CURRENT SURVEYS

Enzymes for trauma

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Summary
We will discuss the mechanism of action, efficacy and side-effects of the proteolytic enzymes. Their exact mechanism of action remains vague which may be partly responsible for the uncertainty about their therapeutic value.

Use of chymotrypsin (Alpha-Chymar) in lens extractions has gained general acceptance and the topical use of trypsin-chymotrypsin (Biozyme), streptokinase-streptodornase (Varidase) and fibrinolytic desoxyribonuclease (Elase) will also be shown to be of some value.

The merits of oral, buccal or intramuscular administration, however, will not be conclusively demonstrated. Studies showing favourable results for non-topically administered enzymes are not completely acceptable, primarily due to the lack of precise techniques of measurement.

The effectiveness of systemically administered preparations of proteolytic enzymes as anti-inflammatory agents will remain to be established.

Introduction

Proteolytic enzymes are defined as physical substances that catalyse the hydrolysis of proteins. In the medical literature of the past ten years, these enzymes have been said to be therapeutically indicated for reducing the soft tissue oedema and inflammation secondary to trauma. Some proteolytic enzymes have also been used clinically as digestants and have been said to be efficacious in aiding or replacing those enteric enzymes necessary for digestion of food. However, this review will treat only the proteolytic enzymes claimed to reduce the soft tissue swelling and oedema of trauma.

Examples of such products marketed in the United States are: (a) a mixture of enzymes extracted from the pineapple fruit called bromelains (Ananase, Rorer); (b) the proteolytic enzyme papain, extracted from the fruit of the papaya tree, Carica papaya (Papase, Warner-Chilcott); (c) chymotrypsin (Alpha-Chymar, Armour; Avazyme, Wampole); and (d) combinations of chymotrypsin and trypsin (Chymolase, Warren Teed; Chymoral, Armour; Orenzyme, National). Other enzyme preparations, streptokinase-streptodornase (Varidase, Lederle) and fibrinolytic desoxyribonuclease (Elase, Parke-Davis), although not chemically proteolytic also will be discussed because they are said to have the same therapeutic indications.

Mechanism of action

The mechanism by which all of the previously mentioned enzymes exert their action is unclear. Various theories have been postulated but firm evidence to support them is lacking. Innerfield (1960) hypothesized that enzymes act as depolymerases which reduce the chain-length of a protein molecule. He proposed that denatured protein macromolecules in the interstices of an inflamed area of soft tissue could be depolymerized by proteolytic enzymes. The permeability of the inflamed area is supposedly increased, facilitating drainage and tissue repair.

The mode of action of streptokinase-streptodornase is thought to differ from that of the proteolytic enzymes in the following manner. Streptokinase activates a normal physiological constituent...
of the body, plasminogen, transforming it into the physiological protease, plasmin. Plasmin actively lyases the fibrin that is the chief substance composing thrombi. Streptodornase acts by directly depolymerizing deoxyribonucleic acid and thus is thought to reduce the viscosity of purulent exudates (Sherry & Fletcher, 1960).

These theories represent current speculation; the exact mechanism by which these products exert their action has not been established as yet.

**Efficacy**

A factor which seems to influence the therapeutic efficacy of these agents is the method of administration. Intraocular use of chymotrypsin (Alpha-Chymar) to facilitate dissection of the lens zonule in intracapsular cataract has been accepted on the basis of considerable experimental and clinical evidence (New Drugs, 1967). Topical use of streptokinase-streptodornase (Varidase), fibrinolysin-deoxyribonuclease (Elase), trypsin-chymotrypsin (Biozyme, Armour) and trypsin (Tryptar, Armour) as debriding agents for removing clotted blood or fibrinous or purulent accumulations present after trauma or inflammation appears to be effective. The above commercial preparations seem to be useful as adjuncts in treating haemothorax, empyema, infected wounds or ulcers and other common supplicative lesions if applied properly.

The value of oral,* buccal and intramuscular administration of these products has not been fully accepted. Since their introduction into therapy, the non-topical dosage forms have been the subject of much controversy. Clinical trials substantiating their efficacy are consistently disputed by numerous clinicians, which may be due in part to difficulties in assessing and quantifying the effectiveness of these enzymes' action. There is no precise method of measuring a given amount of inflammation and oedema. Therefore, most clinical trials have relied on investigators' subjective interpretations of results. Contributing further to this question of efficacy is the absence of evidence showing that enzymes are delivered intact by the circulation to the inflamed area, not having been previously affected by the powerful anti-proteolytic activity of serum (Sherry & Fletcher, 1960).

