Hydroxyethyl Starch

A Current Overview

Editors
P. Lawin, J. Zander and B. Weidler

Contributors

K. van Ackern
M. Albrecht
M. E. Astiz
R. Bach
L. Bette
G. L. Blackburn
J. Boldt
U. B. Brückner
J. Dyckmans
S. Erlenwein
J. Falk
H. Förster
M. Georgieff
M. I. Griffel
A. Grünert
A. Haaß
H. Hahmann
G. Hempelmann
F. Jung
G. Kalff
H. Kiesewetter
H. Köhler
W. Kolepke
J. Koscielny
C. E. Mecher
H.-H. Mehrkens
D. R. Morel
V. K. Puri
E. C. Rackow
P. Satwitz
P. Scheffler
H. Schieffer
W. Schleinzer
K. Sommermeyer
P. M. Suter
W. Vogel
D. Wagner
B. Weidler
M. H. Weil
E. Wenzel
R. Zander

Georg Thieme Verlag
Stuttgart · New York

Thieme Medical Publishers, Inc.
New York

Hydroxyethyl Starch:
A Current Overview

Editors
P. Lawin, J. Zander and B. Weidler

Contributors

K. van Ackern
M. Albrecht
M. E. Astiz
R. Bach
L. Bette
G. L. Blackburn
J. Boldt
U. B. Brückner
J. Dyckmans
S. Erlenwein
J. Falk
H. Förster
M. Georgieff
M. I. Griffel
A. Grünert
A. Haaß
H. Hahmann
G. Hempelmann
F. Jung
G. Kalff
H. Kiesewetter
H. Köhler
W. Kolepke
J. Koscielny
C. E. Mecher
H.-H. Mehrkens
D. R. Morel
V. K. Puri
E. C. Rackow
P. Satwitz
P. Scheffler
H. Schieffer
W. Schleinzer
K. Sommermeyer
P. M. Suter
W. Vogel
D. Wagner
B. Weidler
M. H. Weil
E. Wenzel
R. Zander

101 illustrations and 36 tables

Translated by Alan Ladak

1992
Georg Thieme Verlag
Stuttgart · New York

Thieme Medical Publishers, Inc.
New York

Library of Congress Cataloging-in-Publication Data

Hydroxyethylstärke. English.
Hydroxyethyl starch: a current overview / editors, P. Lawin, J. Zander, and B. Weidler; contributors, K. van Ackern ... [et al.]; translated by Alan Ladak.
p. cm.
Translation of: Hydroxyethylstärke.
Includes bibliographical references and index.
1. Hydroxyethyl starch. 2. Blood plasma substitutes.
I. Lawin, Peter. II. Zander, J. III. Weidler. B. IV. Title.
[DNLM: 1. Hydroxyethyl Starch--pharmacology. 2. Hydroxyethyl Starch--therapeutic use WH 450 H 995]
RM 171.7H8313 1992
615' .39--dc20
DNLM/DLC
for library of congress 92-445
CIP

This book is an authorized translation of the Germand edition published and copyrighted 1989 by Georg Thieme Verlag. Stuttgart, Germany.
Title of the German edition: Hydroxyethylstärke: eine aktuelle Übersicht.

Printed in Germany by Gutmann + Co., Heilbronn

ISBN 3-13-780401-9 (GTV, Stuttgart)
ISBN 0-86577-448-X (TMP. New York) 1 2 3 4 5 6

Hydroxyethyl Starch:
A Current Overview

In memory of Else Kröner

This publication has been made possible by a generous grant from Fresenius AG, Bad Homburg, Germany.

Preface

The present discussion of current approaches to the use of plasma expanders and to the questions that remain as yet unanswered in this field is a stimulating one. The focal point of the discussion is hydroxyethyl starch, but it also embraces the various other plasma substitutes. There are a number of questions: why are three different groups of substances still in clinical use? Does any single one of them really have advantages over the others? The fundamental question is actually whether we need plasma expanders at all, and if so, what the indications are for using them.

