SERRATIOPEPTIDASE

Clinical trials reports

Anti-inflammatory oral enzyme

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Serratiopeptidase was administered for the purpose of suppressing and eliminating the post-operative bleeding and resultant formation of haematoma which are the most serious problems in the field of Orthopaedics. It was also administred for enhancing the action of antibiotics.

The total no. of patients were 29, with major surgery being conducted on 18 and the rest had some form of minor procedures done on them.

No.	Subjects	Diseases	No. Of patients
1.	Inflammatory	Amputation / Skin grafting	6
2.	Swelling and haematoma after injury	Intra-articular fractures contusions	6
3.	Post-operative	Informal fixation/Monisectomy	13
4.	Others		4
Total			29

Administration and dosage:

Each patient was administered 6 tablets per day, in divided doses of 2 tablets three times a day after meals.

The duration of therapy was adjusted according to the local response, mainly the state of tumefaction, induration and flare. The duration varied from 7 days to 10 days depending

on the improvement in each case. However, the dosage (six tablets per day) was not changed in any case.

Results and Conclusion

Considering the results of the trial we have conducted in 29 cases, Serratiopeptidase appears to have afairly good effect in decreasing the swelling, inflammation and enhancement of the antibioic function. The effect of serratiopeptidase on pain was significant, with with 23 of the 29 patients having relief from pain by the 6^{th} day of therapy.

In 11 cases, the swelling subsided by the 6^{th} day, in 12 cases, the swelling subsided by the 6^{th} to 9^{th} day, in 3 cases the swelling took more than 9 days to subside and in the remaining the results were obscure.

Role of Serratiopeptidase in Chronic Sinusitis

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Various surgical means are descirbed in the literature for management of a pateint of chronic sinusitis. These often include invasive techniques form a simple antrum wash out of maxillary sinusitis to a very radical procedure like Caldwel Luc's operation of maxillary sinusitis, ethmoidal exentration / drainage procedures offrontal and sphenoidal sinus and radical exentration / obliteration of frontal sinuses.

These procedures are very demanding both on the part of the an otolaryngologist and the patient. This is one of the reason that some otolaryngologists have again resorted to a more conservative, non-invasive medical approach to the problem.

Out of a long list of medicines used in the management of chronic sinusitis, most common ones used are antibiotics / antibacterials, systemic and local decongestants, analgesics, mucolytics and mucokinetics etc. A relatively new drug, Serratiopeptidase has been used at some places in the world in addition to the medicines already mentioned in the list.

Keeping in mind Serratiopeptidase's strong anti-inflammatory and anti-tumefacient effect which facilitates the expectoration of mucus from the upper and lower respiratory tract, the present study was undertaken.

A total of 200 patients were selected for the study, the socio-economic status and living conditions were as far possible mateched in the paitents studied, and the age ranged between 8 and 57 years.

One group (Serratiopeptidase) comprising 100 patients received 5mg of Serratiopeptidase in those upto 12 years of age and 10 mg Serratiopeptidase in adults orally three times daily after meals. The other group of 100 patients (Placebo Group) also received 1 – 2 tablets three times a day after meals.

In addition, all the patients received systemic antibiotics. Analgesics were also prescribed if needed. No local medication in the form of medicated steam inhalation, nasal drops and nasal sprays were given in any case. The treatment was continued, initially for a period of one week and extended further for one week in those who did not respond as desired.

Results

The table below shows the change in amount of character of nasal discharge:

	Good	Fair	Poor
Serratiopeptidase Group	26	43	31
Placebo Group	12	33	55

Good: Change from purulent to mucopurulent and mucopurulent to mucoid discharge in initial days followed by complete absence of excessive nasal discharge.

Fair: Little change in character but persistence of discharge after full course of treatment

Poor: No change in character and amount of discharge.

Discussion

Serratioepetidase is believed to act mainly in three ways:

1. Elimination of inflammatory oedema and swelling
2. Acceleration of liquefaction of pus and sputum
3. Enhancement of the action of antibiotics

It was seen that the amount and character of nasal and post nasal discharge showed a fair response in 58% of Serratiopeptidase group and only 43% of placebo group. The response was poor in 425 of patients in Placebo group while it was poor only in 19% of those who received Serratiopeptidase. Similarly nasal mucosa showed a change from severe congestion to normal and hypertrophied turbinates showed change to normal size in 26% of Serratiopeptidase group and only 12 % in those who received a placebo only. Here again the poor response was seen in 55% patients in placebo and only 31 % on serratiopeptidase.

It can thus be concluded that in cases of chronic sinusitis, systemic antibiotics along with administration of Serratiopeptidase forms the best mode of conservative therapy presently available.

