ORIGINAL ARTICLE

INTERNATIONAL JOURNAL OF PHARMACEUTICAL RESEARCH AND LIFE SCIENCES

Published by ScienzTech Publication Journal Home Page: www.scienztech.org/ijprls

Impact of Serratiopeptidase on Bleeding and Clotting Time at Therapeutic Dose

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Article History:

Received on: 02 Nov 2022
Revised on: 10 Dec 2022
Accepted on: 22 Dec 2022

Keywords:

Serratiopeptidase, Bleeding Time (BT), Clotting Time (CT), Fibrin, Fibrinolytic Activity, Proteolytic Activity

ABSTRACT

Serratiopeptidase is a proteolytic enzyme that was being used for decades as an anti-inflammatory agent. It was initially synthesized from the larval form of the silk moth. It is ubiquitously prescribed in combination with NSAIDs to relieve pain and inflammation. In addition to desired pharmacological activity, it has some other effects. One among which is fibrinolytic activity. Fibrin is an activated form of fibrinogen formed as a result of injury to mitigate the loss of blood. Inactive plasminogen activates plasmin which is a proteolytic enzyme. As its chemical nature, it solubilizes the fibrin at a specific time to prevent embolism. Serralysin being proteolytic in nature interacts with the fibrin and degrades it into degradation particles which lead to uncontrollable bleeding. This improves the chance of deviation in BT and CT in subjects from initial readings. This analytical study was conducted on 20 participants who are admitted to a public hospital with other ailments and their variations in BT and CT were recorded, analyzed, and represented in the form of charts.

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eISSN: 2321-4589

DOI: https://doi.org/10.26452/ijprls.v11i1.1460

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INTRODUCTION

Serratiopeptidase is also called Serrapeptidase, and Serralysin. This protein-breaking enzyme was 1^{st} isolated in the 1960s from non-pathogenic bacteria (Serratia marcescens) that lies in the intestine of silkworms. This enzyme allows the developing moth to dissolve its cocoon during the life process. Serratiopeptidase is synthesized by purifying Serratia E-15 culture which belongs to the Peptidase M10B family. Numerous strains are present currently, but mostly, E15 is used in the preparation process. The molecular weight ranges from 45000 to 60000 gm/mol. Maximum activity is present at 37^0 - 47^0C at pH 9. Above 57^0 C and in acidic pH, this enzyme gets degenerated [1].

Drug Information

Generic Name: Serratiopeptidase

Brand Name: Amidase, Tolpa

Category/Class: Proteolytic Enzymes

Indication: Inflammation, Pain

Mechanism of Action

Anti-Inflammatory

Cellular damage and inflammation increase concentrations of chemical mediators such as Histamine, Bradykinin, Prostaglandin, and Cytokinin as a defensive mechanism of the body. Even though acute inflammation is a defensive mechanism of the immune system against the infection, it may lead to chronic inflammation. Normal Non-steroidal Anti-Inflammatory Drugs are used to treat acute inflammation but in chronic inflammation steroids along with NSAIDs are prescribed. These steroids were replaced by enzyme-based drugs [2].

Serratiopeptidase binds to the alpha 2-macroglobulin in the blood which is produced by the liver (it prevents coagulation by inhibiting thrombin). Alpha 2-macroglobulin helps to mask serratiopeptidase antigenicity and slowly transfers to the site in inflammation. Serratiopeptidase hydrolyzes bradykinin, histamine, and other chemicals are the reason for swelling. It reduces edema and enhances micro-circulation.

Anti-Biofilm

Bacteria in the group unite and develops a protective shield around them. This biofilm acts as a barrier against antibiotics. This biofilm aids bacteria to multiply rapidly and cause infection. This drug inhibits biofilm formation. Research states that serratiopeptidase improves the efficacy of antibiotics in the treatment of staphylococcus aureus. In-vitro and pre-clinical studies have shown that antibiotics are more effective when combined with serratiopeptidase [3].

Fibrinolytic

Serratiopeptidase can break down an insoluble protein called fibrin. Fibrin is a long fibrous chain-like arranged protein in its inactive state called Fibrinogen. Fibrinogen is a soluble protein produced by the liver and found in blood plasma. When tissue damage results in bleeding. Fibrinogen gets converted to an activated form called fibrin at the site of injury by the thrombin activity. Serratiopeptidase also tears down dead or injured tissue, non-living tissues like mucous, plaques, and blood clots without causing any harm to the living cells. It can dissolve and reduce arterial plaques, fatty cholesterol, calcium, and other foreign protein substances from sticking to the walls of arteries. It might be beneficial in atherosclerosis [Figure 1, Figure 2].

