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Current oral and non-oral routes of antiepileptic drug delivery ☆

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ABSTRACT

Antiepileptic drugs are commonly given orally for chronic treatment of epilepsy. The treatment of epilepsy requires administration of medications for both acute and chronic treatment using multiple types of formulations. Parenteral routes are used when the oral route is unavailable or a rapid clinical response is required. Lorazepam and midazolam can be administered by the buccal, sublingual or intranasal routes. Consensus documents recommend rectal diazepam, buccal midazolam or intranasal midazolam for the out-of-hospital treatment of early status epilepticus. In the United States, diazepam is the only FDA approved rectal formulation. With the lack of parenteral, buccal or intranasal formulations for many of the antiepileptic drugs, the use of the rectal route of delivery to treat acute seizures or to maintain therapeutic concentrations is suitable for many, but not all antiepileptic medications. There is a significant need for new non-oral formulations of the antiepileptic drugs when oral administration is not possible.

Contents

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1. Introduction

Approximately 20–30% of patients with epilepsy have seizures that are refractory to treatment with the currently available antiepileptic drugs (AEDs) and patients will experience break-through seizures. Although the majority of seizures will be self-limiting, seizures that persist for more than 5 min require prompt intervention. In addition, there are circumstances where chronic administration of medications is required but due to lack of oral access and incompatibility with intravenous formulations of medications, alternative routes of drug dosing are required. Therefore, the treatment of epilepsy requires administration of medications for both acute and chronic treatment using multiple types of formulations.

2. Oral administration

2.1. Gastrointestinal absorption

Absorption is defined by the rate at which the drug leaves the site of administration and the extent (bioavailability) to which it occurs. The absorption of a drug is dependent on the anatomy and physiology of the gastrointestinal (GI) tract, the physiochemical properties of the drug (solubility (log P), particle size, chemical form, pka) and the type of dosage formulation. Most drugs are absorbed by passive diffusion in the GI tract, where the rate of absorption is proportional to the drug concentration gradient across the barrier. Other drugs are absorbed by a combination of passive and active transport by proteins that can increase and/or decrease absorption depending on their location and whether they are influx or efflux transporters. For example, the oral absorption of gabapentin is dependent on active transport by the influx L-amino transporter, System-L [1]. Saturation of the L-amino transport mechanism results in decreased absorption with increasing doses of gabapentin [2]. Conversely, p-glycoprotein (Pgp) and other efflux transporters can limit drug absorption by increasing the excretion of drugs into the intestinal lumen from the systemic circulation. Carbamazepine up-regulates the expression of ABCC2 (Pgp) in the liver [3]. A recent study suggested that increased Pgp expression was responsible for the decrease fexofenadine plasma concentrations found when administered concurrently with carbamazepine [4], although plasma concentrations of fexofenadine are dependent on multiple transporters, including Pgp and organic anion transporting polypeptide (OATP) [5] and the contributions of individual transporters have not been defined [5]. Carbamazepine does not affect the pharmacokinetics of digoxin, a common probe for Pgp [6], suggesting that the effect of carbamazepine on fexofenadine is on GI efflux transporters other than Pgp. Orally administered drugs absorbed from the GI tract reach the liver via the hepatic portal vein prior to entering the systemic circulation. First pass metabolism of a drug can occur in the GI tract and in the liver, prior to the drug reaching systemic circulation, resulting in a decreased bioavailability. Both midazolam and stiripentol have low bioavailability due to extensive first pass metabolism (Table 1). Extensive first pass metabolism and/or low GI absorption of a drug increase the possibility of high intersubject variability in the relationship between dose and concentration.

2.2. Oral formulations

Antiepileptic drugs are most commonly given orally for chronic treatment of epilepsy as well as a variety of other non-epilepsy disorders. Oral formulations include solutions, suspensions, tablets, capsules and extended release products. Table 1 summarizes the oral formulations, the bioavailability and the time to maximum concentration (T_{max}) of the commercially available AEDs.

