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Drug-Induced Neurological Disorders

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3rd revised and expanded edition
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Foreword

When a new drug first enters preclinical studies, these are directed to determine the mechanism of primary action, pharmacokinetics, and in vivo toxicity. Though screening tests are undertaken, very little information is usually obtained on secondary activities of the drug and on its interaction with other drugs.

When a potential pharmaceutical compound moves from the preclinical to the clinical phase of study, this introduces another order of complexity, mainly the difference between human metabolism and that of animals. Moreover, the complexity of the human nervous system and human awareness provides the basis for a whole new series of effects and side effects. Some of these become obvious in Phase I trials in humans, but the number of subjects is always small at this stage. As the drug moves into Phase II and Phase III studies, less frequent toxicity reactions begin to be experienced. These include the development of antibodies with a host of immunologically mediated side effects. Additionally, in the human population, there are some individuals with unusual metabolisms who produce abnormal pharmacokinetics, and hence high blood levels of the drugs. Phase III and IV studies that are used to assess efficacy and the risk-benefit ratio of a medication often involve 500 to 5,000 patients. With this number, it might be expected that most of the potential side effects of a drug would have been discovered by the end of this stage of pharmaceutical development.

Unfortunately, this is not so. Some idiosyncratic reactions have an incidence of only 1 in 10,000 or 1 in 100,000 patients. If the idiosyncratic reaction is fatal, even reactions with this rarity may lead to withdrawal of the trial medication. Additionally, many of the uncommon adverse drug reactions (ADRs) go unrecognized for a considerable period after the drug is released. Reasons include that the ADR is very different in type from the primary effect of the drug, that the ADR is very similar to a spontaneous human disease, or that the ADR only results from drug interaction with other drugs or metabolic disorders. It is not until a pattern of such disorders is recognized in a cohort of patients taking a certain drug that it comes under suspicion for being responsible for an ADR.

Post-marketing surveillance by pharmaceutical companies is especially important for recognition of these ADRs. Companies are generally effective in collecting and cataloging such reports. The World Health Organization maintains a registry of adverse drug reactions. The medical/scientific literature is also an important vehicle for reports of potential ADRs, for this is often the mechanism by which clinicians raise the first suspicions that an unusual medical complication might be an ADR. When a very unusual medical condition is first seen, it is never certain whether it is due to a drug or not. When it is seen a second and a third time in relation to treatment with a certain drug, than the association becomes more likely. It is essential that physicians have a high index of suspicion. Undoubtedly, a very large number of such ADRs are missed, either because the physician was suspicious but never saw a second instance of the disorder, or was too busy to report it. The rate of reporting of ADRs is undoubtedly quite low throughout the world.

However, to be set against this low rate of recognition of ADRs is the fact that the literature and pharmaceutical industry data banks are full of single case reports of potential complications of every drug. A glance at the Physicians’ Desk Reference reveals the enormous range of complications of each drug that the practicing physician is warned about. One of the problems of such product information is that ADRs recognized early in the development of a drug, even though they may be extremely rare, tend to get fossilized in this information. No attempt is ever made to eliminate reference to such side effects that turn out to have extremely low frequencies. It is likely that many such reports of apparent ADRs are not due to the drug in question, or are rare idiosyncratic reactions. From a scientific point of view, one would like some index of the frequency of each suggested ADR. Unfortunately, not only is the frequency of reporting low, but certainty of the causality is often absent, and the denominator of drug dose times patient years is unknown. We might hope that patient data banks in this computer age would help. Record linkage studies such as those by Mayo Clinic or in Oxford may help, but rarely are pharmaceutical agents sufficiently clearly targeted for these studies to produce information on more than the common ADRs and common drugs.

Turning to the nervous system, we are all aware that over the last 15 years there has been an enormous explosion in knowledge of basic neurosciences. In particular, enormous strides have been made in the...
understanding of basic neurochemical mechanisms of the action of the nervous system, and the discovery of new classes of receptors, neurotransmitters, second messengers, and fields of neuronal functions. Each discovery has opened the way for the development of new, highly directed, and potent pharmaceutical agents. As the range in potency of these has increased, the potential for drug interaction has also increased exponentially. Such interactions can include the development of excessive therapeutic action, the blocking or abnormal increase in a normal neurological function, or frank neurotoxicity. Again, such changes will not be recognized as a specific ADR without the presence of a very observant neurologist with a high index of suspicion. The complexity of the nervous system and the rapid advance in the development of neuroactive substances explains why neurology is the major discipline experiencing this exponential rise in drug-induced disorders.

How can we improve the dissemination of information about neurological ADRs? One source of information is the Physicians’ Desk Reference. For each drug, there are a reported series of complications divided under region of the body. Under the central nervous system, almost all drugs are reported to cause nausea, drowsiness, dizziness, and tremor. It is interesting that these are also the most frequent side effects experienced by subjects taking placebo medication in double-blind controlled trials. Hence, they may not be due to the specific effect of the drug in question. Another source of information is to review textbooks of disease. In the field of neurology, each chapter or monograph includes some description of drug toxicity affecting this system. Textbooks of neuropharmacology and therapeutics of neurological disease often have important information, but are never comprehensive. They only deal with the most common complications that are well recognized. The data banks of ADRs, such as those of the WHO and individual pharmaceutical firms, can be helpful. However, for the practicing clinician, one has to have developed a suspicion that the unusual neurological reaction is due to a certain drug before one can approach any of these data banks. Access to pharmaceutical company reports may be difficult, for these companies are often unwilling to provide full information, and the rate at which ADRs are reported and their statistical reliability has already been discussed.

