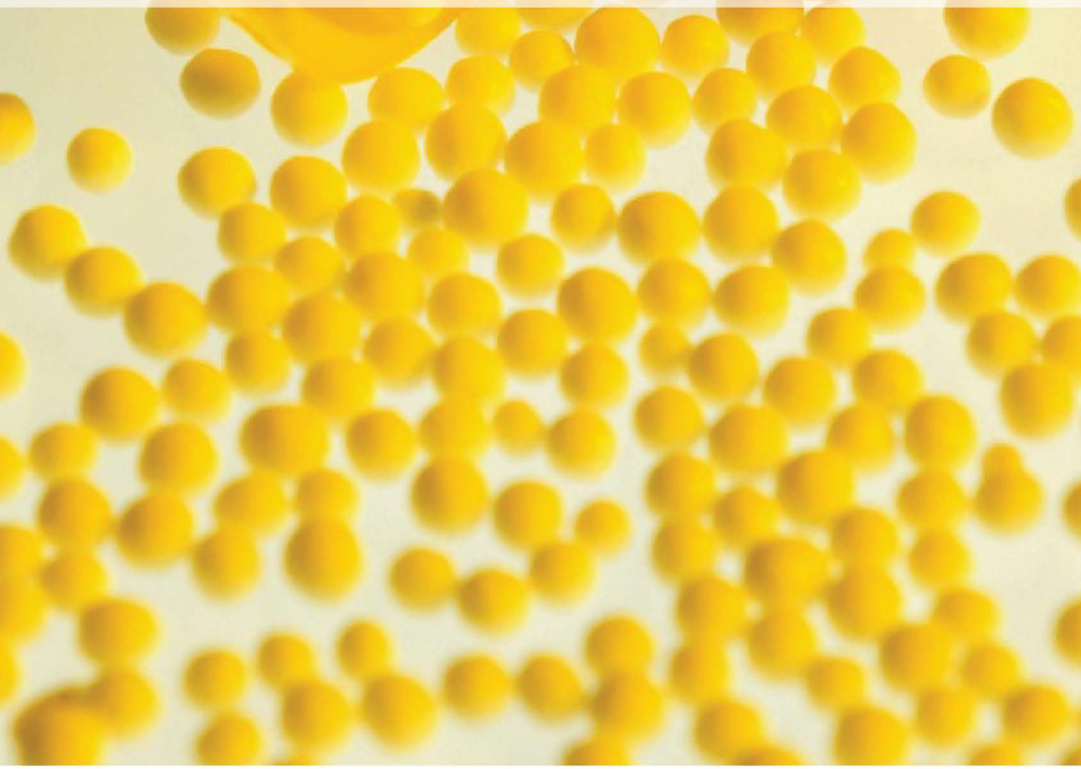
Rationale of Drug of Choice

A Comparative Analysis



P Nirmala
N Chidambaram

Forewords
S Vembar
TR Muralidharan

JAYPEE

Contents

CHAPTER

4

Cholinergic Drugs

1. *Carbachol/Bethanechol in postoperative paralytic ileus and atony of bladder.*

BACKGROUND

Cholinergics increase GIT muscular tone, amplitude, peristalsis and secretions. They cause contraction of detrusor, relaxation of trigone and external sphincter. The responses are mediated through M_3 receptors in GIT and M_2 receptors in bladder. Postoperative paralytic ileus and atony of bladder are due to compromised cholinergic activity. In paralytic ileus, intestinal motility is decreased. Reduced bladder capacity and increased voiding pressure are features of bladder atony. Stimulation of cholinergic receptors promotes motility of bowel and emptying of bladder.

BETHANECHOL

Bethanechol is beta-methyl analog of carbachol, is resistant to cholinesterases and has long duration of action. It also has predominant action on smooth muscles of GIT and urinary bladder. Bethanechol is devoid of unwanted nicotinic action on autonomic ganglia, hence preferred to carbachol. The dose of bethanechol is 10 to 50 mg three to four times a day and should be administered in empty stomach to minimize nausea and vomiting.

CARBACHOL

Carbachol is an unsubstituted carbamoyl ester, resistant to hydrolysis by cholinesterases hence has longer duration of action. It has

a predominant action on smooth muscles of GIT and urinary bladder and has additional nicotinic action that cannot be antagonized completely by atropine.

Drug of Choice: Bethanechol

RATIONALE

The choline esters carbachol and bethanechol are **long acting** drugs as they are completely resistant to inactivation by cholinesterases. They have **equal propensity** for smooth muscles and effectively stimulate GIT and bladder smooth muscles. They are therefore effective in the treatment of postoperative paralytic ileus and atony of bladder. **Carbachol** can stimulate autonomic ganglia as it **has substantial nicotinic action** but bethanechol does not stimulate nicotinic receptors. Hence, bethanechol is preferred.

