Adverse Effects of Antiepileptic Drugs

Dieter Schmidt

with the collaboration of Lee Seldon

Adverse Effects of Antiepileptic Drugs

Dieter Schmidt, M.D.
Assistant Professor of Neurology
Department of Neurology
Free University of Berlin
West Germany

with the collaboration of

Lee Seldon, Ph.D.
Institute of Physiology
Free University of Berlin
West Germany

Raven Press ■ New York

Raven Press, 1140 Avenue of the Americas, New York, New York 10036

Made in the United States of America

Library of Congress Cataloging in Publication Data

Schmidt, Dieter, M.D.
Adverse effects of antiepileptic drugs.

Includes bibliographical references and index.
1. Epilepsy—Chemotherapy—Complications and sequelae. 2. Anticonvulsants—Side effects.
I. Seldon, Lee. II. Title.
RC374.C48S35 1982 616.8'53061 82-14027

Preface

Although any review devoted to adverse effects alone without reference to therapeutic benefits is in danger of exaggerating the side effects of antiepileptic drug therapy, it is reasonable to expect that many of the changes in the neurological, psychological, and medical status of a patient may in fact be due not to epilepsy but rather to the adverse effects of antiepileptic drugs. A growing concern about the adverse effects of antiepileptic drugs has led to many reports on their unintended actions.

This volume presents a comprehensive review of antiepileptic drug-induced disease and the specific side effects of the individual antiepileptic drugs. It provides a source of clinical information on adverse effects of antiepileptic drugs, identifies areas that need further investigation, and suggests guidelines to minimize the side effects of antiepileptic drug treatment.

This work is intended to serve neurologists, pediatricians, and physicians who treat patients with epilepsy. It is further intended to be of use to pharmacologists, toxicologists, and all who are concerned with the recognition, diagnosis, or treatment of adverse effects of antiepileptic drugs.

Berlin
June 1982

Dieter Schmidt
Lee Seldon

Acknowledgments

I am very pleased to acknowledge the important contribution of Lee Seldon who translated a major part of this work and assisted with the editing and final preparation of the manuscript.

I especially wish to thank Dr. Ute Röder who compiled case records of patients with adverse effects. I am also grateful to Professor J. Kiffin Penry for generous support with the literature search and Professor Dieter Janz for his stimulating interest in our work. I would like to express my appreciation to Barbara Herzberger, who translated part of the manuscript, and to Gary Sea, who typed part of it. Monika Dulinsky gave valuable assistance in checking the bibliography. I also wish to thank Doris Schulten for her patience in the search for numerous reprints in various libraries. The publication has been assisted by the capable staff of Raven Press.

Contents

Patient Management

Introduction

It has been increasingly apparent in the last few years that too many patients have suffered as much, if not more, from the treatment than from the disorder.

Reynolds (1978)

Since the thalidomide disaster in 1961, the medical profession and the public have become increasingly sensitive to the problem of adverse effects of drugs. Consequently, a growing concern about the acute and chronic toxicity of antiepileptic drugs has led to many reports on their adverse effects. In these studies adverse effects were defined as any unintended, drug-induced reactions. Accordingly the scope of these investigations ranged from rather rare and mostly unpredictable drug-induced diseases to more frequent, transient, and mostly mild, dose-dependent side effects. This volume presents a review of antiepileptic drug-induced diseases and of dose-dependent, specific side effects of the individual anticonvulsants. The purpose of this review is threefold: to provide a source of comprehensive clinical information on adverse effects of antiepileptic drugs, to identify newly recognized or previously overlooked adverse effects that require further investigation, and to suggest guidelines that help minimize the adverse effects of antiepileptic drug treatment.

It has become increasingly clear that the rate of adverse effects of anticonvulsants can be reduced without compromising seizure control in epileptic patients. The detection and management of dose-related side effects can be improved by monitoring the plasma concentration of antiepileptic drugs. Dose-related side effects can be reduced further by aiming at the lowest effective dose, possibly with only one antiepileptic drug. Unnecessary high dosages and drug interactions have been recognized as leading causes of preventable drug toxicity.

