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Mafenide (Sulfamylon™) Inhibits Plasmin Fibrinolytic Activity

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Key words

Fibrinolysis – Plasmin – Mafenide

Summary

Inflammatory fibrinolysis by plasmin or phagocyte proteases is a major cause of skin graft failure on burn wounds where the primary adherent attachment of the skin grafts is due to the glue-like action of fibrin. We investigated the potential of mafenide acetate solution, an experimental topical antimicrobial used in treating grafted burn wounds, to modify plasmin fibrinolytic activity in vitro and, thus, its potential to alter or modify the integrity of the fibrin glue critical for skin graft viability. Immobilized ^{125}I-fibrin monolayers were used to assay fibrinolytic activity from plasmin or from plasma activated by streptokinase or urokinase and modified by the presence of mafenide or ε-aminocaproic acid (EACA). While streptokinase-activated plasma lysed 52.7 ± 3.9% of the ^{125}I-fibrin, this plasmin activity was more than 80% inhibitable by EACA. Mafenide acetate had no intrinsic fibrinolytic activity (1.5 ± 0.3%) nor activated plasma fibrinolytic potential (2.4 ± 0.5%), but produced significant and dose-related reduction in fibrinolytic activity ($p < 0.001$). Other sulfonamide analogues lacking a para-methylamino reactive group had 10–100 fold less antifibrinolytic potency while lysine, like mafenide, able to compete for plasmin binding sites, could potently block fibrinolysis. Mafenide did not qualitatively alter activation of plasminogen or affect generation of complexes with α_2 antiplasmin complexes. Adding mafenide only minutes following streptokinase-activated plasma or plasmin with the fibrin substrate reduced antifibrinolytic activity, supporting the conclusion that mafenide, like EACA, can modulate the interaction between fibrin and the plasmin reactive sites and thus prevent close plasmin/fibrin apposition. The union of mafenide's potent antimicrobial activity with its antifibrinolytic potential is a fortuitous combination. The beneficial antifibrinolytic effect of mafenide may control inflammatory proteolysis, promote skin graft retention, and support wound healing.

Introduction

Fibrinolytic activity at inflammatory sites involves both intravascular activation of plasminogen to plasmin and also generation of plasmin by proteolytic enzymes from inflammatory cells, complement components and plasma coagulation factors (1, 2). Excess inflammatory fibrinolytic activity may destabilize fibrin formation with resultant hemorrhage. One unique site where fibrin formation serves multiple purposes is in the treatment of burn wounds with split thickness skin grafts. The primary adherent attachment of a skin graft to its prepared bed is due to the glue-like action of fibrin (3). Proteolysis of this fibrin glue may result from endogenous fibrinolytic activation or from inflammatory proteolytic activity which may be enhanced by infection at the burn graft site (4). Proteolysis of the fibrin glue is a major cause of skin graft failure (5).

Mafenide acetate (sulfamylon™ solution) is an experimental topical sulfonamide antimicrobial which has been used in treating deep partial and full thickness burn wounds. Mafenide has broad spectrum antimicrobial activity and penetrates well into the burn sites. In solution (50 g/l; 267 mM) solution, it is applied directly to soak through the burn wound dressings as often as six times daily, saturating the burn site. Because this agent's use in high concentration penetrates the burn graft site, including the fibrin glue critical for graft retention, we sought to determine potential effects of mafenide solution on plasmin fibrinolytic activity *in vitro,* and thus its potential to alter or modify the integrity of the fibrin glue critical for skin graft viability.

Materials and Methods

Fibrinolytic activity was assayed by the proteolytic degradation of ^{125}I-fibrin monolayers as modified from the method of Moroz and Gilmore (6, 7). Polystyrene culture dishes were coated with ^{125}I-fibrinogen (specific activity 191 μCi/mg; Amersham, Arlington Heights, IL) by adding 200 μl of radiofibrinogen (approximately 10^6 cpm/ml) in phosphate buffered saline for 3 h at 25° C. After washing, bovine serum albumin (1 mg/ml in Tris-buffered saline) was overlaid to saturate the nonspecific protein adherence of the polystyrene. After four washes in alkaline Tris saline (pH 9.36), thrombin (approximately 1 unit/well in 500 μl Tris-saline) was added and incubated (5 min, 37° C) to cleave the fibrinogen to ^{125}I-fibrin. After extensive washing, the radio-labelled fibrin wells were stored at 4° C under Tris-saline containing 0.1% sodium azide until ready for use.

