Br. J. Surg. Vol. 68 (1981) 59–60 *Printed in Great Britain*

The effect of intravenous aprotinin (Trasylol) on intraperitoneal adhesion formation in the rat

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SUMMARY

A randomized controlled trial to assess the effect of intravenous Trasylol on postoperative intraperitoneal adhesion formation has been performed in rats. Before undergoing a standard left colonic resection, animals received i.v. Trasylol 10 000 KIU. This dose was repeated 8-hourly for 3 days postoperatively. Control animals received saline placebo. The mean percentage circumference of the anastomosis covered with adhesions in the Trasylol group animals was 20·86 ± 6·08 compared with 45·24 ± 5·97 in the control group ($P < 0·01$).

Significantly more animals treated with Trasylol were completely free of adhesions than those receiving saline. Bursting pressures did not differ between the two groups. Intravenous Trasylol clearly inhibits intraperitoneal adhesion formation in this model.

FIBROUS intraperitoneal adhesions may develop following abdominal operations but their cause is unknown. Whilst some adhesions are transient, those that persist are a common cause of intestinal obstruction (1).

Attempts to prevent adhesions have been made experimentally, and whilst initial success has been reported, other workers have been unable to reproduce results. Intraperitoneal lavage has been used and among the substances introduced into the peritoneal cavity has been aprotinin (Trasylol, Bayer, UK). Trasylol is a proteinase inhibitor obtained from bovine lung sources.

Experimental studies using Trasylol (2, 3) have shown a reduction in the incidence of adhesions when it is given intraperitoneally. Raftery (4), however, was unable to show suppression of adhesion formation, and little reduction in the adhesion incidence. All these studies, however, have utilized Trasylol intraperitoneally; no studies have been reported of the effect of *intravenous* Trasylol. The present study was designed to determine the effect of intravenous Trasylol on intraperitoneal adhesion formation in the rat following laparotomy and left colonic resection.

Materials and methods

Fifty adult female Wistar rats, weighing 250–300 g, were used. The rats were anaesthetized with 0·15 ml Sagatal intraperitoneally. To enable intravenous administration of Trasylol, the right jugular vein was cannulated with a specially designed catheter. This catheter was made from Portex polythene tubing (Portex Ltd, Hythe, Kent) and incorporated a metal insert to which the vein could be tied. The catheter was passed via a subcutaneous tunnel to the nape of the neck.

Each rat was allocated to its treatment group by means of a random envelope system. Rats received 10 000 KIU Trasylol or a similar volume of normal saline placebo immediately before laparotomy.

At laparotomy, through a standard 4·5 cm midline incision, 1 cm of left colon was resected 5 cm from the peritoneal reflection, and an anastomosis using a single layer of 6/0 Mersilk interrupted inverting suture was constructed. The abdominal wounds were closed in layers using continuous 3/0 Dexon.

Immediately postoperatively the rats were inserted into a harness which enabled them to move freely within their cages, but which protected the cannula to allow additional postoperative intravenous infusions. This harness consisted of a sling which encircled the thorax of the animal and to which was attached a flexible metal conduit. The cannula which was connected to a swivel joint mounted 20 cm above the centre of the cage ran through the middle of the conduit. Animals received 10 000 KIU Trasylol i.v. three times a day or similar volumes of placebo for 3 days postoperatively. All rats were sacrificed on the fourth postoperative day.

The analysis of the rats was performed blindly by one of us (H. L. Y.) and consisted of determining the number of gross adhesions present and then determining the percentage of adhesions attached to the circumference of the anastomosis. Gross adhesions were assessed on a scale of 0–3. Following this assessment the colon was removed, with any adhesions, and the proportion of the anastomosis uncovered assessed by measurement of the circumference of the bowel to which no adhesions were attached. The diameter of the colon at the anastomosis was measured and the percentage of the circumference covered by adhesions could thus be mathematically determined.

Bursting pressure studies, using a uniform rate of infusion of water (4·75 ml/min), were also undertaken. These permitted an assessment of whether the presence or absence of adhesions had any detrimental effect upon the integrity of the anastomosis. Because of the disruptive effect of bursting pressure studies, breaking strength studies could not be performed.

Results

At the end of the experimental series the code of treatment was broken and it was noted that 43·5 per cent (10/23) of the Trasylol-treated group of rats had no adhesions compared with 3·7 per cent (1/27) of the placebo-treated group ($P < 0·005$; Student's t test).

There was a significant difference between the mean percentage circumference of the anastomosis covered for those rats that had received Trasylol compared with those that had received placebo: 20·86 ± 6·08, 45·24 ± 5·97 respectively ($P < 0·01$).

There was no significant difference in bursting pressure between the two groups: Trasylol 4·50 ± 0·57 cmHg; placebo 5·70 ± 0·58 cmHg ($P > 0·05$).

In each group there were two rats that had evidence of anastomotic leakage or abscess formation. All these rats, irrespective of their treatment, had dense adhesions covering the whole circumference of the anastomosis.

Discussion

The results show that the proteinase inhibitor Trasylol, given intravenously to rats prior to and following laparotomy and left colonic resection, significantly reduces the incidence of adhesion formation 4 days after laparotomy. In the Trasylol-treated group there was complete absence of adhesions in 43·5 per cent whilst adhesions were invariably present in the rats that received placebo.

Among substances which have been advocated in an attempt to reduce intraperitoneal adhesions are noxythiolin (Geistlich Sons Ltd, Chester) (4, 5) and Trasylol

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(3), both given intraperitoneally. Little work has previously been performed on the effect of Trasylol when given intravenously and no controlled clinical trials have been recorded. Perovic et al. (6) gave children with perforated appendices Trasylol intraperitoneally and had no cases of mechanical ileus. Mooney (7) gave Trasylol intraperitoneally to 20 patients and showed a marked reduction of adhesions in 16 patients who underwent a 'look-back' procedure, but this was an uncontrolled trial. Dai et al. (8), in Vietnam, performed a trial using Trasylol or placebo subcutaneously in dogs and noted a marked reduction in adhesion formation following laparotomy at which deperitonealization of the anterior aspect of the rectum was performed.

The method by which Trasylol might reduce adhesion formation is unknown. Grundmann (3) suggested that inflammatory granulation tissue development was prevented and that there was a reduction in the inflammatory response. Dai et al. (8) suggested that as well as a reduction of the inflammatory response, Trasylol may act as an anti-plasmin and promote the inhibition of fibrin formation.

Intravenous Trasylol probably reaches a higher concentration than can be achieved by the intraperitoneal route, with a consequent increased general inhibitory action, resulting in a decrease of adhesion density.

In this study sutured peritoneal defects, which have been shown to be a stimulus for adhesions (5, 9), were not performed. Instead, a standard left colonic anastomosis was fashioned using a single-layer inverting suture. The strength of the anastomosis was assessed by means of bursting pressure studies to determine whether the presence of adhesions would protect a potentially weak anastomosis. However, the results show no significant difference in bursting pressure measurements in the two groups and the strength of anastomoses with no adhesions matches those with dense adhesions.

The results of this work suggest that intraperitoneal adhesion formation in rats can be significantly reduced or delayed by the administration of intravenous Trasylol and in a number of cases total suppression of adhesions can be achieved.

Acknowledgements

We are grateful to Bayer (UK) Ltd, who generously provided financial support for this study, and to Mrs P. H. Roberts for typing the manuscript.

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Paper accepted 24 July 1980.