Updates in Neurocritical Care

Series Editor Romergryko G. Geocadin

Neuropharmacotherapy in Critical Illness

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edited by
Gretchen M. Brophy

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FOREWORD

Welcome to the second volume in the Updates in Neurocritical Care series, *Neuropharmacotherapy in Critical Illness*.

Updates in Neurocritical Care was developed in response to clinical demands for expertise in neurocritical care. This series bring state-of-the-art knowledge and best practices to the health care providers in the field of neurocritical care. We are excited to bring together leading experts to provide clinicians with the various relevant and practical factors for treating patients with neurocritical illnesses.

We are privileged to have Gretchen M. Brophy serve as the editor of this volume. Dr. Brophy is Professor of Pharmacotherapy and Outcomes Science and Neurosurgery at Virginia Commonwealth University. She is also vice-president of the Neurocritical Care Society (NCS) and the overall chair of the NCS 2017 Annual Meeting.

Dr. Brophy has put together for this book a team of clinical pharmacy specialists that are experts in the field of neurocritical care, and have years of experience in teaching, research and clinical practice.

The clinical practice of neurocritical care addresses neurological illness with the predominant issues not only centered within the nervous system, but also involving complex direct and indirect systemic factors. Management of these complex illnesses requires both understanding the pathophysiology and mastering the neuropharmacology. In this book, Dr. Brophy has assembled pharmacy experts that are in active practice at top medical institutions in the United States. They have extensive knowledge and real-world experience in utilizing the medications relevant to neuerocritical care. These pharmacists practice in a multidisciplinary setting; they are also active in teaching health care professionals, residents, and students about therapeutic entities and management in neurocritical care.

I extend my sincerest appreciation to Dr. Brophy and to the contributors of this volume. I also extend my deep appreciation for the dedication and professionalism of Kel McGowan, Executive Editor for Clinical Health and Medicine, and her team at Rutgers University Press. The development of this series is made possible by the collaboration of the editors, authors, and Rutgers University Press.

Romergryko G. Geocadin, MD FNCS, FANA, FAAN

PREFACE

Neurocritical care patients often pose significant management challenges, which are often commonly complicated by concomitant drug therapies. To avoid unwanted adverse drug effects and drug-drug interactions, it is important to choose the right drug for the right patient. *Updates in Neurocritical Care: Neuropharmacotherapy in Critical Illness* focuses on pharmacotherapeutic strategies in critically ill patients with neurological injuries.

This book is written by a team of clinical pharmacy specialists who are experts in the field of neurocritical care and have years of experience in teaching, research, and clinical practice. These pharmacy experts provide care for neurocritical care patients in institutions all across the United States and have extensive knowledge and experience using the medications that are discussed. In addition, these pharmacists practice in a multidisciplinary setting, teaching health care professionals, residents, and students about neurocritical care therapeutic entities and management strategies at the bedside, as well as in the didactic setting. Each author has contributed a chapter focusing on neurocritical care pharmacotherapies that are clinically relevant, comprehensive, and highly specific to the care of neurologically injured patients.

Therapeutic strategies for the treatment of neurocritical care patients can be variable around the globe but are also similar in regards to the drug class being used for treatment. These common drug classes are discussed in this book and include hyperosmolar therapies for traumatic brain injury, sedation and neuromuscular blockade, antithrombotic therapies for ischemic stroke, coagulopathy reversal strategies for intracranial hemorrhage, pharmacotherapy for vasospasm prophylaxis and treatment in subarachnoid hemorrhage, pharmacotherapy of acute spinal cord injury, hemodynamic management strategies for hypertensive emergencies and shock, antiepileptic agents for seizure prophylaxis and treatment, neurostimulants for acute brain injury, and intraventricular and

intrathecal drug therapies. Evidence-based, clinically significant neuropharmacotherapy pearls on medication mechanisms of action, pharmacokinetics, pharmacodynamics, drug-drug interactions, and adverse drug reactions are provided to assist in optimizing treatment strategies for neurocritical care patients.

GRETCHEN M. BROPHY

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Neuropharmacotherapy in Critical Illness

CONTENTS

Hyperosmolar Therapy in Traumatic Brain Injury

1

Haley Goodwin Gibbs, Jose Guzman Garcia, and Ron Neyens

INTRODUCTION

Severe brain injury results in a complex secondary injury cascade, with ensuing cerebral edema and elevated intracranial pressure (ICP). This process is a common contributor to permanent neurological sequelae and death. Cerebral edema is primarily manifested as 2 distinct physiological processes: vasogenic (eg, capillary permeability) and/or cytotoxic (eg, cellular apoptosis).[1] Osmotherapy is designed to create an osmotic gradient across the blood-brain barrier (BBB), resulting in an intended reduction of brain water content.

