Advanced Drug Delivery Reviews 64 (2012) 896–910

Contents lists available at SciVerse ScienceDirect

Advanced Drug Delivery Reviews

journal homepage: www.elsevier.com/locate/addr

Host factors affecting antiepileptic drug delivery—Pharmacokinetic variability ☆

Cecilie Johannessen Landmark [a,*], Svein I. Johannessen [b,c], Torbjörn Tomson [d]

[a] Dept. of Pharmacy, Faculty of Health Sciences, Oslo University College, Oslo, Norway
[b] The National Center for Epilepsy, Sandvika, Oslo University Hospital, Oslo, Norway
[c] Department of Pharmacology, Oslo University Hospital, Oslo, Norway
[d] Dept. of Clinical Neuroscience, Karolinska Institutet, Stockholm, Sweden

ARTICLE INFO

Article history:
Received 15 July 2011
Accepted 14 October 2011
Available online 21 October 2011

Keywords:
Antiepileptic drugs
Drug delivery
Epilepsy
Host factors
Pharmacokinetics

ABSTRACT

Antiepileptic drugs (AEDs) are the mainstay in the treatment of epilepsy, one of the most common serious chronic neurological disorders. AEDs display extensive pharmacological variability between and within patients, and a major determinant of differences in response to treatment is pharmacokinetic variability. Host factors affecting AED delivery may be defined as the pharmacokinetic characteristics that determine the AED delivery to the site of action, the epileptic focus. Individual differences may occur in absorption, distribution, metabolism and excretion. These differences can be determined by genetic factors including gender and ethnicity, but the pharmacokinetics of AEDs can also be affected by age, specific physiological states in life, such as pregnancy, or pathological conditions including hepatic and renal insufficiency. Pharmacokinetic interactions with other drugs are another important source of variability in response to AEDs. Pharmacokinetic characteristics of the presently available AEDs are discussed in this review as well as their clinical implications.

Contents

☆ This review is part of the *Advanced Drug Delivery Reviews* theme issue on "Antiepileptic Drug Delivery".

* Corresponding author at: Dept. of Pharmacy, Faculty of Health Sciences, Oslo University College, Pilestredet 50, N-0167 Oslo, Norway.
E-mail address: cecilie.landmark@hf.hio.no (C. Johannessen Landmark).

0169-409X/$ – see front matter © 2011 Elsevier B.V. All rights reserved.
doi:10.1016/j.addr.2011.10.003

1. Introduction

Antiepileptic drugs (AEDs) are a group of drugs exhibiting extensive pharmacological variability between and within patients. This pharmacokinetic variability is a major determinant of differences in response to treatment. With a prevalence of 0.6–0.8%, epilepsy is one of the most common serious chronic neurological disorder affecting all ages and without ethnic or geographical boundaries. Hence, age, gender, and ethnicity are all host factors that can be of relevance for variability in AED delivery and response. The pharmacokinetics of AEDs can also be affected by specific physiological states in life, such as pregnancy, as well as by pathological conditions including hepatic and renal insufficiency. Additionally, comorbidities are common among people with epilepsy and these conditions often require treatment with drugs that may interact with the co-prescribed AEDs [1]. The increasing use of AEDs in other disorders such as neuropathic pain, migraine, bipolar disorder and anxiety underline the importance of insight into and understanding of the pharmacological variability of AEDs also in new patient populations [2,3].

Host factors affecting AED delivery may be defined as the pharmacokinetic characteristics that determine the AED delivery to the site of action, the epileptic focus. These are traditionally segregated into absorption, distribution, metabolism and excretion (Fig. 1). In this review, we will discuss each of these pharmacokinetic processes (except delivery to the brain which is covered in a separate chapter) for the presently available AEDs. In doing so, we first provide a general summary of data on individual AEDs followed by a discussion on how the kinetic properties may be affected by individual host factors. The clinical implications will be discussed as well as the possibility to control for pharmacokinetic variability by use of therapeutic drug monitoring (TDM).

1.1. Search criteria and literature review

The present review is mainly based on recently published articles identified by searches in PubMed and Google Scholar from May 2009 to May 2011, in addition to the authors' files. Selected publications with emphasis on the last five years were included. Relevant peer-reviewed articles for the topic in recognized international journals in English were included, and primary sources were preferred. Abstracts were included where a full publication was not found. Review articles giving a broad and updated overview were also included. The SPC (Summary of Product Characteristics) for each of the drugs were used for specific pharmacokinetic parameters. Unpublished or non-English articles and case reports or clinical studies with a minor methodological and clinical value were excluded. Based upon the searches, a selection of relevant articles was chosen as a basis for the present review. AEDs are defined as the drugs classified as N03A in the Anatomical Therapeutic Classification system (ATC) [4]. The following search terms were used: *Category 1*, *AEDs*: Carbamazepine, clobazam, clonazepam, eslicarbazepine acetate, ethosuximide, felbamate, gabapentin, lacosamide, lamotrigine, levetiracetam, oxcarbazepine, phenobarbital, phenytoin, pregabalin, primidone, retigabine, rufinamide, stiripentol, tiagabine, topiramate, valproic acid, vigabatrin, zonisamide.

Category 2, Other terms: Absorption, adverse drug effects, clinical study, distribution, drug delivery, drug development, drug surveillance, efficacy, elimination, excretion, formulation, generic substitution, host factors, metabolism, pharmacokinetics, pharmacology, pharmacogenetics, safety, special populations, therapeutic drug monitoring, teratogenicity, and tolerability.

2. Absorption and bioavailability of antiepileptic drugs

2.1. General aspects

The different routes of administration of AEDs are described in detail in a separate chapter of this volume (R. H. Levy). We here focus on oral administration. In general, absorption is extensive and bioavailability high for most AEDs (Table 1). The rate and extent of absorption can, however, vary with the drug formulation. Slow-, extended-, or sustained-release formulations have been developed for some AEDs. The purpose with such formulations is to prolong the absorption