MEDICAL TOXICOLOGY OF NATURAL SUBSTANCES

Foods, Fungi, Medicinal Herbs, Plants, and Venomous Animals

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Published by John Wiley & Sons, Inc., Hoboken, New Jersey
Published simultaneously in Canada

Library of Congress Cataloging-in-Publication Data:

Barceloux, Donald G.
Medical toxicology of natural substances : foods, fungi, medicinal herbs, plants, and venomous animals / Donald G. Barceloux.
p. ; cm.
Includes index.
ISBN 978-0-471-72761-3 (cloth)
1. Natural products–Toxicology. I. Title.
[DNLM: 1. Plants, Toxic. 2. Animals, Poisonous. 3. Food Poisoning. 4. Furgi. 5. Medicinal Herbs. WD 500 B242m 2008]
RA1211.B285 2008
615.9—dc22

2007051402

Printed in the United States of America

10 9 8 7 6 5 4 3 2 1

To my wife, Kimberly, your loving support and encouragement created the environment to write this book, and your patience allowed me to focus on this book away from what I enjoy most—being with you.

To my son, Colin, your computer expertise has been immensely helpful solving the technical issues in this book, and I admire the application of those skills to the development of your own company, Bookrenter.com.

To my daughter, Shannon, sharing your knowledge for the treatment of animals and your passion for becoming a veterinarian is a great joy for me.

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FOREWORD

Men and women live in a miraculous world, surrounded by natural beauty, diverse environmental conditions and habitats, and evolutionary marvels. Within this intricate assembly of flora and fauna, many plant and animals have evolved that are more than passive inhabitants of this planet. They are endowed with substances both offensive and defensive, namely, potent toxins capable of slowly poisoning or rapidly subduing very large animals, including humans. In addition, modern man utilizes plant and animal products and extracts for commercial, medical, religious, and other purposes. These exposures range from naturopathic cures to a casual encounters with cactus spines during a wilderness expedition, from a diver's encounters with the needles of sea urchins to covert politically motivated assassinations utilizing ricin from castor beans. Wild mushroom foragers grow old only if they are not too bold, while amateur aquarists who reach into their saltwater tanks learn about the toxicity under the cover of lionfish plumage.

We can never learn or know too much about how best to deal with natural toxins, whether we seek to eliminate them from our immediate food supply or treat acutely intoxicated victims. Furthermore, from the understanding of syndromes and therapies, we are offered insights into their possible therapeutic value. No matter what the ultimate fate of man, the seeds, spores, fangs, and venom glands will survive. While the relationship of toxins to humans may not be always be characterized as symbiotic, there will remain a coexistence that is predicted, yet always in part unpredictable.

The medical toxicology of natural substances is predicated upon their existence, which will diminish as humans continue to erode and consume their environment. Until then, we should continue to catalogue, record, evaluate, and teach. Medical practitioners and toxicologists should accept the responsibility to perpetuate these traditions because the wisdom of indigenous shamans is being lost as rapidly as the rainforests in which they reside.

What we do not seek to protect may soon disappear. It is my fervent wish that this book not only serve as a superb medical reference for those who seek to cure, but that all who read it are inspired to preserve the landscapes and seascapes that support the origination of everything that is natural and sustainable upon this Earth.

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PREFACE

Medical Toxicology of Natural Substances: Foods, Fungi, Medicinal Herbs, Plants, and Venomous Animals is designed to provide in-depth, evidence-based coverage of the most important natural toxins. This book is the first of a four volume series in Medical Toxicology, which will include drugs of abuse and psychoactive plants, occupational and environmental exposures, and pharmaceutical overdoses. Scientific knowledge in the field of Medical Toxicology increased considerably since I co-authored the First Edition of *Medical Toxicology: Diagnosis and Treatment of Human Poisoning* with the late Matthew J. Ellenhorn, published in 1988. That book was designed as an authoritative, concise volume for the immediate treatment of poisoning including natural toxins, pharmaceutical agents, and occupational exposures. In the last 20 years, sufficient interest has developed in natural toxins, food contamination, medicinal herbs, chronic occupational exposures, and bioterrorism to justify coverage of the field of Medical Toxicology by a book series rather than a single volume. *Medical Toxicology of Natural Substances: Foods, Fungi, Medicinal Herbs, Plants, and Venomous Animals* retains the consistent, formatted style I developed for the First Edition of *Medical Toxicology: Diagnosis and Treatment of Human Poisoning*. Once the reader is familiar with the templates used in my book series, the consistency of the organization allows the reader quickly to locate the appropriate information necessary for informed decisions regarding the sources, effect, regulation, recognition, and management of toxic exposures.

