ESSENTIALS

ESSENTIAL DENTAL THERAPEUTICS

EDITED BY DAVID WRAY

with website

WILEY Blackwell

Essential Dental Therapeutics

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Edited by

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WILEY Blackwell

This edition first published 2018
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John Wiley & Sons Ltd, The Atrium, Southern Gate, Chichester, West Sussex, PO19 8SQ, UK

Editorial Office: 9600 Garsington Road, Oxford, OX4 2DQ, UK

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Library of Congress Cataloging-in-Publication Data

Names: Wray, David, author.
Title: Essential dental therapeutics / by David Wray.
Description: First edition. | Chichester, West Sussex ; Hoboken : Wiley, 2018. | Series: Essentials | Includes index. |
Identifiers: LCCN 2017014504 (print) | LCCN 2017015962 (ebook) | ISBN 9781119057413 (pdf) | ISBN 9781119057420 (epub) | ISBN 9781119057390 (pbk.)
Subjects: | MESH: Dental Care | Drug Therapy
Classification: LCC RK51.5 (ebook) | LCC RK51.5 (print) | NLM WU 29 | DDC 617.6–dc23
LC record available at https://lccn.loc.gov/2017014504

Cover design: Wiley
Cover image: © Vstock LLC/ Gettyimages

Set in 10/12pt, AGaramondPro by SPi Global, Chennai, India.

10 9 8 7 6 5 4 3 2 1

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Preface

Dentists, along with medical practitioners, are allowed to prescribe all medications although dentists must prescribe only within their competence as part of their clinical practice. Dentists, working within the National Health Service, are restricted to prescribing only those drugs included in the dental list and they must only prescribe generically.

Although the range of medications prescribed by dentists is narrower than their medical counterparts, dentists prescribe drugs to patients with a wide range of medical conditions who may be taking a number of other medications, which will influence dental practice as well as potentially causing interactions among the prescribed drugs.

For these reasons dentists must not only be familiar with the conditions they prescribe for and the drugs they prescribe but also they must be knowledgeable about general medical conditions affecting their patients and have knowledge of the drugs these patients may be concurrently taking.

To this end this textbook, designed to inform both dental students and dental practitioners, aims to provide information about dental prescribing and also general medical conditions, the drugs used to treat them, and their impact on dental practice.

This text does not cover the competencies required by the prescriber since these are detailed in the recently published Prescribing Competency Framework, produced the Royal Pharmaceutical Society under the aegis of NICE. The competencies contained in this Framework should be accomplished by all practitioners seeking to prescribe safely.

Similarly, this text does not detail specific prescribing details. These are comprehensively included in the *British National Formulary* and the *British National Formulary for Children* which are updated electronically, monthly and published in hard copy bi-annually and annually respectively. All prescribers should make reference to these sources when prescribing.

A specific, abridged text, *Drug Prescribing for Dentistry*, is produced by the Scottish Dental Clinical Effectiveness Programme (SDCEP.org.uk), which is also available as an iPhone app (https://itunes.apple.com/gb/app/sdcep-dental-prescribing/id509188306?mt=8). This provides explicit prescribing information for all drugs on the dental list and is designed to help dentists in primary care practice.

About the companion website

This book is accompanied by a companion website:

www.wiley.com/go/wray/dental-therapeutics

This website contains a set of multiple-choice questions for every chapter for students' use.

CHAPTER 1

Introduction to pharmacology and therapeutics – pharmacodynamics

Alan Nimmo

Key Topics

- Introduction to therapeutics – pharmacodynamics and the basis for drug action
- Molecular targets for drug action – receptors, enzymes, ion channels and carrier proteins
- Selective toxicity – the basis of antibacterial, antiviral and antifungal drug action, and cancer chemotherapy

Learning Objectives

- Be familiar with the main types of functional protein that serve as the molecular targets for drug action
- Be aware that in most cases, altering the activity of these proteins alters chemical signaling in the body, and hence control of body function
- Be familiar with how drugs, such as antibiotics, are able to exert a selectively toxic effect
- Be aware of the challenges posed in developing antiviral drugs and drugs for the treatment of cancer

Essential Dental Therapeutics, First Edition. Edited by David Wray.
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Companion Website: www.wiley.com/go/wray/dental-therapeutics

Introduction

Therapeutics has its roots in the historical use of herbal remedies and natural potions. However, the modern practice of therapeutics really began in the twentieth century. The herald for this new era was the German physician, Paul Ehrlich. Ehrlich sowed the seeds for transforming therapeutics into a science by insisting that drug action could be explained in terms of chemical and physical reactions. The understanding of how drugs produce their effects represents the area of therapeutics known as pharmacodynamics.

