Volume 68 No. 3 1995

ISSN 0163-7258

Pharmacology & Therapeutics

An International Review Journal

PERGAMON

Pharmacology & Therapeutics
An International Review Journal

Production Editor: Bruce Cooper, E-mail: B.COOPER@ELSEVIER.COM

Publishing and Advertising Office:
Elsevier Science Inc.
660 White Plains Road
Tarrytown, NY 10591-5153, USA
E-mail Address: ESUK.USA@ELSEVIER.COM

Subscription Office:
Elsevier Science Inc.
655 Avenue of the Americas
New York, NY 10010-5107, USA

Published monthly—twelve issues per annum.

Annual Institutional Subscription Rate (1996): US$2265.00. Prices include postage and insurance and are subject to change without notice.

Second class postage paid at Newark NJ. Postmaster: send address corrections to Elsevier Science Inc., 655 Avenue of the Americas, New York, NY 10010-5107, USA.

At the end of the year, the Subscriber will receive, free, the annual subject index.

Back Issues: Back issues of all previously published volumes are available direct from Elsevier Science Inc.

Pergamon

0163-7258(95)02014-K

Pharmac. Ther. Vol. 68, No. 3, pp. 425–434, 1995

0163-7258/95 $29.00

Associate Editor: M. J. BRODIE

ADVERSE EFFECTS OF ESTABLISHED AND NEW ANTIEPILEPTIC DRUGS: AN ATTEMPTED COMPARISON

BJARKE á ROGVI-HANSEN* and LENNART GRAM

University Clinic of Neurology, Hvidovre Hospital, Kettegaards Alle 34, DK 2650 Hvidovre, Denmark

Abstract—Seizures are but one aspect of the negative impact epilepsy has on patients' lives. Adverse effects of antiepileptic treatment may affect the patient's quality of life to an even greater extent than the occurrence of seizures. Adverse effects of antiepileptic drugs (AEDs) are common, and because the differences in efficacy are often marginal, adverse effects may be the most important factor in choosing the best AED for the patient. The search for more efficient and less toxic agents is constantly ongoing. Current evidence suggests that the new generation of AEDs is as efficient as the established AEDs and exhibits fewer adverse effects, but the scientific evidence from randomised clinical trials comparing established and new AEDs with each other is still pending.

Keywords—Epilepsy, antiepileptic drugs, anticonvulsants, adverse effects, side effects, review.

CONTENTS

1. INTRODUCTION

Depending upon the type of epilepsy, 50–90% of the patients can be "satisfactorily controlled," which means that the balance between seizures and adverse effects is tolerable to the patient. However, more than half of the patients treated with established antiepileptic drugs (AEDs) in monotherapy

*Corresponding author.

Abbreviations—AED, antiepileptic drug; CBZ, carbamazepine; ESM, ethosuximide; GP, gabapentin; HYCZ, 10,11-dihydro-10-hydroxy-carbazepine; LTG, lamotrigine; OXC, oxcarbazepine; PB, phenobarbital; PHT, phenytoin; PRM, primidone; VGT, vigabatrin; VPA, valproate.

will experience adverse effects (Mattson *et al.*, 1985). As differences in efficacy are often marginal, the adverse effects may be the major factor in the choice of an AED.

The search for new and better compounds is constantly ongoing, but the ideal high-efficacy/low-frequency of adverse-effect drugs still need to be identified.

This review focuses on the adverse effects of the best investigated, newly licensed AEDs [oxcarbazepine (OXC), vigabatrin (VGT), gabapentin (GP), lamotrigine (LTG)] compared with established drugs [phenobarbital (PB), phenytoin (PHT), primidone (PRM), ethosuximide (ESM), carbamazepine (CBZ), benzodiazepines and valproate (VPA)].

2. METHODS AND DEFINITIONS

Adverse effects are defined as unwanted insidious or delayed effects of drugs, which can be of four distinct types: (1) acute dose-related, (2) acute idiosyncratic, (3) chronic, and (4) teratogenicity.

