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Evaluation of *Serratia* Peptidase in Acute or Chronic Inflammation of Otorhinolaryngology Pathology: a Multicentre, Double-blind, Randomized Trial versus Placebo

A. Mazzone[1], M. Catalani[2], M. Costanzo[3], A. Drusian[4], A. Mandoli[5], S. Russo[6], E. Guarini[7] and G. Vesperini[8]

[1]Institute of Clinical Otorhinolaryngology, University of Naples, Naples, Italy; [2]Ear, Nose and Throat Department, 'Gradenigo' Hospital, Turin, Italy; [3]Ear, Nose and Throat Department, 'Villa Sofia' Hospital, Palermo, Italy; [4]Ear Nose and Throat Department, Treviso Regional Hospital, Treviso, Italy; [5]Ear, Nose and Throat Department, 'E. Fornaroli' Hospital, Magenta, Italy; [6]Ear, Nose and Throat Department, Lucca Hospital, Lucca, Italy; [7]Ear, Nose and Throat Department, Civil Hospital, Lecce, Italy; [8]Ear, Nose and Throat Department, 'Madonna del Soccorso' Hospital, San Benedetto del Tronto, Italy

The efficacy and tolerability of *Serratia* peptidase were evaluated in a multicentre, double-blind, placebo-controlled study of 193 subjects suffering from acute or chronic ear, nose or throat disorders. Treatment lasted 7 – 8 days, with the drug or placebo being administered at a rate of two tablets three times a day. After 3 – 4 days' treatment, significant symptom regression was observed in peptidase-treated patients. There was also a significant reduction in symptoms after 7 – 8 days for patients in both treatment groups but the response was more marked in those patients receiving the active drug. Statistical comparison between the two groups confirmed the greater efficacy and rapid action of the peptidase against all the symptoms examined at both stages. Tolerance was found to be very good and similar for both groups. It is concluded that *Serratia* peptidase has anti-inflammatory, anti-oedemic and fibrinolytic activity and acts rapidly on localized inflammation.

KEY WORDS: *Serratia* peptidase; anti-inflammatory; fibrinolytic; otorhinolaryngology.

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Address for correspondence: A. Mazzone, MD, Institute of Clinical Otorhinolaryngology, University of Naples, Via Pansini 5, 80131 Naples, Italy.

INTRODUCTION

The use of enzymes with fibrinolytic, proteolytic and anti-oedemic activities has gained increasing support in recent years for the treatment of inflammatory ear, nose and throat (ENT) conditions.[1]

Included among these enzymes is the *Serratia* peptidase (Danzen®), a protease obtained from non-pathogenic enterobacteria of the genus *Serratia*. This proteolytic enzyme, which is available in tablet form to enable it to be absorbed from the intestinal lumen, has been shown to induce intense fibrinolytic, anti-inflammatory and anti-oedemic activity in a number of tissues and results suggest that its anti-inflammatory activity may be of particular use for the treatment of localized or 'closed' forms of inflammation, such as those frequently found in ENT pathologies.[1-6] Another important feature of *Serratia* peptidase is its effect on pain, the enzyme acting by inhibiting the release of pain-inducing amines, such as bradykinin, from inflammed tissue.[1,7]

This peptidase induces fragmentation of fibrinose aggregates and reduces the viscosity of exudates,[1,4,5] thus facilitating the drainage of these products of the inflammatory response and thereby promoting the tissue repair process, and clinical trials have confirmed that the use of *Serratia* peptidase resulted in fast resolution of the inflammatory process.[8-10] The aim of the present placebo-controlled multicentre study was to evaluate the efficacy and tolerability of the *Serratia* peptidase in the treatment of ENT inflammatory conditions.

PATIENTS AND METHODS

Patients

Patients, who were recruited from ENT clinics throughout Italy, were all suffering from inherent acute or chronic inflammatory conditions. Any patients with serious concomitant conditions, such as severe renal and/or hepatic impairments, or who required additional drugs were excluded from the trial, as this could interfere with evaluation of the parameters under examination, and the use of steroids, non-steroidal anti-inflammatory drugs and/or anti-inflammatory/analgesic agents was prohibited. Antibiotics were permitted when deemed necessary.

Treatment

Indistinguishable tablets containing 5 mg *Serratia* peptidase or a placebo were provided in blister packs and patients were randomly assigned to receive two tablets of either drug, which they were instructed to take three times daily after meals for 7 – 8 days.