During the twentieth century, the advent of many effective therapeutic agents began to deliver immeasurable benefits to society. Perhaps the biggest single advance in medicine was the development of antibiotic therapies, exemplified by the work of Florey, Chain and Fleming on penicillin. The introduction of these novel treatments transformed what had previously been fatal or life-devastating diseases into manageable conditions.

However, we cannot be complacent. There are still many areas of practice where our current therapies have limited efficacy, or are associated with unwanted, or side, effects. For example, many cancer therapies come with significant side effects. In dental practice you'll see some of the most severe side effects associated with cancer treatment, such as stomatitis. It will only be through making cancer treatments more specific in the way they target cancerous cells, that we will be able to overcome many of these issues. Another challenge we face is the ability of bacteria to develop resistance to antibiotic therapy. In developed countries, antibiotic-resistant bacteria are now responsible for more deaths than HIV/AIDS. If we do not respond appropriately to these issues, we could return to an era where bacterial infections are no longer treatable. Hence therapeutics is, and needs to be, a constantly evolving science.

In dentistry, therapeutics may not be such a major component of daily practice as compared to general medical practice. However, an understanding of therapeutics is one of the cornerstones of good clinical dental practice. Pain-free dentistry would not be possible without the use of local anaesthetics, while analgesics are used to manage peri- and post-operative pain. In dental practice, the primary approach to managing microbial infection is surgical, however antibiotics do provide an important adjunct therapy, particularly in the case of a spreading infection. Dental practitioners also rely on drugs to manage fungal and viral infections, and inflammation. Other common uses of drugs in the dental clinic are to manage patient anxiety and to provide sedation for patients. However, this is only one side of the coin. Being aware of patients' general medical conditions, and their associated medications, is central to providing safe and effective treatment. Patients' medications may impact directly upon their oral health, for example many common medications cause the problem of xerostomia. In addition, medications may impact upon how a dentist manages a patient within the dental clinic. A significant number of patients may be receiving anticoagulant therapy in order to reduce their risk of a thrombotic event, such as a heart attack. However, a direct consequence of this is these patients will have a tendency to increased bleeding with surgical procedures, and this must be controlled with effective, local measures. Hence, good dental practice relies on a good understanding of therapeutics.

History of therapeutics

The practice of therapeutics is as old as history, and was well documented in ancient Greek and Egyptian civilizations. Throughout history there have been two opposing approaches to therapeutics, a magico-religious approach and an empirico-rational approach. The magico-religious approach is based upon the belief that disease is a supernatural event, and therefore should be managed by such forces, while the empirico-rational approach assumes that disease is a natural process that is best managed by a scientific approach, and evolving treatments in response to careful observation and evaluation of patient outcomes. It is this latter approach that forms the basis of current evidence-based practice.

In itself, the empirico-rational approach is not new. The father of modern medicine was the Ancient Greek physician, Hippocrates (circa 460–370 BCE). Hippocrates is accredited with insisting that disease is a natural process, and should be managed in

a judicious manner. Some of the most basic principles of clinical practice, such as the importance of hygiene, can be traced back to the Hippocratic Works. Hippocrates even suggested that sometimes, 'to do nothing was the best remedy', recognition of the capacity of the human body to fight disease and initiate repair. However, for most of the intervening period between Hippocrates and the twentieth century, the practice of therapeutics was not based upon a scientific rationale. Common practices have included treatments such as bleeding patients, not only through the use of leeches, but also by severing blood vessels. Needless to say, many of these treatments did more harm than good. In fairness, though, a key underlying issue was that the function of the human body, and the basis of disease, was so poorly understood that it impeded a more scientific approach to medicine. It was the Russian physician, Virchow, who indicated that a scientific approach to therapeutics would come through its combination with physiology, and with it an improved understanding of normal body function.