In addition to the question of indications, there are also questions concerning contraindications. Is using crystalline solutions not actually more physiological? Can better results in terms of macrohemodynamics and microcirculation be achieved using crystalline solutions than with colloid solutions?

The answers to these questions are bound to derive from considerations of physiology and pharmacology. The former can provide information on changes in microcirculation, and the latter supplies information on the pharmacokinetics of various substances, above all on their metabolism.

From a clinical viewpoint, the efficacy of the various substrates need to be assessed in relation to various indications, e.g., in vascular disease, in plasma substitution in cases of acute blood loss during surgery or after trauma, or in central nervous system disease resulting from perfusion disturbances. In addition, hemodilution is assuming an increasingly important role in reducing the number of homologous blood donations that are required, and both the quality and the quantity of plasma expanders are under discussion.

It is therefore to be welcomed that respected contributors from the theoretical and clinical spheres have provided here a survey of the current state of knowledge, offering fresh stimulation for future research and clinical applications.

Our special thanks are due to Fresenius Ltd. for their support, and especially to Dr. Weidler, whose input played a decisive role in the preparation of this workshop.

Münster, Winter 1992 *P. Lawin, J. Zander*

Editors

Prof. P. Lawin, M.D.
Director
Clinic and Polyclinic for Anesthesiology and Surgical Intensive-Care Medicine
Westfälische Wilhelms-Universität
Münster
Albert-Schweitzer-Strasse 33
4400 Münster
Germany

Prof. B. Weidler, M.D.
Dept. of Research and Development
Fresenius AG
6380 Bad Homburg
Germany

J. Zander, M.D.
Senior Physician
Clinic and Polyclinic for Anesthesiology and Surgical Intensive-Care Medicine
Westfälische Wilhelms-Universität
Münster
Albert-Schweitzer-Strasse 33
4400 Münster
Germany

Contributors Addresses

M. Albrecht, M.D.
Institute of Anesthesiology
University of Lübeck
Ratzeburger Allee 160
2400 Lübeck
Germany

J. Boldt, M.D., D.Habil.
Dept. of Anesthesiology and
Surgical Intensive-Care Medicine
Justus-Liebig-Universität
Klinikstrasse 29
6300 Giessen
Germany

S. Erlenwein, M.D.
Dept. of Clinical Anesthesiology
and Transfusion Medicine
University of the Saarland
6650 Homburg/Saar
Germany

Prof. H. Förster, M.D.
Dept. of Experimental Anesthesiology
Johann-Wolfgang-Goethe-Universität
Ludwig-Rehn-Strasse
6000 Frankfurt on Main
Germany

M. Georgieff, M.D.
Dept. of Anesthesia
Harvard Medical School
Massachusetts General Hospital
Boston, MA
USA

Prof. A. Grünert, M.D.
Dept. of Experimental Anesthesia
Anesthesiology Clinic
University of Ulm
Oberer Eselsberg 23
7900 Ulm
Germany

Prof. A. Haaß, M.D.
University Neurology Clinic
University of the Saarland
6650 Homburg/Saar
Germany

F. Jung, M.D.
Dept. of Clinical Anesthesiology
and Transfusion Medicine
University of the Saarland
6650 Homburg/Saar
Germany

Prof. G. Kalff, M.D.
Dept. of Anesthesiology
Medical Faculty
Rheinisch-Westfälische
Technische Hochschule
Goethestrasse 27-29
5100 Aachen
Germany

H. Kiesewetter, M.D., D.Habil.
Dept. of Clinical Anesthesiology
and Transfusion Medicine
University of the Saarland
6650 Homburg/Saar
Germany

Prof. H. Köhler, M.D.
Medical Clinic I and Polyclinic
Johannes-Gutenberg-Universität
Langenbeckstrasse 1
6500 Mainz
Germany

Prof. P. Lawin, M.D
Director
Clinic and Polyclinic
for Anesthesiology and
Surgical Intensive-Care Medicine
Westfälische Wilhelms-Universität
Münster
Albert-Schweitzer-Strasse 33
4400 Münster
Germany

