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Transfusion and Apheresis Science 34 (2006) 193–198
TRANSFUSION AND APHERESIS SCIENCE
intl.elsevierhealth.com/journals/tras

The effect of cromoglycate on time-dependent histamine and serotonin concentrations in stored blood products

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Received 4 November 2005; received in revised form 5 December 2005; accepted 15 December 2005

Abstract

Biogenic amines, having vascular and inflammatory effects, are accepted as a potential threat for some non-hemolytic transfusion reactions. The aim of this study was to investigate time-dependent histamine/serotonin levels in stored blood products and to see whether cromoglycate has any effect on these mediators. Either for platelet or whole blood, 10-fold concentrations of cromoglycate (1 μg ml^{-1}, 10 μg ml^{-1}, 100 μg ml^{-1}) with controls prepared as pairs of replicate bags collected from two healthy subjects, separately. By using enzyme immunoassay, histamine and serotonin levels were determined in platelet or blood replicates. Histamine levels increased significantly with time but serotonin remained unchanged during the storage of platelet or blood specimens. Cromoglycate had no effect on these biogenic amines except an increase of serotonin in whole blood specimens containing 100 μg ml^{-1} of it. So, cromoglycate cannot protect blood products against rising levels of histamine or serotonin.

Keywords: Histamine release; Serotonin release; Whole blood; Platelet suspension; Cromoglycate

1. Introduction

Cromoglycate, formerly introduced as "mast cell stabilizing agent", is used mainly in the topical treatment of atopic allergies. Although, its mechanism of action is not known, subsequent investigations showed that this medication had effect on other blood cells, also. Besides the prevention of mediator release from mast cells or basophils [1], it suppresses the activating effects of the chemotactic peptides on human neutrophils, eosinophils, monocytes [2] and inhibits leukocyte trafficking in the mucosal immune system with decreased expression of adhesion molecules [3].

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doi:10.1016/j.transci.2005.12.001

Histamine and serotonin, two of the biogenic amines, have well-known vascular, inflammatory effects. Histamine is synthesized and stored in the granules of mast cells or basophil leukocytes which are the basic reservoir of this pre-formed mediator responsible for the early phase of anaphylactic type hypersensitivity responses. In contrast to some other animal species, serotonin, a neurotransmitter substance found in synapses, is not synthesized by mast cells or basophils in humans and stored in the dens bodies of platelets simply uptaking it from plasma. Time-dependent increases of these mediators were reported due to the storage of blood products [4,5] and incriminated as potential factors responsible for some non-hemolytic transfusion reactions [6–8]. In particular, it was found that patients, who developed reactions which were not accompanied by a change in body temperature, received units with a longer storage time than patients experiencing febrile reactions; in addition, plasma histamine levels of subjects experiencing "anaphylactoid" reactions were higher than those of subjects with febrile or mixed reactions [9].

In this study, considering the junctional role of autacoids in the genesis of anaphylactic and inflammatory responses, we aimed to investigate (1) time-dependent histamine and serotonin concentrations in stored blood products kept in standard conditions used in blood banking practice and (2) if cromoglycate had any effect in inhibiting the release of histamine or serotonin during storage time that might have led to the prevention of some non-hemolytic transfusion reactions. For these purposes, we chose whole blood and platelet suspension as study materials, because, former contains basophils as a source of histamine and latter contains white blood cell-reduced platelets as a reservoir of serotonin.

2. Materials and methods

2.1. Materials

Four healthy individuals were included in the study. By taking their written consent, two of the subjects donated 2 bags of platelet concentrates by apheresis and the other two gave 2 packs of whole blood, 300 ml in each. Platelet concentrates were collected into a closed system apheresis kit (Fresenius HemoCare, Germany) by adjusting the yield of the apparatus (Fresenius AS.TEC 204) to $3.3 \times 10^{11}\,L^{-1}$ so as to achieve a relatively constant concentration in each individual collection. In a second step, every pack of platelet suspensions partitioned into 4 empty bags (PL732, Baxter) equally in aseptic conditions to contain 73 ml in each and labeled as indicated in Table 1. These final 8 working bags were kept in an agitator (Helmer PFS42) at 22 °C in a platelet incubator (Helmer PC900) for 8 days during which time 1 ml samples were taken at 0, 2, 4, 6, 8th days and cultured for bacterial contamination at the end by using BACTEC 9120 system media. Whole blood donated by the other two subjects was collected into 2 separate CPDA-1 bags containing 63 ml of additives[1] and distributed into 4 transfer bags equally to obtain 8 working bags of 73 ml, as described for platelet suspensions above. Eight working bags of whole blood were labeled and stored at 4 °C in a refrigerator (Electrolux MRB1200) for a period of 40 days during which time 1 ml samples were taken at 0, 8, 16, 24, 32, 40th days and cultured for bacterial contamination at the end by using BACTEC 9120 system media.

We prepared a stock and two successive 10-fold dilutions ($37.5\,mg\,ml^{-1}$, $3.75\,mg\,ml^{-1}$, $0.375\,mg\,ml^{-1}$) of sterile cromoglycate solution in buffered saline from a powder (Sigma, product nr: C0399). Two milliliters of these solutions were added to platelet concentrates and whole blood specimens labeled C, B, A in the same order to obtain concentrations of $1\,\mu g\,ml^{-1}$ in all A-labelled bags, $10\,\mu g\,ml^{-1}$ in all B-labelled bags and $100\,\mu g\,ml^{-1}$ in all C-labelled bags. Two milliliters of sterile buffered saline were added to the bags labelled as "control". Some important individual characteristics of the subjects and outline of the study design are shown in Table 1.

[1] 0.299 g citric acid anhydride, 2.63 g natrium citrate dihydrate, 0.222 g natrium dihydrogen phosphate monohydrate, 3.19 g dextrose monohydrate, 0.035 g adenine hydrochloride, ad 100 ml distilled water.