As mentioned earlier, the historical basis of therapeutics lay in the use of natural potions, normally of plant origin. Some of these natural agents were actually very potent and effective. Indeed, there are a number of agents in current, clinical use, which have been used, in crude form, for hundreds, and even thousands of years. Some notable examples include the analgesic, morphine, which comes from the opium poppy, and the muscarinic antagonist, atropine, which comes from the plant, deadly nightshade. Indeed, the first local anaesthetic was cocaine, which comes from the leaves of the cocoa plant. One might assume that the existence of such effective medicinal agents would facilitate a scientific approach to therapeutics but, if anything, they tended to work against it. The issue was that those agents that were effective, produced their effects in such a specific and potent manner, that it was believed their actions could not be explained in terms of physical or chemical reactions. Instead, it was assumed that they must be imbued with some kind of magical, or vital forces. It was Paul Ehrlich, at the beginning of the twentieth century, who insisted that drug action should be understood in terms of normal chemical and physical reactions. In particular, he suggested that drugs are able to produce their specific and selective effects because they bind to specific targets within the body. It is an understanding of these targets, and how drugs interact with them, that underpins modern pharmacology.

Targets for drug actions

Although there are hundreds of different drugs in clinical use, the way in which these drugs are able to produce their effects within the body is limited to a few basic mechanisms. Ehrlich suggested that drugs bind to specific target molecules, and we now recognize that these molecules are primarily key functional proteins, particularly proteins associated with communication within the body. The normal function of the body is under the control of the nervous, endocrine and paracrine systems. These systems use chemical mediators, such as neurotransmitters and hormones, to affect their control. In the same way, many drugs produce their effect by modulating this natural chemical signalling through targeting the functional proteins associated with chemical communication. The other, major way in which drugs act is by being selectively toxic, in other words they are toxic to particular cells or organisms, but are relatively innocuous to healthy human cells.

Receptors

As indicated, the key communication and control systems in the body exert their effects through the release of chemical mediators, such as neurotransmitters and hormones. These mediators are able to produce their effects on their target cells because those cells have receptors, that are not only capable of detecting chemical messages, but are also able to transduce and amplifying that signal to bring about a meaningful response within that cell. In terms of the way in which natural mediators act on these receptors, there are two components to their action. First, they bind to the receptor in question, but coupled to that, they also stimulate that receptor, to bring about a response. The ability of a messenger to bind to a particular receptor is referred to as its affinity, while the ability of the messenger to actually stimulate a receptor, and bring about a response, is referred to as efficacy. An analogy that is commonly

used to describe this mechanism is the 'lock and key' effect. A key must not only have the correct shape to fit into a particular lock (affinity), but it must also have the precise shape that enables it to turn in the lock, and open that particular lock.

In terms of drugs, a number of drugs produce their effects by acting upon receptors, and thereby altering chemical signalling, and with it, control function within the body. Some drugs will produce their effect by mimicking the actions of the natural chemical messengers, in other words they will bind to, and stimulate the specific receptor. Those drugs, which have both affinity and efficacy for a particular receptor, are referred to as agonists. An example of a drug which acts as an agonist is salbutamol, which is used for the management of asthma. Salbutamol is an agonist for the beta2-adrenergic receptor. It mimics the natural actions of adrenaline on the beta2-receptors of airway smooth muscle, relaxing the airways, and thereby relieving an asthmatic attack.

Another way in which drugs can alter chemical signalling at receptors, is to block that receptor. If a drug binds to a receptor, but does not stimulate it, it has in itself no direct action. However, by binding to, and occupying the binding site, it can prevent the natural messenger from producing its effects at that receptor, and hence the drug can prevent a particular, unwanted response. Such drugs, which possess affinity for a receptor, but no efficacy, are referred to as antagonists. Such drugs are often identified by the prefix "anti" or the suffix "blocker", for example antihistamines or beta-blockers. Antihistamines can be used to manage some allergic reactions, such as allergic rhinitis, or hay fever, through blocking the unwanted actions of histamine.

Enzymes

The second class of functional protein that drugs may act upon, is enzymes. Enzymes are obviously essential for catalysing metabolic reactions within the body. However, a number of enzymes are responsible for the synthesis of, and degradation of, chemical messengers. It is particularly this kind of enzyme that serves as a target for drug activity.

The eicosanoids are a family of chemical messengers that are derived from membrane phospholipids. The synthesis of these mediators begins with the liberation of arachidonic acid from membrane phospholipids by the enzyme phospholipase A_2. The arachidonic acid is then metabolized by another enzyme, cyclooxygenase, to give rise to the prostanoids (prostaglandins and thromboxanes). These lipid mediators regulate a number of physiological processes, but are also important inflammatory mediators. The most widely used anti-inflammatory drugs are the non-steroidal anti-inflammatory drugs (NSAIDs), like ibuprofen. They produce their anti-inflammatory effects by inhibiting the cyclooxygenase enzyme, thereby inhibiting the production of the prostanoids.