C.E. Mecher, M.D.
Depts. of Medicine and Surgery
University of Health Sciences
Chicago Medical School
North Chicago, IL
USA

Prof. H.-H. Mehrkens, M.D.
Senior Consultant
Rehabilitation Hospital
Oberer Eselsberg 45
7900 Ulm
Germany

V.K. Puri, M.D.
Critical Care Center
Mount Carmel Mercy Hospital
6071 W. Outer Drive
Detroit, MI 48235
USA

K. Sommermeyer, M.D.
Dept. of Chemical and
Pharmaceutical Research and
Development
Fresenius AG
Borkenberg 14
6370 Oberursel
Germany

Prof. P.M. Suter, M.D.
Soins Intensifs Chirurgicaux
Hôpital Cantonal Universitaire
1211 Geneva 4
Switzerland

Prof. B. Weidler, M.D.
Dept. of Research and Development
Fresenius AG
6380 Bad Homburg
Germany

J. Zander, M.D.
Senior Physician
Clinic and Polyclinic for Anesthesiology
and Surgical Intensive-Care Medicine
Westfälische Wilhelms-Universität
Münster
Albert-Schweitzer-Strasse 33
4400 Münster
Germany

Contents

New developments in the physicochemical characterization of hydroxyethyl starch

K. Sommermeyer

Introduction

If one were to compile a list of the specific physicochemical properties of hydroxyethyl starch (HES) that are essential to give a clear and complete picture of the molecule, they would be as follows:

1. Molecular weight distribution or average molecular weights.
2. Chain length distribution / degree of branching or average chain length.
3. Substitution pattern or degree of substitution.
4. Substitution sequence.

On the one hand, these values determine how easily the molecule is eliminated by the kidneys, by providing information on the average shape and size of the molecules and their solvation state, i.e., how many water molecules are bound to hydroxyethyl starch in different ways (Fig. 1). On the other hand, susceptibility to degradation by α-amylase will also vary with the above characteristics.

Renal elimination and degradation are the main parameters which have an influence on the pharmacokinetics of HES. In addition, it is possible that one of the above-mentioned

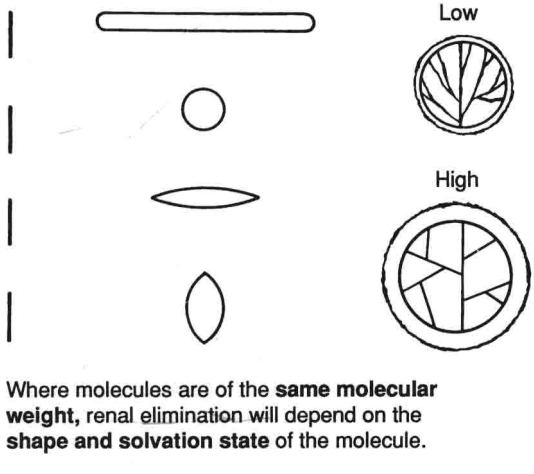

Fig. 1 Renal elimination as a function of the shape and solvation of the molecule

characteristics plays a decisive role in the interim storage of HES in tissue [1]. These characteristics therefore need to be studied and turned into measured and known parameters for clinical applications of hydroxyethyl starch.

I shall report here on the current state of methodology in achieving these aims.

Structure of amylopectin, degree of substitution, and substitution pattern for hydroxyethyl starch species

Hydroxyethyl starch is the hydroxyethyl derivative of degraded amylopectin. Although the branched structure of amylopectin has long been known, the exact architecture is still the subject of research. Figure **2** shows three different models that were proposed during the 1940s. They differ from each other in the branching order of the linear chains, consisting of glucose groups connected by α-1,4-glycosidic bonds. There are α-1,6-glycosidic bonds at the sites of branching. The chains that bear the sole reducing end group of the entire molecule are classed as C-chains [2]. A-chains do not carry any further branching sites. All other chains are described as B-chains.

