Intra-abdominal adhesions and their prevention by topical tissue plasminogen activator

D Menzies MB FRCS **H Ellis** CBE MCh FRCS *Department of Surgery, Westminster Hospital, Dean Ryle Street, London SW1P 2AP*

Keywords: adhesions; intestinal obstruction; tissue plasminogen activator

Summary

Recent work shows that a common pathway in adhesion production is a reduction in local plasminogen activator activity (PAA). This deficit permits deposited surface fibrin to become organized to fibrous adhesions. A rabbit model for adhesion formation was used to assess the effect of replacing the deficit with recombinant tissue plasminogen activator (rt-PA).

Adhesions were produced by stripping peritoneum from corresponding parietal and visceral areas. One week later the adhesions were divided. Either rt-PA or placebo was applied to the divided adhesion. After a further week the animal was killed and the adhesions assessed.

Sixty strips were performed. Fifty-five adhesions were produced (92%). Placebo gel was applied to 28 sides and rt-PA applied to 27. Twenty-two of the placebo group recurred (79%). Two of the rt-PA group reformed (7%, $\chi^2=20.883$, $P<0.001$). Recombinant tissue plasminogen activator is an effective inhibitor of adhesion formation in the experimental animal.

Introduction

Following abdominal surgery the proportion of patients developing intra-abdominal adhesions has been reported to be as high as 93% in those undergoing multiple operations[1]. In our own unit in a series of 210 consecutive laparotomies in patients who had previously undergone at least one abdominal procedure more than 93% had adhesions present at the site of their original surgery or to the undersurface of the wound (unpublished figures).

The number of patients with intestinal obstruction due to adhesions accounts for around 30% of all cases of intestinal obstruction[2,3]. This figure rises to as much as 74% when small bowel obstruction alone is considered[4].

The classical pathway of adhesion formation (Figure 1) has recently been altered by the findings of Buckman[5] and Raftery[6] who have shown a reduction in peritoneal mesothelial plasminogen activator

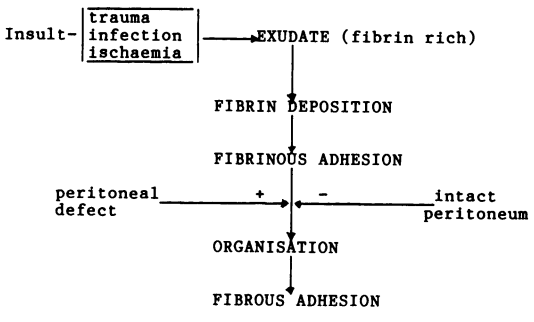

Figure 1. The classical pathway for adhesion formation

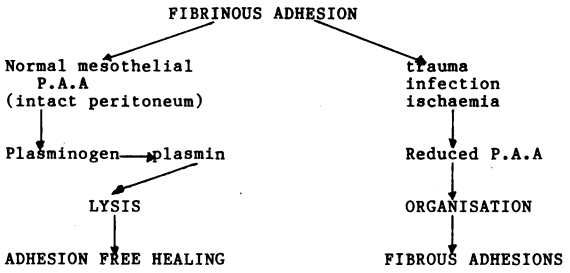

Figure 2. The new pathway for adhesion formation

activity (PAA) in the presence of stimuli known to cause adhesions, and have proposed that it is this abnormality in PAA that is the common link in adhesion formation (Figure 2).

We set out to study the effect of replacing this deficit with recombinant tissue Plasminogen Activator (rt-PA) to try to prevent adhesion formation in an animal model.

Method

A model for adhesion formation was developed using female New Zealand White rabbits. A laparotomy was performed and peritoneum stripped from the caecum at two sites over an area 2×3 cm. The caecum of a rabbit extends across the width of the abdomen so that it was possible to strip peritoneum from the right and the left sides of the caecum. In addition, peritoneum was stripped from the anterior abdominal wall over an area 3×4 cm on the right and left to correspond to the stripped caecum, so that on closure both areas lay in apposition.

Table 1. Grading of adhesions

Grade 1—Separated with gravity
Grade 2—Separated by blunt dissection
Grade 3—Separated by sharp dissection
Grade 4—Difficult sharp dissection

After one week the wound was re-opened, the adhesions assessed for size and grade (Table 1) and divided. Recombinant t-PA (in a hyaluronic acid base) or hyaluronic acid alone was then applied in a blind fashion to the divided adhesion.

After a further week the animal was killed and the adhesions again assessed by size and grade.

Results

A high initial adhesion rate was achieved, with 55 of 60 strips producing adhesions (92%). All of these adhesions were graded as grade 3 or 4 and of a size equal to, or greater than, the original stripped

Paper read to Section of Surgery, 5 October 1988

0141-0768/89/090534-02/$02.00/0

caecal area. The adhesions were divided and the raw surfaces treated; either with rt-PA (27 sides) or hyaluronic acid (28 sides).

Those sides receiving placebo ($n=28$) reformed adhesions on 22 occasions, a reformation rate of 79%. The rt-PA treated sides ($n=27$) only produced two reformed adhesions, a rate of 7% ($\chi^2=20.883$, $P<0.001$).

