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Pharmacology for Dental Students and Practitioners

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The author, editors and publishers of this work have made every effort to ensure that the drug dosage schedules are accurate and in accord with accepted standards at time of publication. However, since drug dosages and contraindications are under constant revision, the reader is advised to consult the drug's package insert or the PDR for the currently correct drug dosages to be certain that changes have not been made in either the recommended dose or contraindications. The author and editors assume no responsibility in this regard; it is the sole responsibility of the student and practitioner. The information presented in this text is deemed accurate only at time of publication; no responsibility is taken for changes in factual information after date of publication.

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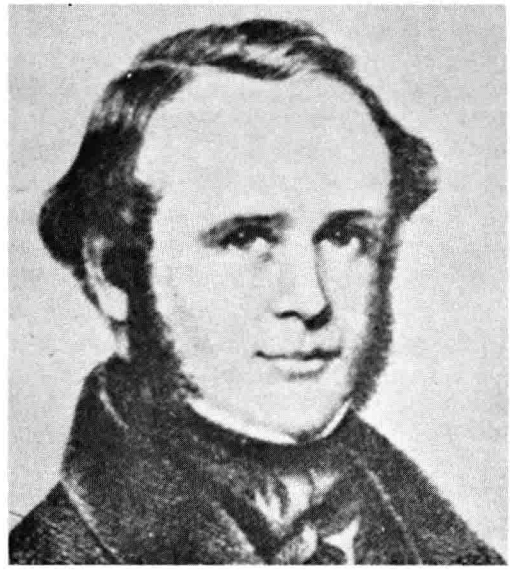
Pharmacology for Dental Students and Practitioners

To Christine, Brian, Jennifer and Robert Pallasch
with love and affection.
And
Horace Wells, D.D.S.
The Father of Anesthesia



Dr. Horace Wells.

Preface

The major difficulty in writing a book on pharmacology is in determining how much information should be included. In other words, how much knowledge of the nature and uses of drugs is "enough" for the dental student and dental practitioner.

Fortunately this dilemma was resolved to some extent by a chapter on pharmacology that I recently contributed to a text entitled: *Review of Basic and Dental Clinical Sciences* edited by Drs. Wells, Reed and Coury and published by Harper and Row. This chapter covers the basics of pharmacology, includes a sample examination and is intended as a study guide in preparing for various board examinations.

So now my conscience is clear. For those individuals preparing for examinations and those whose interests in pharmacology extend only so far as passing tests, help is at hand in the form of the above mentioned chapter. For the other individuals who wish to learn more about drugs even to the point of understanding what drugs really are and what they can and cannot do for us, I have dedicated my efforts in this volume.

I was encouraged to write this particular book by my editors and colleagues at Lea & Febiger who felt as I did that most relevant criticism of my two previous books on pharmacology: *Clinical Drug Therapy in Dental Practice* and *Synopsis of Pharmacology for Students in Dentistry* was that these were separate texts and not in one volume. I have endeavored to retain the spirit of these texts, add and update information where necessary, and include more tables and diagrams of which I am particularly fond since they can say so much in so little space.

I have organized this text in a manner which seems most feasible to me knowing full well that others in this field would have organized it otherwise. I have also written it in a style to which I have become accustomed: lack of excess verbiage. One of the most common criticisms of my previous two books, from my own students, was that "every sentence is a fact." As I glanced through their texts I could appreciate their comments as it seemed that all the pages were a solid yellow color from felt marking pens. To those individuals accustomed to wordy texts, I express my apologies and only hope that they will bear with my style in the interests of financial and literary economy. The references for each chapter were compiled with considerable effort and are complete and current. In the very early stages of this text, I decided to be as thorough as possible. I have a scientific bias against poorly referenced texts as I feel they lack credibility.

It was my original intent to include a section entitled: "Health Status Evaluation via the Drug History." The purpose of this chapter was to have been the listing of various disease states and their drug therapy by both brand and generic names so that the drugs listed by the patient in the health history could be used with a bit of detective work to determine the diseases for which they were being medically treated. This would aid in their physical and medical evaluation prior to and during dental treatment. However, during the writing of this text I discovered that such a chapter would be redundant if the reader were to use the index of the book properly. Towards this end I have included in each chapter all the applicable generic and brand drug names and these are listed alphabetically in the index. To determine the disease for which the patient is under treatment from their medication history, one need only find the drug in the index and consult the page references for the disease(s) for which the drug is intended.

This text is written specifically for persons in the dental profession: dental students, dental practitioners and dental auxiliaries. I would suspect that other allied health professionals might also be interested. In those chapters on drugs not specifically employed in dental practice, I have included within the body of the chapter or at the end of each chapter (whichever best suited the material) information specifically relevant to the dental profession and the patients we see and treat every day. With those chapters directly related to dental practice (General Principles, Toxicology, Prescription Writing and the Drug Control of Anxiety, Pain and Infection), I have followed the pattern established in *Clinical Drug Therapy in Dental Practice* and tailored these chapters specifically to the needs of dentistry. I trust I know whereof I speak since as well as teaching pharmacology and periodontics, I also practice dentistry. I must also "survive in the trenches" as aptly stated by Dr. Frank M. McCarthy.

