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CLINICAL NEUROPHARMACOLOGY

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CHURCHILL LIVINGSTONE

Clinical Neuropharmacology

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Clinical Neuropharmacology

General Editor's Foreword

I remember as a medical student my wonder about the prespicacity of neurologists in the pinpointing of lesions within the central nervous system. Gradually, however, I came to realize that although making the correct diagnosis is a satisfying intellectual exercise and the basis of all therapy, it is of less value if physicians are unable to satisfactorily cure or even ameliorate the associated disorders. I also soon learned there was only minimally effective therapy for the majority of neurological disorders. There is still a long way to go, and the problem is compounded by the lack of regenerative capacity of some nervous tissue components, but significant progress has been made in understanding the pathophysiology of and in developing effective therapy for neurological disorders. An up-to-date accounting of our present knowledge will be found in this monograph.

The first and last chapters deserve special mention. The Introduction, in addition to providing an overview of the current status of treatment of disorders of the nervous system, contains a useful discussion of the general principles and factors affecting drug usage. More and more drugs are being found to have a significant adverse effect on the nervous system. These drugs and the mechanisms involved are discussed in the last chapter along with suggestions for preventing or treating the reactions.

This monograph contains several features that are useful for the practicing physician. For example, for each antiepileptic drug, the factor needed to calculate the conversion of plasma drug levels from μg/ml to μM is given. In the quest for international standardization, the latter unit (not frequently used in the United States) will be seen in the literature more and more.

This monograph will provide therapeutic information for the neurologist as well as the physician involved in general health care delivery. I recommend it to you.

Daniel L. Azarnoff, M.D.

Preface

This book is intended to be of use to students in health fields as well as to physicians concerned with the treatment of disorders of the nervous system. It points out that the physician has perhaps as much to offer in the treatment of neurologic disorders as he does in the treatment of cardiac, renal or endocrinologic disorders. Many of the disorders of the nervous system are chronic conditions requiring continuous supplementative medication which ameliorates but does not cure the disease. The margin between an effective and a toxic dose of medication is often narrow, and considerable expertise and laboratory support may be required in regulating the dosage. There is considerable need for more effective neuropharmacologic treatment with the development of new drugs, new approaches, and new knowledge regarding the pathophysiology of disorders of the nervous system. While waiting for this to develop, the application of the growing knowledge of pharmacokinetic and pharmacodynamic aspects of the available drugs used in the treatment of neurologic disorders, based on monitoring of drug blood levels, has improved the efficacy of therapy of some conditions such as seizure disorders, Parkinson's disease, and nervous system infections. Similar improved efficacy is likely to occur in the treatment of myasthenia gravis, migraine, and movement disorders, as practical methodology for monitoring the concentrations of drugs develops and the empirical data base for effective and toxic drug concentrations accumulates. These aspects of treatment are emphasized in this book along with a warning that, due to variations in the severity of the disease process and acquired tolerance, the effective and toxic drug doses and blood level concentrations vary among individual patients. Thus, in making the clinical decision regarding drug dosage, both clinical findings and laboratory data need to be considered carefully.

Much of what is included in this book is based on personal experience and reflects particular points of view. This, however, is integrated with information and data compiled from the literature listed in the bibliography as well as with that derived from the experience and opinions of our colleagues.

For the physician concerned with the treatment of neurologic disorders, this book should be considered only as a base to enlarge his understanding of treatment through careful attention to the ever expanding neuropharmacologic field and new possibilities for treatment.

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Introduction

Disorders of the nervous system may result from an abnormal process or state in the nervous system itself, or may reflect the response of the nervous system to some systemic abnormal processes. Often, the precise mechanism leading to the disorder is not known, and treatment consists of alleviation of the most disturbing symptoms. There are few disorders in which one course of treatment alone eradicates the cause, thus resulting in cure. The underlying abnormal state or process in many disorders is long lasting once it has developed, and may require prolonged and continuous suppressive or supplementary therapy. In still other disorders, drug therapy may have no effect at all on the cause of the disorder and its symptoms. Thus, effective treatment of neurological disorders with drugs is limited to a relatively few disease entities.

Complete cure may be achieved in some nervous system infections using antimicrobial agents, if therapy is started in time and extensive structural damage to the nervous system has not occurred. Cures can also be achieved with vitamins in some nutritional or metabolic neuropathies and encephalopathies, if the therapy is started before irreversible changes have taken place. The key here is early treatment, because of the poor regenerative potential of the nervous tissues. Therefore the emphasis should be on preventive, more than on curative programs.

