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Review

Pharmacological and clinical aspects of antiepileptic drug use in the elderly

E. Perucca [a,*], D. Berlowitz [b], A. Birnbaum [c], J.C. Cloyd [c], J. Garrard [d], J.T. Hanlon [e], R.H. Levy [f], M.J. Pugh [g]

[a] *Institute of Neurology IRCCS C. Mondino Foundation and Clinical Pharmacology Unit, University of Pavia, Piazza Botta 10, 27100 Pavia, Italy*
[b] *HSR&D Field Program, Bedford VA Medical Center, Bedford, MA, USA*
[c] *Department of Experimental and Clinical Pharmacology, College of Pharmacy, University of Minnesota, Minneapolis, MN, USA*
[d] *Division of Health Services Research and Policy, School of Public Health, University of Minnesota, Minneapolis, MN, USA*
[e] *Institute for the Study of Geriatric Pharmacotherapy, College of Pharmacy, University of Minnesota, Minneapolis, MN, USA*
[f] *Department of Pharmaceutics, University of Washington, Seattle, WA, USA*
[g] *Center for Health Quality, Outcomes, and Economic Research, Boston University School of Medicine, Boston, MA, USA*

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Abstract

The impact of epilepsy on quality of life may have specific features for people in old age. Recent studies conducted in a large population of elderly veterans receiving care within the U.S. Department of Veterans Affairs indicate that people with epilepsy receiving antiepileptic drugs (AED) show important deficits in physical and social functioning compared with age-matched people without epilepsy. To what extent these deficits can be ascribed to epilepsy per se or to the consequences of AED treatment remains to be clarified. The importance of characterizing the effects of AEDs in an elderly population is highlighted by epidemiologic surveys indicating that the prevalence of AED use is increased in elderly people, particularly those living in nursing homes. In a cross-sectional study of 21,551 residents in 346 nursing homes in 24 states of the US, 10.5% of all residents were found to receive at least one AED, which in 65% of the cases was prescribed for a seizure disorder. Both the pharmacokinetics and the pharmacodynamics of AEDs may be altered in old age, which may contribute to the observation that AEDs are among the drug classes most commonly implicated in causing adverse drug reactions in an aged population. Aging-related pharmacokinetic alterations include decreased plasma protein binding, increased volume of distribution for lipophilic drugs, reduced efficiency of drug metabolizing pathways, decreased renal drug clearance, and a prolonged elimination half-life. The unbound drug clearance of most metabolically and renally eliminated AEDs is decreased by an average of 20–40% in the elderly. However, old age is less a period of predictable change than of increased variance between individuals. Age alone is one of several contributors to this variability; other factors include physical frailty, comorbidities, dietary influences, and

* Corresponding author. Tel.: +39 0382 986 360; fax: +39 038 222 741.
E-mail address: perucca@unipv.it (E. Perucca).

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drug interactions. An intriguing observation is that elderly nursing home residents exhibit an unexplained wide intraindividual variability in serum concentration of phenytoin, and possibly other AEDs, despite unchanged daily dosages. This observation suggests that measurement of a single total phenytoin concentration may not be sufficient to assess the size of dosage adjustments in these patients. Additional, well characterized sources of variability are drug–drug interactions between AEDs and drugs administered to treat co-morbid conditions. To a large extent, these interactions can be predicted through knowledge of the isoenzymes responsible for the metabolism of individual drugs coupled with information about the effects of the same drugs on these enzymes.

Keywords: Antiepileptic drugs; Elderly; Clinical pharmacology; Pharmacoepidemiology; Drug interactions

Contents

1. Introduction

Because the incidence of seizure disorders rises sharply after age 60, it is not surprising that the prevalence of antiepileptic drug (AED) use is higher in older people than in the general population. However, the factors affecting the utilization of these agents in different settings, either for epilepsy or for other indications, have not been fully elucidated. Likewise, there is a paucity of studies in which the impact of epilepsy and its treatment on the physical and social functioning of elderly people has been investigated. Because the pharmacokinetics and the pharmacodynamics of AEDs may be altered by advancing age, an understanding of the clinical pharmacology of these agents in elderly people is essential for rational prescribing. These issues were addressed in a special session of the International Geriatric Epilepsy Symposium, which provided researchers with the opportunity to present new findings against the background of currently available information. A summary of these presentations is given in the sections below.

2. The impact of epilepsy and its treatment on older individuals

While many studies have examined the impact of epilepsy in the general population, little attention has been focused on the elderly (Wagner et al., 1996). The needs of the elderly differ from those of younger adults, and physiologic changes that occur with aging complicate this picture. Aging can be considered to be successful when patients are able to remain engaged in life, avoid disease, and maintain high cognitive and physical function (Rowe and Kahn, 1998). Patients with epilepsy are no longer able to avoid disease, so it is even more important to maintain active mental, physical, and social functioning. Dr. Pugh and co-workers at the Boston University School of Public Health and the

Bedford Veterans Affairs (VA) Medical Center recently investigated the potential impact of epilepsy and its treatment on these aspects of successful aging. The study was conducted in a population of older veterans receiving care within the United States Department of VA.

Patients with a diagnosis of epilepsy were identified using national inpatient, outpatient, and pharmacy data from the VA. Those with at least one ICD9-CM code indicative of epilepsy any time between 1997 and 1999 and who also received at least one AED during 1999 were identified as having epilepsy. Individuals who received VA care between 1997 and 1999 and who were first diagnosed in 1999 were identified as newly diagnosed, and those diagnosed in 1997 or 1998 were classified as previously diagnosed. Those with no epilepsy diagnosis were identified as such. Data for these individuals were merged with data from the 1999 Large Health Survey of Veterans, which contained a modification of the Medical Outcomes Study SF-36 for the veteran population (SF-36V). Changes to the role items from dichotomous choices (yes/no) to five ordinal choices (none of the time to all of the time) (Kazis, 2000) improved the precision and discriminant validity of the role scales and the composite physical (PCS) and mental (MCS) component scales. The survey included a nationally representative sample of veterans receiving healthcare within the VA in 1999. Approximately 1.4 million veterans of all ages were sampled, with a return rate of approximately 65% (75% for those $\geq$65 years old). Of those who responded, 436,903 had no diagnosis of epilepsy, 812 had a new diagnosis, and 8258 had a previous diagnosis. Individual SF-36V scale scores and composite scores were calculated for these individuals.

