

Chapter 2

Therapeutic Enzymes Used for the Treatment of Cardiovascular Diseases and Coagulation Disorders

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ABSTRACT

The successful introduction of enzyme replacement therapy opened the way for the use of enzymes, first as crude preparations and later as highly purified enzymes for use in cardiovascular diseases, clotting disorders, etc. Elimination of blood clot is the key factor in thrombolytic therapy and fibrinolytic enzyme therapy can be practiced to remove the clot. Based on the mechanism of action, they are of two types of enzymes: plasminogen activators and plasmin-like enzymes. Plasma products are usually employed as a source of several enzymes used for the treatment of coagulation disorders. While these products have traditionally been purified from blood donations and obtained as foreign proteins obtained from heterogeneous sources, most are now produced by biotechnology. The therapeutic enzymes reviewed in this chapter are used for the treatment of cardiovascular diseases and hereditary diseases leading to coagulation disorders. Enzyme preparations obtained by direct fractionation from a naturally producing source and recombinant enzymes are considered in this chapter.

1. INTRODUCTION

The application of biotechnology to pharmaceutical research, development, and manufacturing is a growing field. Over the last decade, the need of the biopharmaceutical industry for novel, more potent and stable enzyme therapeutics, has increased exponentially.

Enzyme therapies contribute a prominent share in clinical practice these days. Unlike common medicinal products, which can temporarily solve the particular health problems, pharmaceutical enzymes address the underlying cause of health problem and the patient can achieve permanent relief. Enzymes

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can be thought of as protein molecules with a specific mission-to initiate and regulate countless biologic reactions in living organisms. Indeed, the main advantage of an enzyme drug is its specificity. Enzymes specifically bind to target molecules, which make enzymes stand out from any other class of drugs.

The successful introduction of enzyme replacement therapy (ERT) opened the way for the use of enzymes, first as crude topical and oral preparations with proteolytic and hydrolytic activity, and later as highly purified enzymes for use in cancer chemotherapy, metabolic deficiencies, cardiovascular diseases, clotting disorders, etc.

Development of enzyme therapeutics against cardiovascular diseases witnessed a tremendous explosion in the past four to five decades and resulted in the development of the first approved genetically engineered drug against cardiovascular diseases (Activase®) in 1989. Later, many recombinant cardiovascular drugs have been developed and approved for clinical application (Table 1).

Elimination of blood clot or thrombus is the key factor in thrombolytic therapy and fibrinolytic enzyme therapy can be practiced to remove or lyse the clot. Enzymes are used as thrombolytic agents for the treatment of myocardial infarction, thromboembolic strokes, or deep vein thrombosis. Enzymes like Streptokinase, Urokinase, Alteplase, Reteplase, etc are used in the treatment of thrombosis to restore perfusion of the affected tissue. Thrombolytic therapy using fibrinolytic enzyme has an advantage over classical treatments, as the enzymes could act upon the existing clot. Based on the mechanism of action they are of two types; plasminogen activators (e.g. tissue plasminogen activator (tPA) and Urokinase) and plasmin-like enzymes (e.g., Nattokinase and Lumbrokinase) (Table 1). The thrombolytic enzymes are mainly administered by injection or infusion, but some enzymes are used for systemic therapy after oral administration.

Plasma is usually employed as a source of several therapeutic enzymes particularly those used for the treatment of coagulation disorders. The use of whole blood for such purposes would be wasteful if the specific purified component required is already available. Furthermore, fractionation procedures used to produce specific purified blood products considerably reduce the risks of accidental transmission of disease from contaminated blood donations. Most such proteins have been commercially available for many years. While these products have traditionally been purified from blood donations and obtained as foreign proteins obtained from heterogeneous sources, most are now produced by recombinant DNA technology. Despite the advantages of recombinant coagulation factors only a few enzymes were approved by the Food and Drug Administration (FDA). Some adverse events associated with these enzyme drugs is the major setback for their development.

ERT are often complicated by immune responses to the therapeutic enzymes that may cause adverse clinical effects by neutralizing product activity, altering biodistribution and leading to rapid removal and inactivation of enzyme drugs. There may be also problems associated with severe hypersensitivity reactions and immunological reactions. It is for this reason that these enzyme products are administered to patients in very small dose to avoid possible side effects.

The therapeutic enzymes reviewed in this chapter are used for the treatment of cardiovascular diseases and hereditary diseases leading to coagulation disorders. They either have been employed as therapeutic agents in the past or are at a developmental or clinical trial stage as new therapeutics. Enzymes from venomous animals are also reviewed. Enzyme preparations obtained by direct extraction from a naturally producing source and recombinant enzymes are considered in this chapter. This chapter addresses also the issues facing development of ERT for the treatment of some hereditary disorders with inhibitory antibodies.

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