Often the neurologist comes at the situation from a different direction. The patient is exhibiting an unusual neurological syndrome, and the suspicion arises whether this could be due to an ADR. It must be remembered that polypharmacy is the order of the day, particularly in the elderly, where, if there are not five different diseases each receiving three different medications, the individual is quite unusual!

Hence, there is a great need for a monograph such as that of Dr. Jain. This attempts to collate the frequency of the rare drug-induced neurological disorders affecting each area of the nervous system and each of the many neurological functions within each area. Dr. Jain brings an unusual experience to this task. He is a neurosurgeon and neurologist who, for many years, has been a medical advisor to the pharmaceutical industry. He has an understanding of the records of ADRs in the pharmaceutical firms, and hence has access to many that are normally not surveyed in producing a compilation of drug-induced neurological disorders. He has also undertaken a very exhaustive review of the clinical literature dealing with neurological ADRs. The reader is provided with a very succinct collection of this information arranged in the clinically relevant format of individual regions of the nervous system and neurological functions.

Dr. Jain well recognizes the limitations and drawbacks of the data sources concerning ADRs that I have highlighted above. His first chapter on epidemiology and clinical significance is an excellent critical review of this field. The reader will do well to come back again and again to these points in reading the remainder of the book. In summary, there is an enormous amount of information in this book that will be of great use to the practicing neurologist.

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Preface to the Third Edition

A considerable amount of new information on adverse reactions to drugs has been published during the decade since the publication of the second edition. However, most new information could fit into the chapters that appeared in the second edition and only two chapters needed to be added to cover the adverse effects of biological therapies and anesthetics on the nervous system. The style of presentation has changed from the earlier editions and some of the older references to the literature have been deleted. Many of the adverse effects, which were initially supported by publications, are now well recognized in practice. Moreover, it would be impossible to include references to all the case reports as the space for the bibliography would then exceed that for the description of adverse reactions. Many of the well-known adverse effects are no longer being published and the number of publications is not an indication of the frequency of occurrence of a particular event. The bibliography is now more selective and includes approximately 2,000 citations. In addition to more recent publications, some classic papers have been retained.

The author gratefully acknowledges the useful suggestions provided by the readers of the second edition and these were taken into consideration during the preparation of the third edition. I would like to thank Dr. Robert Dimbleby, Managing Editor of Hogrefe Publishing, for his personal attention to this project.

K. K. Jain

Preface to the Second Edition

A considerable amount of new information on adverse reactions to drugs has been published during the four years since the publication of the first edition. The information could fit into the chapters as organized for the first edition and no change was made in the number of chapters. Several new drugs, including some biotechnology preparations, have been introduced in medical practice and their adverse effects have been included in this edition. Considerable new information about older drugs and the pathomechanism of drug-induced neurological disorders is now available. A symptom index has been added to lead the reader to the appropriate table in the text which lists the drugs associated with that symptom or disease. A description of the role of individual drugs can be found in the following text in the same chapter. The bibliography has now been enlarged to include 3,835 citations. There were many more that could not be included due to limitation of space.

The author gratefully acknowledges the useful suggestions provided by the readers of the first edition and these were taken into consideration during the preparation of the second edition. I would like to thank Mr. Robert Dimbleby, Editor, International Division of Hogrefe & Huber, for his personal attention to this project.

Preface to the First Edition

The purpose of this book is to present an account of drug-induced neurological disorders (DIND) which should be considered in the differential diagnosis of various neurological conditions. Although adverse drug reactions are under-reported, there is a vast literature on this subject but hitherto no book has been available on this subject. Publications on this subject are scattered in various journals and monographs, covering several medical subspecialties, and are not easily accessible to a practicing physician.

Using my background knowledge of neurology and of monitoring the safety of pharmaceutical products, I have critically evaluated over 5000 publications on this topic. About 3000 of these have been selected as
references and information has been organized into tables and a readable text. Each disorder is discussed with listing of responsible drugs rather than description of all neurological adverse effects of individual drugs. Some drugs appear in more than one chapter. A physician investigating drug-induced peripheral neuropathy needs only to refer to the relevant chapter which contains cross references to other neurological effects of some of these drugs.

Pathomechanisms of various types of DIND has been discussed as these are important for the understanding, prevention, and treatment. This subject will also be of interest to neurologists as well as health professionals working in the area of drug safety for the pharmaceutical industry and the health authorities.

I would like to acknowledge the useful advice and help of Prof. P. Krupp, Head International Pharmacovigilance, Sandoz Ltd., Basel, during preparation of this book. Finally, I would like to thank both directors of Hogrefe & Huber Publishers, Dr. Christine Hogrefe and Dr. Thomas Tabasz, as well as the editor Mr. Robert Dimbleby for their personal attention to this project.

K. K. Jain
1 Epidemiology and Clinical Significance

Introduction and Terminology

The term “drug-induced neurological disorders (DIND)” as used here refers to unintended or undesirable effects on the nervous system caused by drugs or associated with drug use. Such disorders are classified as iatrogenic disorders, a term which also covers other illnesses such as ones caused by other therapies, e.g., surgical procedures, or even neglect in carrying out treatment which results in harm or injury to the patient. The use of the word “induced” within the term DIND does not necessarily imply a proven causal relationship of the drug to the disorder. The drug may affect the nervous system directly (primary neurotoxicity) or indirectly by other systemic disturbances caused by the drug (secondary neurotoxicity). DIND includes disorders caused by inappropriate use or overdose of a drug or interaction with other drugs but environmental and industrial toxins are excluded.

