(12) PATENT
(19) AUSTRALIAN PATENT OFFICE

(11) Application No. AU 199530256 B2
(10) Patent No. 708409

(54) Title
Pharmaceutical which is suitable for employment as an antidote to blood anticoagulants, and its use

(51)[6] International Patent Classification(s)
A61K 038/36

(21) Application No: 199530256

(22) Application Date: 1995 .08 .24

(30) Priority Data

(31) Number	(32) Date	(33) Country
4430204	1994 .08 .26	DE

(43) Publication Date : 1996 .03 .07
(43) Publication Journal Date : 1996 .03 .07
(44) Accepted Journal Date : 1999 .08 .05

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(56) Related Art
DE 4203965
TABERNER DA ETAL., BRITISH MEDICAL JOURNAL 1976, 2, 83-85

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Abstract of the disclosure

Pharmaceutical which is suitable for employment as an antidote to blood anticoagulants, and its use

A pharmaceutical is disclosed which is used as an antidote to blood anticoagulants and which contains prothrombin.

P/00/011 28/5/91
Regulation 3.2(2)

AUSTRALIA

Patents Act 1990

ORIGINAL
COMPLETE SPECIFICATION
STANDARD PATENT

Application Number:

Lodged:

Invention Title: PHARMACEUTICAL WHICH IS SUITABLE FOR EMPLOYMENT AS AN ANTIDOTE TO BLOOD ANTICOAGULANTS, AND ITS USE

The following statement is a full description of this invention, including the best method of performing it known to us :-

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Pharmaceutical which is suitable for employment as an antidote to blood anticoagulants, and its use

The invention relates to an antidote to blood anticoagulants.

Blood coagulation is a complex process in which plasma proteins and cells are involved. Formation of a wound closure is initiated by rapid adhesion of blood platelets to the damaged surfaces and by proteases and contact factors which are activated successively in a cascade-like reaction sequence. This course of events leads to the production of thrombin which, inter alia, catalyzes activation of fibrinogen to form fibrin.

Proteins such as factors VIII and V contribute, as accelerators, to the efficiency of this system. In addition to the protein C system, inhibitors of the proteases involved essentially regulate the coagulation processes in such a way that, while wound closure takes place, excessive reactions are avoided. Disturbance of this finely tuned equilibrium can lead to fibrin deposition or the formation of thromboses. As is known, the vessel occlusions which result from this are the cause of many pathophysiological processes such as cardiac infarction, in particular. This problem assumes particular importance in those patients who are subject to increased risk of thrombosis, which often represents a post-operative complication.

Various approaches are taken for preventing these pathophysiological processes. Thus, anticoagulants which intervene in different ways in the event of coagulation are often used in clinical practice to prevent the formation of a thrombus or else to support its dissolution (thrombolysis). In addition to reducing or preventing thrombocyte functions (aggregation, adhesion and

activation and the synthesis and secretion of activation products), inhibitors of participating coagulation proteases, in particular of the thromboplastin/factor VIIa complex, of factor Xa and, in particular, of thrombin (factor IIa) are being investigated and applied.

Hirudin, which was originally isolated from the salivary glands of the leech Hirudo medicinalis, is a particularly specific and potent inhibitor of thrombin. In the interim, a variety of different variants, analogs, fragments and mutants of hirudin have become known and are being investigated for their suitability. While hirudin is sulfated in its naturally occurring form, it has been observed that the advantageous biological activity is also retained in the non-sulfated form. As a consequence, hirudin or its derivatives can conveniently be prepared by means of genetic manipulation.

The blood anticoagulants also include heparin, and its fragments and variants, as well as synthetic inhibitors which inhibit the catalytic activity of thrombin and other coagulation proteases, for example factor Xa. These components can also be employed in the prophylaxis and/or therapy of thrombotic or pre-thrombotic complications. The search for ever more specific and potent anticoagulants and antithrombotic agents reflects the unsatisfactory situation that the clinically established substances such as heparins or vitamin K antagonists are either insufficiently effective or else exhibit side effects which are undesirable and in some cases serious. Hirudin is currently the most powerful known thrombin inhibitor which does not also interfere with the other enzymes of the blood coagulation cascade. To date, hirudin has not been observed to have any appreciable side effects on pulse rate, respiration, blood pressure, thrombocyte count or the content of fibrinogen or hemoglobin. For this reason, hirudin is a preferred blood anticoagulant.

The use of anticoagulants or antithrombotic agents in a patient naturally entails the risk of increasing the tendency to bleed which, in extreme situations, for example in association with improper use or dosing, can lead to uncontrolled hemorrhages. In order to be able to counteract the undesirable tendency to bleed in such a situation, it is possible rapidly to remove some substances, whose constitution (molecular weight and structure) permits it, from the blood plasma of the patient by dialysis. However when this is not possible due to the lack of appropriate apparatus or for other reasons, an antidote must be made available.

Some substances or preparations have already been proposed as antidotes. Thus, the thrombins and their blocked variants exhibit a certain hirudin-neutralizing effect; however, on the one hand, the use of active thrombin in patients who are being treated with blood anticoagulants is contraindicated as a rule and, on the other, it is problematic to prepare inactive thrombin using low molecular weight inhibitors which enter into covalent bonds, owing to the toxicity of these substances. In addition, there is a lack of experience with regard to whether these complexes possibly have an antigenic effect. Owing to their nature, these complexes are not suitable for neutralizing low molecular weight (synthetic) antithrombins or antithrombotic agents. While meizothrombin, an intermediate which arises briefly when prothrombin is activated to form thrombin, possesses a certain antagonistic potency, it can transform rapidly into thrombin in vivo and, as such, is contraindicated as a rule.