The endeavor could not have been accomplished without the dedi-

cated help of others. To the School of Dentistry's Word Processing Center personnel, Barbara Anderson, Rhonda Carroll, Beverly Clark, Ramona Conley, Roger Curnock, Elena Selanova, John Slade and Dennis Trujillo, I wish to express my extreme gratitude for turning my illegible scrawl into the neatly typewritten word; in particular I appreciate the efforts of Michele Ripley, for riding herd on this project as Director of the Word Processing Center and to Juniko Moody for her excellent talents in preparing the various figures and diagrams. I fully appreciate my sabbatical leave during which this book was written and without which it could have never been completed; my thanks to the University of Southern California. I am also most grateful for the love, patience and understanding of my wife, Christine, and our children, Brian, Jennifer and Robert, during the times when I was not fit to associate in human circles.

I trust this endeavor expresses my fascination and love for pharmacology. It is a field of never ending change and endless challenge. Constant change is unfortunately anathema to some members of our profession; for the pharmacologist it is a way of life. However, the reader should not be discouraged since this book was written with principles in mind; the drugs may come and go but the principles of pharmacology will always remain.

Finally, as with my other texts, I take all responsibility for any conceptual errors of either omission or commission. It is again hoped that the readers of this book will sympathize with the words of Tai T'ung, the thirteenth century Chinese author, as quoted by Will Durant in the preface to his *Story of Civilization:* "Were I to await perfection, my book would never be finished."

Los Angeles, California THOMAS J. PALLASCH

Contents

my mind" is not unusual.[17] Severe overdosage results in delirium, hyperreflexia, myoclonic convulsions, respiratory and cardiovascular depression.[5]

Bromide intoxication may also be headed towards a revival since bromine is a constitutent of many commonly employed drugs (Dimetane, Romilar, Bromoseltzer, Nervine, Ambodryl).[18] The symptoms of bromism include skin lesions, tremor, ataxia, slurred speech, anorexia, loss of memory, irritability, delirium and hallucinations.[18]

The non-barbiturate sedative-hypnotics do not possess any therapeutic advantages over the barbiturates with the exception of flurazepam which possesses a much higher therapeutic index than other sedative-hypnotics. Chloral hydrate is still an acceptable antianxiety agent and flurazepam is the drug of choice for a nighttime hypnotic prior to dental appointment. None of these drugs are cross-allergenic with the barbiturates.[5]

ANTIANXIETY AGENTS

The antianxiety agents were formerly termed the "minor tranquilizers" and as such intended for the treatment of emotional disorders associated with anxious symptoms: nervousness, fatigue, palpitations, dizziness, weakness, trembling, paresthesias, chest pain and insomnia. These symptoms of anxiety are manifested in simple anxiety states (no apparent reason for anxious symptoms), mixed anxiety and depression, phobic anxiety states and endogenous depression. As stated in Chapter 9, it may be difficult to differentiate anxiety from mental depression on a symptomatic basis only. The antianxiety agents are also of value as part of the drugs required to manage the anxious dental patient.

The antianxiety agents are classically considered to belong to a family of chemicals termed the benzodiazepines. Other agents with relatively non-specific antianxiety properties such as the sedative-hypnotics and the antihistamine, hydroxyzine (Atarax, Vistaril) have declined in popularity with the advent of the benzodiazepines. Meprobamate (Miltown, Equanil) is also an antianxiety agent of decreasing popularity and is considerably more toxic than the benzodiazepines on an acute basis.[19] Beta-adrenergic blocking drugs are also used to a limited extent in treatment of anxiety primarily to decrease the symptoms of cardiovascular beta-adrenergic stimulation. Only the benzodiazepines will be considered below.

General Aspects. The benzodiazepines currently approved for use in the United States for anxious disorders and nighttime hypnosis are listed in Table 5–3. Nitrazepam and medazepam are only employed in Europe. Chlordiazepoxide was introduced in 1960, diazepam in 1963, oxazepam in 1965, flurazepam in 1970, chlorazepate in 1972 and prazepam in 1977. Clonazepam has been approved for use as an

Table 5–3. The Benzodiazepines.