Terms that are used commonly in reference to adverse effects of drugs are defined by the World Health Organization (WHO) as follows:

**Adverse Event/Adverse Experience (AE):** This is any untoward medical occurrence that may present during treatment with a pharmaceutical product but which does not necessarily have a causal relationship with this treatment.

**Adverse Drug Reaction (ADR):** This is an event which is related or suspected to be related to the trial medicine. An ADR is a response to a drug which is noxious and unintended, and which occurs at doses normally used in man for prophylaxis, diagnosis, or therapy of disease, or for modification of physiological function.

**Side Effect:** This is any unintended effect of a pharmaceutical occurring at doses normally used in humans which is related to the pharmacological properties of the drug.

Historical Aspects

The concept of harm resulting from medical treatment is more than 3,500 years old. The Code of Hammurabi in the seventh century BC prescribed penalties for physician errors that resulted in harm. Similarly, the Roman law in the first century AD included penalties for such harms. Complications of medical treatment have been described by all the great medical writers throughout the past centuries. Around the middle of twentieth century, with the development of pharmacotherapy, increasing attention was given to adverse drug reactions. They were not viewed merely as iatrogenic phenomena but rather inevitable consequences of medical progress and introduction of new drugs. Among the earliest adverse effects of therapies to be recognized were those of the nervous system. Polyneuropathies as complications of vaccinations were recognized in 1934 (Cathala 1934) and encephalopathies in 1949 (Globus & Kohn 1949). Payk (1974) was the first to separate complications resulting from treatment of neurological disorders from neurological complications resulting from treatment of other systems. Around the same time pathogenesis of iatrogenic neurologic disorders was discussed under a dozen categories, nine of which concerned adverse drug effects (Yajnik & Solanski 1972). Most of the complications related to antibiotic and hormone therapy. The first work to focus on iatrogenic pathology in neurology was published in 1975 (Arnott & Caron 1975). There was, however, a concern regarding the increasing number of adverse effects and surveillance systems were developed during the past 30 years for collection and analysis of adverse drug reactions.
Epidemiology of DIND

The exact incidence of DIND is unknown. Reported adverse effects of drugs on the nervous system form only a small proportion of all neurological disorders but they are under-recognized and under-reported. ADRs, both from clinical trials and postmarketing surveillance, are usually reported to the manufacturers of the product involved. The manufacturers make the initial assessment of these reports and file the ADRs with the health authorities of the countries involved according to the regulatory requirements. The World Health Organization also maintains a data base for ADRs. The reporting rate of ADRs is low and even in countries with well organized safety surveillance systems, such as Sweden and the United Kingdom, all the ADRs are not reported.

The incidence of ADRs in hospitalized patients has been determined by meta-analysis of 39 prospective studies from US hospitals (Lazarou et al 1998). The overall incidence of serious ADRs was 6.7% and of fatal ADRs was 0.32% of hospitalized patients making these the fourth leading cause of death in the US after heart disease, cancer and stroke. The incidence is much higher than that assumed from the spontaneous reporting system which identifies only about 1 in 20 ADRs. In a study of 18,820 hospital admissions in the United Kingdom, 1,225 were related to an adverse drug reaction, giving a prevalence of 6.5%, with the adverse drug reaction directly leading to the admission in 80% of cases (Pirmohamed et al 2004).

Only a small fraction of the ADRs are published as case reports or as a part of the results of clinical trials of new drugs. Most of the information received by the pharmaceutical companies is inadequate for establishing the diagnosis of drug-induced neurological disorders but it is used for answering questions from physicians and for making decisions for inclusions of adverse reactions in basic drug information and package insert.

Most of the products listed in the Physicians’ Desk Reference include a mention of at least one untoward effect which relates to the nervous system. Entries in the list of adverse reactions is not always based on medical judgment but may be a measure to protect the manufacturer against legal liability by having declared that such an adverse reaction has been reported. The ADR may not be causally related to the drug and this information is not of significant practical value for a neurologist.

The frequency of occurrence of AEs in clinical trials can be calculated and compared with that in the placebo group. An AE is considered to be an ADR only if the relation to the drug is proven or suspected. Because the size of the clinical trials is limited and seldom involves more than 500 patients, rare ADRs cannot be expected to show up in these trials. Postmarketing surveillance continues for the lifetime of a drug to detect such ADRs. The frequency of occurrence of ADRs in this phase is difficult to determine because of poor reporting rate and lack of knowledge of the denominator. The number of patients exposed to the drug is sometimes estimated from the quantity of the drug sold and the standard dose for a patient. These figures are not reliable because the amount of drug used by individual patients varies a great deal and all the drugs sold are not administered to the patients.

Another way to estimate the frequency of drug-induced neurological disorders is to review the case records from hospitals. Of 1,500 neurological consultations at John Hopkins Hospital, 14% of the conditions were iatrogenic but only 1% of these were drug-related (Moses & Kaden 1986). In the UK, 2% of the neurological admissions to a general hospital were drug-induced (Morrow & Patterson 1987). A study from Sweden showed that fatal adverse drug reactions account for approximately 3% of all deaths in the general population, and two thirds of these were due to hemorrhages, of which 29% involved the nervous system (Wester et al 2008). Antithrombotic agents were implicated in more than half of the fatal adverse drug reactions.