Osmotherapy has a long-standing history, with concentrated electrolyte solutions shown to decrease ICP and brain bulk in the early 1900s. It was not until the 1950s before osmotic formulations were routinely used clinically as a therapeutic tool in the management of intracranial hypertension. Initially, formulations of urea were standard therapy, but adverse effects and observations of intracranial pressure rebound limited its use, driving a transition to glycerol and sorbitol in the 1960s, followed by mannitol in the late 1960s and hypertonic saline in the 1990s.[2] The latter 2 osmotic agents now stand as guideline-based recommendations and a major component of neurocritical care treatment strategies for cerebral edema and intracranial hypertension.

MECHANISM

The exact mechanism of ICP reduction with osmotherapy remains ill-defined yet potentially involves several characteristics. The major therapeutic impact is felt to be a complex and dynamic result of osmotic dehydration and rheologically induced cerebrovascular vasoconstriction with reduced cerebral blood volume (CBV).

Osmotic Dehydration

The BBB is a highly selective permeability barrier separating the brain extracellular fluid from the circulating blood. It is composed of endothelial cells, connected by high-density cellular tight junctions. It serves as a self-protective mechanism allowing passive transport of water and small lipid-soluble molecules, as well as active transport of molecules necessary for optimal neuronal function.[3] It relies on the osmotic principle that the BBB allows transport of water from compartments with low osmolality to those with higher osmolality. An induced high-osmole concentration gradient mobilizes water from the interstitial and intracellular compartments of the brain into the intravascular compartment, therefore reducing brain water content, mass effect, and ICP. Clinical practice has evolved to using mannitol and hypertonic sodium solutions as they are more effective osmoles than urea, glycerol, and sorbitol. Therefore, they display low permeability across the BBB, referred to as its reflection coefficient (σ), which is an index of the effectiveness of a solute in generating an osmotic driving force ($\sigma = 1$ for hypertonic sodium solutions and $\sigma = 0.9$ for mannitol on a scale of 0–1, with the most effective being 1). The osmotic model assumes an intact BBB, expressing low hydraulic conductivity.[4] The degree of BBB disruption is not readily determined clinically in the neurologically injured patient. Therefore, the osmotic dehydration effect may occur more effectively in normal rather than injured or impaired brain tissue; however, the clinical relevance remains debatable and ill-defined.[5]

Rheology and Vascular Reactivity

The brain has little capacity to store oxygen, with its survivability dependent on an adequate cerebral blood flow (CBF) and cerebral oxygen delivery (CDO_2). In normal physiological conditions, homeostatic cerebral autoregulation is in place to ensure that supply (ie, CBF and CDO_2) is coupled to meet demand (ie, cerebral metabolic rate for oxygen consumption), despite variations in cerebral perfusion pressure (CPP). This occurs via a tight regulation of cerebral vascular resistance, stimulated by various interrelated processes involving pres-

sure, chemical, and electrical gradients.[6] The rheological principle of osmotherapy relies on its ability to increase red blood cell deformity resulting in reduced blood viscosity, independent of changes in hematocrit.[2] It is proposed that this promotes compensatory vasoconstriction of both arterioles and venules on the surface of the brain to maintain homeostatic CBF and thus reduces CBV and resultant ICP.[7] This model assumes intact vascular reactivity and has been challenged in the pathology of acute brain injury.[8]

Pleotropic

Several other proposed mechanisms exist, including immunomodulatory, free radical scavenging, and neuroendocrine effects.[9–11] With unclear clinical relevance, hypertonic sodium solutions may assist in preserving the BBB by restoring normal resting membrane potential, which is not observed with mannitol.[12]

HYPEROSMOLAR AGENTS

There are several different concentrations of mannitol and hypertonic sodium solutions used in clinical practice. The agents and doses used display variable osmolarities but are believed to yield a therapeutic response via similar principles. For osmotic agents routinely used in clinical practice, see Table 1.1.

Pharmacokinetics and Pharmacodynamics

An optimal dose-response relationship has not been clearly defined, and many of the relevant comparative studies have not used equiosmolar dosing strategies. Based on initial clinical observations, an osmotic gradient of 5 to 10 mOsmol/kg was considered necessary for therapeutic efficacy.[13,14] However, it remains incompletely understood as it is clear that hypertonic sodium solutions effectively reduce ICP, with relatively small total osmole doses (eg, 23.4% 30 mL = 240 mOsm), even in the face of high serum osmolarity (eg, >320 mOsm/L).[15] In addition, it is a common clinical practice that doses of mannitol 20% and hypertonic sodium solutions are often not equiosmolar, yet both are effective at reducing elevated ICPs. An equiosmolar dose of 1 g/kg 20% mannitol is approximately 5.3 mL/kg 3% saline, 3.2 mL/kg 5% saline, 2.1 mL/kg 7.5% saline, 1.6 mL/kg 10% saline, 1.1 mL/kg 14.6%, and 0.69 mL/kg 23.4% saline.

For both mannitol and hypertonic sodium solutions, the effect on ICP tends to be biphasic. The initial rapid ICP reduction, occurring within minutes, is possibly related to the previously mentioned rheological and cerebral vascular