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Review

Drug absorption in the elderly: Biopharmaceutical considerations for the antiepileptic drugs

Barry E. Gidal*

*School of Pharmacy and Department of Neurology, University of Wisconsin, 1032 Rennebohn Hall,
777 Highland Avenue, Madison, WI 53705, USA*

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Abstract

The management of antiepileptic drug (AED) pharmacokinetics remains a challenge in the treatment of patients with epilepsy. Drug characteristics, such as protein binding, mechanisms of drug elimination, and the potential for pharmacokinetic/pharmacodynamic interactions, are important considerations for drug selection and may help determine overall effectiveness. In elderly patients with epilepsy, the likelihood of polytherapy, along with physiological changes associated with aging, can make pharmacokinetic issues even more significant. One aspect of pharmacokinetics that has received less attention is the process of oral drug absorption. Aging can have variable effects on the gastrointestinal system. Some of these physiological changes have the potential to impact absorption patterns of some medications, including AEDs. Altered oral protective reflexes, xerostomia, and delayed esophageal emptying in elderly patients may complicate oral administration of some medications. Altered gastric pH could modify drug absorption, and modified gastric emptying rates can influence the bioavailability of some AEDs. Finally, intestinal transit times may be slower in elderly patients compared to younger patients, possibly altering the absorption of some AEDs. These age-related physiological changes that may affect AED pharmacokinetics should be considered when treating elderly patients with epilepsy.

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* Tel.: +1 608 262 3280; fax: +1 608 265 5421.

E-mail address: beg@pharmacy.wisc.edu.

1. Introduction

A fundamental challenge in the treatment of patients with epilepsy involves management of antiepileptic drug (AED) pharmacokinetics. Individual AED characteristics, such as protein binding, mechanism of drug elimination, and the potential for participating in pharmacokinetic and/or pharmacodynamic interactions, can play a crucial role, not only in drug selection, but also in overall effectiveness of epilepsy treatment. Given the likelihood of comorbid medical conditions requiring polytherapy, as well as the normal physiological changes associated with aging, these issues may be of even greater significance in an elderly patient with epilepsy. One aspect of AED pharmacokinetics that is infrequently addressed is the impact of aging on drug absorption. In part, this is because the physiological changes associated with aging are difficult to study and can be influenced by both comorbid disease states and concomitant medication treatments. Clearly, aging does have an effect on the gastrointestinal (GI) system. The impact of these changes on AED absorption is largely unclear, particularly for the newer generation medications. It is likely however, that changes in drug absorption patterns will be variably altered, and the extent and pattern of these potential changes will be influenced by individual drug pharmaceutical properties and formulation.

Although the GI tract shows remarkable resilience during aging, both healthy and non-healthy aging lead to physiological changes that influence oral and esophageal function, gastric pH, gastric emptying rates, and intestinal transit times (Firth and Prather, 2002; Blechman and Gelb, 1999). These effects, in turn, produce numerous opportunities for AED pharmacokinetic variability due to changes in drug absorption, distribution, and elimination. Of these changes, potential age-related alterations in oral drug absorption have, perhaps, received the least attention from investigators.

2. Oral and esophageal changes

Altered oral protective reflexes and xerostomia may complicate oral administration of certain medications, and a great number of esophageal changes in response to aging have also been documented (Firth and Prather, 2002). Some of these changes include thickening of

the smooth muscle layer, reduced contraction velocity and duration, and delayed esophageal emptying. Advancing age has been associated with an approximate 20–60% reduction in enteric plexus neurons (Dharmarajan et al., 2001). Although these changes likely have no direct effect on absorption, they may impact oral administration of certain dosage forms.

3. Gastric changes

Of all the potential changes in GI physiological function, changes in gastric function are the most likely to influence AED absorption kinetics. In cases where there is a reduction in functional absorptive capacity (e.g., as a result of a reduction in intestinal absorptive cells) one would expect to see a reduction in both rate and extent of drug absorption. Conversely, depending upon the physiochemical characteristics of the particular drug, alterations in gut physiology may actually facilitate drug absorption. In the case of a drug for which formulation dissolution is the rate-limiting step in absorption, a decrease in gastric emptying time may increase the overall extent of absorption and, hence, systemic drug exposure. Aging is frequently associated with increased cholecystokinin levels, which can inhibit distal gastric contractions and slow gastric emptying (MacIntosh et al., 1999). Gastric emptying of both solids and liquids can be delayed.