When animals receiving rt-PA to both sides or hyaluronic acid to both sides are considered; the hyaluronic acid only group ($n=16$) reformed adhesions on 15 occasions (94%) and the rt-PA only group ($n=15$) reformed adhesions on two occasions (13%). The two adhesions that did reform were both graded at grade 2 and were over an area of less than 1/10th of the original adhesion size ($\chi^2=17.099$, $P<0.001$).

There was no evidence throughout the study of excessive haemorrhage or delayed wound healing in any animal receiving rt-PA.

Discussion

Postoperative adhesions form due to organization of fibrinous adhesions produced from the fibrin rich exudate within the abdominal cavity. These convert to fibrous adhesions by invasion of new vessels and fibroblasts. It was originally believed that peritoneum possessed some form of fibrinolytic ability that permitted lysis of the fibrinous adhesions and prevented permanent adhesion formation[7]. This did not explain why a defect of peritoneum, when closed by suturing or grafting, was an even stronger stimulus to adhesions than the bare area itself. It was shown by Ellis that suturing peritoneum produced local ischaemia and it was in response to this ischaemia that adhesions formed[8].

In 1969 Myhre-Jensen[9] showed that the mesothelial cells of the peritoneum were capable of fibrinolysis by activation of plasminogen to plasmin - a powerful endogenous fibrinolytic agent. Subsequently, Gervin[10], Buckman[5] and Raftery[6] have shown that this PAA is reduced in the presence of trauma and ischaemia.

Prevention of adhesions has been the subject of many experiments. Ellis[11] has classified these preventive measures into five groups: (1) instillation of lubricants or distension with gas; (2) enhancement of peristalsis; (3) covering of raw surfaces; (4) enzyme digestion; (5) agents to inhibit deposition of fibrin.

A large number of substances have been used to combat adhesion formation but the majority of these have proven either to be too toxic for use, to possess a too high a complication rate, to be too difficult in application or simply not to work.

The most promising substances so far employed have been povidone iodine[12] and sodium carboxymethyl cellulose[13]. More recently chondroitin sulphate[14] has been reported to be effective. These agents act by mechanical separation of surfaces as well as adding a protective 'finish' to the viscera. Both mechanisms being a feature of their inert nature.

Other thrombolytics, such as streptokinase[15], have been reported to be effective in adhesion prevention but present difficulties with local and systemic administration and the risk of hypersensitivity.

In our study, on only two occasions did adhesions reform despite the use of rt-PA. On each occasion the adhesion was only grade two and substantially smaller than the original adhesion.

Tissue plasminogen activator, by replacing the lower PAA of peritoneum under conditions producing adhesions, corrects the fundamental cause of adhesions and appears to be an effective deterrent of adhesion reformation in an animal model. It can be simply applied at the time of surgery and does not appear to have any systemic complications. Currently clinical trials using rt-PA are planned.

Acknowledgments: We wish to thank Genentech Inc. USA for their support and sponsorship throughout the study.

References

1 Weibel MA, Manjo G. Peritoneal adhesions and their relationship to abdominal surgery. *Am J Surg* 1973; **126**:345-53

2 Ellis H. The causes and prevention of intestinal adhesions. *Br J Surg* 1982;**69**:241-3

3 Perry JF, Smith GA, Yonehiro EG. Intestinal obstruction caused by adhesions; a review of 388 cases. *Ann Surg* 1955;**142**:810-16

4 Bizer LS, Liebling RW, Delany HM, Gieildman ML. Small bowel obstruction. The role of non-operative treatment in simple intestinal obstruction and predictive criteria for strangulation obstruction. *Surgery* 1981; **89**:407-13

5 Buckman RF, Woods M, Sargent L, Gervin AS. A unifying pathogenic mechanism in the aetiology of intraperitoneal adhesions. *J Surg Res* 1976;**20**: 1-5

6 Raftery AT. Effect of peritoneal trauma on peritoneal fibrinolytic activity and intraperitoneal adhesion formation. An experimental study in the rat. *Eur Surg Res* 1981;**13**:397-401

7 Hartwell SW. *The mechanics of healing in human wounds*. Springfield, Illinois: Thomas, 1955:109

8 Ellis H. The aetiology of postoperative adhesions. *Br J Surg* 1962;**50**:10-16

9 Myrhe-Jensen O, Larsen SB, Astrup T. Fibrinolytic activity in serosal and synovial membranes. *Arch Pathol* 1969;**88**:623-30

10 Gervin AS, Puckett CL, Silver D. Serosal hypofibrinolysis, a cause of postoperative adhesions. *Am J Surg* 1973;**125**:80-8

11 Ellis H. Internal overhealing: the problem of intraperitoneal adhesions. *World J Surg* 1980;**4**:303-6

12 Goldberg EP, Sheets JW, Habal MB. Peritoneal adhesions: Prevention with the use of hydrophilic polymer coatings. *Arch Surg* 1980;**115**:776-80

13 Elkins TE, Bury RJ, Ritter JL, *et al.* Adhesion prevention by solutions of sodium carboxymethyl cellulose in the rat. I & II. *Fertil Steril* 1984; **41**:926-32

14 Oelsner G, Graebe RA, Pan S, *et al.* Chrondroitin sulphate—a new intraperitoneal treatment for postoperative adhesion prevention in the rabbit. *J Repod Med* 1987;**32**:812-14

15 James DCO, Ellis H, Hugh TB. The effect of streptokinase on experimental intraperitoneal adhesion formation. *J Path Bact* 1965;**90**:279-87