Nitrate Therapy
& Nitrate Tolerance

Current Concepts and Controversies

Editors Dženan E. Rezaković, Zagreb

78 figures and 45 tables, 1993

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The structure of the nitroglycerin molecule shown on the cover was produced with the aid of the computer program SYBYL from Tripus Inc., USA, using the coordinates published by Espenbetov AA, Filippov VA, Antipin MY, Tsirelson VG, Struchkov YT and Svetlov BS in Izv Akad Nauk SSSR, Ser Khim (7), 1985:1558-1563.

Library of Congress Cataloging-in-Publication Data
Nitrate therapy and nitrate tolerance: current concepts and controversies / editors, Dženan Rezaković, Joseph S. Alpert.
Includes bibliographical references and index, (alk. paper)
1. Nitrates - Therapeutic use. 2. Cardiovascular system - Diseases - Chemotherapy.
5. Nitroglycerin - pharmacology. QV 156 N7314]
RC684.N56N55 1993
Drug Dosage
The authors and the publisher have exerted every effort to ensure that drug selection and dosage set forth in this text are in accord with current recommendations and practice at the time of publication. However, in view of ongoing research, changes in government regulations, and the constant flow of information relating to drug therapy and drug reactions, the reader is urged to check the package insert for each drug for any change in indications and dosage and for added warnings and precautions. This is particularly important when the recommended agent is a new and/or infrequently employed drug.

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Printed in Slovenia on acid-free paper by DAN Printing House, Ljubljana
ISBN 3-8055-5669-1

To all friends and colleagues,
to my daughter Saida and my parents
who have fostered the vision of this book through these hard times.

Dž
enana E. Rezakovi

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Rezakovi
Nitroglycerin has been the oldest known therapy for angina pectoris. Different nitrate compounds have been developed and widely used in the treatment of stable and unstable angina pectoris, acute myocardial infarction and heart failure. At the same time, nitrates have been a source of numerous controversies related to their real efficacy and the mode of administration.

The goal of this book was to present a comprehensive and up-to-date overview on all aspects of nitrate therapy in coronary artery disease as well as proposing a spectrum of opinions on real clinical importance of the nitrate tolerance problem, potential solutions and scientific perspectives for the future.

This complex topic is discussed in all its aspects, strictly scientific and practical clinical issues: pharmacology and mechanisms of action of different nitrate compounds and formulations; different therapeutic indications, clinical results and the effects on mortality; pharmacokinetics of new transdermal systems of nitrate delivery, the results of clinical and multicenter studies and its consequences on the use of nitrates in general.

Finally, based on experimental and clinical results, pharmacological actions and the effects on patients’ symptoms and quality of life, the controversies on nitrate tolerance are discussed. We asked the cardiologists with differing opinions to comment on the problem of the nitrate tolerance. The authors, all outstanding and experienced investigators and clinicians, presented all aspects of the multifactorial nature of the nitrate tolerance phenomenon, its heterogeneity in the appearance in different patient subsets as well as in individual patients.
Different strategies of nitrate administration and solutions for tolerance problem are discussed. We hope that this book will offer a comprehensive documentation about facts, experiences and controversies in nitrate therapy and nitrate tolerance, moreover, we believe that various opinions expressed by the international group of authors will lead to further understanding and discussion of complex aspects of the nitrate therapy.

Preface X

This book would not be possible without the dedicated support and helpful advice of the outstanding cardiologist and experienced investigator, the late Prof. Dr. Jan J. Kellermann, one of Karger’s editors, who generously participated in the creation of the first visions about this book. Finally, the book would not have been written without the work and cooperation of cardiologists and scientists from Europe, Australia, Israel and the USA who promptly and generously responded to the challenges of this important and complex topic.

Dženana E. Rezakovi

Joseph S. Alpert

Some Thoughts on the Birth of a Book

Several years ago I was contacted by Dr. Dženana Rezakovi to contribute a chapter to a very ambitious project - a book that would comprehensively review nitroglycerin and nitrate therapy. This exciting prospect was particularly remarkable because it was directed by a woman cardiologist from the former Yugoslavia who wished to involve many of the world’s experts in nitrate therapy for this project. As time passed, and the beginning of the war and the unravelling of the country took place, I thought more and more about this endeavor. How could someone continue on with such a venture in the midst of destruction, chaos, and tragedy? Furthermore, Dr. Rezakovi became involved in peace and humanitarian actions all over the world as the president of ‘Croatian Physicians for Peace’. It was her personal effort to be a positive force for peace in her homeland, Croatia and Bosnia-Herzegovina. In spite of extraordinary difficulties and great obstacles, she has brought the project to fruition. Like a long and difficult pregnancy, all is forgotten with the birth of a healthy infant.
Here, that baby is a successful book, written and edited during a gestation filled with adversity, and supported by perseverance, inner strength, strong conviction, and a sense of higher ideals. On behalf of all the other authors, I wish to congratulate Dr. Rezakovi and express our deep pleasure, respect and admiration for the privilege of being able to participate in such an effort.

Jonathan Abrams