Whether or not basal or stimulated gastric acid secretion is altered in the aged is controversial. Most studies suggest that, although gastric acid secretion is generally similar in older and younger individuals, the incidence of achlorhydria is approximately 10–20% among elderly patients, compared to less than 1% in younger subjects (Blechman and Gelb, 1999). Hypochlorhydria may be present in approximately 20% of individuals over the age of 70 years (Holt et al., 1989).

Although fasting gastric pH is similar in older and younger individuals, the postprandial pH response may differ significantly (Russell et al., 1993, Table 1). In an evaluation of upper GI pH conducted in a group of healthy elderly subjects, 11% were found to have a median fasting gastric pH greater than 5. Although gastric pH during the consumption of a meal was not significantly different between younger and elderly subjects, the median time for postprandial return for

Table 1
Comparison of gastric pH between young and elderly subjects
(Russell et al., 1993)

	Young (N = 24) ^a	Elderly (N = 79) ^b	P-value ^c
Fasted			
pH, median (range) ^d	1.7 (1.4–2.0)	1.3 (1.1–1.6)	0.014
During the meal			
pH, median (range)	5.0 (4.4–5.6)	4.9 (3.9–5.5)	0.74
Postprandial response, median (range), min			
pH 5	8 (2–17)	23 (6–46)	0.015
pH 4	14 (8–40)	52 (27–115)	0.0002
pH 3	42 (26–83)	89 (44–167)	0.0026
pH 2	100 (44–143)	154 (82–210)	0.026

^a From Dressman et al. (1990).

^b Pooled elderly values include achlorhydric older subjects.

^c Given for the Mann–Whitney *U*-test statistic from comparisons between young and elderly.

^d Values are given as medians, with interquartile ranges in parentheses.

pH values was significantly longer in elderly versus younger individuals. For patients who eat every few hours during the day, low gastric pH may only be found in the early morning, before the first meal of the day. Clinically, these changes may be significant for drugs that display pH-dependent dissolution and/or activation profiles. Elevated gastric pH may also result in impaired oral absorption of minerals such as iron and calcium.

Altered gastric pH could, therefore, modify drug absorption in at least two ways. For drug products that are acid labile, an increase in gastric pH may also result in enhanced drug absorption. Since drugs are more soluble when ionized, increased gastric pH can decrease drug dissolution of weak bases and increase the solubility of weak acids. Weakly acidic drugs dissolve more quickly in environments where pH is higher, and a greater fraction of the drug is in an ionized form. Conversely, weakly basic drugs tend to display a slower dissolution rate at higher gastric pH, since more of the drug exists in its un-ionized form. Clinically, therefore, decreased dissolution and impaired absorption might be seen for weakly basic drugs in patients with elevated GI pH, such as elderly individuals with hypochlorhydria, or perhaps shortly following a meal. Conversely, the dissolution and absorption of a weakly acidic drug may be enhanced in the same situation by virtue of increasing the proportion of drug that exists in the ion-

ized state. Thus, fluctuations in gastric pH may distort the absorption profiles of AEDs, such as phenytoin, and may, in part, explain the observations of variable serum phenytoin concentrations noted by Birnbaum et al. (2003) in elderly nursing home patients.

Changes in gastric pH may also influence the rate and extent of absorption of acid-labile products or prodrugs that require an acidic medium for conversion. The observed impaired absorption of desmethyldiazepam following clorazepate administration that is seen in some older subjects may occur, in part, for this reason. Clorazepate displays acid-dependent hydrolysis and decarboxylation in the stomach to yield desmethyldiazepam, the major active clinical compound found in the systemic circulation following oral clorazepate administration. Studies have demonstrated that, when gastric pH is maintained above 6, oral absorption of desmethyldiazepam is significantly impaired (Abruzzo et al., 1977). This finding may explain the observation of Ochs et al. (1979), who found substantial reductions in systemic desmethyldiazepam concentrations in elderly patients as compared to younger subjects.