Drugs that inhibit enzyme activity can also be used to enhance chemical signalling. Currently, the main agents used to manage Alzheimer's disease are acetylcholinesterase inhibitors. These drugs reduce the breakdown of acetylcholine, thereby increasing its activity in the brain.

Ion channels

The function of nerve and muscle cells is related to the electrical excitability of their cell membranes. For example, the ability of a nerve cell to send signals along the nerve axon is dependent upon its ability to generate action potentials. Membrane excitability is related to the presence of ion channels in the cell membrane. Drugs are able to modify the electrical activity of target cells by altering ion channel activity.

Local anaesthetics, like lignocaine, are the most widely used drugs within the dental clinic. Local anaesthetics produce their effects by blocking voltage-gated sodium ion channels. The opening of voltage-gated ion channels is central to the ability of a nerve to generate action potentials and, consequently, the ability of a nerve to signal. By blocking the transmembrane pore of the sodium ion channel, local anaesthetics inhibit the inward sodium current required to generate action potentials. As such, nociceptive nerves cannot send signals regarding a painful stimulus to the brain, and hence, pain sensations are abolished.

Drugs can also produce their effect by enhancing the opening of ion channels. For example, benzodiazepines, such as diazepam, which may be

used as sedatives within the dental clinic, produce their effect by facilitating the opening of chloride ion channels associated with the $GABA_A$ receptor. GABA (γ-amino butyric acid) is the main inhibitory neurotransmitter in the brain, and its inhibitory effects are enhanced by benzodiazepines, which increase chloride ion channel opening, leading to hyperpolarization of neuronal cell membranes, and hence decreased excitability.

Carrier proteins

The fourth group of functional proteins that serve as a target for drugs are the carrier proteins associated with transmembrane transport. Again, for drugs that act on these targets, their main impact is on cell signalling and chemical communication.

In terms of nerve signalling, once a neurotransmitter has been released from a nerve terminal, there must be some mechanism to terminate the activity of the released neurotransmitter. This primarily happens in one of two ways. There may be enzymic breakdown of the released transmitter, as seen with acetylcholinesterase breaking down acetylcholine. Alternatively, a released neurotransmitter can be 'recycled' through neuronal reuptake involving a specific carrier protein. Such carrier proteins are responsible for the reuptake of catecholamines, such as noradrenaline and serotonin, following release. These carrier proteins serve as an important target for a number of anti-depressant medications. For example, drugs that inhibit the re-uptake of serotonin (selective serotonin reuptake inhibitors (SSRIs), e.g. fluoxetine), increase serotonin activity in the brain, and help enhance mood.

Selective toxicity

The other main way that drugs exert their beneficial effects is by being selectively toxic. As the name suggests, the drug should be toxic to a particular invading organism, but innocuous to healthy human cells. Selectively toxic agents form the basis for antibacterial, antiviral and antifungal drug treatments, as well as the treatment of cancer. The development of selectively toxic treatments relies on exploiting the biochemical differences between particular organisms and cells. This may be 'relatively' easy when one is trying to deal with bacterial and fungal infections within a human, where there are significant differences between the organisms, but it becomes much more difficult when one tries to deal with viral infections and cancer.

Antibacterial drugs

There are significant biochemical differences between prokaryotic cells (bacteria) and mammalian, eukaryotic cells. A number of these serve as effective targets for antibacterial agents. Although not the first antibiotic, penicillin represented a major step forward in terms of being a very effective bactericidal agent. Penicillin, and all β-lactam antibiotics, such as amoxicillin, produce their effects by interfering with the synthesis and integrity of the bacterial cell wall. Because the main component of the bacterial cell wall, peptidoglycan, is not found in human cells, β-lactam antibiotics have a very low toxicity. However, some individuals may develop allergic reactions to penicillins. While severe allergic reactions and anaphylactic shock are rare, they may potentially be fatal.

There are other biochemical targets for antibiotic drugs. Some drugs, such as sulfonamides, can interfere with folic acid synthesis, which subsequently impacts upon nucleotide synthesis in bacterial cells, conferring a bacteriostatic effect. Other antibacterial agents, such as the tetracyclines, target protein synthesis, and in particular the differences between bacterial and mammalian ribosomes. The quinolones, such as ciprofloxacin, target a bacterial enzyme, known as topoisomerase II. These agents have become important in dealing with bacteria that are resistant to agents such as the penicillins.

Antifungal agents

There are a number of agents that can be used to manage fungal infections. Some of these agents, such as amphotericin and nystatin, are naturally occurring, while others, such as clotrimazole and fluconazole, are synthetic. Antifungal agents primarily target the fact that the fungal cell membrane contains the sterol, ergosterol, while animal cells, including humans, contains cholesterol.