The solid phase bioassay of fibrinolysis involved incubation of usually minimally heparinized (1 unit/ml) fresh human plasma with test solutions in the ^{125}I-fibrin wells for 1–3 h at 37° C. The aspirated supernatant radioactivity (including 3 washes, each with 500 μl saline) was quantitated in a gamma counter (Beckman). The radioactivity collected as proteolytic products of the immobilized ^{125}I-fibrin was expressed as a percent of the maximal fibrin proteolysis induced by incubating control wells with trypsin (10 mg/ml) which was used in each experiment as a measure of maximal (100%) fibrinolytic activity. Plasmin was added directly or its activity was generated by streptokinase (150 IU/ml, final concentration) or urokinase (150 IU/ml) activation of heparinized human plasma. Epsilon aminocaproic acid (EACA) (7.6 mM, final) was used as a competitive inhibitor of fibrinolytic activity.

Two-dimensional crossed immunoelectrophoresis of test human plasmas for plasminogen and α_2 antiplasmin (α_2AP) were performed using a modification of the method of Edson et al. (8). In 1% agarose plates, citrated human plasma (with or without streptokinase and/or mafenide) were electrophoresed in buffer (pH 8.6) with Tris-Tricine (α_2AP) or sodium barbital-barbituric acid (plasminogen). Agarose containing antisera was poured surrounding the cutout agarose strips from the first dimension electrophoresis and the second dimension was run. The washed and dried plates were stained with Coomassie blue to reveal the antibody precipitation arc.

Results are expressed as the mean ± the standard error of usually two to five experiments performed in duplicate or triplicate. The student unpaired t-test of significance was used for statistical analysis, where indicated. Streptokinase, plasmin, bovine serum albumin, thrombin, sulfadiazine and sulfamethoxazole were obtained from Sigma (St. Louis, MO). Urokinase was obtained from Abbott Laboratories (North Chicago,

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Table 1 Solid phase fibrinolysis

A.	% Fibrinolysis					
	Saline	Plasma	Mafenide + plasma	Plasmin	Streptokinase + plasma	Trypsin + mafenide
Buffered saline	1.5±0.3	4.2±0.4	2.4±0.5	42.6±0.3	52.7±3.9	100 ±1.7
EACA	1.8±0.5	3.8±0.7	2 ±0.7	4.4±0.1*	6.9±1.1*	100.9±3.3

B.	Fibrinolysis: % Drug-free control		
	Mafenide (mM)	Plasmin	Plasma + urokinase
	0	100 ±1.6	100 ±2.4
	1.3	102.4±1.4	–
	2.7	92.7±3.2*	59.2±1.9*
	5.3	85.2±0.8*	40.7±5.1*
	13.4	75.3±6.4*	28 ±1.8*
	26.7	61.6±4.2*	28.9±3*
	133.5		16.9±0.6*

A. Incubation of ^{125}I-fibrin wells with test solutions shown. Radioactivity released expressed as mean ± SE % maximal fibrinolysis induced by trypsin (see Methods). Mafenide (106.8 mM), streptokinase (150 IU/ml), plasmin (0.5 mU/ml), EACA (7.6 mM), or trypsin (10 mg/ml) were present throughout the incubations. Values marked (*) are significantly ($p < 0.001$) different than the EACA-free control.

B. Fibrinolysis expressed as % of the control incubations free of mafenide. Plasmin (5 mU/well) released 63.8 ± 1% of the trypsin-released radioactivity while plasma + urokinase (150 IU/ml) released 31.9 ± 0.8%. Values marked (*) are significantly ($p < 0.001$) different than the control.

IL). EACA was obtained from Lederle Laboratories (Pearl River, NY). Carzenide was obtained from Aldrich (Milwaukee, WI). Rabbit anti-human plasminogen and anti-human α_2AP were obtained from Calbiochem Behring (San Diego, CA). Mafenide acetate solution was obtained from Winthrop Laboratories (New York).

Results

When tested in the solid phase fibrinolytic assay, mafenide acetate solution (1–250 mM) had no intrinsic fibrinolytic activity. As shown (Table 1), buffered saline, heparinized human plasma, and mafenide acetate solution plus plasma all induced less than 5% release of radioactivity from the ^{125}I-fibrin wells (p = NS). Streptokinase-activated plasma induced release of 52.7 ± 3.9% of the radioactivity releasable by trypsin, comparable to that from plasmin. Three fourths of the eventual fibrinolysis was completed by 30 min of incubation and no additional fibrinolysis was observed after 60 min (data not shown). This activity was nearly completely inhibited by the addition of EACA. Mafenide had no effect on the proteolytic digestion of the ^{125}I-fibrin by trypsin and thus no broadly reactive anti-protease activity.