Evaluation of treatment

Clinical signs and symptoms were assessed on days 0, 3 – 4 and 7 – 8 of treatment on a scale of 0 – 3 (0, absence of the symptoms; 3, maximum severity). Clinical parameters recorded were as follows: pain; quantity of secretion; difficulty in swallowing; nasal obstruction; anosmia; and body temperature. The appearance of the secretion was also recorded on a scale of 0 – 3 (0, normal; 1, mucoid; 2, mucopurulent; 3, purulent). All evaluations were performed by an ENT specialist unaware of the treatment given.

Evaluation of tolerability

Tolerability of *Serratia* peptidase was evaluated on the basis of the presence, absence or severity of side-effects, recorded on the patients' data-collecting forms.

Statistical analysis

All data were analysed by the most appropriate statistical tests (χ^2-test and Student's *t*-test).

RESULTS

A total of 193 subjects (96 males, 97 females), aged between 12 and 77 years (mean ± SD 38 ± 15.7 years), with acute or chronic ENT pathologies were recruited to the trial. Of these 193 cases, 97 (43 males, 54 females; mean ± SD 37.3 ± 15.2 years) were placed in group A and 96 (53

Danzen® is a registered tradename of Takeda Italia Farmaceutici SpA, Italy.

males, 43 females; mean ± SD 38.8 ± 16.2 years) in group B.

All subjects, including those who only completed 1 day of treatment, were evaluated for drug tolerance and all who completed the trial were evaluated for efficacy. A total of 24 cases who had been assigned to the *Serratia* peptidase treatment group and 29 assigned to receive placebo were subsequently excluded from the trial. The reasons for exclusion were as follows: treatment with different dosages; ineligibility due to lack of necessary details in the records; treatment interrupted on day 1; and incomplete study data. Of the 140 subjects entered for evaluation of efficacy, therefore, 73 received the active peptidase and 67 placebo. The two treatment groups were statistically uniform in terms of demographic data, the incidence of disease type and severity of disease prior to treatment. The mean treatment period was 7.8 days for *Serratia* peptidase and 7.9 days for group B, with the dosage regimen having been followed by all the patients. The incidence of use of an antibiotic was 25% for patients treated with *Serratia* peptidase and 27% for those treated with placebo, reinforcing the comparability of the groups.

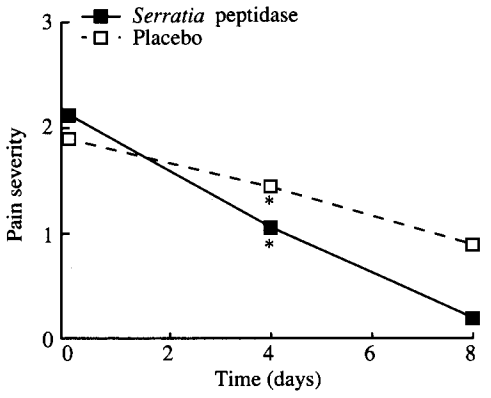
There was a significant ($P < 0.001$) reduction in severity of pain (Fig. 1), amount of secretion (Fig. 2), purulence of secretions (Fig. 3), difficulty in swallowing (Fig. 4), nasal dysphonia (Fig. 5), nasal obstruction (Fig. 6), anosmia (Fig. 7) and body temperature (Fig. 8) both after 3 – 4 days and at the end of treatment with *Serratia* peptidase; final average residual severity scores for individual symptoms were between 0 and 0.5 in each case.

In the placebo-treated patients, responses were generally less marked and there were no significant effects of placebo on the quantity of secretion and nasal dysphonia. The scores in the placebo treatment group were much higher (1 – 2) for all symptoms,

Table 1
Side-effects reported in patients (n = 140) with acute or chronic ear, nose and throat pathologies treated with 5 mg/day *Serratia* peptidase or placebo for 7 – 8 days

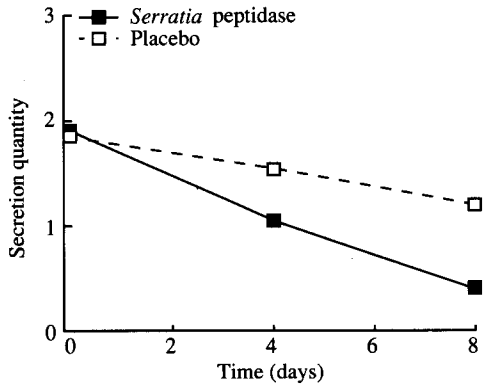
Treatment	Sex[a]	Age (years)	Side-effect	Duration (days)	Severity	Correlation with drug
Serratia peptidase	M	41	Gastric pain	2/3	Slight	Doubtful
	F	46	Gastric intolerance	2	Slight	Doubtful
	F	30	Gastric pain	<1[b]	Moderate	Possible
	M	52	Gastric pain	1	Moderate	Possible
	M	12	Gastric pain	4	Moderate	Certain
	F	23	Intermittent	1	Moderate	Possible
Placebo	F	41	Gastric pain	2	Serious	Possible
	F	37	Gastric pain	5	Slight	Possible
	M	60	Nausea	2	Slight	Possible
	F	30	Gastric pain	4	Moderate	Possible
	F	18	Glossitis	2	Slight	Possible
	F	62	Gastric pain	7	Moderate	Possible

