A PROTEASE THERAPY FOR CHRONIC SINUSITIS

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On review of the recent literature no report of an attempt to treat cases of chronic sinusitis with a proteolytic enzyme was found. The authors present account of the favourable treatment of cases of chronic sinusitis with the oral administration of Pronase-P, a proteolytic enzyme, seems to be the first report in the literature.

Of 318 cases of chronic sinusitis given Pronase-P therapy orally, 68% showed some improvement of their symptoms and about 30 per cent excellent symptomatic relief. It was also observed that those cases whose symptoms showed little or no improvement, responded favourably to this medication on further administration in combination with an antibiotic.

Regarding possible adverse effects of enzyme therapy, out of 708 cases receiving this drug only three noted slight nasal bleeding after blowing the nose. Oral administration of Pronase-P to 27 rats for 5—7 consecutive days in an average daily dose of 26 mg (44 times the human therapeutic dosage in mg. per kg. of body weight), resulted in no adverse effects. On autopy no hemorrhage or other pathologic changes were observed in the stomach, in the inner membrane of intestines, or in any other organ.

Twelve patients with chronic sinusitis who were given the same dosage of Pronase-P for 7—14 consective days revealed, with one exception, no increase in serum plasmin activity over the pre-administration stage.

On post-operative observations of patients with chronic sinusitis who were given Pronase-P therapy, a gradual improvement of inflammation was observed. Histologically on H. E. stain there was seen a disappearance of edema, an increase in round cells in the sub-epithelial stroma. A regeneration of blood vessels and a dissolution of fibrin were demonstrated with Van Gieson's stain, a regeneration of blood vessels and an increase in polysaccharides were revealed on PAS stain, an increase in acid muco-polysaccharide was demonstrated with colloidal iron stain and metachromasis in toluidine blue stain.

For the present study enzyme activities in the blood serum and in normal human organs were determined in order to confirm the fact that Pronase-P entered the blood stream through the bowel wall.

LAP in the portal vein was quantitatively determined in 14 normal rats as a control. It was also determined in 14 rats, following a consecutive 5—7 days administration of enteric coated Pronase-P at a daily dosage of 200—400 mgr. The group to which the Pronase-P had been administered showed an increase of about 30% in enzymatic activity over the control group. However,

oral administration of Pronase-P to humans or to rabbits resulted in no increase of LAP or caseinolytic activity in serum.
Histologically in rats and rabbits to whom orally had been administered Pronase-P, examined a week later no changes in non-inflammatory tissues as in the kidneys, adrenals, intestines or liver and no increased tissue enzyme activity was found.
Studies were then made on casein dissolution and LAP determination after Pronase-P was added to human or rabbit serum. It was found that the addition of Pronase-P to such serum inhibited the enzyme activity of Pronase-P by 60—80%. It was concluded that the blood must contain a powerful inhibitory agent against Pronase-P. (Table 1). It was also revealed that repeated oral administrations of Pronase-P for a one to two week period had little effect on the powerful inhibition of this agent by the blood serum. No increase in enzymatic activity in the urine was observed in human or rabbits following administration of Pronase-P.

Table 1.

Inhibitory effect of serum on enzyme activity of Pronase-P ®

INHIBITOR		ENZYME ACTIVITY
rabbit serum	—	100 ✱
	+	19 ✱
human serum	—	100 ✱ ✱
	+	35 ✱ ✱

✱ LAP activity
✱ ✱ caseinolytic activity

The enzymatic activity of inflammed nasal and nasal mucous membrane: Surgically removed mucous membranes in the nasal and the nasal sinus cavities were arbitrarely divided into three gross types: edematous, fibrinous and polypoid. Determinations of LAP and caseinolytic activity of these membranes were made. Six cases of chronic hypertrophic rhinitis (histologically and edematous, infiltrative type) showed on an average, 3.35 OD/mgN for LAP, seven cases of nasal polyposis showed 2.57 OD /mgN. The mucous membrane of the sinus maxillaris showed 4.25 OD/mgN in 15 cases of the edematous type, 4.59 OD/mgN in 17 cases of the fibrinous type and one case with polypoid mucosa showed 5.10 OD/mgN. As for caseinolysis, cases of hypertrophic rhinitis on an average showed 0.499 OD/mgN, and seven cases of nasal polyposis showed 0.300 OD/mgN. Fifteen cases of the edematous type of mucous membrane taken from the sinus maxillaris showed 0.506 OD/mgN; 17 cases of the fibrinous type showed 0.370 OD/mgN, and one case of the polypoid type showed 0.022 OD/mgN.
The enzymatic activity of normal mucous membranes of the nasal and nasal sinus cavity: Mucous membrane and polypi were surgically removed in cases of unilateral hypertrophic rhinitis and nasal polypi and chronically diseased

mucosa were removed from sinuses with almost an indentical bilateral involvement, after Pronase-P had been orally administered in daily doses of 45 mg for a week. The contralateral mucous membrane and / or polypi were allowed to remain.
The specimens removed were studied as to their comparative LAP and caseinolytic activity. Cases of hypertrophic rhinitis and nasal polypi revealed no marked changes in LAP or caseinolytic activity following administration of Pronase-P. In the mucous membrane of the sinus maxillaris, LAP showed no change but caseinolytic activity showed a significant increase following administration of Pronase-P. (table 2).

Table 2

Caseinolytic activity of sinus mucous membranes treated with Pronase-P ®

		Caseinolysis OD/mgN	LAP OD/mgN
		before after	before after
	edematous type		
No.	1	0.104 < 0.161	2.83 > 4.60
	2	0.505 < 0.603	3.55 > 2.48
	3	0.517 = 0.540	3.65 = 3.57
	4	0.657 < 0.820	4.76 = 4.69
	5	0.133 < 0.162	4.93 > 2.77
	6	0.491 = 0.536	5.15 < 5.90
	7	0.505 > 0.231	5.16 < 9.43
	8	0.559 > 0.456	4.64 < 5.70
	9	0.295 = 0.273	7.77 < 8.81
	fibrinous type		
	10	0.289 < 0.746	3.98 ≦ 5.41
	11	0.430 < 0.586	6.25 > 5.21
	12	0.306 < 1.019	6.67 < 8.27
	13	0.271 < 0.410	4.69 = 4.81
	14	0.426 < 0.820	6.67 > 5.41
	15	0.268 < 0.513	5,11 > 4.32
	polyp type		
	16	0.022 < 0.212	5.10 = 5.20

SUMMARY

Favourable results were obtained in approximately 70 per cent of patients with chronic sinusitis by treatment with oral administration of Pronase-P. They were all free from adverse side effects such as bleeding. Pronase-P seemed to decrease edema in the mucous membrane of sinus maxillaris produce a dissolution of fibrin and anti-inflammatory re-actions such as an increase in the infiltration of cells.

Pronase-P did not interfere with serum, normal tissue or normal organ: neither did it increase the enzymatic activity nor increase plasmin activity, possibly because of the presence of a substance inhibiting the action of Pronase-P in

the blood. However, an increase in caseinolysis was observed in the inflammatory mucous membrane following oral administration of Pronase-P. It was assumed that this increase in the enzymatic activity might improve symptoms of "chronic sinusitis".

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