However, when mafenide was added to the streptokinase/plasma incubations in the radiofibrin wells, it produced significant and dose-related inhibition of fibrinolytic activity. As shown (Fig. 1), at concentrations tested between 2 and 200 mM mafenide, there was statistically significant reduction in fibrinolytic activity at all doses shown (all $p < 0.001$). Mafenide solution is used clinically to soak the burn graft dressings at 267 mM concentration, even above the highest inhibitory dose tested.

In comparison, mafenide also produced dose-related inhibition of fibrinolysis induced by plasmin or by urokinase-activated plasma (Table 1B). Fibrinolysis activated by streptokinase was similarly sensitive to mafenide ($IC_{50} \sim 6.8$ mM) and urokinase-induced activity ($IC_{50} \sim 4.7$ mM) while direct plasmin activity was at least 10-fold less sensitive ($IC_{50} > 50$ mM). This enhanced inhibitory activity observed in the presence of plasma (with streptokinase or urokinase) may reflect synergistic fibrinolytic inhibition between mafenide and plasma inhibitors (9, 10).

Structure-Activity Relationship

Mafenide differs from other sulfonamides by containing a para-methylamino group, rather than a para-amino group (Fig. 2). The

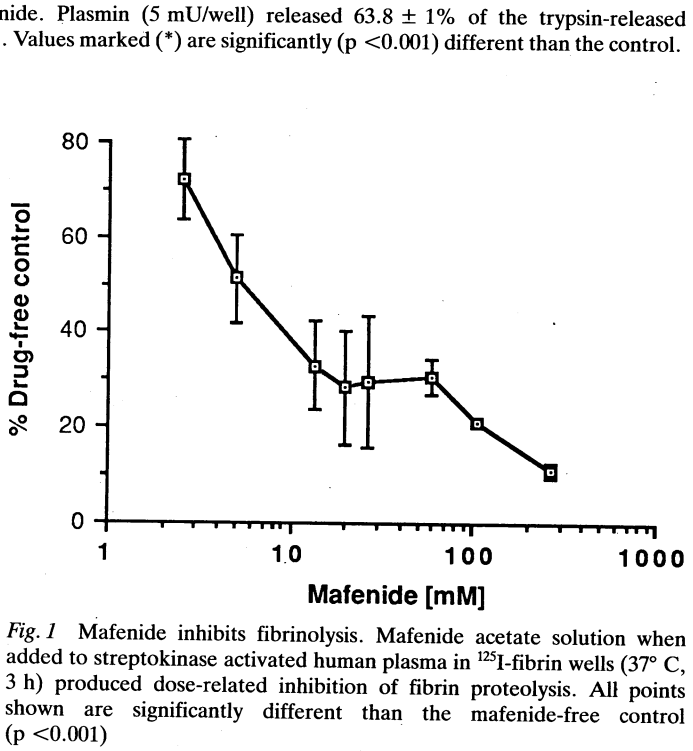

Fig. 1 Mafenide inhibits fibrinolysis. Mafenide acetate solution when added to streptokinase activated human plasma in ^{125}I-fibrin wells (37° C, 3 h) produced dose-related inhibition of fibrin proteolysis. All points shown are significantly different than the mafenide-free control ($p < 0.001$)