Investigation of factor VII as a hirudin antidote in appropriate models failed to provide satisfactory results. European Patent Application EPA 89.810733.9 describes the use of factor VIII, or fragments of factor VIII, as antidotes to blood anticoagulants. It is also known that substances, such as, for example, desmopressin

(Mannucci, P.M., Progress in Haemostasis and Thrombosis, 8 (1986), pp. 19-45), can be used which increase the concentration of factor VIII in the blood.

However, since even these antidotes are not adequate for all areas of application, there is still the need to make available antidotes to blood anticoagulants, antithrombotic agents and platelet antagonists which are more effective and have fewer side effects.

Within the scope of the present application, anticoagulatory or antithrombotic substances are understood to mean glycosaminoglycans and sulfated polysaccharides, including heparins, in particular unfractionated and low molecular weight (LMW) pentosan polysulfate, heparan sulfate, dermatan sulfate or chondroitin sulfate, and also hirudins and their fragments, for example hirugen (J. Biol. Chem. 265 (1990), 13484-13487; EP-A-0 333 356), analogs or mutants, for example Hirulog® (WO 92/13952), coupled hirudins, for example PEG-hirudin or hirutonins, natural or synthetic inhibitors of the thromboplastin/factor VIIa complex, of factor Xa or of thrombin, components of the protein C system, namely activated protein C, protein S and thrombomodulin, inhibitors of fibrin aggregation or crosslinking, substances from the vitamin K antagonist group, substances which have an effect on platelet activation and/or platelet aggregation or else platelet adhesion, such as, in particular, fibrinogen receptor antagonists, or which are able to increase the endogenous capacity for fibrinolysis, such as, in particular, PAI-1 inhibitors, or stimulators of the synthesis and secretion of plasminogen activator inhibitors, and thus have an indirect antithrombotic effect.

It is particularly important to provide a suitable antidote to the said coupled hirudins, for example PEG-hirudin, since these coupled hirudins can only be removed from the organism with difficulty.

It has been found, surprisingly, that prothrombin (factor II) is highly effective as an antidote to blood anticoagulants.

The present invention therefore relates to a pharmaceutical which contains prothrombin for antagonizing blood anticoagulants, it being possible for these blood anticoagulants to be selected from the group consisting of glycosaminoglycans and sulfated polysaccharides, and also hirudins, and their fragments, analogs or mutants, natural and synthetic inhibitors of the thromboplastin/factor VIIa complex, of factor Xa or of thrombin, components of the protein C system, namely activated protein C, protein S and thrombomodulin, inhibitors of fibrin aggregation or crosslinking, substances from the vitamin K antagonist group, substances which have an effect on platelet activation and/or platelet aggregation and also platelet adhesion, such as, in particular, fibrinogen receptor antagonists, or which are able to increase the endogenous capacity for fibrinolysis, such as, in particular, PAI-1 inhibitors or stimulators of the synthesis and secretion of plasminogen activator inhibitors.

Within the scope of the present invention, prothrombin is also understood to mean active fragments or variants which can be prepared conventionally or, in particular, by genetic manipulation.

In the pharmaceutical according to the invention, prothrombin is employed in a concentration of from 1 to 2000 international units (IU) per kilogram of the bodyweight of the patient to be treated, with concentrations of from 10 to 1000 IU/kg being particularly preferred.

The invention also relates to the use of prothrombin as an antidote to blood anticoagulants.

The invention furthermore relates to a process for preparing a pharmaceutical which contains prothrombin for antagonizing blood anticoagulants.

The present invention is illustrated further by the following example.

Example

Standard human plasma (SHP) to which 20 µg/ml hirudin were added was investigated in the aPTT test for the antagonizing effect of prothrombin (F II). The coagulation times shown in the table verify the effectiveness of prothrombin.

Table

	aPTT (sec)
Control	>2000.0
2 IU factor II	258.7
2 IU factor V	>2000.0
2 IU factor VII	>2000.0
2 IU factor VIII	>2000.0
2 IU factor IX	>2000.0
2 IU factor X	>2000.0

THE CLAIMS DEFINING THE INVENTION ARE AS FOLLOWS:

1. Use of prothrombin FII in the absence of other coagulation factors for the preparation of a pharmaceutical for antagonising blood anticoagulants.

2. The use as claimed in claim 1 wherein the prothrombin FII is present in a concentration of from 1 to 2000 international units (iu) per kilo of the bodyweight of a patient to be treated with said pharmaceutical.

3. The use as claimed in claim 1 or 2 wherein the prothrombin FII is present in a concentration of from 10 to 1000 iu/kg of the bodyweight of a patient to be treated with said pharmaceutical.

4. The use as claimed in claim 1 wherein the prothrombin FII is produced by genetic manipulation.

5. The use as claimed in claim 1 wherein the blood anticoagulant is hirudin, an analogue, mutant or derivative thereof.

6. A method for treatment of blood anticoagulation in a patient requiring an anticoagulation antidote, including administering to said patient an effective amount of prothrombin FII in the absence of any other coagulation factor.

7. A method as claimed in claim 6 wherein the prothrombin FII is administered in an amount of 1 to 2000 international units (iu) per kilo of the bodyweight of said patient.

8. A method as claimed in claim 6 or 7 wherein the prothrombin FII is administered in an amount of 10 to 1000 international units (iu) per kilo of the bodyweight of said patient.

9. A method as claimed in claim 6 wherein the prothrombin FII is produced by genetic manipulation.

10. A method as claimed in claim 6 wherein the blood anticoagulant is hirudin, an analogue, mutant or derivative thereof.

DATED this 11 day of June, 1999.
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