Clinical drug trial of Serratiopeptidase for Chest Disorder

Dr. S. K. Chhabra and Prof. M.P.S. Menon, Clinical Research Centre,
V.P. Chest Institute, University of Delhi, New Delhi.

This study is concerned with the evaluation of its effects in obstructive disorders of lungs, associated with hypersecretion of tenacious sputum, chronic obstructive pulmonary disease and bronchial asthma. Effective clearance of thick sputum is often a problem and a source of discomfort for these patients. Thus an agent which could decrease this hypersection would be a welcome addition to the existing drug armamentarium.

A total of 20 patients were studied. 13 cases had "cold" and 7 had "Bronchial Asthma". All the patients of theophylline compounds and salbutamol and were clinically stable. These were continued as before.

Serratiopeptidase was administered as 2 tablets thrice daily after meals for 14 days.

Assessment of Effects:

Sputum charts were maintained which recorded amount and state of sputum daily.

Symptomatic status in terms of dysponea and cough was also noted.

Adverse effects assessment:

During trial a watch was kept for any adverse effect that might be due to this new drug such as bleeding tendency, fever, skin rash or gastro-intestinal upset. Haematological and chemical parameters were investigated again after the trial to look for any significant alterations.

Results:

Group of Patients	Effectiveness of Serratiopeptidase			
	Markedly Effective %	Effective %	Relatively Effective %	Ineffective %
Cold	10	46	16	38
Bronchial Asthma	6	50	50	-

Markedly Effective: Sputum decreased to nil.
Effective: Sputum persisted, but less, viscocity decreased.
Relatively effective: Sputum amount same or increased, viscocity decreased.
Ineffective: No effect on amount of sputum or viscocity.

1. The amount of sputum decreased in 15 patients, remained as before in 2 and increased in the remaining 2.
2. Sputum viscocity was markedly different.
3. Haematological and biochemical parameters were not significantly altered.
4. In 16 out of 19 patients it was possible to obtain spirometric data. Most (14) showed improvements in atleast one of the three indices measured.
5. No adverse effect was recorded.
6. Serratiopeptidase was judged to be effective as above.

Remarkable features:

- Decrease in sputum viscocity
- All the patients found it much easier to expectorate than before.
- All patients felt that their cough and the subjective sensation of dysponea was lesser than before.

Application

- **Trauma Surgery :** In sports injuries, sprains, laceration, fractures and dislocation. It reduces inflammation and helps faster healing and repair.
- **Surgery :** Reduces Post Operative Edema at injection sites. Reduces internal tissue edema caused at post operative handling. Reduction in edema reduces chances of rupture at tissue site as well as risk of graft rejection.
- **Plastic Surgery :** Reduces Post Operative Edema and restores microcirculation at the site of graft rejection.
- **Respiratory Medicine :** Breaks down complex sputum molecules in smaller peptides with lower viscosity, helping in expectorating them more easily. Reduced viscosity of secretion helps in better antibiotic penetration to enable control over stubborn infections like bronchitis, lung abscess and bronchectasis.
- **Infections :** Mucolytic activity in sinuses, ear cavities and anti-inflammatory activity in upper respiratorytract organs help in faster resolution, better antibiotic bioavailability and faster cure rates.
- **Male Genital Infection :** Restores microcirculation and augments antibiotic penetration in these organs which are known to produce poor antibiotic availability.
- **Dermatology :** Used in acute painful inflamed dermatoses.
- **Dentistry :** Helps better control over dental infections.
- **Obestetrics & Gyaenacology :** The anti-inflammatory activity helps in resolution of post-partum haematomas, breast engorgements and pregnancy related thromboplbitis.

Storage Conditions

Conditions for storing Serratiopeptidase is as for any othe enzyme. It should be stored at cool temperature. Away from direct sunlight.

Latest developments on Serratiopeptidase

Further studies carried out on Serratiopeptidase have revealed new and more interesting applications for Serratiopeptidase in the field of pain management and transferance of antibiotics.

SERRATIOPEPTIDASE AND PAIN MANAGEMENT

The treatment of diverse inflammatory conditions require a comprehensive approach that is aimed at not only controlling pain, but also relief from swelling and edema associated with these disorders. **Hence, to ensure relief, a more efficacious approach would be to prescribe both a NSAID (non-steroidal anti-inflammatory drug) and a proteolytic enzyme.**

Studies on Serratiopeptidase's various activities – caseinolytic activity, fibrinolytic activity and bradykinin decomposing activity indicate that serratiopeptidase is more potent than chymotrypsin, bromeline and pronase.