Dramatic symptomatic relief can be achieved with drug therapy in several disorders of the nervous system. These include seizure disorders, extrapyramidal syndromes, facial pain and migraine headaches, as well as myasthenia gravis and some spastic states. With the exception of migraine, the relief of symptoms in these disorders requires continuous administration of drugs over

long periods of time. The drugs are usually needed until spontaneous remission of the disease process occurs; or sometimes, for the rest of the patient's life.

Drug treatment is modestly effective in cerebrovascular disease, where it may alleviate the outcome or diminish the occurrence of vascular occlusions to some extent in some patients. In multiple sclerosis, drug therapy can beneficially influence the course of an acute exacerbation but has little, if any effect on the long-term, general course of the disease. Recent advances in the chemotherapy of malignant brain tumors are encouraging, but at best can only prolong the survival time by a modest degree.

The course of degenerative and/or hereditary diseases such as amyotrophic lateral sclerosis, Friedreichs' ataxia, olivo-ponto-cerebellar degeneration and muscular dystrophies, has remained virtually unaffected by any of the currently available chemotherapeutic agents.

This somewhat pessimistic picture may improve as continuing research efforts clarify the mechanisms of the disease processes and develop new therapeutic agents.

GENERAL PRINCIPLES OF TREATMENT

Pharmacodynamic Aspects

The pharmacodynamic aspects deal with the biological effects of the drug, including the therapeutic and the toxic effects.[16] In the laboratory, under experimental conditions one can accurately establish the minimal effective dose of the drug and show an increasing therapeutic effect with increasing the dose, as well as define the toxic range of the dose. The dose-response principle holds true in clinical situations in general. It would be desirable to be able to carry out pharmacodynamic measurements, i.e., to quantitate the severity of the disease process and the therapeutic and toxic effects of drugs in patients. This would allow valid comparison of the existing effective drugs and be useful in the development of new drugs. Numerical values of drug effects can be obtained in some clinical situations such as prothrombin time with anticoagulants. More often than not, however, measuring the therapeutic and toxic effects in patients, poses various problems. Thus, an epileptic patient may not remember all the generalized tonic-clonic seizures he has had; and the observer may lose count of the absence episodes. Prolonged electroencephalographic recording and telemetry will provide accurate seizure counts, but due to the complexity of the apparatus, are not generally applicable yet. It is also not easy to accurately quantitate the clinical manifestations of intoxication due to high doses of some drugs such as anticonvulsants. Here, one may use numerical

grades on, for instance, a scale of 0 to 5 in estimating the severity of sedation or equilibrium disturbances.

With some drugs, the therapeutic and toxic effects correlate to some extent with the concentration of the drug in the blood.[2,9,14] Thus, the blood levels can be used as rough guidelines in evaluation of the pharmacodynamic parameters. One must realize, however, that the severity of the disease process varies among individual patients, as does the tolerance to intoxication. Therefore, a universally applicable therapeutic dose and blood concentration for a drug is not expected.[14]

The aim in the therapy is to match the severity of the disease with a dose that renders effective drug concentrations. In patients with very severe disease process, this may require doses and concentrations which cause intoxication or other intolerable side effects. A compromise dosage that produces the greatest benefit and the least intoxication or side effects may have to be settled for in these patients. Adjusting the dose to achieve effective concentration of the drug is facilitated by knowledge about some aspects of the pharmacokinetics of the drug.

Pharmacokinetic Aspects

Pharmacokinetic aspects deal with the fate of a drug in the organism and are reflected mainly by the measurements of concentrations of the drug (and its metabolites) in the available body fluids and tissues.[3,6,16] Knowledge of the fate of the drug is helpful in obtaining the best possible therapeutic effect with an agent. The pharmacokinetic aspects relevant in treatment are (1) absorption (indicating how soon to expect the effect), (2) elimination (indicating how long the effect may last), and (3) distribution (indicating when and how much of the drug might reach the desired location).

Absorption There are two major concerns regarding drug absorption: (1) the time at which the peak blood level occurs following oral ingestion and (2) the total amount absorbed from a dose. A rapid absorption peak is desirable with analgesics and antimigraine drugs. Incomplete absorption may necessitate parenteral administration.[3,6]

Many drugs used in the treatment of disorders of the nervous system are well absorbed. These include most of the antiepileptic drugs, cholinergic drugs and antimicrobial agents. Anticholinesterases, on the other hand, are incompletely absorbed, and the oral dose greatly exceeds the parenteral dose.

The rate and completeness of absorption generally depends upon the physical-chemical properties of a drug such as solubility, ionization and particle size.[3,16,21] Furthermore, the absorption of a drug can be enhanced or inhibited by the previous or simultaneous ingestion of other substances. For instance, the

absorption of ergotamine is enhanced by caffeine. The absorption of phenytoin, on the other hand, may be inhibited by simultaneously ingested antacids; thus, a treatment failure with an otherwise effective agent can result from poor absorption in an individual patient, a situation which can be remedied by removing the inhibiting agent. Taking drugs with meals generally does not reduce the total amount absorbed, but tends to delay the absorption peak.