Demographic characteristics included age, sex, race, education level, marital status, and living arrangements (i.e., live alone versus with others). The physical and mental comorbidity index scores developed by Selim et al. (2002) were used to control for overall disease burden, as these indices were developed to adjust for disease burden in SF-36V. The impact of epilepsy on older veterans was assessed by calculating the SF-36V scale scores and the physical and mental composite scores for those with no epilepsy diagnosis, those with newly diagnosed epilepsy, and those previously diagnosed. Scores adjusted for demographics and comorbidities were also compared among the groups by analysis of covariance (ANCOVA). Responses on questions regarding change in physical and mental health over the past year and participation in physical activity were compared using χ^2 analysis.

Mean scores for individual scale and mental and physical composite scores are presented in Table 1. In almost all instances, individuals without epilepsy had higher levels of health status than those with epilepsy, and those with newly diagnosed epilepsy had worse health status than those with previously diagnosed epilepsy. Results from the ANCOVA indicated that even when demographic factors and comorbidities were controlled, older veterans with epilepsy experienced lower levels of physical and mental health status than older veterans without epilepsy ($p < 0.01$). Moreover, individuals who were newly diagnosed reported significantly lower levels of physical functioning, social functioning, mental health, and vitality, and had lower scores on the mental component summary than those who were previously diagnosed ($p \leq 0.01$).

Table 2 demonstrates that older patients with newly diagnosed epilepsy were more likely to experience decrements in physical ($p < 0.001$) and mental ($p < 0.001$) health in the past year, and were more likely to have no participation in regular physical activity than those with either no epilepsy or those previously diagnosed ($p < 0.001$).

These analyses indicate that the impact of epilepsy on older individuals is substantial and that differences are not only statistically significant, but also clinically important. Because the VA population has similar demographic characteristics and comorbidity profiles to the general geriatric population, the results may be generalizable (Hauser, 1997). Further research is needed to more clearly define the impact of epilepsy on older patients. Because the elderly are more susceptible to adverse effects of drugs including AEDs (Cloyd et al., 1994), research on the specific adverse effects of AEDs in the elderly may help providers understand the effect of these drugs in long-term use.

3. Pharmacoepidemiology of AED use in the elderly

Surveys of both community-dwelling elderly and nursing home residents indicate that as many as 1.6 and 10%, respectively, take one or more AEDs (Lackner

Table 1
Health status of older veterans with and without epilepsy

V/SF-36 scale	Observed (S.D.)	Adjusted (S.D.)
Physical function		
No epilepsy	46.14 (29.35)	46.04 (12.76)
New epilepsy	29.47 (28.84)	37.46 (12.76)
Previous epilepsy	36.61 (29.99)	41.19 (12.10)
Role physical		
No epilepsy	27.21 (37.34)	27.12 (11.98)
New epilepsy	10.50 (29.59)	17.88 (14.10)
Previous epilepsy	17.61 (33.97)	21.87 (13.53)
General health		
No epilepsy	45.45 (23.82)	45.36 (8.99)
New epilepsy	31.41 (21.52)	37.92 (11.12)
Previous epilepsy	17.61 (33.97)	21.87 (13.53)
Bodily pain		
No epilepsy	47.92 (26.78)	47.89 (8.97)
New epilepsy	38.03 (26.73)	40.28 (11.18)
Previous epilepsy	42.60 (27.36)	43.60 (10.42)
Physical composite scale		
No epilepsy	32.95 (11.02)	32.93 (3.99)
New epilepsy	28.00 (9.73)	29.95 (4.66)
Previous epilepsy	30.11 (10.36)	31.16 (4.53)
Mental health		
No epilepsy	67.22 (22.29)	67.14 (9.10)
New epilepsy	52.95 (24.05)	60.02 (12.87)
Previous epilepsy	59.21 (23.71)	63.29 (11.06)
Role emotional		
No epilepsy	49.27 (48.69)	49.13 (16.66)
New epilepsy	24.25 (42.67)	36.77 (20.80)
Previous epilepsy	35.17 (46.48)	41.91 (18.91)
Vitality		
No epilepsy	41.85 (24.13)	41.78 (8.55)
New epilepsy	28.96 (21.88)	34.78 (10.77)
Previous epilepsy	35.13 (23.14)	37.85 (9.92)
Social functioning		
No epilepsy	60.59 (30.93)	60.45 (11.18)
New epilepsy	40.44 (30.94)	50.51 914.84)
Previous epilepsy	48.33 (32.00)	55.01 (13.35)
Mental composite scale		
No epilepsy	46.07 (12.94)	46.02 (5.12)
New epilepsy	38.01 (12.70)	42.09 (7.05)
Previous epilepsy	41.37 (13.02)	43.80 (6.16)

et al., 1998; Nitz et al., 2000). Because phenobarbital (PB) and phenytoin (PHT) are potentially problematic drugs for treating epilepsy in the elderly (Mattson et al., 1985; Smith et al., 1987), expert consensus recommendations favor the use of lamotrigine (LTG), gabapentin (GBP), or carbamazepine (CBZ) as first line agents in these patients (Scottish Intercollegiate Guidelines Network, 2001). Yet, experience suggests that these less problematic medications are being used relatively infrequently in actual practice (Lackner et al., 1998; Nitz et al., 2000). Two recent pharmacoepidemiologic surveys have investigated the extent to which expert recommendations are being translated into clinical practice in epilepsy patients.