Assessment of Adverse Drug Reactions

Causality Assessment

Several methods of causality assessment of adverse drug reactions (ADRs) are in use which include questionnaires, algorithms, and computerized Bayesian approach. None of these methods have found universal application because they are tedious, time consuming, and expensive. Stephens (1987) reviewed 22 methods of causality assessment and concluded that Bayesian approach (Naranjo et al 1992) was the only reliable method. In practice causality is usually assessed by global judgment, i.e., opinion of the causal relation of the drug to the event after taking into consideration the available relevant information.
such as the temporal relationship, results of dechallenge (discontinuation of the medication) and rechallenge (re-exposure to the medication), etc. The importance attached to each of these factors varies among the assessors and often no reason is given why a particular causality rating was assigned to an AE. In order to standardize the assessment of AEs, Jain (1995) has devised a method of triage of the AEs using a questionnaire with the following seven questions:
1. Is there a biological explanation (pathomechanism) for the AE?
2. Is the AE temporally related to the drug AE?
3. Is dechallenge positive?
4. Is rechallenge positive?
5. Is the event already known and documented?
6. Is the AE known to occur during the course of the natural disease?
7. Is the AE known with the concomitant drug?

The answers are weighted and scored to allocate the ADRs to the following categories: A (Probable); B (Possible); O (Unlikely or insufficient information for assessment). These are approximate terms because of soft nature of the data available. The term definite is used rarely. Possible means that such a reaction can take place with the drug and sometimes this term is used simply because the possibility cannot be excluded.

Diagnostic Assessment

ADRs are often reported as symptoms and these should be linked to a provisional neurologic diagnosis. There are two limitations to this assessment:
1. The assessor does not have access to the patient and further information is usually difficult to obtain.
2. Drug safety specialists are rarely neurologists and the average medical assessor does not have adequate neurological knowledge to carry out this step.

Evaluation of Literature

Publications showing the association of various drugs with DINDs fall into the following categories:
– Single case reports. This is the weakest evidence, particularly if the case is not well documented. Unfortunately this constitutes the bulk of the literature on adverse reactions to drugs. Such case reports are usually not peer-reviewed. Reputable journals insist on minimum essential information before publishing these reports but many inadequately documented reports also get published in obscure journals. Whether the causal relationship is proven or not, such reports cannot be ignored. Some of these reports may encourage other physicians to submit similar unreported cases for publication.
– Multiple case reports. This is a stronger evidence than that provided by single case reports.
– Reports of clinical trials of new drugs. These provide a useful source of AEs for assessment.
– Drug safety reviews. These serve a useful purpose of analyzing the cumulative evidence in literature. A good review should provide a critical analysis of the information, comments on pathomechanisms of DIND, and possibly suggestion for prevention and treatment.
– Toxicology studies. Animal experimental studies provide toxicological information which may or may not be relevant to humans DINDs but may provide an insight into pathomechanisms.
– Epidemiological studies. These are the most useful source of information, particularly if they are properly designed prospective studies.
– Textbooks on adverse drug reactions. Some well known DINDs are listed in recognized textbooks of adverse drug reactions and can be quoted even though reference to the original source is not always provided.

Some authors have attempted to stratify the information on ADRs according to the strength of evidence into various levels. The major drawback is that a rigid system of evaluation cannot be applied to “soft” data that is available from drug safety literature. The quality of information available varies from one drug to another and application of strict criteria of evaluation might exclude information which may be useful even though it is anecdotal. Evidence is presented as available and pathomechanisms are described where possible. Drugs frequently mentioned and reported in relation to certain disorders are marked with asterisks in various tables and the readers are left to make their own judgment.

Clinical Significance

Drug-induced neurological disorders (DIND) can mimic neurological disorders due to other causes.
However, when there is a reasonable suspicion of association with a drug or a known or plausible pathomechanism for DIND, the drug should be considered in the differential diagnosis. For practical purposes ADRs in the categories A (probable) and B (possible) are taken into consideration.

DINDs are presented according to various neurological systems. It has the advantage that a physician or a neurologist who is investigating a patient with a neurological problem has access to information about drugs which can cause that problem. One drawback is that ADRs seldom involve only one neurological system. There may be involvement of other systems of the body or involvement of another neurological system.

Assessment of a DIND in a patient receiving a multimodal treatment is difficult. Patients undergoing organ transplants are liable to neurological complications of the primary disease, the procedure and the drugs which include immunosuppressants and antibiotics which are liable to induce neurological disorders. Critical decisions need to be made in case of liver and heart transplants. For this an understanding of the pathomechanism of neurological disorders and their natural history is important. An immunosuppressant may not need to be discontinued if the evidence for causal relationship is weak and the neurological complications are transient. In a study on liver transplant, the time of occurrence of CNS complications and the risk factors identified suggest that the pre-transplant condition and the surgical phase are the two most critical periods for developing CNS complications. Patients undergoing liver transplant with a severe pre-transplant medical disorders are at higher risk of experiencing CNS complications.