While a dose reduction is sufficient to correct side effects in most patients, the development of drug-induced disease is usually not primarily dependent on the

administered dose. However, it has become apparent in recent years that some of the more frequent drug-induced diseases, e.g., osteomalacia or malformations in the offspring, develop more frequently in high-risk subgroups of epileptic patients. The identification of specific risk factors prior to the administration of the drug will help reduce the rate of drug-induced disease and improve our understanding of the risk–benefit ratio of the proposed treatment in the individual patient.

1

Mechanism of Adverse Effects of Antiepileptic Drugs

From a clinical viewpoint, any unintended reaction to a drug may be seen as an adverse effect. The various adverse effects differ in their morbidity, mortality, predictability, and pathogenesis. Essentially all adverse effects can be classified in one of two categories. There is a small number of rather rare but sometimes fatal and mostly unpredictable drug-induced diseases (Reynolds, 1975). However, the vast majority of adverse effects may be classified as side effects and develop much more predictably due to their dose-dependency. They are mostly mild and reversible (Plaa, 1975). Furthermore, drug-induced diseases and unwanted side effects differ in their pathogenesis.

DRUG-INDUCED DISEASES

The pathogenesis of antiepileptic drug-induced diseases involves pharmacological and clinical factors. The pharmacological factors include the pharmaceutical, pharmacokinetic, and pharmacodynamic properties of the drugs.

Pharmacological Factors

Pharmaceutical Factors

There is little evidence that pharmaceutical factors, e.g., additives, solvents or expedients, are responsible for drug-induced diseases. However, phenytoin solutions have been found to have a hypotensive effect. Louis et al. (1967) have shown that propylene glycol, the solvent for parenteral phenytoin, contributes to the drop in blood pressure that may occur during intravenous injection or infusion of phenytoin.

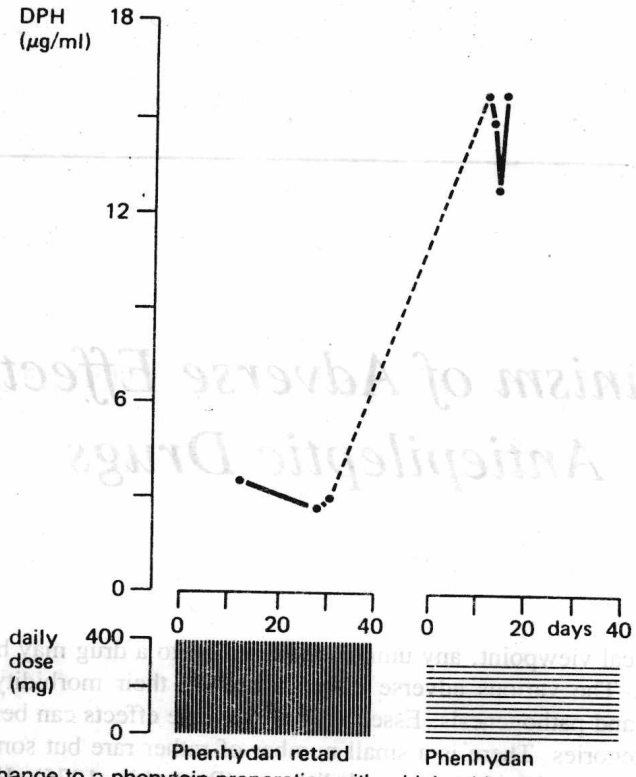

FIG. 1.1. A change to a phenytoin preparation with a higher bioavailability led to an increase in the plasma concentration and clinical drug toxicity with nystagmus and ataxia (from Schmidt, 1981a, with permission).

Pharmacokinetic Factors

It seems possible that metabolites of antiepileptic drugs may cause drug-induced diseases. The toxicity of mephenytoin may be explained by the accumulation of its primary metabolite, 5-ethyl-5-phenylhydantoin (Kupferberg, 1982).

Pharmacodynamic Factors

We are familiar with only a few examples in which disease is caused or aggravated by an altered target organ response of the individual. The precipitation of acute porphyria with enzyme-inducing antiepileptic drugs is such an example (Magnussen et al., 1975). Myasthenia gravis may be worsened by the intake of antiepileptic drugs, especially hydantoins (Brumlik and Jacobs, 1974).

