ABSTRACT

At least 10% of nursing home patients are prescribed antiepileptic drugs. These drugs have complex properties and most pharmacokinetic studies have been performed on a much younger population. Although theoretically, the elderly experience a series of physiological changes that would have expected effects on pharmacokinetics, in practice, the appearance of these changes is highly variable. Therefore, each patient must be individually dosed and monitored. Special attention must be paid to poorly absorbed drugs such as phenytoin and carbamazepine because of marked variations in plasma concentrations caused by daily changes in gastrointestinal absorption. Antiepileptic drugs have important adverse effects that must be taken into consideration along with seizure control. Given the likelihood for cognitive deficits in the elderly, it is critical to monitor for the possibility of a negative cognitive impact caused specifically by the antiepileptic drug alone. Finally, antiepileptic drugs can have significant drug interactions in terms of adverse cognitive effects and, in the case of enzyme inducers and inhibitors, can increase or decrease metabolism of concomitant drugs, potentially altering response. All of these factors must be considered while caring for this patient population.

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ANTIEPILEPTIC DRUGS (AEDs) are widely used in nursing homes. On admission, 6% to 7% of patients are already taking an AED, and within a year, an additional 3% are placed on AED therapy. Thus, approximately 1 in 10 nursing home residents are prescribed 1 or more AEDs. The most commonly prescribed AEDs in this group are phenytoin and carbamazepine, which are used to treat epilepsy. AEDs, particularly valproic acid and gabapentin, are also used to manage pain and agitation.

FACTORS AFFECTING PHARMACOKINETICS AS A FUNCTION OF AGING

AED pharmacokinetics can differ in the elderly compared with younger individuals. Most clinical studies, however, have been performed in younger individuals. Elements affecting drug distribution in the elderly include variable gastrointestinal (GI) absorption and decreases in serum albumin, lean body mass, liver function, and kidney function. Theoretically, drug absorption is decreased in the elderly because of decreased GI blood flow and loss of intestinal mucosal surface. There is emerging evidence that absorption of poorly water-soluble drugs is highly variable in older individuals, particularly those with fluctuating GI function such as nursing home residents.

Concomitant therapies can also alter absorption. Drug distribution is strongly affected by lean body mass and by serum albumin levels. Adiposity rises from 18% in young adults to 36% in elderly men and 48% in elderly women. This increases the volume of distribution for lipid-soluble drugs such as the benzodiazepines that can extend elimination half-life. Serum albumin declines with age with as much as a 25% change from young adults. This can result in lower total drug concentrations while unbound plasma concentrations remain unchanged. In this situation, clinicians may misinterpret drug level measurements and make unnecessary dosage adjustments.
Because drug metabolism primarily occurs in the liver, it is strongly affected by changes in hepatic function. Liver mass (numbers of hepatocytes) and blood flow decrease with aging. Phase 1 metabolic pathways, such as microsomal oxidation, are decreased, although the rate of decrease varies with the individual as does microsomal enzyme induction. Phase 2 conjugation reactions are purported to be less affected by aging, although there are several reports involving valproate and lamotrigine that show an age-related decline in clearance. Finally, kidney function declines at a rate of approximately 1% per year from age 40 for men and women, resulting in a commensurate decrease in the clearance of drugs that are renally eliminated. These changes can be exacerbated or masked by the presence of other diseases and the drugs used to treat these diseases.

Currently, there are few studies that characterize AED pharmacokinetics in the elderly, making management of AED therapy in this group difficult. Perhaps the most useful pharmacokinetic concept to consider when selecting an AED is linearity in the relationship between dose and concentration. Drugs that follow linear pharmacokinetics will exhibit a proportional relationship between an increase (or decrease) in dose and the resulting plasma concentration. Drugs following nonlinear pharmacokinetics will exhibit a disproportional relationship between changes in dose and concentration. Among the AEDs, all 3 possible dose-concentration relationships exist as shown in Figure 1. For the majority of AEDs, the extent of absorption, protein binding, and clearance remain constant as dose increases, giving rise to linear kinetics (Figure 1, curve B). This is the case for ethosuximide, felbamate, levetiracetam, lamotrigine, phenobarbital, pregabalin, tiagabine, topiramate, and zonisamide. Phenytoin is metabolized through a saturable pathway, causing drug levels to increase more rapidly at higher doses (Figure 1, curve A). Finally, there are several drugs in which concentration does not increase in proportion with dose (Figure 1, curve C). AEDs in this class include carbamazepine, gabapentin, and valproate. For each of these drugs, the underlying pharmacokinetic mechanism for nonlinearity differs. Carbamazepine induces its own metabolism. Gabapentin absorption is saturable. Valproate protein binding is saturable, resulting in disproportional total drug concentration while unbound levels increase in proportion with dose. For each of these 3 drugs, as the dose is increased, there will be a less-than-proportional increase in total drug concentration.