### Neurologic Symptoms as ADRs

ADRs can present with a neurologic symptom which may be an entity in itself with several mechanisms and a number of widely differing pharmaceutical agents may be the causative agents. An example is headache which is discussed in Chapter 6. The following are some of the symptoms and their causes which can be ADRs of drugs:

#### Drop Attacks and Falls

The following can be considered in the investigation of a patient with drop attacks and falls:
- Behavioral toxicity
- Dementia
- Movement disorders, e.g., parkinsonism
- Loss of consciousness due to syncope or seizures
- Transient ischemic attacks
- Neuromuscular disorders: neuropathy and myopathy
- Myelopathy
- Cerebellar disorders
- Vestibular disorders

**Neurogenic Bladder.** A patient who presents with neurogenic bladder dysfunction can have any of the following drug-induced causes:
- Encephalopathy
- Myelopathy
- Autonomic neuropathy

**Ataxia.** A patient presenting with ataxia may have the following drug-induced causes affecting different parts of the CNS:
- Cerebellar: degeneration or hemorrhage
- Cerebral: encephalopathy
- Spinal cord: myelopathy with posterior column involvement
- Brainstem: transient ischemic attacks
- Frontal lobe lesions in encephalomyelitis

**Vertigo and Dizziness.** Different drugs may produce these symptoms by a number of neurological as well as systemic disturbances, such as the following:

**Neurological:**
- Vestibulotoxicity, e.g., aminoglycoside antibiotics
- Cerebellar dysfunction, e.g., anticonvulsants
- Depression of central integrative centers, e.g., hypnotics

**Systemic:**
- Hypotension
- Vasculitis
- Hematological disorders

**Dysarthria.** This is disturbance of normal speech articulation and can be affected by drugs acting at different levels of the nervous system:
- Cerebral cortex. Slurring of speech can be due to effect of sedative-hypnotic drugs on the cerebral control of speech.
- Central anticholinergic effect of some drugs such as tricyclic antidepressants can lead to speech block, i.e., halt in normal speech patterns.
- Cerebellum. Scanning speech can result from drugs such as lithium and phenytoin which have a toxic effect on the cerebellum.
Neuromuscular blockade, an adverse effect of drugs such as aminoglycoside antibiotics, can produce a myasthenic syndrome and cause fatigability of speech.

Oro-facial movement disorder in tardive dyskinesia due to neuroleptic therapy can make articulation difficult.

Vomiting. Nausea and vomiting are prominent symptoms of a variety of neurological disorders. No clear protective role, such as that of vomiting associated with gastric irritants, can be defined for this. The pathomechanism of vomiting is neurological: stimulation of the vomiting center in the brainstem. Vomiting is associated with the following neurological disorders which can be drug-induced:

- Raised intracranial pressure: benign intracranial hypertension
- Encephalopathy
- Aseptic meningitis
- Headache

Some drug-induced disorders are distinct neurological syndromes, such as tardive dyskinesia, serotonin syndrome, and eosinophilia myalgia syndrome. However, they need to be differentiated from naturally occurring neurological disorders.

Concluding Remarks

Drug-induced neurological disorders may be more frequent than they have hitherto been considered. They can mimic naturally occurring neurological disorders or induce drug-specific syndromes. Further studies are required to determine the pathomechanisms and the incidence of these disorders. The current methods of data collection for adverse effects of drugs are inadequate. In order to improve the current situation, it would be important to establish registries for drug-induced neurological disorders.

References


Pathomechanisms of Drug-Induced Neurological Disorders

Introduction

Pathomechanisms of drug-induced neurological disorders (DINDs) vary considerably and most of them remain unexplored. The mechanisms of toxicity associated with drugs can be grouped into pharmacologically mediated and those that are non-pharmacological. Pharmacologically mediated mechanism is defined as the interaction of the drug with its intended target or relevant receptor. Interaction with this intended target can result in an anticipated biological effect, such as the reduction in blood glucose by insulin, or in a previously unanticipated effect. Nonpharmacological effects are those unrelated to the interaction with the intended target, e.g., hypersensitivity reactions secondary to an immune response to the drug. It is sometimes difficult to draw a line between the desirable and undesirable effects of a drug for a neurological disorder. For example, intravenous diazepam may control status epilepticus but will make the patient drowsy for a while. Such transient neurological disturbances are considered a minor inconvenience, leave no permanent sequelae, and are outweighed by the therapeutic benefits of the drug. On the other hand, the central nervous system (CNS) may be affected by a drug for disorders of other systems. The various pathomechanisms of DINDs will be discussed under the following three categories:

- Direct mechanisms or primary neurotoxicity
- Indirect mechanisms, i.e., neurotoxicity is due to drug-induced disturbances of other organs
- Predisposing or risk factors for DIND: (i) related to the patient, or (ii) related to the drug

These mechanisms are discussed briefly in this chapter and further details are given in chapters dealing with individual disorders.

Direct Neurotoxicity

Role of the Blood-Brain-Barrier (BBB)

This barrier usually prevents the access of drugs to the fluid spaces of the brain. For direct neurotoxic effects the drugs usually have to cross the BBB. Despite this barrier, lipid-soluble molecules such as benzodiazepines readily enter the brain. A drug has to have the property of crossing the BBB to have a therapeutic effect on the CNS.

Damage to the BBB facilitates the passage of drugs which normally do not cross the BBB. Diseases in which the BBB is damaged, such as multiple sclerosis, malignant brain tumors and meningitis, would facilitate the direct neurotoxic effect of drugs. This point is discussed in further detail under the factors related to the patient.

Damage to the BBB

The access is facilitated if the BBB is damaged and the effect of drugs is seen in areas which lack the BBB. Drugs may bypass the BBB by retrograde intra-axonal transport. In the case of peripheral nerves, the BBB may be deficient in posterior root ganglia and perineurium making them susceptible to peripheral neuritis. Damage to the BBB can occur in a number of diseases which can predispose the patient to DIND when a neurotoxic drug is administered. Adriamycin, when injected into the cerebral ventricles of mice, passes into the surrounding parenchyma and is detected in the nuclei of both neurons and neuroglia. Therefore, it can be assumed that when adriamycin is given to patients with disturbance of the BBB, the drug may spread to the brain in the same way.

