PHARMACOKINETIC PROFILE OF THROMBOLTYICS

	Sk	APSAC	Uk	rt-PA
Dosage by I.V. adminisrtation	1.5 million units	30 units	2 million units	100 gm (58 million units)
Infusion time(min)	30-60	5	20-90	180
Plasma elimination half-life (min)	23	90	16	5
Heparin infusion received	0	0	0	Yes
Cost (MIMS JAN 1990)	£85	£495	£198	£816

TABLE 3 *Clinical profile of thrombolytics.*

CLINICAL PROFILE OF THROMBOLYTICS

	Sk	APSAC	Uk	rt-PA	rPRO-UK
Reperfusion% (patients treated within 3 hrs)	65	68	66	70	67
Time to Reperfusion (min)	45+–	45+–	45+–	45+–	45+–
Bleeding complications following invasive prodedures	Yes	Yes	Yes	Yes	Yes
Re-occlusion%	15+–	10+–	10+–	20+–	–

Other major studies with streptokinase include Gruppo Italiano per lo studio della streptochinase nell'infarto miocardico-Gissi (4,5) (11,806 patients). ISAM (6) (1,741 patients); Kennedy et al (7) (368 patients) and White et al (8). The results of these trials are summarized in Table 4.

r TISSUE PLASMINOGEN ACTIVATOR (rtPA) ASSET. (ANGLO-SCANDINAVIAN STUDY OF EARLY THROMBOSIS) (10).

In this study 13,318 patients with suspected AMI were admitted to the participating hospitals; 8307 (62%) were excluded by protocol criteria (Table 5). The remainder received either rtPA plus heparin or placebo plus heparin. The fatality at one month was 245/2253 (9.8%) in patients given placebo and 183/2330 (7.3%) in those given rt-PA (26% reduction). Adverse effects included a slight excess of major bleeds (defined as bleeding from the gut or urinary tract, but not necessarily requiring transfusion) in the group given rt-PA, and an increase also in minor bleeds mainly from venepuncture sites. Other studies include the ECSG (European Co-operative Study Group for streptokinase treatment in acute myocardial infarction) study (11).

ANISOYLATED DERIVATIVE OF THE LYS-PLASMINOGEN STREPTOKINASE COMPLEX (APSAC)

AIMS (APSAC in myocardial infarction study) (12). This study investigated 1004 patients in a randomized double blind, placebo controlled trial. Criteria for inclusion included AMI onset within 6 hours, major symptoms of at least 30 min duration; age, 70 years or under, and no contraindications to thrombolytic therapy. The results indicated that 32/502 (6.4%) of patients died following APSAC compared with 61/502 (12.2%) following placebo. This represented a reduction of 47.5% in mortality. This trial was terminated; the estimated 1 year mortality rates were 10.8% on APSAC and 19.4% on placebo (a 43.5% reduction).

COMPARATIVE STUDIES

A number of smaller studies have compared SK and rtPA on the early mortality rate in patients with AMI. The overall figures indicated that 36/443 patients on streptokanse died compared with 24/442 on rtPA (13) (14) (15) (16).