Model 3 is currently considered the most likely model. Details of the structure have been elucidated by applying enzymatic degradation methods and chromatographic separation

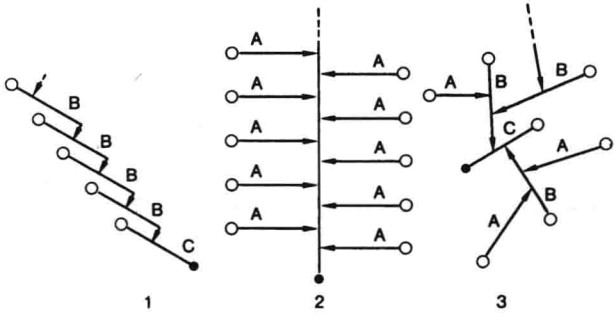

Fig. **2** Three different proposed structures for amylopectin
○ = Terminal, non-reducing end group
● = Reducing end group
→ = α-D-(1→6) bond
— = A chain of 20 to 25 α-D-(1→4) bonded D-glucose molecules

methods to maize starch, which consists of 99% amylopectin and therefore forms the starting-point for the production of hydroxyethyl starch.

Figure **3** shows a more refined model, published in 1987, showing the average chain length, broken down into inner and outer, short and long A and B chains [3].

The scope of the present chapter does not permit any more detailed analysis of these results. The average chain length of 18.5 anhydroglucose units, 10.0 for the outer chain length

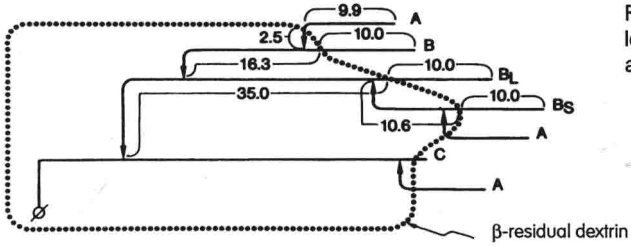

Fig. 3 Outer and inner chain length distribution of amylopectin

and 8.5 for the inner chain length, should be noted. More recent work has shown that the amylopectin molecule has regions with a very high degree of branching alongside almost linear chains (i.e., heterogeneous branching) [6].

The hydroxyethyl groups are more or less randomly distributed over the partially degraded amylopectin molecule. They may occupy positions 2, 3 and 6 of the anhydroglucose units (Fig. 4).

Substituting hydroxyethyl groups already introduced is equally possible. One relatively

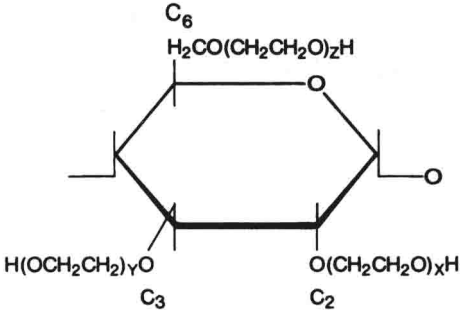

Fig. 4 An anhydroglucose unit with α-1,4-glycosidic bonding

simple way of recording and describing substitution by hydroxyethyl groups is to use the degrees of substitution DS and MS, while neglecting the recording and quantifying of individual substitution positions. MS (molar substitution) is defined as the average number of hydroxyethyl groups per anhydroglucose unit. It is therefore a statistical value, determined by the total number of hydroxyethyl groups in a sample, which is then applied to all anhydroglucose units present. By contrast, DS (degree of substitution) is defined as the ratio of substituted anhydroglucose units to the total number of anhydroglucose units, regardless of whether these are single or multiple substitutions. From these definitions it may be seen that MS > DS for polysubstitution. Where there is only monosubstitution, i.e., each substituted anhydroglucose unit carries only one hydroxyethyl group, then MS = DS.

Far more informative than the MS and DS data is the substitution pattern, i.e., the recording of individual, variously substituted anhydroglucoses, randomly distributed over individual polymer molecules.

These include the monosubstituted units 2-0- or 3-0- and 6-0-hydroxyethyl