[a]M, male; F, female.
[b]Side-effect was experienced for 1 h.



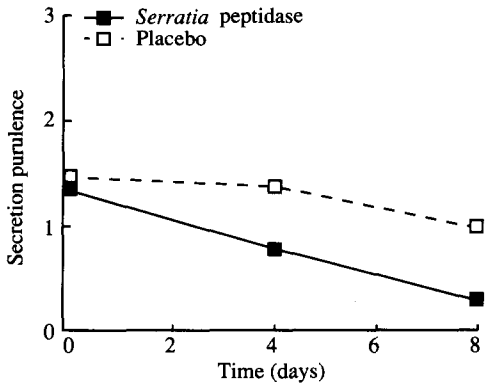
Comparison	*P*-value
Day 3-4 vs day 0	
Serratia peptidase	< 0.001
Placebo	< 0.001
Day 7-8 vs day 0	
Serratia peptidase	< 0.001
Placebo	< 0.001
Serratia peptidase vs placebo	
Day 0	NS
Day 3-4	< 0.01
Day 7-8	< 0.001

Fig. 1. Severity of pain on a scale of 0 – 3 (0, normal; 3, maximal severity) in patients (n = 140) with acute or chronic ear, nose and throat pathologies treated with 5 mg/day *Serratia* peptidase or placebo daily for 7 – 8 days.



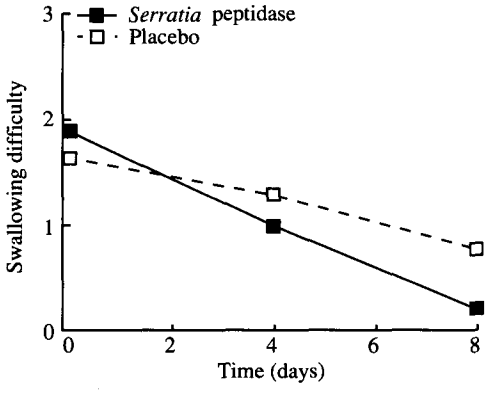
Comparison	*P*-value
Day 3-4 vs day 0	
Serratia peptidase	< 0.001
Placebo	< 0.001
Day 7-8 vs day 0	
Serratia peptidase	< 0.001
Placebo	< 0.001
Serratia peptidase vs placebo	
Day 0	NS
Day 3-4	< 0.01
Day 7-8	< 0.001

Fig. 2. Quantity of secretion on a scale of 0 – 3 (0, normal; 3, maximal severity) in patients (n = 140) with acute or chronic ear, nose and throat pathologies treated with 5 mg/day *Serratia* peptidase or placebo for 7 – 8 days.



Comparison	*P*-value
Day 3-4 vs day 0	
Serratia peptidase	< 0.001
Placebo	NS
Day 7-8 vs day 0	
Serratia peptidase	< 0.001
Placebo	< 0.001
Serratia peptidase vs placebo	
Day 0	NS
Day 3-4	< 0.001
Day 7-8	< 0.001

Fig. 3. Secretion scores on a scale of 0 – 3 (0, normal; 1, mucoid; 2, mucopurulence; 3, purulent) in patients (n = 140) with acute or chronic ear, nose and throat pathologies treated with 5 mg/day *Serratia* peptidase or placebo for 7 – 8 days.



Comparison	*P*-value
Day 3-4 vs day 0	
Serratia peptidase	< 0.001
Placebo	< 0.01
Day 7-8 vs day 0	
Serratia peptidase	< 0.001
Placebo	< 0.001
Serratia peptidase vs placebo	
Day 0	NS
Day 3-4	NS
Day 7-8	< 0.001

Fig. 4. Difficulty in swallowing on a scale of 0 – 3 (0, normal; 3, maximal severity) in patients (n = 140) with acute or chronic ear, nose and throat pathologies treated with 5 mg/day *Serratia* peptidase or placebo for 7 – 8 days.

except for body temperature which dropped to a final mean score of 0.2 points compared with 0 for peptidase-treated patients. Mean clinical scores for all symptoms were lower following peptidase rather than placebo treatment (Fig. 9).