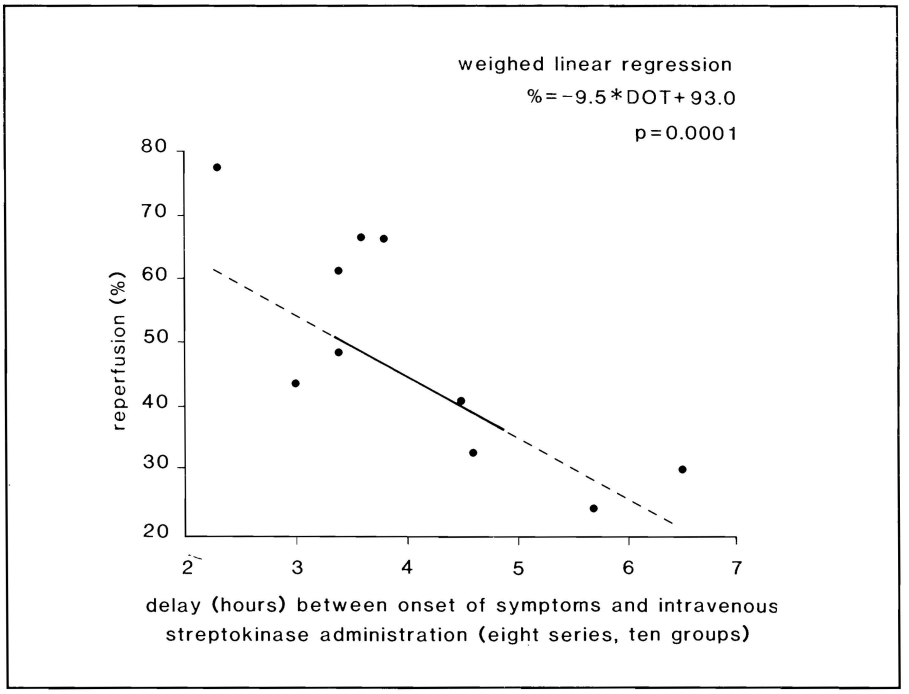

Figure 5 *Relationship between reperfusion and delay in administration of streptokinase. (Permission from Boissal).*

Problems with thrombolytics

1. With thromoblytics, bleeding complications are related more to the presence of an underlying vascular injury and of superimposed anti-coagulant therapy than to the hemostatic defect. The incidence as mentioned above appears to be much the same for all compounds. Other in-hospital complications are shown in Table 6. Other problems include coagulation defects and rethrombosis. It is suggested that coagulation defects are more common with SK, APSAC and UK rather than rt-PA and rPro-UK. Platelet defects with rt-PA have also been reported with activation of thrombospendin-bound, platelet-bound and endothelial cell-bound plasminogen (1).
2. Exclusion criteria, e.g. the ASSET study excluded 61% of patients. The overall mortaity rate in this group was 13.1% (17.1% in patients with myocardial infarction), Table 5. While this was greater in the placebo group (9.8%) for those patients included in the study, one wonders if some of the exluded patients could have benefited.
3. Adjuvant Therapy Heparin has been administered concurrently with rt-PA and rpro-UK with the aim of enhancing their action and reducing the incidence of rethrombosis. However, its use in this situation remains open for discussion (1). It is more likely that aspirin will be used; with the thrombolytic agent acting on the erythrocyte rich whole blood clot and aspirin action on the platelet risk thrombosis.
4. Time of therapy after onset of symptoms

The clinical outcome with thrombolytics appears to depend on the time of onset of symptoms to when the patient receives therapy. The relative efficacy of rtPA and SK falls from 81% and 55% and 42% respectively, when therapy is less than 3 hours compared to 3-6 hours. A curvilinear relationship between risk reducton and delay of treatment has been demonstrated (Figure 5) (18). This had led to calls for the use of i.v. thrombolytics outside hospital; the risks associated with this still have to be assessed. However, the AIMS study and the ISIS-2 study have confirmed significant reductions in mortality well beyond the period of demonstrable improvement in myocardial function attributable to thrombolytic therapy (the mechanisms are unknown).

THROMOLYTIC THERAPY IN THE TREATMENT OF ACUTE MYOCARDIAL INFARCTION IN MALTA

Thrombolytic Therapy in the treatment of Acute Myocardial Infarction was first used in Malta in March, 1989. The

TABLE 4 *Major placebo controlled clinical trials with intravenous thrombolytic therapy in acute myocardial infarction.*

Major placebo controlleld clinical trials with intravenous thrombolytic therapy in acute myocardial infarction

Study	Patient Number	Adjunctive Therapy Aspirin	Heparin	Major Bleeding(%) Placebo	Active	Neurological Event Definition	Rate (%) Placebo	Active	Early Mortality Endpoint	Rate (%) Placebo	Active	
A. Streptokinase												
GISSI (4) (5)	11,806	14%	21%	?	0.3	Stroke SK-CVA	0.9 0.2	1.1	21d	13.0	10.7	0.0002
ISAM (6)	1,741	+	+	?	0.8	ICB	0	0.5	21d	7.1	6.3	NS
W.WASH (7)	368	?	+	(0.7)	(13)	ICB	0	0.5	14d	9.7	6.3	NS
N.ZEALAND (8)	219	+	+	0	1	ICB	0	0	30d	12.9	2.5	0.012
ISIS-2 (3)	17,187	+/–	–	0.2	0.6	Stroke SK-ICB	0.9	0.8 0.1-0.2	35d	11.7	8.9	0.0001
B. rt-PA												
ECSG (19)	721	+	+	1.9	3.7	Stroke ICB	0.5 ?	2.0 1.4	14d	5.7	2.8	0.053
ASSET (10)	5,111	–	+(24hr)	0.4	1.4	Stroke	1.0	1.1	30d	9.8	7.2	0.0002
C. APSAC												
AIMS (12)	1,004	?	+	?	?	Stroke	1.0	0.4	30d	12.2	6.4	0.0016