Amphotericin and nystatin will preferentially bind to fungal cell membranes and form a transmembrane pore, disrupting the fungal cell. In contrast, the synthetic azoles still target ergosterol, but do so by inhibiting a fungal cytochrome enzyme responsible for ergosterol synthesis.

As a generalization, antifungal agents are safe and effective for use on topical, including oral infections, but require careful management when used for systemic infections in order to manage potential side effects.

Antiviral drugs

Historically, viral infections have been difficult to target with drug treatment. In themselves, viruses just consist of nucleic acid (either DNA or RNA) enclosed in a protein coat, or capsid. In order to replicate, viruses have to attach to, and enter a living, host cell. Having infected a host cell, the virus then uses the host cell's metabolic machinery to replicate. As such, there are very few biochemical differences between healthy human cells and those that are infected with a virus. However, in recent years, there has been a significant increase in the number of effective antiviral agents. This has occurred following the recognition that infected cells may contain virus-specific enzymes that are required for the replication and release of the virus particles. Aciclovir (zovirax) represented a major step forward in terms of developing effective antiviral agents. The drug itself is activated by one viral enzyme, viral thymidine kinase, and it subsequently inhibits another viral enzyme, viral DNA polymerase, that is required for viral replication. This two-step process gives aciclovir a high degree of selectivity in terms of inhibiting viral as opposed to human DNA polymerase. It is effective against infections caused by the herpes simplex and zoster viruses, including cold sores.

Cancer chemotherapy and treatment

Perhaps the hardest cells to target through a selectively toxic action are cancerous cells, since the biochemical differences between healthy and cancerous human cells are minimal. Historically, cancer treatments have primarily exerted a cytotoxic effect, targeting cells that are actively dividing. However, this does not represent a target that is selective for cancer, since many cells in the body are actively dividing in order to replace cells that have a high turnover rate. It is this, non-selective action that accounts for the many, significant side effects seen with cancer chemotherapy. Indeed, the epithelial cells that line the oral cavity have one of the highest turnover rates in the body, and as such, cancer chemotherapy can have marked effects in the oral cavity, causing problems such as stomatitis.

There is a constant drive to develop more selective drug treatments for cancer. Some success has been achieved by targeting growth-promoting signals that are overactive in some cancers. For example, in approximately 25% of breast cancers, the human epidermal growth factor receptor 2 is overexpressed, giving an increased growth-promoting stimulus (HER2+ve breast cancer). Trastuzumab (Herceptin) is a monoclonal antibody that binds to the HER2 receptor, and interferes with the growth stimulus produced by epidermal growth factor. However, perhaps the biggest conceptual breakthrough has come with the development of imatinib (Gleevec). Imatinib is a tyrosine-kinase inhibitor that is used in the treatment of a number of cancers, including chronic myelogenous leukemia. Imatinib inhibits a specific form of tyrosine kinase, BCR-Abl, which activates the signalling pathway responsible for the cancerous cells' growth. Because this tyrosine kinase is only found in certain cancerous cells, imatinib has a truly selectively toxic action against cancerous cells. As a result, imatinib is devoid of the significant side effects commonly associated with cancer treatment.

Conclusion

Antibiotic drugs, like penicillin helped revolutionize clinical practice, enabling the safe and effective management of conditions that had been previously fatal. Now, new antiviral and anticancer agents are showing that it is possible to achieve a similar, effective medical management of these conditions. However, we cannot be complacent, and we need strategies to manage problems like increasing antibiotic resistance in order to maintain the effectiveness of therapeutics.

CHAPTER 2

Introduction to pharmacology and therapeutics – pharmacokinetics

Alan Nimmo

Key Topics

- Introduction to pharmacokinetics and the factors that affect drug concentration within the body
- Drug diffusion and partitioning within the body
- Elimination of drugs from the body – metabolism and excretion
- Routes of drug administration
- Quantifying drug kinetics

Learning Objectives

- Be familiar with the factors that influence the concentration of a drug within the body
- Be aware of factors, such as regional differences in pH, which may influence the distribution of drugs within the body
- Be aware of the mechanisms involved in eliminating drugs from the body, and the potential for drug interactions and toxicity
- Be familiar with the main routes of drug administration
- Be aware of some of the basic approaches used to quantify drug kinetics

Essential Dental Therapeutics, First Edition. Edited by David Wray.
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