Retrograde Axonal Transport

It is a well established fact that neurons have the capacity to incorporate substances at the periphery...
of the axons and that material can be transported within the axons to the perikaryon by means of retrograde axonal transport. When toxic substances are picked up by axons and transported to perikaryon, death or degeneration of the neuron results, a phenomenon called “suicidal axonal transport.”

Direct Mechanisms of Neurotoxicity

These mechanisms are listed in Table 2.1. Because some of the drugs used for treatment of neurologic disorders target receptors in the nervous system, there remains the possibility of direct neurotoxic effect. For example, dopamine receptors, which are profusely expressed in the caudate-putamen of the brain, represent the molecular target of several drugs used in the treatment of neurologic disorders such as Parkinson disease. Although such drugs are effective in alleviating the symptoms of the disease, their long-term use could lead to the development of severe side effects (Lebel et al 2007).

Disturbances of Brain Energy Metabolism

These play an important role in drug-induced neurotoxicity. Various disturbances of brain energy metabolism are:

<table>
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ATP Synthetase Inhibition

Adenosine triphosphate (ATP) plays an important role in the brain. Under normoxic conditions ATP is synthesized almost exclusively by oxidative phosphorylation in the mitochondria and only a small portion comes from glycolysis. The rate of ATP production varies with rapid synthesis in areas of higher functional activity. ATP level is a reliable indicator of pathological events such as hypoxia, ischemia, hypoglycemia, seizures, and toxic effects of drugs, which may disrupt the homeostasis of brain metabolism by hindering energy production or enhancing energy consumption. Oligomycin is an example of a drug which inhibits ATP synthetase.

Uncoupling

There must be an adequate rate of electron flow and oxygen delivery as well as efficient coupling between electron transport and oxidative phosphorylation to maintain a balance between energy production and utilization. Uncoupling is dissociation of oxidative phosphorylation following its inhibition, for example, by barbiturates.

Disturbance of Oxygen Consumption

Oxygen deficiency, whether due to hypoxia, ischemia or drug effects, leads to depletion of glycogen stores and impaired mitochondrial respiration. ATP production is decreased. The resulting neuronal damage may be transient, reversible, or irreversible depending on the duration and extent of hypoxia. Oxygen transport from the blood to the tissues becomes impaired after chronic exposure to ethanol resulting in oxygen deficiency which restricts the synthesis of ATP.

Enzymatic Disturbances

Adenosine which is formed by enzymatic dephosphorylation of adenosine monophosphate (AMP) has an inhibitory effect on the central nervous system. The action of this enzyme is inhibited by theophylline intoxication leading to convulsions (Jensen et al 1984).

Selective Vulnerability of the Central Nervous System

Brain cells are selectively vulnerable because they express specifications which mediate essential functions, for example, neurotransmitter uptake. Neurons at specific sites are more vulnerable than those in other areas.
Sequelae of Disturbances of Brain Energy Metabolism

Sequelae of metabolic disturbances of the brain are: Ca\(^{2+}\) entry into neurons, free radical formation, and excitatory amino acids.

**Ca\(^{2+}\) Entry in Neurons**

Ca\(^{2+}\) normally acts as a second messenger and plays an important role in membrane stabilization and regulation as well as neurotransmitter release. However, it can also cause cell death under certain circumstances. Ca\(^{2+}\) enters the postsynaptic neurons mostly through receptor operated calcium channels which lie on dendrites. The most important transmitters are glutamate and related amino acids. The best known is N-methyl-D-aspartate (NMDA) receptor linked to calcium channels. Stimulation of this receptor allows mainly Ca\(^{2+}\) and some Na\(^{+}\) to enter the cell. Inside the neuron Ca\(^{2+}\) is a signal which is changed into various cell responses. During energy deficit Ca\(^{2+}\) may rise manifold and set off metabolic reactions with formation of free fatty acids (FFA) and cell destruction. Increased level of Ca\(^{2+}\) in mitochondria activates various dehydrogenases and alters the metabolic flux into the citric acid cycle. Cell viability is threatened when calcium homeostasis fails and calcium-activated reactions run out of control. There is considerable evidence for a link between Ca\(^{2+}\) influx and neuronal necrosis.

**Free Radicals**

A free radical is an agent with an unpaired electron in its orbit. Oxygen radicals are produced by normal cellular metabolism but are usually kept under control by several defense mechanisms. Such defense mechanisms may be overwhelmed when there is increased production of oxygen free radicals by hypoxia and disturbance of cellular metabolism. The central nervous system is particularly vulnerable to free radical damage because of its high lipid content.

Superoxide radical is water soluble but it can cross membranes through the anion channels and enter the extracellular space. Seizures are one manifestation of the attack of free radicals on neuronal membranes. Drug-induced seizures lead to increase of brain levels of FFA. Superoxide may arise from further metabolism of FFA. Oxygen radicals may also increase the permeability of BBB. Free radical mechanisms may contribute significantly to the expression of harmful properties of diverse, unrelated neurotoxic agents.