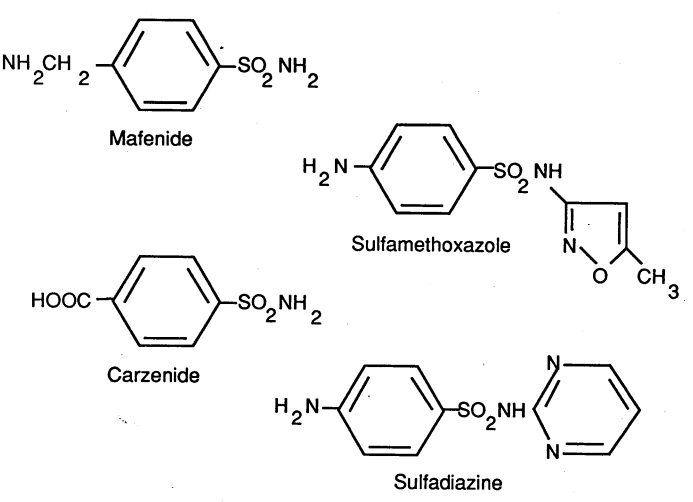

Fig. 2 Structure of mafenide analogues

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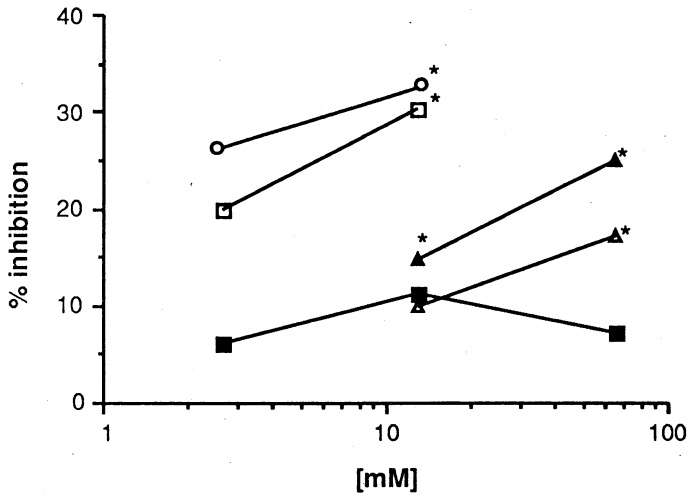

Fig. 3 Structural analogues of mafenide: Inhibition of fibrinolysis. Mafenide (open squares), lysine (open circles), sulfadiazine (solid triangles) and sulfamethoxazole (open triangles) or the mafenide metabolite carzenide (solid squares) were incubated with streptokinase activated plasma in radio-labelled fibrin wells (3 h, 37° C). The results are expressed as the percent inhibition from the individual drug-free control. Results shown are the mean of two experiments, each done in duplicate. Points marked (*) are significantly different than control ($p < 0.01$).

antifibrinolytic activity of EACA is apparently due to its reactive epsilon amino group (11, 12) and perhaps to its spatial separation from the alpha carboxyl group (13). We reasoned, therefore, that this methylamino site may contain the antifibrinolytic activity we observed in mafenide, perhaps by competing with the reactive lysine groups on fibrin and fibrinogen for plasmin binding. As shown in Fig. 3, lysine was roughly equipotent with mafenide at inhibiting plasmin fibrinolysis. In contrast, sulfadiazine and sulfamethoxazole with para-amino reactive sites and substituted bulky sulfonamide groups were at least one to two orders of magnitude less active at inhibiting *in vitro* fibrinolysis. In contrast, carzenide, the major circulating metabolite of mafenide in the plasma, which has a carboxyl group replacing the methylamino site in the para-position, had no significant fibrinolytic effect over almost three orders of magnitude tested.

Mechanism of Antifibrinolytic Activity

We next explored the potential mechanisms of mafenide antifibrinolytic activity. As shown in Table 2A, pre-incubation of streptokinase-activated plasma in polystyrene before plating into the radiofibrin coated wells failed to modify the fibrinolytic activity. Addition of either mafenide or EACA to the incubations before plating blocked over 80% of the fibrinolytic activity. Because pre-incubated streptokinase-activated plasma still contained fibrinolytic activity inhibitable by addition of mafenide, we further assessed some aspects of the mechanism underlying this inhibition.

If mafenide prevented generation of fibrinolytic species by blocking streptokinase activation of plasminogen, similar loss of fibrinolysis would be observed. To probe whether mafenide qualitatively altered plasminogen activation or generation of complexes with α_2 anti-plasmin, we performed two-dimensional crossed immunoelectrophoreses of citrated, minimally heparinized fresh human plasma after incubation alone, with streptokinase, and with streptokinase plus mafenide (Fig. 4). As shown, two-dimensional immunoelectrophoresis of plasminogen (panel A) shows nearly complete conversion of native plasminogen after activation with streptokinase (2A). Mafenide addition to this incubation (3A) shows the same complete depletion of the native plasminogen, implying near complete conversion of plasminogen and the formation of plasmin or streptokinase/plasminogen and streptokinase/plasmin α_2AP complexes of altered mobility shown. Mafenide and related lysine analogue antifibrinolytics may interact with these plasminogen and plasmin complexes potentially altering their affinity both for activator and for the fibrin substrate (10). Such alterations would not necessarily be reflected by this immunoelectrophoretic analysis.

