The Effect of Oral D-Penicillamine on Intraperitoneal Adhesions

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Abstract
Objectives: The most common cause of intraperitoneal adhesion bands is previous abdominal surgery. Postoperative adhesion formation results from a fibroproliferative inflammatory reaction. The possibility of involvement of fibrogenic process in adhesion formation and the antifibrogenic effect of D-penicillamine led us to test the effectiveness of this drug as a possible preventive method for intraperitoneal adhesions.

Methods: Eighty female rats were randomly divided into four equal groups of 20 rats. Generation of adhesion in rats introduced by intra peritoneal injection of 2.5 millilitre of a 10% sterile talc solution. The first group served as control, group 2 received oral D-penicillamine 35 milligram per kilogram per day, group 3 received oral colchicines 0.02 milligram per kilogram per day and group 4 received both drugs for three weeks. Formation of adhesion bands was then quantitatively graded in each group according to Nair classification.

Results: Severe adhesions (grade 3 and 4) were found in 20% of the D-penicillamine administered group (group 2), whereas these types of adhesions were observed in 33% and 84% of colchicine administered groups (group 3) and the control group (group 1) respectively (p<0.003). Group 4 that had received both D-penicillamine and colchicine was omitted from the study due to a high mortality rate. Adhesion bands in D-penicillamine group were thinner and smoother in comparison to other groups.

Conclusion: Lower grades of adhesions were found in the D-penicillamine group in comparison to the colchicine and control groups. Therefore it seems that D-penicillamine may be effective in the prevention of formation of adhesion bands in the rat.

Key words: Adhesion band, colchicine, penicillamine.

Introduction
Surgical procedures are the most common causes of intra-abdominal adhesion band formation, resulting in small bowel obstruction. Adhesion bands are a major cause of morbidity and mortality in surgical patients. Numerous attempts have been made to prevent or reduce the incidence of peritoneal adhesions. However, limited success have been achieved until now. For example, removal of fibrinous exudates by peritoneal lavage with or without the use of various. Proteolytic enzymes, prevention of fibrin deposition using anticoagulation and Anti-inflammatory agents, separation of surfaces by stimulation of peristalsis with prostigmine to prevent prolonged contact between adjacent loops of intestine, use of substances such as olive oil or liquid paraffin (which prevent adhesions formation by limiting tissue apposition during the initial phases of peritoneal repair).
inhibition of fibroblastic proliferation with antihistamines, steroid and cytotoxic agents, and enhancement of peritoneal fibrinolytic activity (which decreases after local peritoneal insult), with application of recombinant tissue plasminogen activator.13

The pathogenesis of adhesion between serosal surfaces is usually explained as follow: the surfaces are injured and therefore become inflamed; fibrinogen oozes out; a fibrin clot glues the injured areas together, and fibrous attachment becomes organized into a permanent fibrous band.5

The possibility of inhibition rate of collagen synthesis by D-penicillamine in scleroderma and it’s anti-fibrogenic effect12 (since it can cleave bands and partially inhibit collagen synthesis), led us to use it for prevention or reduction of adhesion band formation.

Materials and Methods
Eighty female rats with mean weight of 200-220 grams were divided randomly into four equal groups of control, D-penicillamine, colchicine, and D-penicillamine and colchicine. Adhesions were induced by intraperitoneal injection of 2.5 cc of 10% sterile talc solution.

The control group received no drug. In group two, 35 mg/kg/day of penicillamine was administered. Group three received 0.02 mg/kg/day of colchicine which was dissolved in distilled water and was administered by a long metal oral gavage. Group four received both drugs, but due to high mortality rate this group was omitted from the study. All animals received medications for 3 weeks, and at the end of the fourth week they were sacrificed. Their abdominal cavities were explored and the number and degree of adhesions were recorded according to the Nair classification (Table-1). The result was analysed statistically by Kruskalwallis test. Standard photographs were taken.

Result
At the end of the fourth week in group one, 19 rats survived and 16 rats (84%) developed severe adhesion bands (Grade 3 and 4). In group two, only 4 rats (20%) developed high grade adhesion bands. In group 3, six rats (33%) developed high grade adhesion (Fig.-1) (p=0.003). Mortality rates were 5% and 10% in group 1 and 3, respectively. No mortality was seen in group 2.

Adhesions in group 2 were thinner and looser in comparison to other groups. Grade 4 adhesion was seen in 5% of D-penicillamine administered group and about 70% had one or two loose bands. Grade 4 adhesion developed in 4 rats (22.2%) in group 3 and 8 rats (42.1%) in group 1, respectively.

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Discussion
Peritoneal adhesions are a consequence of an inflammatory reaction and a healing process following damage to the peritoneum, e.g.: trauma or during surgery. Fibroblasts proliferation and secretion of collagen are probably involved in the pathogenesis of adhesion bands. Colchicine has been investigated previously as a potential anti-adhesion formation agent because of it’s anti-histaminic and antimototic effect.14,3

D-penicillamine has been used in the treatment of progressive systemic sclerosis, where it’s mechanism of action has been proposed to be interfering with collagen synthesis. It also inhibits the proliferation of several cultured cell types, such as fibroblasts and T-lymphocytes. Due to these observations the effect
of penicillamine on peritoneal adhesion formation was examined.

![Figure 1: Grades of Adhesion Bands in Groups 1,2,3.](image)

Many efforts have been made to elucidate the cause and prevent the development of abdominal adhesions, such as usage of intra-abdominal methylene blue, vitamin E, allopurinol, colchicine, usage of peritoneal barriers and abdominal adhesions, such as intra-peritoneal barriers (proteoglycan), fibrolamellar agents, inhibition of insulin-like growth factor 1 activity, selective immuno-suppression at molecular level, and anti-inflammatory agents (oxyphosphotamide). However, complete success has not been achieved.

The result of this study, showed that D-penicillamine markedly reduces severe adhesion band formation and loosens it in comparison to colchicine. Administration of both agents is not recommended because of high mortality rate. In those rats who survived in this group (group 4) and were explored, severe adhesions (grade 3 and 4), multiple interloop collection and bowel obstruction were later seen. Before death, rats presented with anorexia and decreased activity and 24 to 48 hours later they did. The cause may be due to sepsis, collection or obstruction. Although no specific interaction of D-penicillamine and colchicine has been previously reported, however, unknown interaction and animal intolerance may be the cause of the high mortality rate in this group.

**Conclusion**

Oral D-penicillamine is more effective than oral colchicine in reduction of peritoneal adhesion band formation. Use of D-penicillamine for this purpose should be weighed against its side effects. Also administration of both agents is not recommended.

**References**

1. Ran-Brin-Abraham, Tel - Hashomer, Yoram Kiger: Reduction of surgery induced peritoneal adhesions by methylene blue.


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