Elimination The rate and mechanism of the elimination of a drug depends basically upon its physical-chemical properties. Many drugs must undergo extensive and nearly complete biotransformation before they can be eliminated, while others are excreted unchanged in large amounts.[3,4] The rate of elimination of the active drug determines the duration of the effect of a single dose and influences the extent of accumulation of the drug in the body during chronic administration. The elimination rate to some extent parallels the plasma half-life.

The plasma *half-life* is defined as the time it takes for the plasma level to decline 50 percent from a previous value.[16,21] That decline is usually exponential. Drugs with a short half-life such as anticholinesterases need to be given frequently, if continuous, effective concentration is to be maintained. Several antiepileptic drugs have long half-lives and can be given once a day. Following the onset of chronic administration of drugs, there is a rise of drug concentration in the body over a period of days, until the intake and output are in balance and a plateau or steady state is achieved. Only then can one expect to see the maximum effect of a given dose. Empirically, it has been proven that the time it takes to reach the steady state or maximum concentration with a given dose is 4 to 6 times the half-life. Thus, if the half-life of phenobarbital is approximately 3 days, the achievement of steady state takes over 2 weeks. Although the half-life of a drug in the majority of patients falls into a definable range of values, it is important to know that variations among individuals can be considerable; and that the half-life of a drug can change with age[20] in the same individual. The half-life and the rate of elimination of a drug can be influenced by a variety of factors. Thus, alkalinization enhances the elimination of phenobarbital, while phenobarbital, in turn, can enhance the elimination of other drugs by inducing enzymes that are involved in their biotransformation.

Biotransformation of drugs usually effects an increase in the solubility of the drug, thus preparing it for elimination.[4,16] Frequently occurring metabolic steps include hydroxylation, followed by conjugation with glucuronic acid or sulfate. In this process, the drug also becomes inactivated. Drugs that carry alkyl radicals such as methyl are usually first dealkylated. The des-methyl or "nor" intermediary metabolites are usually pharmacologically active until they are further metabolized and eliminated.

The biotransformation of drugs is carried out largely in the liver by the

microsomal enzyme system. The rate of activity of these enzymes is determined in part by genetic make-up of the patient, but it can also be influenced by environmental factors. Among the environmental factors of clinical significance are other drugs that can either enhance or inhibit the enzymes involved in the biotransformation of the primary drug. These drug-drug interactions at the drug biotransformation stage are seen with some antiepileptic drugs[12] and with coumarine anticoagulants[19] leading to a change in the half-life and the rate of elimination, and consequently to a change in dosage requirement.

Distribution After absorption the drugs distribute from the blood into the tissues according to their ability to penetrate the various compartments and the existing drug concentration gradients.[16,18] Active transport mechanisms through the cell membranes may be involved in the distribution of some drugs. With the majority of drugs used in the treatment of nervous system disorders, it is important that they can penetrate into the nervous tissue. The ability to pass the blood-brain barrier depends upon the physical-chemical properties of the drug and generally increases with increasing lipid solubility of the agents. Most antiepileptic drugs reach the brain easily in concentrations equal to concentrations in the blood or higher. The speed of entry, however, varies among drugs. For instance, diazepam concentration in the brain reaches maximum within 5 minutes after intravenous injection, that of phenytoin takes 10 to 20 minutes, while phenobarbital concentration reaches maximum in about 30 minutes. This is relevant when treating status epilepticus with phenobarbital in that repeating the phenobarbital dose too soon because of lack of rapid action, may, eventually, result in overdosing. Many antimicrobial agents, on the other hand, pass the blood-brain barrier or spinal fluid barrier modestly or poorly, although that passage may be enhanced considerably by inflammation. Those antimicrobial agents that penetrate poorly, even in the presence of inflammation, need to be given intrathecally or intraventricularly (if they are the only agents to which the infecting organism happens to be sensitive).

Low ability to enter the central nervous system may also be an advantage. Such is the case with some anticholinesterases. They can be given to patients with myasthenia gravis in large amounts without causing central nervous system related side effects.

Penetration of levodopa into the brain is modest, and necessitates a relatively high dose and blood concentration to achieve therapeutic effect. This creates a problem because the peripheral dopa decarboxylase then produces large amounts of dopamine outside the nervous system which leads to systemic side effects such as vomiting and hypotension. The situation can be alleviated, fortunately, by using dopa decarboxylase inhibitors which do not enter the brain, thus preventing excessive systemic dopamine formation.