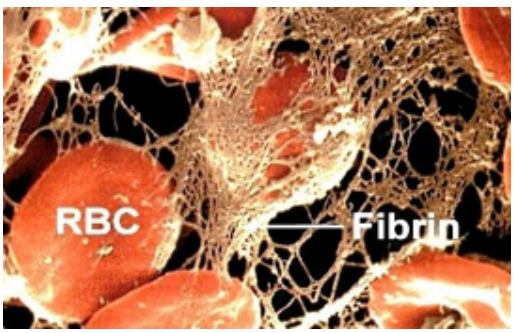

Figure 1: Fibrinolysis Mechanism

Pharmacokinetics

Absorption

Serratiopeptidase is orally absorbed and also dissolves in the intestines not in the stomach due to its acidic pH. So, the drug is enteric coated in preparation and is always found in combination with NSAIDs due to its anti-inflammatory property. It is also often combined with antibiotics to enhance the tissue penetration property.

Distribution

Through plasma and lymph.

Peak Plasma Concentration

15 to 30 minutes.

Duration of Action

6 hours.

Half-Life

1-4 hrs.

Contraindications

Pregnant and lactating women, and patients with bleeding disorders.

Dose

Normal adult dose of serratiopeptidase is 10mg 3 times a day. However, a dose of 15 mg is also accessible. Serrapeptidase is administered for a week to get desired anti-inflammatory effect. For mucolytic effect, it is prescribed for 2 weeks.

Fibrinolysis Mechanism

Fibrinogen was degraded to fibrinogen degradation products (FDPs) by plasmin. These FDPs again convert in thrombin when needed. Unstable fibrin also gets converted to degradation products called Fibrin degradation products. D-dimer is formed from stable fibrin. Tests for these degradation products reveal the fibrinolytic property of the test drug. The range of proportion of fibrinolytic activity of the test drug can be identified by the D-dimer test.

Background Information and Need for this Research

Publication in The Asian journal of pharmaceutical sciences by Manju Tiwari stated that “Serratiopeptidase is a natural molecule that is being used for decades, hence generally considered as safe. The safety of this enzyme in different areas of therapeutics was supported by several studies in which no side effects or adverse events were reported”. However, some studies have reported adverse effects of this molecule but at a rare frequency. An explanation of the same has been tried to provide in this study [4].

Another evidence-based study by Gavin Van De Walle shared that ”It’s thought to act by breaking down dead or damaged tissue by fibrin. This could enable serratiopeptidase to dissolve plaque in arteries or dissolve clots that may lead to stroke or heart

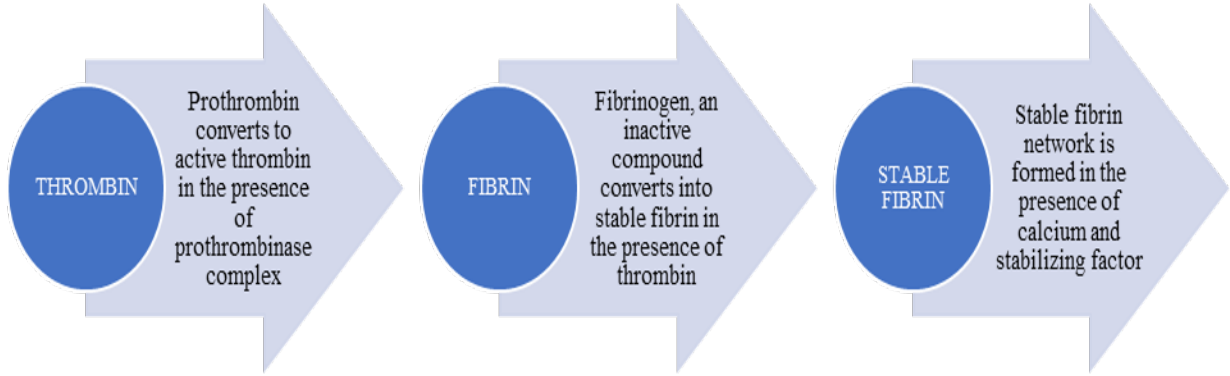

Figure 2: Blood Clotting Mechanism

attack." However, much information on its ability to dissolve clots is based on personal stories rather than facts. Therefore, detailed research is necessary to determine what role (if present) serratiopeptidase plays in treating clots [5].

About this Study

This study is needed to shed light on the fibrinolytic activity of serratiopeptidase. This study was conducted in individuals who were administered serratiopeptidase at least twice a day for three consecutive days and the range of difference in their bleeding and clotting time before and after the therapy were recorded and results were interpreted.

METHODOLOGY

Study Site

This study was conducted in the department of Orthopedics in the Government hospital, Chittoor.

Study Duration

3 Months.

Size

20 Patients of both genders.

Study Design

This is an Observational analytical study.

Study Materials

Patient case sheet, Researcher data collection form, lab reports.

Study Criteria

Inclusion Criteria

Patients above the age of 16 of both genders were included in the study.

Exclusion Criteria

Patients above the age of 80 and subjects with other comorbidities which would affect bleeding and clotting time were excluded.