Clinical Factors

There is clinical evidence that antiepileptic drug-induced osteomalacia develops more frequently in patients with vitamin D deficiency, lack of sun exposure, and

lack of physical activity. These clinical factors, which may lead to the development of osteomalacia even without antiepileptic drug treatment, are relevant risk factors, contributing to the development of disease in predisposed individuals. Another example is the increased hepatic toxicity of antiepileptic drugs in epileptic patients receiving concomitant antituberculosis chemotherapy (Dodd and Reichenmiller, 1969).

DOSE-DEPENDENT SIDE EFFECTS

Four factors may be partly or wholly responsible for the development of adverse side effects of antiepileptic drugs.

Pharmaceutical Factors

Differences in pharmaceutical preparation may result in a sudden increase in the amount of antiepileptic drug available to the blood and the brain. An often quoted example is the increased incidence of phenytoin intoxications in an Australian city when calcium sulfate was exchanged for lactose as an excipient (Bochner et al., 1972). Phenytoin intoxication was described in another case when a conventional preparation was substituted for a slow-release tablet (Schmidt, 1981a) (Fig. 1.1).

Pharmacokinetic Factors

Individual differences in absorption, distribution, and elimination result in differences in drug concentrations in plasma and at the site of action. Enhanced absorption or impaired elimination cause an increase in drug concentrations in plasma and brain and may precipitate intoxication. Inhibition of biotransformation

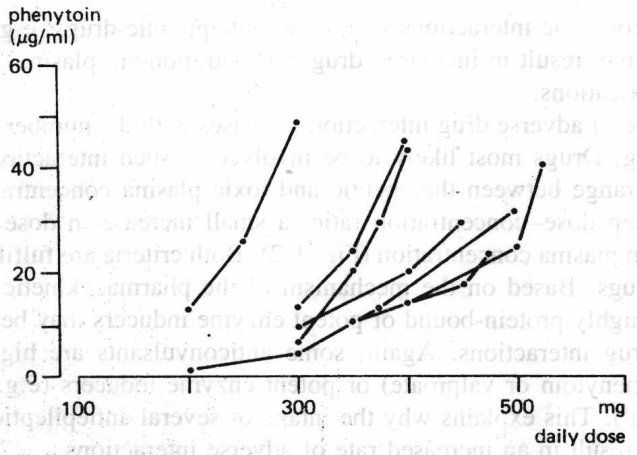

FIG. 1.2. Dose/plasma level relationship in seven patients in whom steady-state concentrations of phenytoin were measured at various doses of the drug. Note the increasing steepness of the relationship with higher doses. A small increase may lead to a disproportionally large increase in plasma concentration and to subsequent clinical intoxication (from Schmidt, 1981a, with permission).

TABLE 1.1. *Therapeutic and toxic plasma concentrations of anticonvulsants*[a]

Medication	Range of therapeutic levels (μg/ml)	Range of toxic levels (μg/ml)	References
Phenytoin	10 (3–23)	>20	b,d,n,s,u
Phenobarbital	20 (10–40)	>50	e,u
Carbamazepine	4 (4–12)	>8	f,g,h,l,o,q,t,w,x,y
Ethosuximide	40 (30–120)	>100	c,v
Valproate	40 (40–300)	>120	j,p
Clonazepam	(13–72)[b]	>80[b]	i
Diazepam	(200–500)[b]	>1000[b]	a,k,r
Methsuximide	(0.1–1.4)		r
	(10–40)[c]	>60[c]	
Lidocaine	(2–5)	?	m
Trimethadione	(>20)		
	(>700)[d]	>1500[d]	r

[a]From Schmidt (1981a), with permission.
[b]ng/ml.
[c]Desmethylmethsuximide.
[d]Dimethadione.

a—Booker and Celesia (1973); b—Borofsky et al. (1973); c—Browne et al. (1975); d—Buchthal et al. (1960); e—Buchthal et al. (1968); f—Cereghino et al. (1974); g—Cereghino et al. (1975); h—Dam et al. (1975); i—Dreifuss et al. (1975); j—Gram et al. (1977); k—Knudsen and Vestermark (1978); l—Kutt et al. (1975); m—Lemmen et al. (1978); n—Lund (1974); o—Mehta (1977); p—Meinardi et al. (1974); q—Monaco et al. (1976); r—Pippenger et al. (1978); s—Reynolds et al. (1976); t—Rodin et al. (1974); u—Schmidt and Janz. (1977); v—Sherwin et al. (1973); w—Simonsen et al. (1975); x—Troupin et al. (1975); y—Troupin et al. (1977).

due to pharmacokinetic interactions with other antiepileptic drugs, e.g., sulthiame or disulfiram, may result in increased drug concentrations in plasma and possibly in clinical intoxications.