3.1. AED use in community-dwelling elderly patients with epilepsy

The study, coordinated by Dr. Berlowitz and coworkers at the Bedford VA Medical Center, focused on elderly patients cared for within the VA network. Demographic, diagnostic, and utilization data were obtained from the Outpatient Clinic File and the inpatient Patient Treatment File of the VA national databases for 1997–1999. Types of medication dispensed were obtained from the Pharmacy Benefits Management database. A patient was considered to have epilepsy if there was at least one ICD9-CM code suggestive of epilepsy between 1997 and 1999 and the patient received at least one AED in 1999. The diagnosis of epilepsy was considered new if it was first made in 1999 and the patient had received previous VA care between 1997 and 1998.

Out of a total of 1,130,155 veterans aged 65 or older, 20,558 (1.8%) were identified as having epilepsy. Of those, 9.2% were first diagnosed in 1999 (Pugh et al., 2003). Both newly diagnosed and previously diagnosed epilepsy patients had significantly more comorbid illnesses than patients without epilepsy. For example, cerebrovascular disease was present in 41, 31, and 9% of newly diagnosed, previously diagnosed, and patients without epilepsy, respectively, and dementia was present in 21, 17, and 5% of the patients in each group. Cardiovascular and psychiatric diagnoses were also significantly more frequent in patients with epilepsy.

Approximately 80% of the epilepsy patients were on monotherapy and 20% on combination therapy with two or more drugs. PHT was the most commonly prescribed monotherapy, used in almost 70% of previously and newly diagnosed patients (Fig. 1). PB monotherapy use was somewhat less than 10% in both previously and newly diagnosed patients, while CBZ was prescribed in slightly more than 10%. Even among newly diagnosed

Table 2
Other components of health status for older veterans with and without epilepsy

	No epilepsy (%)	Newly diagnosed (%)	Previously diagnosed (%)
How would you rate your physical health in the past year?			
Worse	40.64	61.78	48.94
About the same	45.76	29.70	39.02
Better	13.56	8.51	12.04
How would you rate your mental health in the past year?			
Worse	23.51	43.42	32.55
About the same	62.78	45.38	54.74
Better	13.71	11.2	12.7
About how often do you participate in regular physical exercise such as walking briskly, biking, or swimming (times per week)?			
0	44.57	68.09	59.27
<1	13.19	10.96	10.6
1–2	15.04	5.89	11.46
3–4	15.1	7.72	10.22
>5	12.1	7.32	8.44

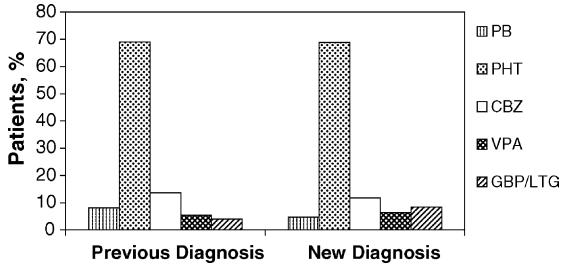

Fig. 1. AED monotherapies used in previously and newly diagnosed elderly patients from the VA database.

patients, GBP and LTG were prescribed in fewer than 10% of the cases. For patients on combination therapy, nearly 50% of those previously diagnosed, and 25% of those newly diagnosed, were on PHT and PB (Fig. 2). Thus, approximately 15% of patients overall were receiving PB.

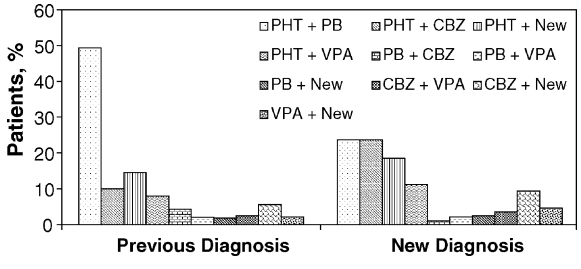

Fig. 2. AED combinations used in previously and newly diagnosed elderly patients from the VA database. "New" denotes either gabapentin or lamotrigine.

Analysis based on logistic regression models showed that PB monotherapy or combination therapy among newly diagnosed patients, as well as PHT monotherapy, were less likely to be used in patients seen by a neurologist. There was no clear association between neurologic conditions that are likely causes of epilepsy and type of medication taken. Similarly, other non-neurologic comorbidities were rarely associated with therapy decisions.

These results highlight that epilepsy is a frequent problem among elderly veterans living in the community. Moreover, a large gap exists between expert recommendations concerning AED therapy and actual treatment decisions made in clinical practice.

3.2. AED use in elderly nursing home residents

Five percent of all Americans reside in a nursing home at any point in time and, at 65 years of age, an estimated 43% are likely to enter a nursing home at some time before they die (Kemper and Murtaugh, 1991). It is important to assess whether nursing home admissions differ in use of AEDs from their community-based counterparts or from a cross-section of elderly already residing in these facilities. It is also relevant to determine in what proportion of patients AED therapy is initiated following entry into a nursing home. Two studies by Dr. Garrard and co-workers (2000, 2003) have addressed these issues.

The cross-sectional study was based on 21,551 residents in 346 nursing homes in 24 states in 1995. The subsequent study of AED use at entry was based on 10,318 admissions in 1999 to 510 nursing homes in 31 states. Both studies used convenience samples of nursing homes located throughout the US. Secondary source data included a federally mandated assessment form, the Minimum Data Set (MDS), administered at admission, and physicians' orders for all medications. Prevalence and incidence data for AED use were determined, followed by logistic regression analysis of patient-level factors from the MDS, including demographics (age, gender, race), clinical conditions (epilepsy/seizure disorder and comorbidities), and cognitive and functional assessments.

In the cross-sectional study, 10.5% of all residents in the 346 nursing homes received at least 1 AED, of whom 65% had an indication of epilepsy/seizure disorder. Factors associated with AED use included (i) a diagnosis of epilepsy/seizure disorder, with AED use being substantially greater among these patients (Fig. 3); (ii) geographic region, with AED use being greater among residents in northeastern states than in those living in southern states; and (iii) age, with AED use declining with increasing age (Fig. 3). The most commonly used AED was PHT, which was taken by 60% of users, followed by CBZ (18%), PB (17%), and valpnoic acid (VPA) (9%). Fourteen percent of residents received a combination of at least two AEDs, PHT/PB being the most common combination.