2. *Neostigmine/Pyridostigmine in myasthenia gravis.*

BACKGROUND

Myasthenia gravis is an autoimmune disease, characterized by muscular weakness and fatigue. The defect lies in synaptic junction of neuromuscular transmission. Cholinergic receptors in postjunctional motor end plate are involved. Development of antireceptor antibodies to nicotinic cholinergic receptors is the most common immunological cause seen in myasthenia gravis. It may be congenital in 10% of patients due to mutations in acetylcholine receptors. Although subjective improvement is more prominent in autoimmune type, drugs effectively alleviate the symptoms in congenital type. Anticholinesterases are effective and improve skeletal muscle weakness. Neostigmine and pyridostigmine are used for symptomatic treatment in myasthenia gravis. They prolong the presence of acetylcholine in neuromuscular junction.

PYRIDOSTIGMINE

The duration of action of pyridostigmine is 3 to 6 hours but it is available as sustained release preparation containing 180 mg as tablets. Of the 180 mg, 60 mg is released immediately and the

remaining 120 mg is released slowly. Sustained release preparation improves the compliance of patients and also reduces muscle fatigue for a longer period.

NEOSTIGMINE

The duration of action of neostigmine is only 2 to 4 hours so it needs to be administered every 6 hours for effective relief. It improves symptoms due to muscle fatigability only when administered four times a day but frequent dosage results in plasma fluctuations. Since it has to be frequently administered it is not preferred.

Drug of Choice: Pyridostigmine

RATIONALE

Myasthenia gravis, the **autoimmune disorder** is characterized by muscle weakness and fatigue. Anticholinesterases lead to the accumulation of acetylcholine in neuromuscular junction. When compared to neostigmine, **pyridostigmine** has **longer** duration of **action**. Neostigmine has to be given four times a day which results in plasma level fluctuations. Pyridostigmine is available as **sustained release** preparation and **once daily dose will suffice**. It alleviates symptoms of myasthenia gravis and improves the compliance of patients. Hence, pyridostigmine is preferred.

3. *Edrophonium/Neostigmine for diagnosis of myasthenia gravis.*

BACKGROUND

History, signs and symptoms may help in the diagnosis of myasthenia gravis but it is necessary to differentiate it from severe muscular weakness of cholinergic crisis. The symptoms of cholinergic crisis are due to excessive cholinergic stimulation causing generalized depolarization of motor end plate.

EDROPHONIUM

Edrophonium is a short acting reversible anticholinesterase drug. A rapid IV infusion of 2 mg of edrophonium improves the symptoms.

If the symptoms do not improve, an additional dose of 8 mg should be administered after 45 seconds. Edrophonium aggravates symptoms due to cholinergic crises and results in predominant lingual fasciculation. Muscle strength worsens but it does not cause respiratory paralysis as it is short acting. Improvement in muscle strength indicates the diagnosis of myasthenia gravis.

NEOSTIGMINE

Although a reversible anticholinesterase agent, neostigmine is longer acting than edrophonium so should not be used for diagnosis of myasthenia gravis. In cholinergic crisis, neostigmine may exaggerate the symptoms and may result in respiratory paralysis since it has long duration of action.

Drug of Choice: Edrophonium

RATIONALE

Muscular weakness can occur either due to myasthenia gravis or cholinergic crisis. In case of myasthenia gravis, it is due to defective neuromuscular transmission while the symptoms of cholinergic crisis are due to excessive cholinergic stimulation. Since the pathophysiology is diagonally opposite, the treatment also differs. Myasthenia gravis requires administration of anticholinesterases while cholinergic crisis requires withholding of anticholinesterases. **Neostigmine** is longer acting than edrophonium and **worsens** the symptoms in **cholinergic crisis**, potentiating life-threatening **respiratory paralysis**. Hence, neostigmine should not be used. **Edrophonium** is **short acting**, will **improve** symptoms in myasthenia gravis and it **will not aggravate** the symptoms in cholinergic crisis. So edrophonium is the drug of choice for definitive diagnosis.

4. *Physostigmine/Neostigmine in the treatment of atropine poisoning with central symptoms.*

BACKGROUND

Atropine poisoning is characterized by both central and peripheral symptoms. Peripheral symptoms are dryness of secretions,

redness, fever and blurring of vision. Central symptoms are excitement, ataxia, delirium, restlessness and irritability. Physostigmine and neostigmine are reversible anticholinesterase drugs and are competitive antagonists of atropine. Reversible anticholinesterases antagonize the binding of atropine at muscarinic receptors.