Conversions for length and temperature in metric and imperial systems are provided to ease the use of this book by an international readership, whereas the metric system for mass and concentrations are retained to limit any confusion about doses in the United States.

The following provides organizational details on the material under the headings for each toxin:

History provides interesting historical facts involving the use and recognized effects of the toxicity of natural substances.

Identifying Characteristics and **Botanical Descriptions** helps the reader identify the characteristics and geographic distribution of the specific toxin (e.g., venomous animal, toxic plant).

Exposure discusses the sources, uses, and regulation of exposures to these toxins.

Principal Toxins identifies the main toxins in the natural substances and provides data on the chemistry, structure, and physical properties of the toxin that are important for the reader's understanding of the clinical response to the toxin. This part discusses the basic science and the composition of the toxins along with factors that affect the delivery of the toxin including discussions of the venom apparatus and seasonal variation in the locations of the toxins. Additionally, this part covers the biochemical and pathophysiological basis for the toxic responses.

Dose Response covers data on the lethality and clinical effects of the toxin both in animals and in humans as well as factors that affect the potency of the toxin. The emphasis is on dose-related effects, but important adverse and idiosyncratic reactions are also discussed.

Toxicokinetics discusses the disposition of the principal toxins in the body including the distribution, absorption, and elimination of the principal toxins. The emphasis is on human data, but animal data may be included when human data are sparse.

Clinical Response provides data on the clinical features of poisoning following exposure to the toxin including the onset, duration, and type of clinical effects.

Diagnostic Testing covers information important to the interpretation of the clinical significance of the laboratory data. This section includes current laboratory methods to determine the presence of the toxin, effects of storage, biomarkers of exposure in blood, urine, and postmortem material, and the laboratory abnormalities detected by imaging studies and ancillary tests.

Treatment provides details on current methods to treat the poisoning including information important for first responders, life-threatening problems associated with the poisoning, the use of antidotes, and measures of supportive care.

Medical Toxicology of Natural Substances: Foods, Fungi, Medicinal Herbs, Plants, and Venomous Animals focuses on scientifically validated facts about specific toxins based on clinical experience and the medical literature. References are documented to validate the statements and to provide sources for further inquiry. The interdisciplinary, evidence-based approach is designed to reach beyond clinical settings to increase the scientific understanding of those in associated fields (analytical laboratories, universities, regulatory agencies, coroner's offices) involved with decisions regarding toxic exposures. My hope is that increased scientific communication between the fields aligned with Medical Toxicology will inspire more inquiry into the pathophysiology, clinical effects, biomarkers, treatment, and prevention of toxic exposures.

Donald G. Barceloux, MD

June 12, 2008

ACKNOWLEDGMENTS

I deeply respect the expertise and appreciate the dedication of the following people for their help in improving the quality, depth, and accuracy of my book, *Medical Toxicology of Natural Substances: Foods, Fungi, Medicinal Herbs, Plants, and Venomous Animals*.

Bob Esposito, Senior Editor, John Wiley & Sons
His belief in the importance of my Book Series to the medical literature and his guidance made this book a reality.

Kate McKay, Text Editor
Her outstanding editorial comments, meticulous style, and judgment substantially improved the consistency and clarity of the text.

Ed Wickland
His support and astute advice on the medical publishing field was an essential part of the placement of this book series.

Donna Seger, MD, Managing Editor
Her management skills and resources for the arduous task of developing this book were an invaluable contribution.

Rob Palmer, PhD, Illustration Editor and Analytical Toxicology Reviewer
His breadth of analytical knowledge, clinical judgment, and artistic expertise were important contributions to the interdisciplinary approach of this book.

Cyrus Rangan, MD
His scholarly chapters on food contamination, food additives, and bacteria were vital contributions to the content of this book.

Rune Midtgaard
The sharing of his exquisite photographs from the professional gallery at Nature's Window (www.natureswindow.dk) was extremely generous.

Review Panel
The critical reviews and clinical insights of the Review Panel were an essential part of the scientific basis of this book.