As established, AEDs arbitrarily are considered drugs marketed in the period from 1912 (PB) to 1979 (VPA).

3. COMMON ADVERSE EFFECTS OF ESTABLISHED ANTIEPILEPTIC DRUGS

3.1. Phenobarbital

PB was the first effective AED to be marketed more than 80 years ago and is still used worldwide. It exerts its anticonvulsive effect by a GABA-agonistic, glutamate-antagonist mechanism (Morselli and Lloyd. 1985).

PB is 40–60% protein-bound and has a half-life of about 100 hr. It is extensively metabolised by the cytochrome P450 system in the endoplasmic reticulum of the liver cells and exhibits considerable autoinduction (Kutt and Paris-Kutt, 1982). This induction results in an increase of the elimination rate of many endogenous and exogenous substances, including other AEDs such as PHT and VPA (Park and Breckenridge, 1981).

The knowledge of PB's efficacy stems more from clinical practice than from clinical trials, but it seems to be as effective as other, newer established agents (Cereghino *et al.*, 1975; Benassi *et al.*, 1980; Mitchell and Chavez, 1987).

The most predominant dose-dependent acute adverse effect, experienced in almost 70% of patients, is sedation, to which partial tolerance develops during chronic treatment (Prichard and Mattson, 1986). Coarsening of facial features and Dupuytrens' contracture frequently is associated with PB treatment, but it is potentially reversible (Schmidt, 1983). Other toxic symptoms are lethargy, dysarthria, and lack of coordination (Loiseau and Duché, 1991). Subnormal folate levels are a relatively common feature during PB treatment (Reynolds, 1975), as is a hemorrhagic diathesis in neonates of mothers given PB (Griffiths, 1981), but other clinically relevant toxic hematological symptoms are rare. The widely acknowledged cognitive adverse effect of PB, in comparison with other established drugs, is most likely due to a depression of cerebral glucose metabolism (Theodore *et al.*, 1986). Loiseau and Duché (1991) found that the cognitive adverse effects may be overemphasised.

Teratogenicity seems to be as low, or lower than, with other AEDs (Shapiro *et al.*, 1976).

3.2. Phenytoin

PHT was synthesized in 1908 as a result of a search among nonsedative structural analogues of PB. The drug stabilises neuronal membranes by adjusting the transmembrane resting fluxes of sodium, as well as the flow of calcium and sodium during depolarization (Woodbury, 1980).

PHT has a limited aqueous solubility, and is metabolised by 0-order kinetics, which means that an increase in dose in a patient already saturated with PHT may increase the plasma level disproportionately (Browne and Chang, 1989). PHT is bound extensively to plasma proteins (about 90%) and metabolised in the liver by glucuronidation to its inactive metabolite, which is excreted in the urine. This biotransformation is influenced by a variety of drugs, resulting in accumulation

(*e.g.*, CBZ, disulfiram, isoniazid, cimetidine) or increased excretion (*e.g.*, clonazepam, chronic use of ethanol) (Kutt, 1991). PHT also influences the elimination of other drugs (*e.g.*, CBZ, digoxin, anticoagulants) and, most importantly, steroids in fertile women taking oral contraceptives (Perucca, 1982).

Central and peripheral nervous toxicity is the most predominant effect of overdosage. Cerebellar-vestibular symptoms, such as ataxia, diplopia, nystagmus, and vertigo, are common. Cerebellar atrophy has been associated with chronic PHT treatment, but whether this atrophy is caused by the treatment or seizures is disputed (Dam, 1977; Koller *et al.*, 1981). Behavioral effects include confusion, drowsiness, hyperactivity, and hallucinations. When PHT is administered intravenously, cardiac arrhythmias, with or without hypotension, may occur.

During chronic administration, cosmetic changes, such as hirsutism, gingival hyperplasia, and facial coarsening, make this agent especially troublesome in the treatment of young women. Gastrointestinal symptoms are often seen. Moderate elevation of hepatic enzymes are common, but do not necessitate withdrawal of the drug.