In the study that assessed AED use at admission, 7.7% of all elderly admitted to the 510 nursing homes during the first quarter of 1999 were already using one or more AEDs and, of these, 58% had documentation of epilepsy/seizure disorder. The most commonly used AEDs were PHT (52% of patients), VPA (19%), GBP (16%), CBZ (11%), and PB (8%), and 10% of patients received AED combinations. Logistic analysis revealed an epilepsy/seizure disorder and age interaction: in patients with no documentation of epilepsy/seizure disorder, AED use declined with age; however, when an epilepsy/seizure disorder was present, there was no difference among the three age groups. A diagnosis of bipolar depression was independently associated with higher AED use. The relationship between AED use and cognitive performance was complex. When epilepsy/seizure disorder was present, AED use decreased with worsening cognitive performance; however, without epilepsy/seizure disorder, AED use increased with worsening cognitive performance. In the same study, an assessment could be made of changes in AED therapy during the first 3 months after admission. One or more AEDs were initiated for 3% of admissions who had not been on AEDs at entry. Of these patients, 21% had an epilepsy/seizure disorder. Factors associated with a higher rate of AED initiation included (i) epilepsy/seizure disorder; (ii) bipolar depression, (iii) lower age. AEDs most commonly initiated included PHT (38%), VPA (33%), GBP (31%), CBZ (11%), and PB (4%). AED combinations were used in 20% of these patients. The comparison of these two groups, at entry and during the post-admission period, is shown in Fig. 4.

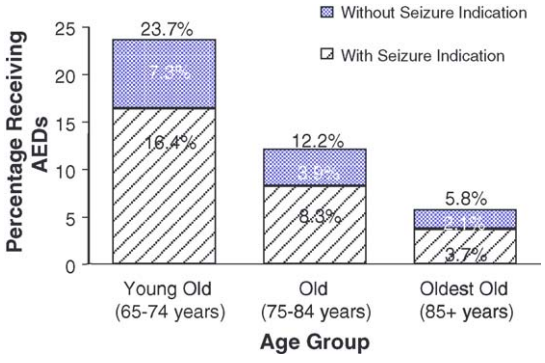

Fig. 3. Percentage of nursing home residents receiving an AED within each age group, by seizure indication.

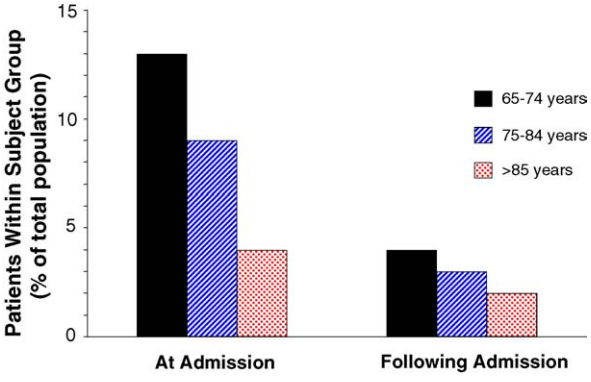

Fig. 4. AED use by age group in two groups of nursing home elderly: at admission and following admission. Data following admission refer to patients not taking AEDs at the time of admission.

Overall, these results indicate that, although different factors are associated with AED use by nursing home elderly, epilepsy/seizure disorder is clearly a dominant indication. Bipolar depression emerged as an independent factor associated with AED use.

4. Age-related changes in AED pharmacokinetics

4.1. Overview of available data

Available information on the pharmacokinetic properties of most therapeutic agents refers mostly to patients aged less than 70 years, despite the fact that they are mainly needed by elderly people. AEDs are no exception, and the paucity of data on AED pharmacokinetics in old age contrasts with the high prevalence of AED use among elderly patients, both for the treatment of epilepsy and for other indications.

Aging has a considerable influence on pharmacokinetic processes, often to an extent that requires dosage adjustments. Aging-related pharmacokinetic alterations include decreased plasma protein binding, increased volume of distribution (for lipophilic drugs only), reduced efficiency of drug metabolizing pathways (particularly those involving CYP enzymes), decreased renal drug clearance, and prolonged elimination half-life (Bernus et al., 1997). The unbound drug clearance of most metabolically and renally eliminated AEDs is decreased by an average of 20–40% in the elderly (Table 3). However, old age is less a period of predictable change than of increased variance between individuals. Age alone is one of several contributors to this variability. Other factors include physical frailty, comorbidity, dietary influences, and drug interactions (Hammerlein et al., 1998).

Predicting the pharmacokinetic behavior of an AED in an elderly individual is a challenging task. For highly protein-bound drugs (e.g., PHT and VPA), changes in unbound fraction can be predicted to some extent by measuring serum albumin concentration and creatinine clearance (Perucca, 1980; Perucca et al., 1984). There is, however, no single test or combination of tests that can be used to predict hepatic drug metabolic capacity in a single individual (Hammerlein et al., 1998). Although for highly metabolized AEDs population pharmacokinetics can be a useful tool to estimate individual drug clearance, the predictive accuracy of this approach leaves much to be desired. Our ability to predict changes in drug clearance is greater for renally eliminated than for extensively metabolized drugs (Haegele et al., 1988). In fact, the aging-associated pharmacokinetic changes of many renally excreted AEDs can be predicted on the basis of creatinine clearance, although this approach is not without pitfalls (Fliser et al., 1999).