CEP America
The support and shared clinical experiences of my medical colleagues have been indispensable to the completion of my book: Wes Curry, President; James Kim, Medical Director; Ken Moore, former Medical Director; Ken Nakamoto, Vice President of Medical Affairs; Phil Piccinni, Regional Medical Director; Emergency Department physicians, Mark Boettger, Ivan Schatz, Richard Dorosh, Greg Burke, Greg Murphy, Howard Friedman, Marc Eckstein, Matt Janssen, Geoffrey Pableo, John Lee, Tom Umemoto, Ali Jamehdor, Ludwig Cibelli, Brian Rhee, Vicki Shook, Hanne Rechtschaffen, Susan Salazar, Tom Edholm; and physician assistants, Anne Castle, Glenn deGuzman, Jaison Fraizer, Erin Merchant, Janet Nakamura, Frank Pastor, and Erik Smith.

Pomona Valley Hospital Medical Center
I admire the incredible hard work and dedication of the Emergency Department nurses and support staff in the care of a community challenged by difficult medical and social problems.

UCLA Emergency Department Colleagues
I appreciate all those who shared their expertise and clinical experience at UCLA Toxicology Rounds especially Marshall T. Morgan, Director of the Emergency Medicine Center and David A. Talan, Chairman, Department of Emergency Medicine, Olive View-UCLA Medical Center.

UCLA/Pomona Librarians
The writing of this book required the review of thousands of references and the technical assistance of the UCLA Biomedical and Pomona Valley Hospital Medical Center libraries, particularly Glenn Sato, Joseph Babi, and Debra Klein.

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PART 1

FOODBORNE and MICROBIAL TOXINS

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Chapter 1

FOOD CONTAMINATION

Cyrus Rangan, MD, FAAP

Records of outbreaks of human illness caused by toxic contaminants in foods appeared at least several centuries BC, when mad honey poisoning was associated with an illness among troops under the command of the Greek historian and mercenary, Xenophon.[1] One of the first recorded foodborne outbreaks of ergotism occurred in Limoges, France during the Capetian Dynasty in 994 AD.[2] The ingestion of rye bread contaminated with ergot alkaloids during this epidemic caused the deaths of approximately 20,000–50,000 victims. Numerous episodes of ergotism have occurred throughout history. Although ergotism is a possible explanation for the bizarre behavior that occurred before and during the Salem Witch Trials of 1692, there is no definite evidence that ergotism was a contributing factor.[3] In the 1950s, mining operations in the Toyama region of Japan released cadmium into the Jinzu River. The use of this water for drinking and for irrigation of nearby rice fields resulted in a disease called *itai-itai* (translation: "ouch-ouch"), manifest by osteoporosis and renal dysfunction primarily in middle-aged women.[4] In the same decade, numerous neonates born near Minamata Bay, Japan, developed birth defects and neurological abnormalities after pregnant women were exposed to seafood contaminated by methyl mercury released into the bay from a local factory. A methyl mercury-based fungicide caused an outbreak of mercury poisoning in Iraq in 1971 after grain seeds treated with the fungicide were inadvertently used for food manufacturing instead of planting.[5] Prominent outbreaks of illnesses associated with chemical contamination of cooking oils include tri-*ortho*-cresyl phosphate-induced neuropathy (Morocco, 1959),[6] yusho ("rice oil disease," Japan, 1968), yu-cheng ("oil disease," Taiwan, 1979), toxic oil syndrome (Spain, 1981), and epidemic dropsy (India, 1998). Some contaminants are unavoidable in food manufacturing. In the United States, the Food and Drug Administration (FDA) imposes "Current Good Manufacturing Practices" (CGMP) on food manufacturers. These mandatory codes enable the FDA to cite food products as *unfit* if an unavoidable contaminant poses a risk of harm by violating a standard or action level for that unavoidable contaminant (e.g., aflatoxin). Food products are considered *adulterated* when concentrations of avoidable contaminants (e.g., pesticides) exceed established standards, sometimes prompting food recalls after sale and distribution.

Metal contaminants such as lead, mercury, arsenic, and cadmium come from factory emissions, mining operations, and metal-containing industrial products used in food production. Methyl mercury found in commercially sold seafood is deemed an unavoidable contaminant because contamination preexists in the raw material; therefore, the contamination does not result from food processing or distribution. Fish and shellfish acquire methyl mercury primarily from microorganisms that methylate environmental inorganic mercury compounds released primarily from industrial sources.