Plasma protein binding has some effect on drug distribution. Many drugs are bound to plasma proteins, mostly albumin, to a greater or lesser extent.[8,10] For instance, of the total phenytoin concentration in plasma, 90 percent is bound. This leaves 10 percent free to penetrate into the tissues. A decrease of phenytoin binding to 80 percent, as is often seen in patients with chronic uremia or liver disease,[17] doubles the amount of free drug to enter the brain. The clinical corollary to that is, that often in uremic patients very low total plasma phenytoin concentrations may be effective.

Pharmacogenetic Aspects

Pharmacogenetic factors are relevant in drug therapy of nervous system disorders mainly by their influence upon the activity of enzymes involved in the biotransformation of some drugs.[1,7,22,23] For instance, there is a (rarely occurring) familial incidence of individuals who can metabolize and eliminate only small amounts, (100 to 200 mg), of phenytoin per day. The common dose of 300 mg daily constitutes an overdose to those slow phenytoin metabolizers, and leads to severe drug accumulation and intoxication. Conversely, other individuals may metabolize phenytoin rapidly and thus require higher than average doses to maintain average effective drug concentrations in the blood.[11]

The genetic make-up of a patient can influence his response to phenytoin indirectly, via his phenotype regarding isoniazid inactivation. Isoniazid strongly inhibits phenytoin biotransformation. Its concentration with the common clinical doses, however, in moderate and fast isoniazid inactivators remains too low to have a significant effect upon phenytoin biotransformation. In the very slow isoniazid inactivators, on the other hand, concentrations of active isoniazid that are sufficient to cause marked phenytoin accumulation and intoxication can be present. Thus an epileptic, who is otherwise an average phenytoin metabolizer, becomes a slow phenytoin metabolizer if he acquires tuberculosis, is given isoniazid, and happens to be a very slow isoniazid inactivator. His phenytoin dose then needs to be adjusted downward accordingly.[13] The slow isoniazid inactivator is also liable to other complications related to isoniazid per se, such as peripheral neuropathy and hepatitis.[7]

Another (rarely occurring) genetic anomaly is associated with abnormal pseudocholinesterase. Patients thus inflicted have an exaggerated response to succinylcholine when, for instance, treated with this agent for tetanus.[15]

There is some evidence that the degree by which hepatic drug metabolizing enzymes can be induced by the "inducer" drugs is influenced by the genetic factors.[24,25] It has been demonstrated that the degree of acceleration of aminopyrine metabolism by phenobarbital is identical in identical twins but may vary considerably in non-identical twins. Based on clinical observations, it appears that the phenobarbital effect upon the biotransformation and elimina-

tion of other drugs also varies considerably among individuals. Addition of phenobarbital may cause a considerable decline of phenytoin blood level in some rare patients but may have little, if any, effect in the majority.[11,12] It may increase the requirement of coumarine anticoagulant dosage in some patients and have little effect in others. It is fair to assume that these individual differences are at least in part influenced by the genetic make-up of the patients.

BLOOD LEVELS

Clinical experience has shown that monitoring of drug blood levels can be useful for obtaining the optimal therapeutic success. This is particularly true with those drugs that need to be given continuously to control symptoms of an established disease process.[2,9,14,26] The usefulness of application of drug blood levels in the clinical management of patients has evolved and gained recognition during the past decade and a half. This has prompted increasing numbers of clinical laboratories to set up capability for performing these assays. There are currently available, assays of many drugs that produce concentrations in the blood in the microgram per milliliter range. Availability of blood levels of drugs found in nanograms or picograms per milliliter is still limited.

Of the drugs used for the treatment of nervous system disorders, blood level determinations are now generally available for most major antiepileptic drugs and some analgesics, antimicrobial agents and vitamins. Less readily available at the present time are measurements of ergot preparations, anticholinesterases and levodopa. The reliability of these assay values depends upon the methods used and the experience and the strictness of the quality control of the laboratory.

The rationale of the application of blood levels in clinical management is based on the following empirical findings.

(1) Pharmacokinetic findings: There is a reasonably good correlation between the dose and the blood level of many drugs in most individual patients. When the dose is increased, the blood level rises fairly proportionately until the dose becomes high enough to saturate the elimination mechanism; then a disproportional upswing of blood level occurs. The same dose does not usually produce the same blood level in all individuals. The differences in blood levels with the same dose may reflect individual differences in absorption, biotransformation and/or elimination, and may be caused by genetic or environmental factors. There is, however, a definable range of blood levels from a given dose. Defining the range of blood levels to be expected in the majority of patients with a dose is clinically useful. If the observed blood level value in a particular patient is well below or above the level range expected from his dose, one may