Table 3
Average changes in apparent oral clearance of older and newer AEDs in elderly patients

Drug	Effect of old age on drug clearance	Reference
Carbamazepine	Decrease by 25–40%	Battino et al. (2003)
Felbamate	Decrease by 10–20%	Richens et al. (1997)
Gabapentin	Decrease by about 30–50%	Boyd et al. (1999)
Lamotrigine	Decrease by about 35%	Posner et al. (1991)
Levetiracetam	Decrease by about 20–40%	Patsalos (2004)
Oxcarbazepine	Decrease by 25–35%[a]	van Heiningen et al. (1991)
Phenobarbital	Decrease by about 20%	Messina et al. (2005)
Phenytoin	Decrease by about 25%[b]	Bachmann and Belloto (1999)
Tiagabine	Decrease by about 30%	Snel et al. (1997)
Topiramate	Decrease by 20%	Doose et al. (1998)
Valproic acid	Decrease by about 40%[c]	Perucca et al. (1984)
Vigabatrin	Decrease by 50–85%[d]	Haegele et al. (1988)
Zonisamide	No data	

Interindividual variation may be considerable in relation to age and other factors.
[a] Data refer to the active metabolite monohydroxycarbazepine.
[b] Decrease in clearance of unbound drug may be greater.
[c] Decrease in unbound drug clearance. Clearance of total (unbound + protein bound drug) may not change.
[d] These patients, who had various pathologies, were preselected to cover a wide range of impaired renal function.

There is clearly a need for improved methodology in the assessment of aging-related changes in pharmacokinetics. Formal pharmacokinetic studies involving extensive sampling in a limited number of subjects yield precise information, but they tend to underestimate interindividual variability due to rigid inclusion criteria. Studies based on serum drug concentrations at steady state may yield valuable information but, for the many AEDs that exhibit dose-dependent pharmacokinetics, results may be biased by non-randomized dose allocation, particularly with drugs that are routinely monitored (Battino et al., 2003).

In the therapeutic setting, measurement of serum AED concentrations can be valuable in individualizing dosage in an elderly person, even though it should be remembered that for drugs that are highly bound to plasma proteins the total serum concentration might underestimate the level of unbound, pharmacologically active drug. Because aging is also associated with important pharmacodynamic changes, pharmacokinetic measurements alone are not a substitute for careful monitoring of clinical response and appropriate dosage adjustment.

4.2. A study of steady-state serum PHT concentrations in elderly nursing home residents

Although approximately 10% of elderly nursing home residents in the US receive AEDs (Cloyd et al., 1994; Lackner et al., 1998; Garrard et al., 2000), few data exist on AED dose and serum concentrations in these patients. These factors were evaluated by A. Birnbaum and co-workers at the University of Minnesota (Birnbaum et al., 2003a) in a study that also assessed intraindividual variability in total serum drug concentrations (Birnbaum et al., 2003b).

The investigation was conducted at 119 nursing homes between June 1998 and December 2000, with a minimum of 6 months observation for each resident. To be included residents had to be at a nursing home for at least two months, aged 65 years or older, not residing in a subacute care unit, taking an AED for any indication, and have total PHT, VPA or CBZ serum concentrations documented in their medical record. For the cross-sectional part of the study, the descriptive information provided was based on data from only the first steady-state blood draw. The actual dose given 24 h prior to the blood sample was used in the calculation of doses. Data for the intra-resident variability in total PHT, VPA, and CBZ concentrations were only from individuals who had three or more concentrations while on the same dose of AED, who had been on this dose for at least 4 weeks, and who were not receiving any medications that could alter AED metabolism. Results for PHT concentrations are available, while those for VPA and CBZ concentrations are being evaluated.

A total of 387 residents (age: 79.4 ± 7.8 years) receiving PHT had sufficient data for analysis. Women received higher daily PHT doses than men (5.1 ± 1.8 mg/kg, $n = 259$ versus 4.6 ± 1.6 mg/kg, $n = 128$; $p = 0.017$) to achieve similar serum concentrations (women, 11.6 ± 6.4 μg/mL versus men, 12.0 ± 6.6 μg/mL). Daily PHT doses (mg/kg) and total serum PHT concentrations among age groups (65–74, 75–84, and ≥85 years) were similar. There were no differences in daily PHT doses (mg/d or mg/kg) or total serum PHT concentrations by the presence of concomitant medications known to inhibit or induce PHT metabolism, or in relation to differences in albumin levels. Most residents exhibited a steady-state PHT concentration between 5 and 15 μg/mL; however, 45% had levels below and 9% had levels above the suggested optimal range of 10–20 μg/mL.

Fifty-six residents had three or more total PHT concentrations measured (total, 285 concentrations) and were included in the intra-resident variability data set. Ages ranged from 65–100 years (mean, 80.1 ± 8.1 years) at the time of entry. The mean daily dose was 4.9 ± 1.5 mg/kg. There was a remarkable variability in serum PHT concentrations within patients who were on a stable PHT dose for at least 4 weeks. The range of total PHT concentrations in an individual was as narrow as 10.0–10.4 μg/mL to as wide as 9.7–28.8 μg/mL. Over time, 12 of the 56 residents had at least one PHT concentration higher than 20 μg/mL and 39 had at least one lower than 10 μg/mL. Six residents had both at least one higher than 20 μg/mL and one lower than 10 μg/mL. No factor could be identified that would account for such large intraindividual variability. Serum PHT concentrations in elderly nursing home residents appeared to be more variable than serum VPA or CBZ concentrations.

In conclusion, this study demonstrated that elderly women residing in nursing homes received higher doses of PHT than men to achieve similar total serum PHT concentrations. The majority of PHT levels were

outside the suggested optimal range (10–20 μg/mL), and the number of residents in the potentially toxic range (>20 μg/mL) was similar to that observed in a 1995 cohort of nursing home patients aged 20–107 years (Schachter et al., 1998). Serum PHT concentrations in nursing home residents varied 2–3-fold despite unchanged daily dose, a finding similar to observations made previously in a smaller group of elderly patients (Mooradian et al., 1989). These results have important clinical and public health implications, and suggest that measurement of a single total PHT concentration should not be used in determining dose changes in these individuals.

4.3. A preliminary study of PHT pharmacokinetics in community dwelling elderly patients

Most AED pharmacokinetic studies in the elderly have been based on oral administration of a single dose and typically included relatively healthy patients between 65 and 74 years, an age range in which pharmacokinetic changes are expected to be minimal. Information on steady-state elimination half-life is mostly unavailable, because therapy cannot be interrupted to allow adequate collection of blood samples. Moreover, few studies have characterized potential alterations in gastrointestinal absorption and in drug binding to plasma proteins, despite evidence that these can be affected by aging (Hammerlein et al., 1998).

