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CLINICAL PHARMACOKINETICS OF NEW ANTIEPILEPTIC DRUGS

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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, ralitoline, remacemide, stiripentol, tiagabine, and topiramate). In addition, we have compared the prodrugs eterobarb 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 ralitoline and stiripentol have the least favourable.

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

CONTENTS

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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.

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.

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