PHYSOSTIGMINE

Physostigmine is a tertiary amine which crosses the blood brain barrier. It counteracts the central symptoms but causes undesirable CNS side effects in their absence. Therefore, it is reserved only for counteracting the central symptoms of atropine overdose.

NEOSTIGMINE

Neostigmine is a quaternary ammonium compound. It does not cross the blood brain barrier due to its bigger molecular size. Hence, neostigmine is not effective in antagonizing the central symptoms but it can block the peripheral symptoms of atropine poisoning.

Drug of Choice: Physostigmine

RATIONALE

In severe atropine poisoning with central symptoms, **physostigmine** is the specific antidote. Physostigmine is a **tertiary amine**, **crosses blood brain barrier** and antagonizes the central effects of atropine. **Neostigmine** is a quaternary ammonium compound, **does not enter CNS** hence not useful in blocking central symptoms though effective in the treatment of peripheral symptoms. However, physostigmine should be reserved for use only in case of central excitatory symptoms since it can cause undesirable centrally mediated side effects in the absence of central symptoms of atropine poisoning.

5. *Physostigmine/Neostigmine in the treatment of glaucoma.*

BACKGROUND

Anticholinesterase drugs are not the first line drugs in the treatment of glaucoma. Glaucoma can cause irreversible blindness, if left

untreated. Increased intraocular pressure can damage optic nerve. The three types of glaucoma are primary, secondary and congenital glaucoma. Anticholinesterases are used to manage primary glaucoma and in some secondary types such as glaucoma after cataract surgery or aphakic glaucoma. Chronic wide angle glaucoma has a gradual or insidious onset. It is managed by other drugs and anticholinesterases are reserve drugs. Reversible anticholinesterases are mainly indicated for those with chronic wide angle glaucoma, resistant to first line drugs.

PHYSOSTIGMINE

Physostigmine is effective in the treatment of glaucoma. It is a tertiary amine administered topically as eye drops. It is highly lipophilic, achieves high ocular concentration and is useful in glaucoma. It increases ciliary muscle tone and trabecular patency facilitating effective drainage of aqueous humor resulting in reduction of intraocular pressure. It causes miosis, minimal visual acuity and brow pain due to persistent spasm of iris and ciliary muscles.

NEOSTIGMINE

Neostigmine is a quaternary ammonium compound and does not penetrate through corneal membrane. Neostigmine is not used as it is not effective.

Drug of Choice: Physostigmine

RATIONALE

Anticholinesterases are miotics and used as **reserve drugs** in the management of chronic wide angle glaucoma. Physostigmine and neostigmine are **reversible** anticholinesterases. Physostigmine is **lipophilic**, a tertiary amine, achieves **higher ocular concentration**, increases tone of ciliary muscle, increases trabecular patency, facilitates effective drainage of aqueous humor and reduces intraocular pressure. It can cause brow ache, minimal visual acuity

and miosis. **Neostigmine** is not effective as it **does not penetrate** corneal membrane due to its particle size. Hence, physostigmine is preferred to neostigmine in the treatment of glaucoma.

6. *Neostigmine/Physostigmine in postoperative decurarization.*

BACKGROUND

D-tubocurarine is a competitive neuromuscular blocker used during surgery. It results in persistent postoperative curarization as it is long acting. Reversible anticholinesterases antagonize the actions of d-tubocurarine.

NEOSTIGMINE

Neostigmine is a reversible anticholinesterase and effectively antagonizes the symptoms of curarization. It blocks the actions of the competitive blocker, d-tubocurarine by displacing it from its binding site at N_M receptors. Neostigmine has higher affinity to nicotinic receptors than physostigmine and prolongs the presence of acetylcholine at motor end plates. It has additional direct action at neuromuscular junction and reverses the blockade but may induce muscarinic side effects. Either atropine or glycopyrrolate can be co-administered with neostigmine to prevent such side effects. Neostigmine is also effective in cobra bite as it reverses the curarimimetic effects of the venom.

PHYSOSTIGMINE

Physostigmine is not used in d-tubocurarine overdose and is less effective in antagonizing the blockade because it does not act directly on nicotinic cholinergic receptors. Its affinity to nicotinic N_M receptors is inferior to neostigmine.

Drug of Choice: Neostigmine

RATIONALE

D-tubocurarine is a long acting skeletal muscle relaxant and its actions need to be reversed by a cholinergic agonist. Neostigmine

is a reversible anticholinesterase that potentiates the action of acetylcholine at nicotinic cholinergic receptors. It also acts directly on the nicotinic receptors. It is co-administered with a muscarinic antagonist like atropine or glycopyrrolate for preventing muscarinic actions and side effects. Physostigmine cannot be used as it does not act directly on nicotinic receptors and neostigmine is a better choice.