To investigate in greater detail the effect of age on PHT pharmacokinetics at steady-state, Dr. Cloyd and colleagues developed and administered parenteral formulations of stable-labeled PHT (SL-PHT) and fosphenytoin (SL-FOS) to adults (age 18–64 years) and elderly patients (>65 years) on maintenance PHT regimens. To enter the study, patients had to be free of cardiac disease and not taking medications known to interact with PHT. A 100-mg dose of either SL-PHT or SL-FOS was infused intravenously over 20 min under blood pressure and ECG monitoring. Subsequently, the patient's morning dose, less 100 mg, was administered by the oral route. Blood samples were collected just prior to the infusion and for 192 h thereafter. A gas chromatographic-mass spectroscopy assay was used to simultaneously determine labeled and unlabeled serum PHT concentrations. Unbound PHT was separated from bound drug by ultrafiltration. The study was carried out under steady-state conditions, allowing the use of a linear pharmacokinetic model to analyze the data. Pharmacokinetic parameters were determined by noncompartmental analysis using WinNonlin®.

Table 4
Pharmacokinetic parameters of PHT in adults and elderly patients as determined by use of stable labeled PHT under steady-state conditons

	Adults ($n = 9$)	Elderly ($n = 21$)
Dose (mg/kg)	5.7 ± 1.0	4.7 ± 1.2
F (bioavailability)	0.82 ± 0.22	0.85 ± 0.22
Total concentration (μg/mL)[a]	15.9 ± 7.3	11.7 ± 4.6
Unbound concentration (μg/mL)[a]	2.3 ± 1.5	1.7 ± 0.8
Percent unbound (%)[a]	12.8 ± 3.2	13.3 ± 3.6
Serum albumin (gm/dL)	3.6 ± 0.3	3.7 ± 0.4
Volume of distribution (L/kg)	0.74 ± 0.2	0.87 ± 0.28
Total clearance (L/kg/h)	0.016 ± 0.013	0.029 ± 0.015
Unbound clearance (L/kg/h)[a]	0.17 ± 0.19	0.23 ± 0.14
Half-life (h)	44.3 ± 29.1	44.3 ± 20.8

[a] Adult, $n = 8$; elderly, $n = 18$.

Preliminary results are available for 30 subjects (non-elderly: five women and four men, aged 34.1 ± 10.4 years; elderly: eight women and 13 men, aged 76.1 ± 7.9 years). Compared with younger adults, elderly patients took smaller doses and had lower total and unbound serum PHT concentrations (Table 4). Half-lives were similar, whereas for distribution volume, unbound fraction, and total and unbound drug clearance there was a trend for higher values being found in the elderly.

Because PHT exhibits Michaelis–Menten kinetics, its clearance decreases with increasing drug concentration and, therefore, the higher clearance of the drug found in the elderly could be explained by the lower unbound concentration in this age group. The mean bioavailability (percent of dose absorbed) for both age groups was somewhat lower than that listed in the product labeling and the variability among patients was substantial. Overall, the one point measurement of bioavailability ranged from 46 to 115%. Three of the nine younger adults and 10 of the 21 elderly patients absorbed less than 80% of their daily dose (Fig. 5).

Although these results suggest that PHT pharmacokinetics are comparable in non-elderly adults and relatively healthy elderly patients, other investigations and indirect evidence do, in fact, indicate that the rate of PHT metabolism may decrease with advancing age. Fig. 6 shows a simulation of PHT concentration-dose relationships using previously reported V_{max} and K_m

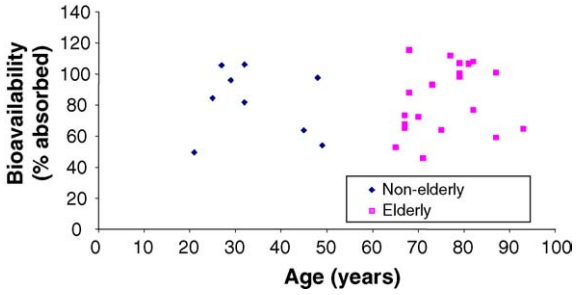

Fig. 5. Relationship between phenytoin bioavailability (% absorbed) and age in nine non-elderly and 22 elderly patients on maintenance phenytoin therapy.

values from adults and elderly patients (Bauer and Blouin, 1982; Cloyd et al., 1978). If PHT pharmacokinetics were unchanged in old age, the simulation (curve for adult patients shown in Fig. 6) predicts that the mean daily dose taken by the elderly patients in the study described above would result in a steady-state serum PHT concentration of 6.5 μg/mL. In fact, the elderly patients in the study had observed mean serum PHT concentration of 11.7 μg/mL (Table 4), suggesting that either K_m increases and/or V_{max} decrease in old age. On the other hand, elderly patients would have had higher serum PHT concentrations than those actually observed if their V_{max} and K_m values were similar to those reported by Bauer and Blouin (1982). This suggests that PHT pharmacokinetics for the elderly group included in the Cloyd study are intermediate between previously reported values for adults and elderly.

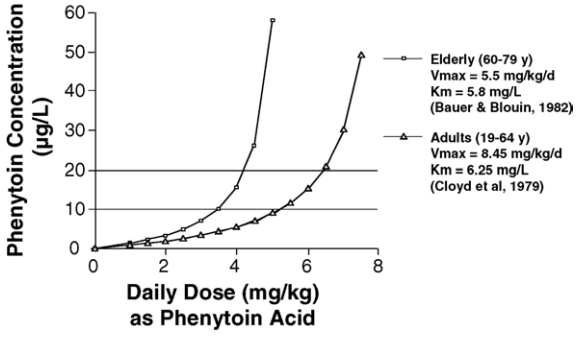

Fig. 6. The effect of age on phenytoin pharmacokinetics. The serum concentration–dose curves were simulated using a rearrangement of the Michaelis–Menten equation: $C_{pss} = K_m \times \text{daily dose}/(V_{max} - \text{daily dose})$, using data taken from the literature (see references Bernus et al., 1997 and Cohen et al., 2000).