**Excitatory Amino Acids**

Current evidence suggests that poorly controlled release of these amino acids, their insufficient clearance from the extracellular space and the breakdown of surrounding GABA-ergic inhibition transform the excitatory transmitters into potential toxins. Pathogenesis of excitotoxic cell damage is shown in Figure 2.1.

**Mitochondrial Dysfunction**

Mitochondrial DNA is susceptible to mutations by endogenous as well as exogenous factors. Increased sensitivity to mutagenic factors may account for the mitochondrial DNA polymorphism within ethnic groups and mitochondrial disease associated with all mitochondrial DNA mutations, including DNA depletion. Mitochondrial damage is known to be caused by classic poisons such as cyanide and carbon monoxide.

**Neurotransmitter Disturbances**

Neurotransmitter disturbances are an important pathomechanism of adverse reactions of several drugs such as antidepressants which are aimed at manipulating this system for therapy. Some neurotransmitters involved in DIND are: serotonin (5-HT), norepinephrine (NE), dopamine (DA), and acetylcholine (ACH).

**Serotonin (5-HT)**

Both excess and depletion of this neurotransmitter can produce neurological disorders. Examples of drugs which produce depletion of serotonin are substituted amphetamine derivatives: 3,4-methylenedioxyamphetamine (MDMA), ecstasy, p-chloramphetamine (PCA), and fenfluramine.
All of these drugs release serotonin and cause depletion of 5-HT from most axon terminals in the forebrain. Decrease in brain levels of serotonin are considered to be due to drug-induced degeneration of 5-HT neurons or their projections to the brain. Anatomical and neuroimmunocytochemical studies have provided evidence for the axonal degeneration as well as reinnervation but it is not known if a normal pattern is established. MDMA use has been shown to produce depletion of dopamine and produce parkinsonism.

There is controversy regarding the effect of fenfluramine. Low doses of this drug which are effective in suppressing food intake in rats do not have an effect on the integrity of the 5-HT terminals in spite of increases in the brain levels of 5-HT. Higher doses, however, deplete brain 5-HT and produce toxic effects. Dexfenfluramine, a drug used as an appetite suppressant, was withdrawn from the market as an antiobesity drug. The drug is said to “prune” neurons and result in depletion of serotonin in the brain. Anti-depressants which block serotonin uptake increase brain levels of serotonin and may produce serotonin syndrome.

Pathogenesis of serotonin syndrome by drug-induced excess of serotonin is described in Chapter 21.

**Norepinephrine**

Blockage of NE uptake by antidepressants can cause tremor.

**Dopamine**

Blockage of dopamine uptake by antidepressants can lead to psychomotor activation and aggravation of psychoses. Dopamine depletion may result from enhanced metabolism of dopamine via MAO activity. This may explain why neurotoxicity of levodopa can be reduced by MAO-B inhibitor deprenyl.

**Acetylcholine**

ACh binding sites on cholinergic nerve terminals or sites postsynaptic to cholinergic neurons (nicotine receptors) are well known targets of neurotoxins. Atropine is an example of such a drug which can produce memory impairment by reducing ACh in the brain.

**Metabolite-Mediated Neurotoxicity**

The best example of metabolite mediated neurotoxicity is the use of designer drugs containing the contaminant MPTP. Their use results in severe Parkinsonian syndrome. MPTP leads to selective destruction of dopamine cell bodies in the substantia nigra and the loss of the striatonigral pathways. MPTP is not a neurotoxin itself; it is converted in the glia to 1-methyl-4-phenylpyridinium ion (MPP⁺) by monoamine oxidase B (MAO B) via the intermediate MPDP. MPP⁺ is a substrate for the dopamine re-uptake systems and accumulates within dopaminergic neurons, where it binds to neuromelanin, a black pigment found in the nigral nerve cells of primates. MPP⁺ is then concentrated in the mitochondria where it is thought to inhibit oxidative phosphorylation, leading to ATP depletion and changes in intracellular calcium concentration with subsequent cell death.

**Astrogliosis**

Traditionally the induction of gliosis has been regarded as a relatively late step in the cascade of events that follow neural cell damage. Gliosis, as measured by an increase in glial fibrillary acidic protein, can coincide with the earliest evidence of cell damage, often within hours of toxin exposure. Perhaps a signal common to a variety of toxicants initiates this response and further investigations are worthwhile for determining the common mediators of neurotoxicity.

**Drug-Induced Selective Cell Death**

Drugs may induce death of a selective population of neurons. Cyclosporine-induced selective cell death of oligodendrocytes in cortical cell cultures may help to explain the involvement of brain white matter in cyclosporine toxicity in humans. Pharmacological strategies, such as the use of neurotrophic factors, may prove useful in enhancing the benefit-risk ratio of using this drug.

**Unknown Mechanisms**

Some drugs such as fluorinated quinolone antibiotics are associated with neurotoxicity but PET scanning shows no abnormality of cerebral blood flow and metabolism. The mechanism of several other DINDs remains unknown.
Multiple mechanisms of neurotoxicity from drugs

An example of this is neurotoxicity of amphetamine. Mechanisms that mediate this damage involve oxidative stress, excitotoxic mechanisms, neuroinflammation, the ubiquitin proteasome system, as well as mitochondrial and neurotrophic factor dysfunction (Yamamoto et al 2010). These mechanisms are also involved in the toxicity associated with chronic stress and HIV infection, both of which have been shown to enhance the toxicity to methamphetamine.