Idiosyncratic cutaneous reactions involving skin, liver, and bone marrow are infrequent, but often necessitate drug withdrawal.

The teratogenicity of PHT is well-described, and a "fetal hydantoin syndrome" has been described (Kutt, 1991).

3.3. Primidone

The anticonvulsant effect of PRM is partly due to its active metabolites, especially PB, which accumulates during chronic medication. Protein binding is 20–30%, with a half-life of 4–12 hr.

When PRM is administered in combination with other enzyme-inducing drugs, the PB/PRM ratio is increased from the normal 1–2:1 to levels where mainly PB is responsible for the clinical effects (Reynolds *et al.*, 1972).

The dose-dependent adverse effects show a complex picture because of the several active compounds and the gradual development of tolerance, but without doubt, PRM exhibits adverse affects of its own (Leppik *et al.*, 1984), leading to a feeling of intoxication, sedation, nausea, vertigo, and diplopia—symptoms that can be attenuated by a slow build up of dosage. Mattson *et al.* (1985) found that PRM was associated with significantly more adverse effects than PB (gastrointestinal symptoms and loss of libido), which makes the use of PRM instead of PB questionable (Brodie, 1990). On the other hand, in a comparative study, Herranz *et al.* (1988) found that the overall rates of adverse effects leading to discontinuation (8–10%) resembled those of VPA and PHT. Idiosyncratic adverse effects, such as skin rash, thrombocytopenia, lupus, and lymphadenopathy, appear seldom.

3.4. Ethosuximide

The succinimides were synthesised in the search for less toxic agents to treat absence seizures in children.

ESM is not protein-bound, has a half-life of 20–60 hr, and its inactive metabolites are excreted by the kidneys. The indication is absence seizures. Large interindividual differences in drug disposition have been noticed (Goulet *et al.*, 1976).

ESM seems to exert a synergistic effect with VPA in otherwise refractory absence seizures (Rowan *et al.*, 1983). CBZ—and probably other enzyme-inducing agents, such as PHT, PB, and PRM—tend to increase the metabolism of ESM (Warren *et al.*, 1980).

Adverse effects are reported in 0–44% of the patients in different studies (Dreifuss, 1982), gastrointestinal symptoms being the most common besides drowsiness, lethargy, euphoria, and headache.

Idiosyncratic adverse effects seldom observed are skin reactions, thrombocytopenia, and bone marrow depression.

In animal models, ESM is less teratogenic than most other AEDs (Sullivan and McElhatton, 1977), but human experiences are too limited to generalise (Kuhnz *et al.*, 1984).

DOCKET ALARM

Explore Litigation Insights

Docket Alarm provides insights to develop a more informed litigation strategy and the peace of mind of knowing you're on top of things.

Real-Time Litigation Alerts

Keep your litigation team up-to-date with **real-time alerts** and advanced team management tools built for the enterprise, all while greatly reducing PACER spend.

Our comprehensive service means we can handle Federal, State, and Administrative courts across the country.

Advanced Docket Research

With over 230 million records, Docket Alarm's cloud-native docket research platform finds what other services can't. Coverage includes Federal, State, plus PTAB, TTAB, ITC and NLRB decisions, all in one place.

Identify arguments that have been successful in the past with full text, pinpoint searching. Link to case law cited within any court document via Fastcase.

Analytics At Your Fingertips

Learn what happened the last time a particular judge, opposing counsel or company faced cases similar to yours.

Advanced out-of-the-box PTAB and TTAB analytics are always at your fingertips.

API

Docket Alarm offers a powerful API (application programming interface) to developers that want to integrate case filings into their apps.

LAW FIRMS
Build custom dashboards for your attorneys and clients with live data direct from the court.

Automate many repetitive legal tasks like conflict checks, document management, and marketing.

FINANCIAL INSTITUTIONS
Litigation and bankruptcy checks for companies and debtors.

E-DISCOVERY AND LEGAL VENDORS
Sync your system to PACER to automate legal marketing.