The incidence of adverse drug interaction increases with the number of drugs the patient is taking. Drugs most likely to be involved in such interactions are those with a narrow range between therapeutic and toxic plasma concentrations (Table 1.1), and a steep dose–concentration ratio; a small increase in dose results in a large increase in plasma concentration (Fig. 1.2). Both criteria are fulfilled by some antiepileptic drugs. Based on the mechanism of the pharmacokinetic interaction, drugs that are highly protein-bound or potent enzyme inducers may be expected to be active in drug interactions. Again, some anticonvulsants are highly protein-bound (e.g., phenytoin or valproate) or potent enzyme inducers (e.g., phenytoin or phenobarbital). This explains why the intake of several antiepileptic drugs may be expected to result in an increased rate of adverse interactions.,

If drugs other than antiepileptic agents are prescribed, twofold adverse drug interactions may occur: 1) The other drug may be rendered less active by antiepileptic agents. A well-known example is the reduced contraceptive action of oral contra-

ceptive steroids when antiepileptic drugs are taken in addition (Janz and Schmidt, 1974). 2) Anticonvulsants may become less effective when taken together with other drugs. An example is the decreased phenytoin plasma concentration when antacids are taken.

Genetic, environmental, and clinical factors may influence pharmacokinetics. Patients with impaired biotransformation caused by liver disease or old age run a higher risk of intoxication owing to increased plasma and brain concentrations. For antiepileptic drugs, variability among patients and within the same patients is so great that it is now unacceptable to prescribe standard doses for chronic treatment without individual dose adjustment. The individualization of drug dosage is greatly improved by the monitoring of plasma levels of the medications. This contributes considerably to the prevention of dose-related drug toxicity.