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YUSHO and YU-CHENG

HISTORY

The first known case of yusho (rice oil disease) involved a 3-year-old girl in northern Kyushu, Japan, who had an acute onset of an acneiform rash (chloracne) in June, 1968. Her family members, followed by other familial clusters, presented to a single clinic with complaints of acneiform rash, hyperpigmentation, and eye discharge over the next 2 months. By January 1969, 325 cases were reported. After a small minority of patients initially identified rice oil as the causative agent of yusho, Kyushu University convened the *Study Group for Yusho* to investigate yusho; about 2,000 afflicted patients were subsequently identified. The clinical features of yusho included fatigue, headache, cough, abdominal pain, peripheral numbness, hepatomegaly, irregular menstrual cycles, nail deformities, and hypersecretion of sebaceous glands. A field survey of canned rice oil associated the disease with the use of "K Rice Oil" produced or shipped by the K Company on February 5–6, 1968.[7] The yu-cheng epidemic involved over 2,000 individuals in Taiwan in 1979, when an accidental leakage of thermal exchange fluid resulted in the contamination of rice-bran oil with polychlorinated biphenyls (PCBs), dibenzofurans (PCDFs), and quaterphenyls (PCQs).[8] The clinical features of yu-cheng and yusho were similar.

EXPOSURE

Source

Polychlorinated biphenyls (PCBs) and polychlorinated dibenzofurans (PCDFs) are thermal heat exchanger compounds used in food processing machinery. Leakage of these compounds into rice oils during manufacturing led to the yusho and yu-cheng outbreaks.

YUSHO

Epidemiological studies revealed that 95.7% ($p < 0.01$) of surveyed patients recalled consumption of rice oil from K Company in Western Japan.[7] A case-control study revealed rice oil as the only associated etiologic factor, and a cohort study demonstrated a 64% risk of yusho in K rice oil consumers compared with no risk for nonexposed individuals.[7] Food engineers confirmed the leakage of dielectric thermal exchange fluid (Kanechlor 400) containing PCBs into the rice oil. This contaminant contained PCB compounds, primarily tetra-chlorinated biphenyls. In 1969, the Study Group initially concluded that PCBs caused yusho.[9] However, a lack of similar symptoms (besides chloracne) in PCB workers who had significantly higher tissue burdens (mean blood PCB level: 45 ppb) contradicted this conclusion. Furthermore, the dermatological lesions could not be reproduced in animals following the oral administration of PCB compounds or by Kanechlor 400, and the severity of the clinical features of yusho did not correlate to serum concentrations of PCB compounds. Therefore, other compounds (e.g., polychlorinated dibenzofurans) in the adulterated rice oil probably contributed to the development of yusho.[10,11]

YU-CHENG

As with the yusho incident, the suspected causative agents of yu-cheng were PCDFs rather than PCBs.[12] Contamination of the cooking oil occurred when PCBs used for the indirect heating of rice-bran oil leaked into the cooking oil. Repeated heating of the partially degraded PCBs produced PCDFs, as well as polychlorinated terphenyl and polychlorinated quaterphenyl compounds.[13]

Food Processing

High temperatures (>200 °C) in dielectric thermal exchange fluid during the deodorization step of oil refining contributed to the development of yusho and yu-cheng by degrading PCBs in the contaminated rice oil to PCDFs, PCDDs (polychlorinated dibenzo dioxins), and PCQs (polychlorinated quaterphenyls).[14]

DOSE RESPONSE

Exposure to toxic contaminants in the rice oil from the yusho and yu-cheng epidemics was assessed by recording the lot numbers of purchased oil containers and comparison of the volume of oil purchased to the volume of oil remaining in the containers retrieved from affected households. Consumption of the contaminated rice oil by household members was estimated by proportional distribution to each family member. Positive relationships were observed between estimated individual oil consumption and incidences of yusho and yu-cheng.[15,16] The mean concentrations of PCBs, polychlorinated quaterphenyls (PCQs), and PCDFs in five samples of contaminated cooking oil from the yu-cheng outbreak were 62 ppm, 20 ppm, and 0.14 ppm, respectively.[17] The congeners of these compounds were similar in the cooking oils from these two outbreaks, but ye-cheng cooking oil