In addition to gastric pH changes, modified gastric emptying rates can significantly influence the bioavailability of certain drug products, depending upon their physiochemical properties. Alterations would generally be expected to impact drugs that were either very soluble or poorly soluble. The hindered gastric emptying that may present in some elderly patients (Clarkston et al., 1997) could restrict the speed and onset of absorption for highly soluble compounds. Conversely, delays may actually facilitate the dissolution and consequent absorption of poorly soluble drugs. Solid dosages are more susceptible to these effects than those in liquid form.

4. Intestinal changes

It is important to recognize that the GI tract is best viewed as a heterogeneous organ system, and that physiological properties, such as gut motility and number of villi and microvilli, may change across the length of the gut (Martinez and Amidon, 2002).

In addition to possible changes seen in the stomach, age-related changes may also be seen in the intestine. Although enterocytes are essentially unchanged in the

elderly individual, reduced numbers of myenteric neurons have been noted in the small intestine. Differences in duodenal pH are minimal between young and elderly subjects (Russell et al., 1993).

Changes in manometric patterns, including decreased postprandial contractions and reductions in the frequency of migrating motor complexes, have been seen, prompting questions about altered GI transit times in some individuals (Firth and Prather, 2002). Delayed colonic transit times have been noted in otherwise healthy elderly patients who become inactive (Liu et al., 1993). These changes are relatively minor and would not be expected to alter absorption of most drugs significantly, but there may be exceptions. In particular, absorption of some extended-release AED formulations is likely sensitive to GI transit times, although the clinical significance is still unclear. In one evaluation of an osmotically controlled release formulation of carbamazepine, systemic exposure varied substantially as a function of the transit time from stomach and small intestine (Wilding et al., 1991). In this study conducted in young subjects, total GI transit time for this formulation was found to range between 10 and 60 h. Overall, drug release was greatest in subjects with the longest transit times, while up to 30% of the drug was not released in the subjects with the fastest gut transit times. Therefore, as gut transit times may be altered in elderly patients, dose formulations and delivery devices might be expected to influence the absorption patterns of poorly soluble AEDs such as carbamazepine.

Elderly patients may also have diminished rectal compliance and reduced sphincter tones. Delayed colonic transit times, particularly in the distal colon and rectum, along with changes in anorectal function may contribute to the high incidence of constipation seen in elderly (particularly inactive elderly) patients (Firth and Prather, 2002). Whether these changes or the increased incidence of constipation in older patients results in altered rectal drug absorption is not clear.

Although the overall extent of intestinal drug absorption is primarily determined by the physiochemical characteristics mentioned above (e.g., solubility, dissolution, permeability, and acidic stability), in many cases transport proteins involving both drug influx and efflux are likely involved. Protein transporters can include (but are not limited to) organic anionic

and cationic transporters, amino acid transporters, P-glycoprotein, vitamin transporters, and intestinal dipeptide transporters (Martinez and Amidon, 2002). P-glycoprotein is located on the villus tip of the apical brush–brush membrane (Lin and Yamazaki, 2003). Its distribution tends to progressively increase from the stomach to colon. Many drugs that are substrates for the cytochrome P450 isozyme system are substrates for this transporter. Whether there are clinically meaningful age-related declines in the activity of this transporter is still unclear (Rosati et al., 2003).

Gabapentin absorption utilizes the amino acid transporter system L, and considerable absorption variability has been observed among even young, healthy subjects. There do not appear to be marked differences in gabapentin absorption in elderly patients as compared to younger subjects however (Boyd et al., 1999). How the activity of these other various transporters influence drug absorption and may respond to intestinal changes associated with aging is an area of increasing research interest.

5. Conclusion

Drug absorption is a complex process that involves the interaction of numerous physiological variables. In many cases, the impact of both healthy and unhealthy aging on various GI functions is incompletely characterized. Currently, there is an increased research focus on AED pharmacokinetics in the elderly, often centered on changes in drug elimination processes. However, the absorption kinetics of certain drug products may be substantially affected by age-related changes in GI function as well.

Although generally resistant to the effects of aging, certain physiologic changes in GI function may occur. When considering the impact of these changes on treatment of the elderly epilepsy patient, it is important to realize that the GI tract is not a homogenous, static organ. For example, while fasting gastric pH is similar in older and younger individuals, postprandial return to basal levels slows with age. Similarly, enterocytes are generally unchanged in elderly patients, but intestinal transit may be slowed. These effects, and many others, could beget modified drug solubility, altered transport protein activity, and other consequences that reshape drug absorption profiles among the elderly.

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