Methods of Assessing Neurotoxicity

Study of adverse effects of chemical, physical, or biological factors on the function and/or structure of the nervous system is called neurotoxicology and is a branch of toxicology. Most of the studies on neurotoxicology have taken place within the last two decades. Most of the studies in neurotoxicology concern exposure to environmental and industrial chemicals and measurement of effect in experimental animals. The information accumulated in this fashion is not necessarily relevant to the study of neurological adverse effects resulting from the use of therapeutic substances in human patients. Nevertheless, the methods used are important for the investigation of the potential neurotoxicity of a drug. Some of these methods are used for testing neurotoxicity in the preclinical stage of drug development. These methods are listed in Table 2.2.

A discussion of these methods of assessing neurotoxicity is beyond the scope of this work. Some of the approaches will be mentioned briefly here.

Immunohistochemistry

This is a powerful tool for evaluating neurotoxic effect of drugs. It allows one to demonstrate neurotoxic effects of a substance through altered morphology or loss of stained structure as in the classical methods of histochemistry. In addition it can reveal the neurochemical identity of the affected structures. This technique has been used for demonstrating neurotoxicity of fenfluramine. It is a versatile and sensitive technique for localizing antigens of interest in the central nervous system with a high degree of resolution. Depletion of antibodies may not necessarily indicate neurotoxicity and this is a limitation of this technique. Immunohistochemistry is also being used to examine functional neuroanatomy by elucidating changes in the expression of proteins which appear to relate to drug treatment or neuronal injury.

In situ Hybridization Histochemistry

This methods utilizes standard physicochemical rules for DNA and RNA duplex formation, allowing one to form hybrids between mRNA molecules and labeled probes with complementary nucleotide sequences within the tissues. This technique is reviewed in more

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Neurotoxicoproteomics

Neurotoxicant-induced changes in protein level, function, or regulation could have a detrimental effect on neuronal viability. Direct oxidative or covalent modifications of individual proteins by various drugs are likely to lead to disturbance of tertiary structure and a loss of function of neurons. The proteome and the functional determinants of its individual protein components are, therefore, likely targets of neurotoxicant action, and resulting characteristic disruptions could be critically involved in corresponding mechanisms of neurotoxicity. Neuroproteomic studies can provide an overview of cell proteins, and in the case of neurotoxicant exposure, can provide quantitative data regarding changes in corresponding expression levels and/or posttranslational modifications that might be associated with neuron injury.

Biomarkers of neurotoxicity

A variety of classic proteomic techniques (e.g. LC)/tandem mass spectroscopy, 2DG image analysis) as well as more recently developed approaches (e.g. two-hybrid systems, antibody arrays, protein chips, isotope-coded affinity tags, ICAT) are available to determine protein levels, identify components of multiprotein complexes and to detect posttranslational changes. Proteomics, therefore, offers a comprehensive overview of cell proteins, and in the case of neurotoxicant exposure, can provide quantitative data regarding changes in corresponding expression levels and/or posttranslational modifications that might be associated with neuron injury.

Human embryonic stem cell (hESC)-based test systems, based on neuronal differentiated murine ESCs and quantitative differential proteomic display techniques, can be used to identify biomarkers for neurotoxicity. Results are superior to those of conventional array technologies (nucleic acids), because the proteomic analysis covers posttranslational modifications. It is possible to identify toxicity biomarkers without using animal-based in vitro or in vivo systems. To circumvent serious neurotoxicity, while taking advantage of the antitumor activities of the platinum agents, efforts to identify mechanism-based biomarkers are under investigation. These data from the study of genetic biomarkers associated with neurotoxicity induced by single-agent and combination platinum chemotherapy have the potential for broad clinical implications if mechanistic associations lead to the development of toxicity modulators to minimize the noxious sequelae of platinum chemotherapy (McWhinney et al 2009).

Glial fibrillary acidic protein as biomarker of neurotoxicity. The glial reaction, gliosis, represents a hallmark of all types of nervous system injury. Therefore biomarkers of gliosis can be applied for assessment of neurotoxicity. The astroglial protein, glial fibrillary acidic protein (GFAP), can serve as one such biomarker of neurotoxicity in response to a panel of known neurotoxic agents. Qualitative and quantitative analysis of GFAP has shown this biomarker to be a sensitive and specific indicator of the neurotoxicity. The implementation of GFAP and related glial biomarkers in neurotoxicity screens may serve as the basis for further development of molecular signatures predictive of adverse effects on the nervous system.

Single-stranded DNA as a biomarker of neuronal apoptosis. Single-stranded DNA (ssDNA) is a biomarker of apoptosis and programmed cell death, which appears prior to DNA fragmentation during delayed neuronal death. A study investigated the immunohistochemical distribution of ssDNA in the brain to investigate apoptotic neuronal damage with regard to the cause of death in medicolegal autopsy cases (Michiue et al 2008). Neuronal immunopositivity for ssDNA was globally detected in the brain, independent of the age or gender of subjects and postmortem interval, and depended on the cause of death. Higher positivity was typically found in the pallidum for delayed brain injury death and fatal carbon monoxide intoxication, and in the cerebral cortex, pallidum and substantia nigra for drug intoxication. For mechanical asphyxiation, a high positivity was detected in the cerebral cortex and pallidum, while the positivity was low in the substantia nigra. The neuronal ssDNA increased during the survival period within about 24h at each site, depending on the type of brain injury, and in the substantia nigra for other blunt injuries. The neuronal positivity was usually lower for drowning and acute ischemic disease. Topographical analysis of ssDNA-positive neurons may contribute to investigating the cause of brain damage and survival period after a fatal insult.