Serratiopeptidase administered orally supresssed that vascular permeability in an inflammation model. It has also been shown to inhibit the inflammatory edema following administration of substances such as carragenan, dextran and bradykinin. In vitro studies indicate that the bradykinin decomposing activity is far superior to other proteolytic enzymes.

STUDIES	RESULTS
Preventive edema protection using serratiopeptidase after standardised one-stage osteotomy procedures of third molars was verified by means of an opto electronic measuring instrument.	Statistically significant reduction in soft tissues swelling was observed demonstrating the cliinical efficacy of serratiopeptidase in reducing post-operative edema.
Using a quantitative standardised procedure, the swelling of the ankle produced by supination trauma was measured in 66 patients with fresh rupture of the lateral ligament after administration of serratiopeptidase	The swelling was reduced by 50 %; thus the patients receiving the test substance became pain-free more rapidly.
The efficacy and tolerability of serratiopeptidase was evaluated in a multi-centred, double-blind, placebo-controlled study of 193 subjects suffering from acute or chronic ear, nose or throat disorders. Treatment lasted 7-8 days.	After 3-4 days treatment, significant symptom regression was observed in enzyme-treated patients. From the study it was concluded that Serratiopeptidase has anti-inflammatory, anti-oedemic and fibrinolyitc activity and acts rapidly on localised inflammation

SERRATIOPEPTIDASE AND ANTIBIOTIC TRANSFERANCE

Serratiopeptidase has been shown to be effective in transferring various antibiotics such as Penicillin G, Ampicillin, Gentamicin or Cefotaxim to the site of infection *(Okumura et al 1977; Ishihara 1983)*

The following papers detail the use of serratiopeptidase in treating sinusitis, in combination with antibiotics.

Sinusitis - Inspecting the causes and treatment

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United States
Ear, Nose and Throat Journal (EAR NOSE THROAT J.) (United States)
1992, 71/6 (258-262)

In summary, sinusitis is a common disease caused by viruses, bacteria and the accumulation of excessive secretions and inflammatory mediators that impair the function of the mucociliary transport.

Combination treatment is usually necessary to treat the cause and relieve the symptoms of sinusitis.

Therapy aims at eliminating causative bacteria with antibiotics, decongesting edematous membranes, and thinning mucus with use of a mucolytic-expectorant. Improving the rheology of mucus by thinning abnormally thickened secretions may improve mucociliary transport and enhance penetration of antibiotics. Acute sinusitis usually responds to treatment within 2 weeks.

Studies carried out by Prof. Mohd. Maqbool, of Govt. Medical College, Srinagar, have shown that Serratiopeptidase acts in three ways in the treatment of chronic sinusitis.

4. Elimination of inflammatory oedema and swelling
5. Acceleration of liquefaction of pus and sputum
6. Enhancement of the action of antibiotics

Augmentation by serrapeptase of tissue permeation by cefotiam

Koyama A; Mori J; Tokuda H; Waku M; Anno H; Katayama T; Murakami K; Komatsu H; Hirata M; Arai T; et al
Jpn J Antibiot (JAPAN) Mar 1986, 39 (3) p761-71, ISSN 0368-2781

Cefotiam (CTM) is a new cephalosporin with a broad spectrum of activity against both Gram-positive and Gram-negative microorganisms. Cephalosporins are widely used for prophylaxis of infections in patients undergoing thoracotomy. Augmentation by serratiopeptidase on tissue permeation of CTM was examined in 35 thoracotomy patients with lung cancer. The subjects were divided into two groups according to the method of the administration of CTM. Group I consisted of 17 subjects, each of whom received a single dose of 2 g of CTM alone by an instillation for 30 minutes. Group II consisted of 18 subjects, each of whom received a combination of CTM and serrapeptase; serrapeptase was given 2 tablets (10 mg) each time for three times/day until the day before surgery, and then CTM was administered by the same procedure.

The following results were obtained:

Individual difference was observed for the permeation of CTM into tissues. Pathologic differences also affected the permeation. Nevertheless, the CTM levels in pulmonary tissues reached about a half of those in the blood in both the single dose group and the combination group, hence sufficient concentrations exceeding MIC80 for main microorganisms that caused infections in the lung were obtained. The concentrations of CTM in inflammatory tissues have showed lower levels than those of normal tissues in both CTM single dose and the combination groups. Decrease of blood flow volume may have contributed to the reduction in levels of CTM in the inflammatory tissues. The ratio of the concentration of the drug in pulmonary tissues to that in the blood was 29.1 +/- 2.5% in the single dose group, and 44.2 +/- 6.0% in the combination group, the latter showing quite a significant increase (P less than 0.05).