Abbreviations: *ICB: intracerebral bleeding; CVA: cerebrovascular accident; SK-CVA: associated with streptokinase therapy; Sk-ICB: ICB associated with SK therapy; rt-PA ICB: ICB associated with rt-PA therapy.
Collen and Gold (9)

TABLE 5 *ASSET mortality in excluded patients.*

Reason	% Exclusion	% Dead
duration symptoms > 5 hrs	73.5	10.6
age > 75 yrs	8.3	26.2
recent haemorhage, ulcer bleeding diathesis	5.9	12.1
other serious disease	5.4	13.5
refused consent	4.3	8.0
receiving warfarin	4.2	10.0
emergency CPR	4.1	28.7
recent stroke, trauma or surgery	3.6	14.3
lives away	3.6	7.4
high systolic BP	2.2	3.8
proliferative retinopathy	1.5	18.5
pregnancy	0.3	3.6

Hampton (17)

TABLE 6 *In-hospital complication other than strokes.*

	rt-PA n	%	Placebo n	%
Recurrent MI	97	(3.9)	111	(4.5)
Ventricular arrhythmias (day 1)	149	(5.8)	107	(4.3)
Ventricular fibrillation	94	(3.7)	120	(4.8)
Asystole	100	(3.9)	124	(5.0)
Pulmonary embolism	11	(0.4)	15	(0.6)
Other embolism	12	(0.4)	19	(0.8)
Cardiogenic shock	96	(3.8)	131	(5.2)
Heart failure	453	(17.9)	466	(18.6)

Hampton (17)

TABLE 7 *Cost per administration of thrombolytic agent.*

THROMBOLYTIC AGENT	COST PER ADMINISTARTION IN LM*
Streptokinase	33
Urokinase	158
APSAC	275
rt-PA	453

* Source: last tender for SK & UK Mims Jan. 1990 for APSAC & rt-PA

Thrombolytic agent used then was Streptokinase.

According to the policy (19) adopted by the Department of Medicine, St Luke's Hospital, the indications for using thrombolytic therapy in AMI are as follows:-

- Age: < 65 years (the age limit is only a guideline, the decision is at the discretion of the admitting consultant)
- Diagnosis: (a) typical chest pain > 30 minutes
  (b) ECG: ST > 1mm in 2 or more limb leads
  > 2mm in 2 or more precordial leads
- Time factor: treatment must be initiated within six hours of onset of the pain.
- Negative test to nitrates: no modification of ST elevation five minutes after the administration of sublingual GTN.

To date (April 1990), a total of about 150 patients suffering from AMI were treated with Streptokinase. Urokinase has been recently made available in St Luke's Hospital. The use of Urokinase in the treatment of AMI is being restricted to those patients who suffer a further AMI after 8 days to within 6 months following the previous one. At present,it is estimated that about 12 patients will benefit from the use of Urokinase per year.

Streptokinase is administered in a dose of 1.5 million units over 45 minutes in 60mls of 5% dextrose. It is used in conjunction with other therapy as follows:-

- Hydrocortisone 200mg IV
- +/- Lignocaine 100mg IV bolus
- +/-B Blockers (early)
- Heparin 1000 units/hour, started one to two hours after the end of Streptokinase infusion. It is continued for six days, the dose being adjusted to keep APTT at 1.5 - 2 x normal value.
- Aspirin 75mg daily

If reinfarction occurs within seven days of the use of Streptokinase, it may be used again together with a high dose of corticosteroids.

Urokinase in administered in a dose of 1.5 million units over 30 - 40 minutes in the same way as Streptokinase with the exception of corticosteriods which are not required with Urokinase.

Although the Medical Department is well aware of the other thrombolytic agents now on the market, eg. APSAC and rt-PA, and the possible advantages they offer, the cost involved must also be considered (Table 7).

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