The anti-proteolytic activity of serum was investigated by Grob (1943). Subsequently Tauber (1950) demonstrated a specific inhibition by serum of chymotrypsin. Silverman, Livingston & Lipshitz (1966) measured an increase in the serum's chymotrypsin-inhibiting ability after administration of chymotrypsin intramuscularly but these authors did not find such an elevation after oral administration. Such results suggest a lack of absorption of the oral form of chymotrypsin from the intestine.

Oral chymotrypsin (Avazyme) and trypsin-chymotrypsin combinations (Chymolase, Chymoral, Orenzyme) are marketed as enteric-coated tablets in order to prevent hydrolysis by gastric juice and to permit absorption from the intestine.

The stability of these enzymes in human intestinal juice has been investigated. Wohlman, Kabacoff & Avakian (1962) found that trypsin retained only 8% of its activity, while chymotrypsin retained as much as 63% after ½ hr of incubation in human intestinal juice. At the end of 2 hr 30% of the proteolytic activity of chymotrypsin still remained. Inasmuch as the trypsin-chymotrypsin preparations for oral use contain 68–84% trypsin and 16–23% chymotrypsin, possibly a preparation containing only chymotrypsin may be more efficacious.

Despite the apparently destructive properties of intestinal juice, other investigators have been able to substantiate the presence of enzymes in the circulation following oral administration. Various techniques of measurement were used. Ambrus, Lassman & DeMarchi (1967) substantiated the absorption of oral trypsin-chymotrypsin (Chymoral) by identifying shifts in blood esterase levels. Miller, Williard & Polachek (1960) confirmed the absorption of trypsin from the intestinal tract after labelling the enzyme with U. Miller & Opher (1964) demonstrated absorption of oral bromelains (Ananase) by these enzymes' ability to lyse casein in serum.

These studies demonstrate only that the enzyme or some derivative of it was absorbed. They do not demonstrate that the amount or the form of the absorbed enzyme was able to exhibit a significant proteolytic effect in traumatized areas.

**Clinical trials**

Numerous controlled double-blind studies are reported confirming the efficacy of the proteolytic enzymes. Boutselis & Sollars (1964) found that papain (Papase) increased the rate of resolution of swelling following perineal episiotomy. Zatuchni & Columbi (1967) found similar effects in post-partum patients with the use of bromelains (Ananase). Soule, Wasserman & Burstein (1966) found trypsin-chymotrypsin (Chymoral) effective in reducing oedema and ecchymosis in patients after mediolateral episiotomy. Favourable results with the use of proteolytic enzymes were also shown for other conditions such as sinusitis (Taub, 1967; Seltzer, 1967); certain oral surgery (Metro & Horton, 1965; Magnes, 1966); and surgical and accidental trauma of the face, head and neck (Lewis & Grossman, 1965); hand (Lie, Larsen & Posch, 1967); foot (Frank, 1965); and abdomen (Thorek & Pandit, 1964).

* Oral administration refers to preparations that are swallowed and does not include those intended for buccal administration.
Controlled double-blind trials showing no significant difference between enzymes and placebos have also been reported. Gylling et al. (1966) measured the effect of bromelains (Ananase) on post-operative oedema after plastic surgery, and could show no significant difference between the enzyme preparation and a placebo. Sherman & Ellison (1961) found that patients could not differentiate between trypsin-chymotrypsin (Orenzyme) and a placebo in relieving the pain of episiotomy. Huntsinger & Leberz (1966) found chymotrypsin (Avazyme) no different from a placebo in alleviating the pain, oedema and inflammation induced by episiotomy.

The conflicting results of these clinical trials are not entirely unexpected. Substantiating a clinical effect due to the proteolytic enzymes relies on the observers' subjective interpretation. A reliable means of measuring the clinical effects, if any, of the enzyme preparations remains to be developed and this seems to be the major obstacle to the acceptance of the efficacy of the enzymes. Sherry & Fletcher's 1960 statement concerning the clinical value of the enzymes still appears to be true, 'The evidence supporting the existence of an anti-inflammatory effect in man for such enzymes as trypsin, chymotrypsin and streptokinase ... is still unsatisfactory and ... the burden of responsibility for proving this effect remains upon those who advocate their use.'

Side-effects

The incidence of side-effects reported with the oral or buccal administration of proteolytic enzymes is remarkably low. They include gastro-intestinal upset (oral) or local tissue irritation (buccal) and mild allergic manifestations (rash, urticaria, itching). Intramuscular injection and directinstillation into closed body cavities may cause febrile reactions; anaphylactic reactions have been reported following intramuscular use.

References