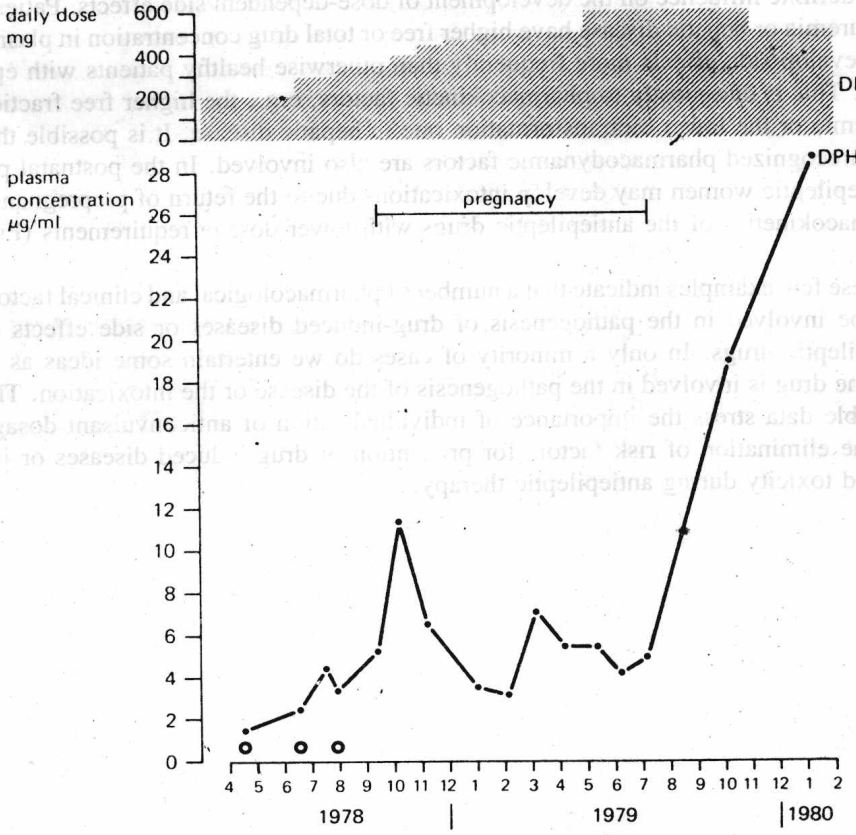

FIG. 1.3. Plasma concentrations of phenytoin in a patient before, during and after pregnancy. The plasma concentration decreases during pregnancy despite a higher dose. The patient was free of generalized tonic–clonic seizures (o) following the dosage increase. After delivery, the patient developed nystagmus and ataxia as signs of a phenytoin intoxication (from Schmidt, 1981c, with permission).

Pharmacodynamic Factors

An altered target response may be based upon pharmacodynamic mechanisms, which currently are not well understood. For instance, identical plasma concentrations of diazepam have a stronger sedative action in older patients than in younger ones (Schmidt, 1982a). The type of epilepsy may influence the development of immunological deficiencies during treatment with antiepileptic drugs. Patients with primary generalized epilepsy do often have low IgA levels prior to treatment and are more prone, when compared to other epileptic patients, to develop IgA deficiency during treatment (Fontana et al., 1976).

Clinical Factors

The presence of another disease or change in the functional state of the individual has a definite influence on the development of dose-dependent side effects. Patients with uremia or hepatic disease have higher free or total drug concentration in plasma and develop side effects more frequently than otherwise healthy patients with epilepsy. This is due mostly to pharmacokinetic factors, e.g., the higher free fraction in uremia or the lower biotransformation rate in hepatic disease. It is possible that yet unrecognized pharmacodynamic factors are also involved. In the postnatal period, epileptic women may develop intoxications due to the return of prepregnancy pharmacokinetics of the antiepileptic drugs with lower dosage requirements (Fig. 1.3).

These few examples indicate that a number of pharmacological and clinical factors may be involved in the pathogenesis of drug-induced diseases or side effects of antiepileptic drugs. In only a minority of cases do we entertain some ideas as to how the drug is involved in the pathogenesis of the disease or the intoxication. The available data stress the importance of individualization of anticonvulsant dosage and the elimination of risk factors for prevention of drug-induced diseases or increased toxicity during antiepileptic therapy.

2

Disorders of the Nervous System

The adverse effects of antiepileptic drugs on the nervous system include so-called encephalopathies with transient deterioration of mental functions and the development of cerebellar and brainstem dysfunction. In addition, isolated extrapyramidal disturbances, polyneuropathy, and cerebellar disturbances have also been associated with anticonvulsant treatment. Furthermore, anticonvulsants may influence the electroencephalogram.

ENCEPHALOPATHY

A number of drug-induced neurological syndromes may be observed in patients receiving high doses of antiepileptic drugs (Kutt et al., 1964a,b; Kokenge et al., 1965; Nozue et al., 1973; Umeda and Sakata, 1977). The clinical features are quite variable. Best known are drug-related cerebellar and brainstem dysfunction with disorders in equilibrium, gait and speech, and with gaze nystagmus (Umeda and Sakata, 1977). They develop with increasing plasma concentrations of phenytoin, carbamazepine, or other antiepileptic drugs, as outlined in Chapters 16–27 on side effects of the individual drugs. In addition, some authors have used the terminology of anticonvulsant encephalopathy to denote a reversible syndrome that includes progressive mental deterioration, brainstem and cerebellar signs, EEG changes, and an increase in seizure frequency. These disturbances were described during treatment with phenytoin (Levy and Fenichel, 1965; Engel et al., 1971; Vercelletto, 1977; Meistrup-Larsen et al., 1979), carbamazepine (Salcman and Pippenger, 1975), and valproate (Chadwick et al., 1978; Coulter and Allen, 1980b). The increased seizure frequency may, however, be coincidental, and some of the reported seizures are difficult to distinguish from hysterical attacks. In some patients with increased seizure frequency, no other signs of clinical toxicity were noted, despite high plasma phenytoin concentrations, which led to the suggestion of a paradoxical intoxication (Troupin and Ojemann, 1975). Furthermore, some antiepileptic drugs—e.g., diazepam or nitrazepam—are thought to be able to induce tonic seizures or even