Parallel immunoelectrophoresis of these same samples for α_2AP (panel B), the major plasma antiplasmin factor, demonstrates alteration of native α_2AP after incubation with streptokinase (2B). The α_2AP is significantly depleted and travels with

Table 2 Mafenide effects on fibrinolysis: Time course

A. Pre-incubation before plating

	% Fibrinolysis		
Plating after	Buffer	Mafenide	EACA
5 min.	49 ±2.4	8.7±1*	6.4±1.5
15 min.	46.4±1.1	9.2±2.7*	8.1±0.9

B. Late addition of inhibitor

	% Fibrinolysis					
	Plasma + streptokinase			Plasmin		
Time added (min)	Buffer	Mafenide	EACA	Buffer	Mafenide	EACA
0	51.5±2.7	8.2±0.6[1]	5.7±0.5[1]	63.8±1.0	39.3±2.7[1]	22.1±1[1]
1	–	11.3±2.3[1]	6.8±0.4[1]	–	40.7±0.7[1]	20.4±1.3[1]
3	–	17.6±0.6*[1]	15.1±1.8*[1]	–	–	–
5	–	33.3±0.5*[1]	30.4±0.7*[1]	–	43 ±0.4[1]	24.9±1.4[1]
10	–	–	–	–	44 ±1.4[1]	41.8±0.1*[1]
15	55 ±1.7	53.4±1.8*	56 ±2.7*	63.1±0.8	49.5±1.4*[1]	46 ±3.3*[1]

A. Streptokinase plus plasma ± mafenide (26.7 mM) or EACA (7.6 mM) was incubated in polystyrene tubes at 37° C for the indicated time and then added to ^{125}I-fibrin wells. After 60 min, the percent of fibrinolysis was determined. Values marked (*) are significantly different than the buffer control ($p < 0.001$).

B. Streptokinase (150 IU/ml) plus plasma or plasmin (5 mU/well) was added to ^{125}I-fibrin wells at time 0. At the indicated time, the buffer or the fibrinolytic inhibitor (mafenide 20 mM or EACA 7.6 mM) was added. After 60 min total incubation, the percent of fibrinolysis was determined. Values marked (*) are significantly different than zero time ($p < 0.001$). Values marked ([1]) are significantly different than the inhibitor-free controls ($p < 0.001$).

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altered electrophoretic mobility – compatible with the generation of plasmin/α_2AP complexes. The pattern is similar in the mafenide/streptokinase/plasma incubations (3B). Therefore, though mafenide might kinetically alter the activation of plasminogen by streptokinase, the generated products and subsequent complexes with α_2AP are of similar electrophoretic mobility.

The antifibrinolytic activity of mafenide and EACA was critically time dependent. As shown in Table 2B, when mafenide was added later following the addition of streptokinase-activated plasma or plasmin to the radiofibrin wells, time dependent reduction in fibrinolysis was observed. Progressively later addition of the mafenide to the streptokinase plasma incubations resulted in significant reductions in the amount of antifibrinolytic activity observed. For its inhibitory activity to be fully expressed, mafenide must apparently be present before the interaction of the streptokinase-generated fibrinolytic species (e.g., SK-plasminogen, SK-plasmin, or plasmin) and the fibrin substrate. These results are consistent with earlier observations on various ω-aminocarboxylic acids reported to react with plasmin-plasminogen species producing reduced affinity for fibrin (10). EACA, as shown, displayed similar time dependent requirements for its inhibitory activity against streptokinase-generated fibrinolysis to be expressed.

In contrast, the inhibitory impact of mafenide and EACA on plasmin activity was manifest differently over time (Table 2B). Addition of either inhibitor up to 15 min into the reaction still resulted in significant reduction in plasmin fibrinolysis compared to the inhibitor-free control, suggesting that this fibrinolytic activity was still vulnerable to neutralization by either mafenide or EACA even late into the reaction. Delayed addition of mafenide (15 min) or EACA (10 min) resulted in significantly less antiplasmin activity compared to the zero-time control.