Rationale of Drug of Choice
A Comparative Analysis

Rational prescription of drugs based on 'Evidence-Based Medicine' determines the success of the therapy. Quick development of drug resistance necessitates the pragmatic use of drugs with the application of pharmacokinetic and pharmacodynamic principles. The drug chosen for the therapy should maximize the clinical benefits and minimize the unwanted side effects. An ideal prescription should focus on a patient's compliance and success rate of therapy. Rational prescription of drugs at right dose through optimal route of administration with required frequency and duration is the ultimate objective of this book. Hence, this book deals with the selection of a rational drug from the current list of approved drugs. This book emphasizes on the therapeutic approach with the basic input about the essential characteristics of drugs and provides an easy understanding to impart a better knowledge to the readers.

P Nirmala MD (Pharmacology) PhD (Pharmacology) is currently the Professor and Head, Department of Pharmacology, Rajah Muthiah Medical College, Annamalai University, Chidambaram, Tamil Nadu, India. She is the Professor of Pharmacology for the past 16 years and Head of the Department of Pharmacology for the past 11 years. Dr Nirmala is an experienced teacher with 30 years of teaching and 20 years of research experience in pharmacology. Her field of specialization is colon cancer. Dr Nirmala has published 31 research articles in 28 international and 3 national journals. She has been awarded the 'Best Researcher' award for the medical faculty of Annamalai University for the year 2012 and 'Merit Certificate' for best research publications for the period between 2012 and 2016 for the medical faculty of Annamalai University in 2016.

Dr Nirmala has delivered 6 invited lectures and chaired sessions in 2 national and 3 international conferences. She has served as the expert member of research committee of Annamalai University for the year 2016. Dr Nirmala is a life member of Indian Pharmacology Association and Indian Medical Association. She is also the member of Institutional Human Ethics Committee, Institutional Animal Ethics Committee, Pharmacovigilance Committee, Board of Faculty of Medicine, PG Committee, and Board of Studies for Pharmacy. Dr Nirmala has so far guided 8 MD students and 2 PhD students. Her area of interest is Drug of Choice and Drug-Drug Interaction.

N Chidambaram MD FRCP (Glasg) FACC is currently the Professor and Head, Department of Cardiology, and Dean, Faculty of Medicine, Rajah Muthiah Medical College, Annamalai University, Chidambaram, Tamil Nadu, India. He is the Professor of Medicine for the past 19 years as well as Professor and Head of Cardiology for the past 10 years. Dr Chidambaram has received the Best Doctor Award from The Tamil Nadu Dr MGR Medical University, Chennai, Tamil Nadu, India in 2012, Lifetime Achievement Award from Delhi Tamil Sangam in 2016, Dr Radhakrishnan Memorial National Best Teacher Award from India International Center, New Delhi in 2016 and Professor G Ananthasubramanian Gold Medal Oration Award for the Tamil Nadu Chapter in 2012.

Dr Chidambaram is a seasoned academician and an experienced researcher, teacher and a keen planner. A lead investigator of several research projects with an ability to collaborate with National and International funding agencies. At present, he has six MoUs with institutions in Canada, USA, Japan and in India to his credit. So far, Dr Chidambaram has guided 22 MD students. He has published research articles in 44 International and National journals. Dr Chidambaram has delivered invited lectures in 6 International and 26 National conferences. He has presented papers in 10 International and 25 National conferences.

Dr Chidambaram has served as a member of senate and syndicate of Annamalai University. He is the vice-president of professional academic bodies, such as Indian Medical Association, Chidambaram, and Indian Society of Hypertension, Lucknow, Uttar Pradesh, India. He is a life-member of Indian Medical Association, Indian Society of Hypertension, Indian Society for Atherosclerosis Research, Indian Academy of Echocardiography, Indian Society of Pediatric Cardiology, International Medical Sciences Academy, and Indian Society of Cardiology. He is the chairman of Board of Faculty of Medicine, Institutional Animal Ethics Committee, Academy of Medical Sciences, Pharmacovigilance Committee, Board of Studies, Medical Education unit, vice-chairman of Rajah Muthiah Heart Foundation, and convener of Deans Committee, Publication Committee and Annamalai University,

Shelving Recommendation
PHARMACOLOGY

ISBN 978-93-5270-134-6

JAYPEE BROTHERS
Medical Publishers (P) Ltd.
www.jaypeebrothers.com

Join us on facebook.com/JaypeeMedicalPublishers