Overall, the results of this preliminary investigation indicate that PHT pharmacokinetics exhibit greater variability than previously reported, which can make dose standardization difficult, particularly in the elderly. This also suggests that PHT therapy in the elderly may require more intense monitoring than in younger patients.

5. AEDs and adverse drug reactions in the elderly

Ramsay et al. (1994), in a post-hoc analysis of several large multicenter, controlled clinical trials comparing CBZ and VPA, found that elderly patients are more often seizure free at lower serum AED concentrations, but they also tend to have adverse effects at lower drug concentrations. While the benefits of AED therapy in the elderly are substantial, the risks of adverse drug reactions (ADRs) in this age group are equally important. Indeed, AEDs have been found to be among the most common sources of ADRs in old people.

In a survey conducted in nearly 3000 elderly patients from 18 nursing homes in Massachusetts, ADRs to any prescribed medication were determined through chart review and staff reports, and were evaluated by pairs of physicians (Gurwitz et al., 2000). A total of 546 ADRs were identified over a year, which corresponds to a rate of 1.89/100 resident months. Fifty percent of ADRs were preventable, i.e., associated with administration, adherence, or prescribing errors. The most common drug classes involved in ADRs were, in rank order, antipsychotics, antibiotics, antidepressants, sedative/hypnotics, anticoagulants, and AEDs. The same investigators also evaluated ADRs in nearly 30,000 elderly outpatients from a multispecialty clinic in central Massachusetts (Gurwitz et al., 2003). ADRs were identified by screening of voluntary reports, computer generated lab and medical records signals, and review of emergency department and hospital discharge summaries. Case reports were written by a blinded pharmacist and evaluated by a pair of physicians. They detected 1523 ADRs over a year, for a rate of 50.1/1000 person years. Twenty-eight percent of ADRs were preventable. The most common drug classes involved were, in rank order, cardiac drugs, diuretics, non-opioid analgesics, hypoglycemics, opioids, and AEDs.

There have been several studies examining the relationship between AED therapy and mobility problems (i.e., falls and fractures) in the elderly. A study of nearly 8000 elderly community dwelling women examined the association between CNS medications and risk of falls (Ensrud et al., 2002). The risk of any fall was found to be increased by 175% in women taking AEDs, even after controlling for other risk factors, including seizure diagnosis. The use of AEDs was also associated with an increase in the risk of frequent falls, with an adjusted odds ratio (adj. OR) of 2.56. Another study examined the association between medications and non-vertebral fractures in 2590 community dwelling elders (Bohannon et al., 1999). Due to low prevalence of the use of AEDs other than PHT, meaningful data could not be obtained for others. Patients taking PHT had a three-fold increased risk of any non-vertebral fracture (adj. OR, 3.06). For non-hip fractures, the increase in risk among PHT users was even higher (adj. OR, 3.74).

Based on these data, further studies are indicated to examine the appropriateness of AED use in the elderly and interventions to minimize their risks.

6. Pharmacokinetic drug interactions in the elderly: risk and predictability

Many AEDs are involved in clinically important drug interactions because of their ability to induce or inhibit metabolizing enzymes. Geriatric patients with epilepsy are particularly vulnerable to drug interactions because they are often taking many other medications for concurrent diseases (Lackner et al., 1998) and they are more sensitive to side effects, especially cognitive impairment and cardiac conduction abnormalities (Turnheim, 2003).

AED effects on cytochrome P450 (CYP) and other drug metabolizing enzymes can be summarized as follows (Patsalos and Perucca, 2003a,b): CBZ, PHT, PB, and primidone (PRM) are broad-spectrum inducers of CYP enzymes, including CYP1A2, CYP2C9, CYP2C19, and CYP3A4, and they also induce glucuronyl transferases (UGT) responsible for glucuronide conjugation. Oxcarbazepine (OXC) is a less potent inducer of CYP3A4 than CBZ, and it is an inhibitor of CYP2C19. Topiramate (TPM) also inhibits CYP2C19. VPA is known to inhibit CYP2C9 and UGT enzymes responsible for glucuronidation. Conversely, LTG, GBP, levetiracetam (LEV), tiagabine (TGB) and vigabatrin (VGB) have not been reported to alter enzyme activity, except for a recent study in which LTG, 300 mg/day, was found to increase the clearance of the progestagen component of a contraceptive pill (Lamictal prescriber's information).

The enzymes involved in the metabolism of AEDs have been well established. CBZ, TGB, ethosuximide (ESM), and zonisamide (ZNS) are predominantly metabolized by CYP3A4. PHT and PB are metabolized by CYP2C9 and CYP2C19. VPA, LTG and the active metabolite of OXC are mostly metabolized by glucuronidation. GBP, LEV and VGB are not metabolized to a clinically important extent in humans. TPM is also predominantly excreted without metabolism unless potent enzyme inducers are co-administered.

The literature concerning pharmacokinetic drug interactions between AEDs and some cardiovascular and CNS-acting drugs commonly used in the elderly was recently analyzed using the Drug Interaction Database (http://depts.washington.edu/didbase) and MEDLINE. When no reported interactions were found, the potential for drug interactions was evaluated using available literature on the metabolic behavior of the compounds and established principles for predicting metabolic drug interactions.

The antidepressants recommended for use in elderly patients with epilepsy (mostly SSRIs) have favorable safety profiles, and their metabolism is not highly sensitive to the inducing/inhibitory effects of AEDs. However there are a few reports of alterations in the pharmacokinetics of AEDs associated with co-administration of antidepressants. In vitro and in vivo studies indicate that fluoxetine inhibits several cytochrome P450 isoforms (CYP1A2, CYP2C9, CYP2C19, CYP2D6 and CYP3A4). Moreover, fluoxetine and its active metabolite norfluoxetine (which also inhibits CYP2D6) have long half-lives. Fluoxetine inhibits CBZ, PHT and VPA metabolism (Grimsley et al., 1991; Patsalos and Perucca, 2003b) and also interacts with many beta-blockers (Graff et al., 2001), antiarrhythmics (Cai et al., 1999) and warfarin (Dent and Orrock, 1997). Paroxetine is a narrow spectrum inhibitor (CYP2D6): it does not affect the plasma concentrations of CBZ, PHT and VPA (Andersen et al., 1991) while it interacts with beta-blockers and antiarrhythmics (Hemeryck et al., 2000a,b). Sertraline is a less potent CYP2D6 inhibitor.