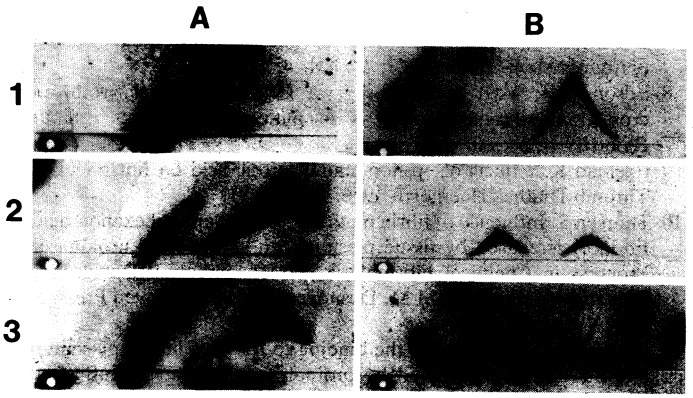

Fig. 4 Immunoconversion of plasminogen and α_2 antiplasmin: Effect of streptokinase and mafenide. Incubation of fresh plasma (1A, 1B): streptokinase + plasma (2A, 2B); Mafenide (26.7 mM) with streptokinase + plasma (3A, 3B) (all 5 min, 37° C). Two-dimensional crossed immunoelectrophoresis of each sample for plasminogen (panel A) or α_2 antiplasmin (panel B)

Discussion

Mafenide acetate solution at concentrations used clinically is a potent and apparently competitive inhibitor of plasmin fibrinolysis. While possessing no intrinsic fibrinolytic potential, and having little qualitative effect on either the activation of plasminogen or the interaction of plasmin with α_2AP, mafenide can protect human fibrin from proteolysis by plasmin or by urokinase and streptokinase-generated proteolytic species. Okamoto and colleagues, in an extensive study of several hundred synthetic compounds for antifibrinolytic potential, previously recognized the antifibrinolytic potential of mafenide and some related sulfonamides (13).

While the structural and kinetic interactions of these synthetic lysine analogues with fibrinolytic components are complex (15) and inhibitory mechanisms are controversial, the present study offers several new insights, though derived in a simplified experimental system. Mafenide's full inhibitory effect requires its presence throughout the incubation of the lytic species (plasmin or activator generated complexes) and the fibrin substrate. In view of this prominent requirement for mafenide to be present during the interaction of plasmin with fibrin, we suggest that the mafenide inhibitory activity, like that reported for other ω-aminocarboxylic acids (10, 11), involves alteration of the interaction between plasmin and fibrin, in addition to any effects on the generation of plasmin activity from plasminogen. Since later addition of mafenide cannot as effectively prevent fibrinolysis by streptokinase-activated plasma compared to plasmin, these data are consistent with a hypothesis that mafenide may not as potently modify this functional interaction of SK-generated fibrinolysins with fibrin.

Assessment of related, but structurally distinct, sulfonamides demonstrated that the antifibrinolytic activity of mafenide rests primarily in its para-methylamino group. Its structure and active site is thus similar to free lysine, to the reactive site on fibrin, to various synthetic organic acid antifibrinolytics and to EACA, a well-known and clinically useful fibrinolytic inhibitor (10–14). Mafenide's major plasma metabolite, lacking the para-methylamino group, contains none of the antifibrinolytic potency. The clinical use of mafenide topically, therefore, could modulate antifibrinolytic activity locally, but any mafenide which was absorbed systemically and metabolized to carzenide would not induce systemic fibrinolytic inhibition, and thus no systemic tendency to thrombosis.

Since activation of fibrinolysis at inflammatory sites, particularly at infected burn graft sites, may be induced by bacterial or granulocytic proteases (4), the union of potent yet safe antimicrobial activity with coincidental antifibrinolytic activity is a fortuitous combination. The antimicrobial activity can contain infection, thus reducing granulocytic infiltration and lysosomal enzyme proteolytic cleavage of fibrin while concurrently counteracting any endogenous plasmin fibrinolysis. This dual activity could help maintain the fibrin network critical for burn graft retention, for fibroblast and epithelial migration and proliferation, and thus for wound healing. Similarly, the inactivity of its prime metabolite at blocking plasmin activity suggests that no systemic fibrinolytic inhibition would ensue. Further studies of this potentially beneficial side effect of mafenide may allow greater exploitation of its antifibrinolytic potential in vivo.

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Haemoccult Screening for the Early Detection of Colorectal Cancer

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Carcinoma of the colon is now the second commonest cause of death from cancer in the western world.

There has been little change in the survival rates of symptomatic cancer over the last 20 years, the results of treatment being disappointing as the majority of patients present with tumours that have already spread beyond the bowel into the draining lymph nodes and liver.

The Haemoccult faecal occult blood test has now been used for population screening for colorectal cancer for over 10 years and evidence has accumulated to show that the use of this test results in the diagnosis of a greater number of early stage cancers limited to the bowel wall. Control trials are now in progress to demonstrate the likely resultant improvement in survival.

The objectives of this Workshop are to record the studies using Haemoccult in Europe and to provide an opportunity for the discussion of these results.