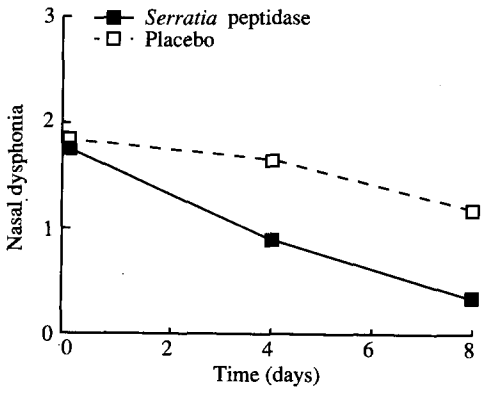
The doctors' assessments of efficacy of treatment were excellent or good for 97.3% of patients treated with *Serratia* peptidase compared with only for 21.9% of those treated with placebo.

No significant differences in the side-effects were found between patients treated with the peptidase and those treated with placebo. There were no changes in blood and clinical measures, and both the drug and the placebo were found to be well-tolerated. Side-effects experienced during the course of the trial were uniformly distributed between the two treatment groups, with an incidence of 6.1% in the *Serratia* peptidase-treated patients and 6.2% in the placebo-treated patients. The main side-effects were slight or moderate gastric pain, being attributed with certainty to *Serratia* peptidase in one case only. In the placebo treatment group, one case of glossitis was reported.

DISCUSSION

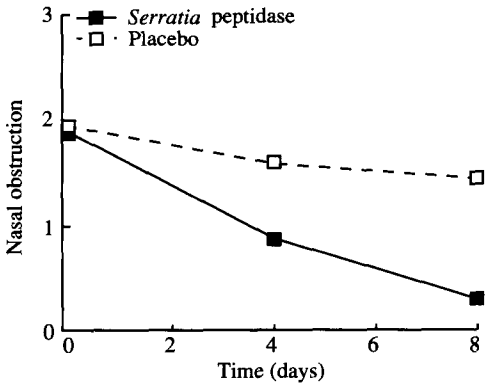
Treatment of patients suffering from ENT pathologies, including laryngitis, catarrhal rhinopharyngitis and sinusitis, with *Serratia* peptidase produced a rapid effect with a significant improvement of symptoms after 3 – 4 days. By comparison, placebo had only a moderate effect on individual symptoms and improvement in symptoms was much slower and the incidence of satisfactory clinical results was lower in placebo-treated patients compared with those treated with the active drug.

The findings of the present study are in agreement with previous double-blind, placebo-controlled trials of *Serratia* peptidase for the treatment of patients with inflammatory ENT conditions.[11 – 13] In one trial, for example, involving subjects with chronic sinusitis it was demonstrated that the peptidase significantly improved nasal obstruction and mucolytic activity,[11] and improvements



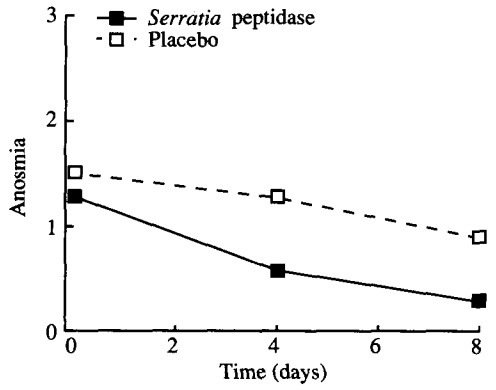
Comparison	*P*-value
Day 3-4 vs day 0	
Serratia peptidase	< 0.001
Placebo	NS
Day 7-8 vs day 0	
Serratia peptidase	< 0.001
Placebo	< 0.01
Serratia peptidase vs placebo	
Day 0	NS
Day 3-4	< 0.001
Day 7-8	< 0.001

Fig. 5. Nasal dysphonia on a scale of 0 – 3 (0, normal; 3, maximal severity) in patients (n = 140) with acute or chronic ear, nose and throat pathologies treated with 5 mg/day *Serratia* peptidase or placebo for 7 – 8 days.