Solutions are absorbed most rapidly, as the rate-limiting step in the absorption of the drugs is predominantly due to gastric emptying. For drugs that are not completely aqueous soluble, and are in a suspension formulation, absorption is dissolution rate-limited. In most cases, a well-formulated suspension has superior bioavailability characteristics compared to a tablet or capsule. However, shaking an oral suspension prior to each administration is important in order to accurately administer the dose. Otherwise, theoretically, precipitation in the suspension will result in doses lower than expected initially and then higher than expected as the bottle empties.

Compressed tablets with or without coating are the most widely used oral dosage form. A coating is used to mask unpleasant taste, to protect ingredients from decomposition during storage, or to improve appearance of the tablet. The disintegrating tablet is designed to be dissolved on the tongue rather than swallowed whole. Clonazepam and lamotrigine are available as disintegrating tablets and are bioequivalent to their immediate release formulations.

Sprinkle capsules are formulations in which the capsules can be opened to release small pellets of drug that can be sprinkled onto food or can be swallowed whole. Both disintegrating tablets and sprinkle capsules serve as alternative formulations for infants, children, and patients with dysphagia (difficulty swallowing), which is relatively common in the general population. The prevalence of dysphagia significantly increases in the elderly patient population.

Sprinkle capsules can contain either immediate-release or extended-release formulated drug, and it is important to identify the type of content of the sprinkle capsule. Topiramate and valproate are both available as sprinkle capsules. Valproate (divalproex sprinkle capsule) contains modified-release granules and the rate and extent of absorption are equivalent to other sustained-release formulations. Therefore,

Table 1
Antiepileptic drug oral formulations.

Antiepileptic drug	Oral formulations	Oral F[a] (%)	T_{max} (IR) (h)	References
Carbamazepine	Suspension, syrup, tablet, chewable tablet, SR tablet, ER tablet, ER capsule	70–95	2–8 [a]	[85,86]
Clobazam	Tablet	87	1–3	[87]
Clonazepam	Suspension, tablet, disintegrating tablet	90	1–4	[88]
Diazepam	Suspension, tablet	100	0.5–1.5	[15,89]
Ethosuximide	Syrup, capsule	>90	3–5	[90]
Felbamate	Suspension, tablet	>90	1–3	[91]
Gabapentin	Solution, tablet, capsule	30–60	2–3	[2]
Lacosamide	Solution, tablet	100	1–4	[92]
Lamotrigine	Tablet, chewable tablet, disintegrating tablet, ER tablet	98	1–3	[93]
Levetiracetam	Solution, tablet, ER tablet	100	0.5–2	[94]
Lorazepam	Suspension, tablet,	>90	1–2	[24]
Midazolam	Syrup, solution	30	0.5	[95]
Oxcarbazepine	Suspension, tablet	>90	4–6[b]	[96]
Phenobarbital	Suspension, tablet, chewable, capsule, elixir, ER tablet, ER capsule, SR tablet	>95	0.5–4	[97]
Phenytoin	Suspension, tablet, chewable tablet, capsule	90–100	3–12	[98]
Pregabalin	Solution, capsules	>90	0.5–1.5	[99]
Primidone	Suspension, tablet, chewable tablet	>90	3–6	[100,101]
Rufinamide	Suspension, tablet	85	4–6	[102]
Stiripentol	Capsule	30–70	1–3	[103]
Tiagabine	Tablet	90	0.5–3	[104]
Topiramate	Tablet, capsule, sprinkle capsule	80	1–4	[105]
Valproate	Syrup, tablet, sprinkle capsules, DR tablet, ER tablet	90	2–4	[106]
Vigabatrin	Powder for solution or suspension, tablets	>90	0.5–2	[107]
Zonisamide	Capsules	>90	1–3	[108,109]

Abbreviations used: F = oral bioavailability, IR = immediate release (includes capsules, tablets, syrups, suspensions, solution, disintegrating and chewable tablets), ER = extended release, DR = delayed release and SR = sustained release.
[a] Peaks as late as 26 h have also been rarely found.
[b] Peak concentration of monohydroxycarbazepine (MHD) as oxcarbazepine is a pro-drug.