

Pharmacology & Therapeutics

An
International
Review Journal

Executive Editors:

W.C. Bowman, A.M. Breckenridge, A.C. Sartorelli

ine
enzo-p-

ains and
tion of

stracted in:
Biosis Data.,
Sci., CABS,
I. Sci. Rev.,
i. Cit. Ind.,
I Ind. Med.

RY

89052645975



b89052645975a



PERGAMON

Argentum Pharm. v. Research Corp. Techs., IPR2016-00204

Aims and Scope

Pharmacology & Therapeutics presents lucid, critical, authoritative and current reviews of all branches of science that impact on pharmacology. The articles are normally specially commissioned, although uninvited review papers are occasionally published.

Invitation to Authors

While the majority of articles are commissioned, unsolicited reviews will be welcomed for editorial consideration and authors should write to the relevant Executive Editor to obtain guidance on how to prepare their manuscripts prior to submitting their reviews.

© 1995 Elsevier Science Inc.

Whilst every effort is made by the publishers and editorial board to see that no inaccurate or misleading data, opinion or statement appears in this journal, they wish to make it clear that the data and opinions appearing in the articles and advertisements herein are the sole responsibility of the contributor or advertiser concerned. Accordingly, the publishers, the editorial board and editors and their respective employees, officers and agents accept no responsibility or liability whatsoever for the consequences of any such inaccurate or misleading data, opinion or statement.

Drug and dosage selection: The authors have made every effort to ensure the accuracy of the information herein, particularly with regard to drug selection and dose. However, appropriate information sources should be consulted, especially for new or unfamiliar drugs or procedures. It is the responsibility of every practitioner to evaluate the appropriateness of a particular opinion in the context of actual clinical situations and with due consideration to new developments.

It is a condition of publication that manuscripts submitted to this journal have not been published and will not be simultaneously submitted or published elsewhere. By submitting a manuscript, the authors agree that the copyright for their article is transferred to the publisher if and when the article is accepted for publication. However, assignment of copyright is not required from authors who work for organisations which do not permit such assignment. The copyright covers the exclusive rights to reproduce and distribute the article, including reprints, photographic reproduction, microform or any other reproduction of similar nature and translations. No part of this publication may be reproduced, stored in a retrieval system or transmitted in any form or by any means, electronic, electrostatic, magnetic tape, mechanical photocopying recording or otherwise, without permission in writing from the copyright holder.

Photocopying information for users in the USA: The Item-Fee Code for this publication indicates that authorization to photocopy items for internal or personal use is granted by the copyright holder for libraries and other users registered with the Copyright Clearance Center (CCC) Transactional Reporting Service provided the stated fee for copying, beyond that permitted by Section 107 or 108 of the United States Copyright Law, is paid. The appropriate remittance of \$29.00 per article is paid directly to the Copyright Clearance Center, 222 Rosewood Drive, Danvers, MA 01923.

Permission for other use: The copyright owner's consent does not extend to copying for general distribution, for promotion, for creating new works, or for resale. Specific written permission must be obtained from the publisher for such copying.

The Item-Fee Code for this publication is: 0163-7258/95 \$29.00

©™ The paper used in this publication meets the minimum requirements of American National Standard for Information Sciences—Permanence of Paper for Printed Library Materials, ANSI Z39.48-1984.

D. J. K. Balfour
L. Z. Benet
P. N. Bennett
K. D. Bhoola
I. S. Blagbrooke
M. J. Brodie
D. B. Calne
M. P. Caulfield
P. K. Chiang
District of Columbia
J. G. Cory
P. G. Davey
C. R. W. Edwards
D. Grunberg
A. L. Harvey
J. A. Hickman
E. Huberman
M. Kimura
P. Köhler
D. Kupfer

G. E. Adams
R. Auerbach
D. N. Bateman
C. Bell
J. C. Buckingham
J. M. Carney
C. E. Cass
M. Colvin
L. C. Erickson
J. S. Fedan
G. Gillies
M. P. Hacker
E. Hamel
J. N. Hathcock
C. J. Hawkey
A. M. Heagerty
J. L. Holtzman

Pharmacology & Therapeutics

An
International
Review Journal

UW PHARMACY LIBRARY

Volume 67 No. 3

1995

Contents

- H. R. Matthews 323 Protein kinases and phosphatases that act on histidine, lysine, or arginine residues in eukaryotic proteins: A possible regulator of the mitogen-activated protein kinase cascade
- M. C. Walker and P. N. Patsalos 351 Clinical pharmacokinetics of new antiepileptic drugs
- F. Dauphin and E. T. MacKenzie 385 Cholinergic and vasoactive intestinal polypeptidergic innervation of the cerebral arteries
- R. E. Appleton 419 Treatment of childhood epilepsy
- C. R. Sirtori 433 New targets for lipid lowering and atherosclerosis prevention

PHTHDT 67(3) 323-448 (1995)



PERGAMON

This journal is indexed/abstracted in:
Curr. Cont. ASCA, Biosis Data.,
Chem. Abstr., Curr. Cont./Life Sci., CABS,
Excerpt. Med., Curr. Cont. Ind. Sci. Rev.,
Curr. Cont. ISI/BIOMED Database, Curr. Cont. Sci. Cit. Ind.,
Curr. Cont. SCISEARCH Data and Ind. Med.