RESULTS

85% subjects of the study turned out to be males and only 3 were females with ages ranging from 18 to 80 years. Where most of them are adults and middle age adults. Subjects' BT and CT were recorded before and post-therapy, and later results were compared.

There was a maximum inclined variation in bleeding and clotting time of 2 minutes and 3 minutes respectively in some patients. Surprisingly few subjects had their readings dropped to 30 seconds from the initial recordings in BT and 15 seconds in CT. Usually, BT and CT get affected by many factors. Hence, an accepted possible average deviation due to Serratiopeptidase on BT and CT is needed.

According to this study, there would be a possible variation of BT in an individual subject was nearly half a minute (28 sec) and almost a minute (57 sec) in CT after taking medication for 2 days [Figure 3, Figure 4 and Figure 5].

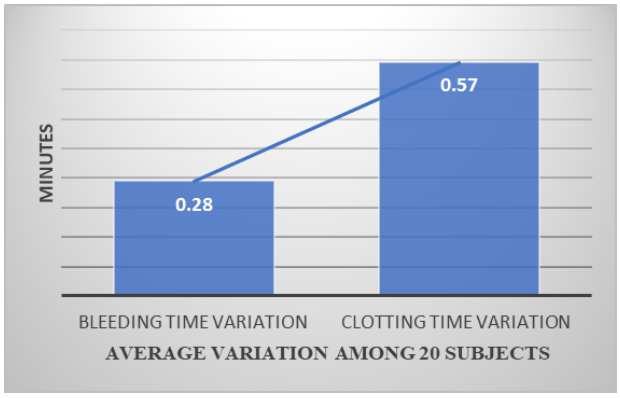

Figure 3: Impact of Serratiopeptidase After Therapy

Limitations

1. The results presented in this study were obtained by an Activated clotting time machine

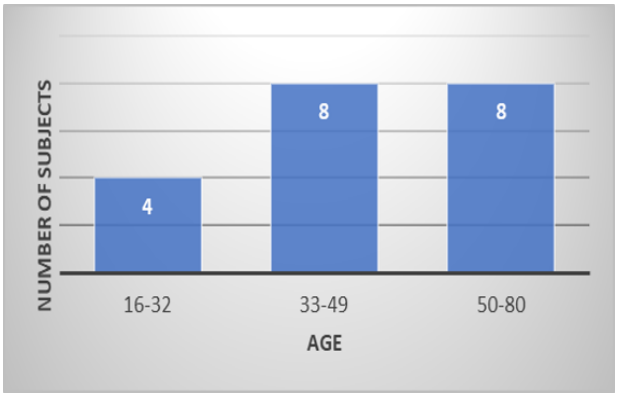

Figure 4: Age Chart

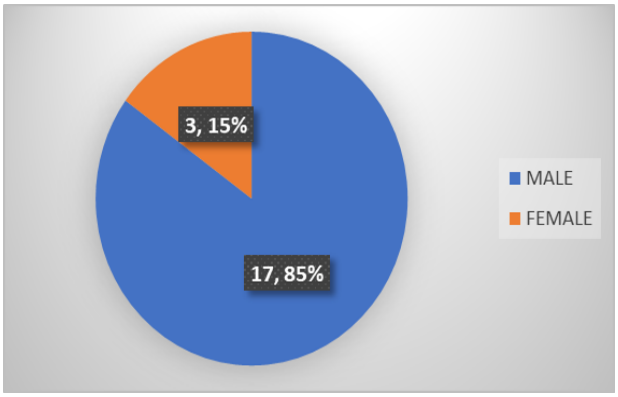

Figure 5: Gender Chart

at the research site. Results may differ with a different procedure like Duke, Ivy's Method.

2. Larger the sample size, the different the data.
3. Diet and other medications may also affect BT and CT.

CONCLUSION

This study was an attempt to estimate the fibrinolytic activity of the drug serratiopeptidase. Though there are different ways of estimating its proteolytic property like PT INR (Estimation of prothrombin time), this was a different kind of approach. 20 subjects with general ailments are admitted and their BT, and CT were compared before and post administration of SP. Serratiopeptidase was being used for decades thus, is considered to be safe. This trial is done to find out whether the changes in BT and CT were in the normal range or not. The normal range of bleeding time and clotting times are 2-7 min and 8-15 min respectively. All the subjects had altered timings, and most of them had increased in values as expected. Only a few showed a slight fall in findings. Although, the altered timings are within the normal range serratiopeptidase might still cause blood disorders in hyperlipidemic patients and exacerbates the patient's condition, when prescribed for a longer period.

Funding Support

The authors declare that they have no funding support for this study.

Conflict of Interest

The authors declare that there is no conflict of interest.

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Cite this article: Jothieswari D, Srihari M V, Karthik R, Praveen Kumar V, Sumit Giri. **Impact of Serratiopeptidase on Bleeding and Clotting Time at Therapeutic Dose**. Int. J Pharm. Res. Life Sci. 2023; 11(1): 1-4.