Confirmatory in vivo studies did not demonstrate an inhibition of CBZ and PHT metabolism by sertraline; however, there are case reports of CBZ, PHT and LTG toxicity when sertraline was administered concomitantly (Joblin, 1994; Haselberger et al., 1997; Kaufman and Gerner, 1998). The antidepressants with least potential for metabolic drug interactions are escitalopram and citalopram (Jeppesen et al., 1996). Venlafaxine and duloxetine are expected to have a minimal effect on AED metabolism (Albers et al., 2000; Amchin et al., 1998, 2001; Skinner et al., 2003; von Moltke et al., 1997; Wilkander et al., 1995).

The cholinesterase inhibitors used in the treatment of dementia have little potential for significant interactions with AEDs because they have limited effects on metabolic enzymes. Similarly, memantine is predominantly eliminated without being metabolized.

Warfarin is a significant concern in an elderly population with epilepsy because it has a narrow therapeutic index, it is metabolized predominantly through CYP2C9 and CYP3A4, and there is a significant age-related decline in warfarin metabolism. In addition, the elderly have a higher risk of bleeding. Older AEDs have reported interactions with warfarin (Nappi, 1979; Patsalos and Perucca, 2003b), while LEV, LTG, GBP, TGB and TPM have low potential for drug interactions. Although OXC (450 mg twice daily for 1 week) did not alter the anticoagulant effect of warfarin in healthy volunteers (Kramer et al., 1992), there is potential for interactions with this drug since it is a mild inducer of metabolic enzymes.

There are no published reports on the effects of AEDs on ticlopidine metabolism. However, ticlopidine is an inhibitor of CYP2C19 and there are case reports of PHT and CBZ toxicity with concomitant administration (Brown and Cooper, 1997; Donahue et al., 1999).

Hydrophilic beta-blockers such as atenolol and sotalol are not metabolized and therefore they have little potential for drug interactions. In contrast, lipophilic beta-blockers such as propranolol, metoprolol and timolol are extensively metabolized and there are reports of their metabolism being accelerated by enzyme inducing AEDs (Mantyla et al., 1983). ACE inhibitors are either prodrugs that are not metabolized by CYP enzymes or they are renally eliminated and there are no reported interactions between these agents and AEDs. Thiazide diuretics are not metabolized and similarly there are no reported interactions with AEDs.

On the other hand, there are significant risks of interactions between AEDs and calcium channel blockers. Diltiazem and verapamil are CYP3A4 inhibitors and there are reports of increased CBZ levels with both diltiazem (Eimer and Carter, 1987) and verapamil (Macphee et al., 1986). Elevations of PHT levels have also been reported with these drugs (Bahls et al., 1991). Several studies have shown that the concurrent use of older enzyme inducing AEDs result in marked decreases in the serum levels of dihydropyridine calcium antagonists such as felodipine, nimodipine, nivaldipine and nisoldipine, all of which are CYP3A4 substrates (Tartara et al., 1991; Michelucci et al., 1996; Yasui-Furukori and Tateishi, 2002). Oxc has a smaller enzyme inducing effect on calcium channel blockers (Zaccara et al., 1993).

The HMG-CoA reductase inhibitors atorvastatin, lovastatin, and simvastatin are metabolized predominantly by oxidation (CYP3A4) and glucuronidation (UGT1A1/1A3 for atorvastatin and simvastatin). In a recent study in healthy volunteers, CBZ was found to reduce the area under the serum concentration curve of simvastatin and its active metabolite simvastatin acid by 75 and 82%, respectively (Ucar et al., 2003). There is also one case report of loss of efficacy when PHT was co-prescribed with atorvastatin and simvastatin (Murphy and Dominiczak, 1999). Fluvastatin is metabolized by CYP2C9, and there is a case report that PHT alters fluvastatin metabolism (Murphy and Dominiczak, 1999). Pravastatin and rosuvastatin are not extensively metabolized. There are no reports of newer AEDs affecting statin metabolism and there is little potential for such interactions. Atorvastatin, lovastatin and simvastatin are weak inhibitors of CYP3A4 (Cohen et al., 2000). Although there are no reports of inhibition of the metabolism of AEDs that are CYP3A4 substrates (e.g., CBZ and ZNS), the potential does exist. Fluvastatin inhibits CYP2C9 probe substrates in vitro and it could potentially inhibit PHT metabolism, but no cases have been reported. Another lipid lowering drug, gemfibrozil, is glucuronidated by UGT2B7 and is an inhibitor of CYP2C9, CYP2C19, CYP2C8 and UGTs (Prueksaritanont et al., 2002; Wen et al., 2001). There is a potential for inhibition of PHT metabolism by gemfibrozil, but there are no reports of such interaction in the literature.

In summary, many drugs commonly prescribed in geriatric patients have significant proven or potential

interactions with AEDs. This is most marked for older AEDs, particularly CBZ, PHT and PB. These interactions should be taken into account when prescribing concomitant medications, and drug levels may need to be monitored more closely.

7. Conclusions

AED use is common in the elderly, and is complicated by age-related changes in pharmacokinetics and pharmacodynamics. AEDs are a common class of drugs involved in adverse drug reactions, and in elderly persons they have been associated with mobility problems and with an adverse impact on several domains of health-related quality of life. The elderly are also at increased risk for clinically important drug interactions due to their frequent use of multiple medications to treat multiple morbidities. Further studies are needed to better characterize the comparative impact of different AEDs on clinical outcome in patients with seizures in old age.

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