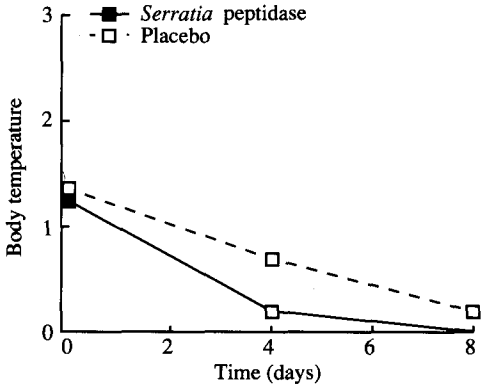
Comparison	*P*-value
Day 3-4 vs day 0	
Serratia peptidase	< 0.001
Placebo	< 0.05
Day 7-8 vs day 0	
Serratia peptidase	< 0.001
Placebo	< 0.001
Serratia peptidase vs placebo	
Day 0	NS
Day 3-4	< 0.001
Day 7-8	< 0.001

Fig. 6. Nasal obstruction on a scale of 0 – 3 (0, normal; 3, maximal severity) in patients (n = 140) with acute or chronic ear, nose and throat pathologies treated with 5 mg/day *Serratia* peptidase or placebo for 7 – 8 days.



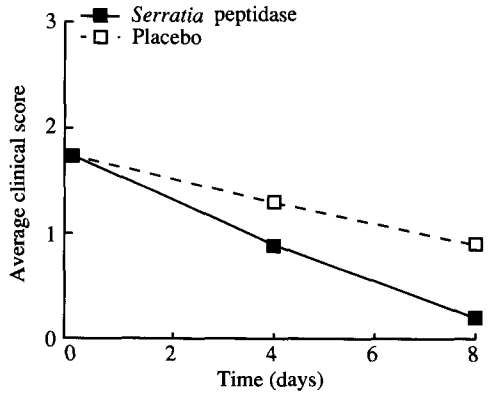
Comparison	*P*-value
Day 3-4 vs day 0	
Serratia peptidase	< 0.001
Placebo	< 0.05
Day 7-8 vs day 0	
Serratia peptidase	< 0.001
Placebo	< 0.001
Serratia peptidase vs placebo	
Day 0	NS
Day 3-4	< 0.001
Day 7-8	< 0.001

Fig. 7. Anosmia on a scale of 0 – 3 (0, normal; 3, maximal severity) in patients (n = 140) with acute or chronic ear, nose and throat pathologies treated with 5 mg/day *Serratia* peptidase or placebo for 7 – 8 days.



Comparison	*P*-value
Day 3-4 vs day 0	
Serratia peptidase	< 0.001
Placebo	< 0.001
Day 7-8 vs day 0	
Serratia peptidase	< 0.001
Placebo	< 0.001
Serratia peptidase vs placebo	
Day 0	NS
Day 3-4	< 0.01
Day 7-8	< 0.01

Fig. 8. Body temperature scores on a scale of 0 – 3 (0, normal; 3, maximal severity) in patients (*n* = 140) with acute or chronic ear, nose and throat pathologies treated with 5 mg/day *Serratia* peptidase or placebo for 7 – 8 days.



Comparison	*P*-value
Day 3-4 vs day 0	
Serratia peptidase	< 0.001
Placebo	< 0.001
Day 7-8 vs day 0	
Serratia peptidase	< 0.001
Placebo	< 0.001
Serratia peptidase vs placebo	
Day 0	NS
Day 3-4	< 0.001
Day 7-8	< 0.001

Fig. 9. Average of clinical scores on a scale of 0 – 3 (0, normal; 3, maximal severity) in patients (*n* = 140) with acute or chronic ear, nose and throat pathologies treated with 5 mg/day *Serratia* peptidase or placebo for 7 – 8 days.

in chronic sinusitis were also shown by Cocchiola and Beltrami.[12] Furthermore, Passali *et al.*[14] when studying children reported improvements in otitis media, measured using audiometry and typano metry.

It should be noted that in the present trial the concomitant use of antibiotics was permitted and this could explain the high incidence of satisfactory clinical response reported. It has previously been demonstrated that the simultaneous use of the peptidase and an antibiotic has resulted in increased concentrations of the antibiotic at the site of infection.[15]

Previous studies have suggested that *Serratia* peptidase has a modulatory effect on specific acute phase proteins, which are involved in the inflammatory process. This is substantiated by a report of significant reductions in C3 and C4 complement, increases in opsonizing protein (α_2-H5-glycoprotein) and reductions in concentrations of haptoglobin, which is a 'scavenger' protein that inhibits lysosomal protease.[16]

It is concluded from the present studies, therefore, that *Serratia* peptidase, with or without concomitant antibiotics, because of its ability to reduce rapidly pain, oedema and inflammation followed by the rapid reabsorption and elimination of protein residues in the localized inflammatory process, is useful for the treatment of otorhinopharygeal disorders.

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