0163-7258(1995)67:3;1-H



Associate Editor: M. J. BRODIE

CLINICAL PHARMACOKINETICS OF NEW ANTIEPILEPTIC DRUGS

M. C. WALKER and P. N. PATSALOS*

*Epilepsy Research Group, University Department of Clinical Neurology,
Institute of Neurology, London, WC1N 3BG, UK*

Abstract—We have reviewed the pharmacokinetics of six antiepileptic drugs that are marketed (felbamate, gabapentin, lamotrigine, oxcarbazepine, vigabatrin, and zonisamide) and six drugs that are undergoing evaluation (levetiracetam, raltitoline, remacemide, stiripentol, tiagabine, and topiramate). In addition, we have compared the prodrugs etorobarb and fosphenytoin and the controlled-release formulations of valproic acid and carbamazepine with their parent compounds. Finally, we have devised a scoring system to compare the pharmacokinetics of new antiepileptic drugs. Using this system, vigabatrin, levetiracetam, gabapentin, and topiramate appear to have the most favourable pharmacokinetic profiles, whilst raltitoline and stiripentol have the least favourable.

Keywords—Epilepsy, new antiepileptic drugs, pharmacokinetics, controlled-release, prodrugs.

CONTENTS

1. Introduction	352
2. Drugs That Have Been Marketed	354
2.1. Felbamate	354
2.1.1. Absorption	355
2.1.2. Distribution	355
2.1.3. Elimination	355
2.1.4. Age and disease-related effects	355
2.1.5. Drug interactions	355
2.1.6. Drug monitoring and dosaging	357
2.2. Gabapentin	357
2.2.1. Absorption	357
2.2.2. Distribution	357
2.2.3. Elimination	358
2.2.4. Age and disease-related effects	358
2.2.5. Drug interactions	358
2.2.6. Drug monitoring and dosaging	358
2.3. Lamotrigine	359
2.3.1. Absorption	359
2.3.2. Distribution	359
2.3.3. Elimination	359
2.3.4. Age and disease-related effects	360
2.3.5. Drug interactions	360
2.3.6. Drug monitoring and dosaging	360
2.4. Oxcarbazepine	361
2.4.1. Absorption	361
2.4.2. Distribution	362

*Corresponding author.

Abbreviations—AED, antiepileptic drug; AUC, area under the curve; CSF, cerebrospinal fluid; GABA, γ -aminobutyric acid; GABA-T, GABA-transaminase; MHD, monohydroxy derivative of oxcarbazepine; MMMP, *N*-monomethoxymethylphenobarbitone; NMDA, *N*-methyl-D-aspartate.

2.4.3. Elimination	362
2.4.4. Age and disease-related effects	362
2.4.5. Drug interactions	363
2.4.6. Drug monitoring and dosaging	363
2.5. Vigabatrin	363
2.5.1. Absorption	364
2.5.2. Distribution	364
2.5.3. Elimination	364
2.5.4. Age and disease-related effects	365
2.5.5. Drug interactions	365
2.5.6. Drug monitoring and dosaging	366
2.6. Zonisamide	366
2.6.1. Absorption	366
2.6.2. Distribution	367
2.6.3. Elimination	367
2.6.4. Age and disease-related effects	367
2.6.5. Drug interactions	367
2.6.6. Drug monitoring and dosaging	367
3. Drugs Undergoing Clinical Trials	368
3.1. Levetiracetam	368
3.2. Ralitoline	368
3.3. Remacemide	369
3.4. Stiripentol	369
3.4.1. Absorption	370
3.4.2. Distribution	370
3.4.3. Elimination	370
3.4.4. Drug interactions	370
3.4.5. Drug monitoring and dosaging	371
3.5. Tiagabine	371
3.6. Topiramate	371
4. Improving the Pharmacokinetics of Established Antiepileptic Drugs	372
4.1. Prodrugs	372
4.1.1. Eterobarb	372
4.1.2. Fosphenytoin	373
4.2. Controlled-release formulations	373
4.2.1. Carbamazepine	374
4.2.2. Valproate	374
5. Comparative Pharmacokinetics	375
6. Conclusion	376
Acknowledgement	376
References	376

1. INTRODUCTION

Approximately 1% of the general population has active epilepsy or will be taking antiepileptic drugs (AEDs) (Sander and Shorvon, 1987); of these, approximately 80% are well controlled on one medication and 20% require polytherapy (Reynolds and Shorvon, 1981). At present, only a small proportion of patients with drug-resistant epilepsy are amenable to epilepsy surgery. New AEDs have been developed to provide drugs with fewer side effects and greater efficacy than those currently available and also to help treat those patients with refractory epilepsy. Although from the introduction of phenobarbitone in 1912 up until recent times, new AED development had been sporadic—a new AED was introduced every 10–20 years (see Table 1), this apparent inactivity belies crucial advances that were being made in the pharmacological treatment of epilepsy. These have included the testing of compounds in animal seizure models, a greater understanding of the molecular basis of seizures and, importantly, a greater understanding of clinical pharmacokinetics. It is these developments that have formed the basis of the recent acceleration in the evolution of new AEDs.

An understanding of clinical pharmacokinetics has resulted in the improved clinical use of established AEDs, modifications of established AEDs to create drugs with better pharmacological profiles, and the early characterisation of the clinical pharmacokinetic profiles of new AEDs.

The ideal oral absorption (this increase permits release (both of which no such drug the development long half-life. In this release licensed in which there AEDs. Further available ph In presence age- and d concentrate shown in Table bioavailability calculated by preparations drug is often a drug is not by the liver circulation under the control with dose, dose (first

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.