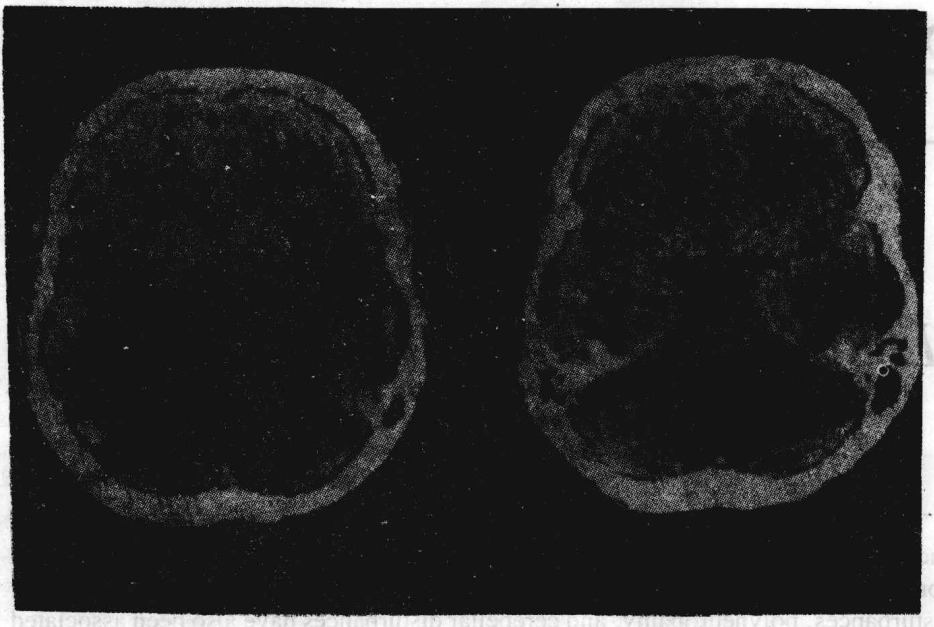

FIG. 2.1. Cerebellar atrophy as shown by cranial computer tomography in a 21-year-old epileptic patient with elementary focal seizures, generalized tonic–clonic seizures, and severe cerebellar ataxia. The epilepsy began at the age of 5 years. There is no apparent etiology, and the family history for epilepsy and cerebellar disorders is negative. At age 14, the patient began to experience progressive gait ataxia. In spite of this, it appears that phenytoin was gradually increased; it was not until three years later that phenytoin was discontinued. The significant findings on neurological examination were those of marked nystagmus in all positions of gaze and a prominent cerebellar ataxia with gait disturbance and dysarthric speech. No other abnormalities were detected on neurological examination. The cerebellar syndrome remained unchanged despite the withdrawal of phenytoin. In addition, the patient suffers from hypogonadism. This case demonstrates how difficult it may become to evaluate the pathogenetic role of phenytoin in this case, but it may have contributed to the development of the cerebellar syndrome. (Computer tomographic illustration, courtesy Dr. W. Kluge.)

status epilepticus in isolated cases, mostly in patients with Lennox syndrome (Prior et al, 1972; Tassinari et al, 1972; Bittencourt and Richens, 1981).

In addition to these neurological syndromes, a variety of isolated neurological abnormalities has been reported, usually as single cases and sometimes with a doubtful relationship to drug treatment.

Postural tremor may develop during valproate treatment (Hyman et al., 1979). A flapping tremor was seen during phenytoin treatment (Gitlin and Morris, 1976) and in one patient who had renal insufficiency and received primidone and cimetidine (Forman et al., 1979). Isolated reports on the development of transient hemiplegia and pathological grasp reflexes are difficult to relate to drug treatment (Morris et al., 1956; Moling and Posch, 1957). Transient changes in CSF protein and cell count and meningeal irritation have also been associated with phenytoin treatment (Dutton, 1958; Logan and Freeman, 1969). A transient, total external ophthalmoplegia may develop in comatose patients with phenytoin or primidone