An anti-inflammatory effect of serratiopeptidase in the respiratory system is expected, and in addition, the combined use of CTM and serratiopeptidase should stimulate permeation of the antibiotic into tissues.

Jpn J Antibiot 1983 Oct;36(10):2665-70

[Experimental studies on distribution of cefotiam, a new beta-lactam antibiotic, in the lung and trachea of rabbits. II. Combined effects with serratiopeptidase].

[Article in Japanese]

Ishihara Y, Kitamura S, Takaku F

Plasma levels and distribution in pulmonary and bronchial tissues of CTM following injection into the jugular vein were investigated in rabbits with experimental pleuritis or pneumonitis as well as in normal rabbits. The experiments also included the assessment of the effect of concomitant administration of serratiopeptidase (TSP). The pneumonitis + TSP group, pleuritis group and pleuritis + TSP group showed a tendency to delayed dissipation of CTM from the plasma, as compared with controls. The CTM concentrations in tissues from the apical region of upper lobe (L1), lateral region of middle lobe (L2) and diaphragmatic region of lower lobe (L3) 30 minutes after injection did not differ significantly between the control and the TSP group, pleuritis group or pleuritis + TSP group. In the pneumonitis group, the tissue CTM concentrations at all 3 sites (L1, L2, L3) were lower than those in the control group. They were increased by the concomitant administration of TSP, with statistical significance of increase in regions L2 and L3. Thirty minutes after the injection of CTM, the pneumonitis group and

pneumonitis + TSP group displayed essentially comparable CTM levels in pleural fluid, whereas the CTM concentrations in the pleural fluid were prone to be increased in the pleuritis + TSP group as comparing with the pleuritis group. CTM levels in the tissues of trachea (B0), right and left main bronchi (B1) and lobar bronchi (B2) 30 minutes after the injection did not show any significant difference between control and TSP-treated normal groups. CTM concentrations tended to be increased, yet not significantly, in all these regions in the rabbits with pleuritis administered TSP, compared to those without TSP.

Jpn J Antibiot 1980 May;33(5):623-35

[Studies on the distributions of antibiotics in the oral tissues: Experimental staphylococcal infection in rats, and effect of serratiopeptidase on the distributions of antibiotics].

[Article in Japanese]

Aratani H, Tateishi H, Negita S

1) A focal infection was prepared by inoculation of staphylococci into rat gingiva. Then, concentrations in oral tissues (gingiva, tongue and masseter), serum and liver of the infected rats which were given ciclacillin, ampicillin, cephalexin and minocycline in a dose of 100 mg/kg p.o. were investigated and effects of serratiopeptidase (20 mg/kg) on these concentrations were studied. 2) Concentrations of ciclacillin in the oral tissues were approximately 10% of a serum level. A gingival concentration was elevated 8.5-fold by pretreatment with serratiopeptidase. A concentration in infected gingiva was 2.5-fold of that of another side of gingiva. 3) Concentrations of ampicillin in the oral tissues were approximately 15% of a serum level. A gingival concentration was elevated 5.7-fold by pretreatment with serratiopeptidase. A concentration in infected gingiva ws 2.2-fold of that of another side of gingiva.

4) Concentrations of cephalexin in the oral tissues were approximately 3 to 5-fold of a serum level except that in masseter. A gingival concentration was slightly elevated (1.1-fold) by pretreatment with serratiopeptidase. A concentration in infected gingiva was 1.7-fold of that of another side of gingiva. 5) Concentrations of minocycline in the oral tissues were 1.3 to 7.2-fold of a serum level. A gingival concentration was elevated 2.2-fold by pretreatment with serratipeptidase. A concentration in infected gingiva was 3.1-fold of that of another side of gingiva. 6) Gingival concentrations of antibiotics were higher than those of tongue and masseter and serratiopeptidase elevated gingival concentrations.

Jpn J Antibiot 1977 Mar;30(3):223-7

Effects of a proteolytic-enzyme preparation used concomitantly with an antibiotic in osteoarticular infections.

Okumura H, Watanabe R, Kotoura Y, Nakane Y, Tangiku O

Studies were performed in 8 patients with osteoarticular infections to examine the concentrations of sulbenicillin in the venous blood and exudate following administration and the concentrations of the antibiotic in the exudate when serratiopeptidase was orally administered concomitantly with the antibiotic. The results of the examination indicated that the transfer of sulbenicillin into the exudate tended to increase when 30 mg/day of serratiopeptidase was concomitantly given for 6 days, though further examination was thought necessary by increasing number of subjects and elaborating on the methodology.

Jpn J Antibiot 1980 May; 33(5):623-35

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Commercially available serratiopeptidase combination drugs

1. Emanzen D – Emcure Pharma
2. Serronac – Stedman

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