Diazepam (Valium)	Lorazepam (Avitan)
Chlordiazepoxide (Librium)	Prazepam (Vestran)
Oxazepam (Serax)	Flurazepam (Dalmane)
Chlorazepate (Azene)	

anti-epileptic agent for the treatment of myoclonic, atonic, infantile spasm and absence seizures.[20] Tens of millions of prescriptions for these drugs are written every year almost solely by internists and general medical practitioners. As long ago as 1972, 77 million prescriptions for the benzodiazepines were written annually[21] in the United States and the number has risen. At least 5 to 15% of all Americans take antianxiety agents in a single year.[4] In 1979, diazepam was the number one prescribed drug and chlordiazepoxide was number three.

Mechanism of Action. The precise locus and mechanism of action of the benzodiazepines is still presently unknown. It is widely assumed that these agents act on brain areas involved with our emotions such as the limbic system and the thalamus, however, the drugs are widely distributed throughout the central nervous system and do not selectively localize in the limbic system.[4] The benzodiazepines have been termed "limbic system sedatives" as they impair nerve discharge in the amygdala and amygdala-hippocampus nerve transmission.[4] Specific receptors for the benzodiazepines have been located within the central nervous system.[22,23] The benzodiazepines possess a high affinity for binding to proteins of synaptic membranes in the CNS.[24]

It is probable that the benzodiazepines enhance synaptic inhibition by facilitating the release of gamma-aminobutyric acid (GABA), a known inhibitory neurotransmitter,[24] increasing the efficiency of gabaminergic transmission, and increasing the affinity of the GABA receptor for GABA. The benzodiazepines do not possess any GABA-like effects, but potentiate the physiologic actions of GABA. Other possible neurochemical actions which may result in reduced anxiety include inhibition of phosphodiesterase (thereby increasing cyclic AMP), reduction in ATP-ase activity and serotonin antagonism.[4]

Pharmacologic Actions. The most prominent pharmacologic effect of the benzodiazepines is one of "taming": a reduction in aggression and hostility.[21] Another prominent effect is "disinhibition": restoration of behavior suppressed by punishment or lack of reward or a reduction in behavior motivated by punishment.[4] Most interestingly, when aggression or hostility are inhibited ("held in check") by fear or anxiety a "paradoxical" increase in hostility or aggression may be seen after benzodiazepine ingestion (release of "anxiety-bound" hostility). Other CNS depressants also reduce aggression and produce disinhibitory effects but only at doses which also produce somnolence and motor

incoordination.[4] The disinhibition dose of the benzodiazepines is less than required to induce sleepiness and ataxia.[21]

The benzodiazepines do not possess any analgesic effects but may alter the "reaction" component of the pain experience (see Chapter 6) by reducing concomitant anxiety. The benzodiazepines are also skeletal muscle relaxants by an effect on CNS supraspinal polysynaptic neurons.[4] The benzodiazepines are extremely effective as anticonvulsants and inhibit seizures in tetanus, some forms of epilepsy and those due to local anesthetics (see Chapter 7), strychnine, picrotoxin and pentylenetetrazol. Their antiseizure effects may be related to an increase in brain GABA levels.[4]

Absorption, Distribution, Metabolism and Excretion. Most of the benzodiazepines are well and rapidly absorbed from the gastrointestinal tract. After a single dose administration, the peak blood levels for diazepam occur in 2 hours and for chlorodiazepoxide in 4 hours.[4,21] The peak blood levels of oxazepam occur between 1 and 4 hours; prazepam is slowly absorbed over 4 to 6 hours.[4] The intravenous absorption of diazepam is considered below.

A most important clinical factor in the use of the benzodiazepines is their rate and pattern of liver metabolism. All the benzodiazepines except oxazepam and nitrazepam are biotransformed to metabolites which are as pharmacologically active as the parent drug.[4]

The half-life of diazepam is 20 to 50 hours with considerable biologic variability among patients.[4] The drug rapidly disappears from the blood due to distribution to other areas within 4 hours and then is slowly biotransformed over the next 20 to 50 hours. A "resurgence" of diazepam effects is sometimes observed at 6 hours after the dose possibly due to release from the bile via enterohepatic circulation or release from tissue depots. The serum half-life of chlordiazepoxide is between 6.6 and 28 hours and for oxazepam between 3 and 21 hours.[4] The half-life of lorazepam is 22 hours.[11] These long half-lives of the benzodiazepines predispose to cumulation and persistent effects.

To further compound this problem, the metabolites of the benzodiazepines are also pharmacologically active and some possess an extremely long half-life. The major metabolite of diazepam is desmethyldiazepam which may possess a half-life up to 96 hours. The active metabolite of flurazepam has a half-life ranging from 47 to 100 hours. It should be remembered that it usually requires a time equal to 5 half-lives of a drug to completely eliminate it from the body. Therefore, serious questions must now be raised regarding the duration of action of the benzodiazepines and their metabolites and persistent motor incoordination. When can the patient safely drive an automobile or perform complex psychomotor tasks? To date no one knows. The best present advice is to utilize oxazepam for oral premedication since it possesses a relatively short half-life and has no pharmacologically active metabolites.