One can compare the first-generation AEDs (carbamazepine, phenytoin, phenobarbital, and valproate) with the second-generation AEDs (gabapentin, lamotrigine, levetiracetam, oxcarbazepine, pregabalin, topiramate, and zonisamide) to make some important generalizations. The first-generation AEDs, in general, are highly bound to plasma proteins, making interpretation of plasma drug concentrations more difficult if plasma protein levels change. All undergo cytochrome P450 metabolism and all are involved in clinically significant drug interactions, either by strongly affecting other therapies or, in turn, being affected by other drugs. In contrast, the second-generation drugs are less bound to plasma proteins and, with the exception of gabapentin, are much more consistently absorbed. Several (gabapentin and pregabalin) are eliminated solely through the kidney. Levetiracetam is eliminated in part through the kidney and in part through nonhepatic enzymes that do not change through induction. This would indicate that the second-generation AEDs, in general, have a superior pharmacokinetic profile as compared with first-generation AEDs.

**Antiepileptic Drug Pharmacokinetics: Special Issues in Elderly Patients**

There are 3 important parameters when discussing AED pharmacokinetics in the elderly: absorption, protein binding, and metabolism. Poorly water-soluble drugs such as phenytoin are especially sensitive to small changes...
in GI absorption. In a study by Birnbaum et al, phenytoin levels were followed in 56 patients from 32 nursing homes. These patients were on no other medications and remained on the same dose of phenytoin throughout the study. Yet, when drug levels were compared, they were found to vary tremendously over the period of measurement as shown in Figure 2. The period of time during which these measurements were made was likely too short for changes in serum protein or metabolism to explain these data, leaving variable absorption as the only plausible mechanism. Two important points that can be taken from this are: (1) variable absorption can change a therapeutic dose into a toxic or a subtherapeutic dose; and (2) a single measure of plasma phenytoin concentration is insufficient to obtain an accurate sense of the average plasma concentration achieved at a particular dose.

Changes in serum protein binding can also confuse matters. The age-associated decrease in serum proteins can cause an apparent drop in the total plasma drug concentration. However, it is important to remember that brain concentrations are proportional to the free drug as opposed to total drug. Total plasma drug concentration can drop while the free drug remains constant. It is quite possible when measuring blood levels of highly bound drugs to consider that the dose needs to be altered but, in fact, this is not the case. AEDs that bind extensively to plasma proteins include carbamazepine, valproate, and phenytoin.

Finally, we will consider metabolism. Theoretically, metabolism decreases with age along with clearance, leading to a greatly increased half-life. However, in a recent study relating the half-life of phenytoin with age, it was observed that the difference between young and old groups was rather small. Additionally, the half-life was 40 to 50 hours, several times greater than the 8 to 25 hours listed in textbooks. Thus, as dose is changed, the onset of effect and alterations in effect may be prolonged for some patients, given that 4 to 5 half-lives must elapse before the full effect of a dose change is known.

EFFICACY AND SAFETY OF ANTIPILEPTIC DRUGS IN OLDER PATIENTS

It is generally assumed that elderly patients respond to AED therapy at lower concentrations, but that they have an increased risk of adverse effects. The VA Cooperative Study 428, a trial designed to compare 2 newer AEDs—lamotrigine and gabapentin—to carbamazepine, raised an interesting point in this regard. When the number of patients remaining in the trial were compared for the 3 drugs, the data showed clearly that more patients dropped out from the carbamazepine arm as compared with the lamotrigine and gabapentin arms, primarily because of adverse effects. When considering seizure control, all 3 drugs had similar efficacy. Interestingly, the response rate in the study patients was similar to that seen for a younger population. When plasma drug levels associated with seizure control were examined, they also appeared similar to those levels observed in a younger patient population. Hypersensitivity was seen more often with carbamazepine than with the newer drugs, a side effect attributed more often to lamotrigine in other studies.

Cognition

It is well established that epileptic seizures and AEDs have negative effects on cognition. However, there are significant differences in this effect among AEDs. Numerous studies have investigated AED effects on cognition and a subset of these will be listed here to illustrate the data used to rank order groups of AEDs. Cognition...
is a complex set of processes that is measured through variables grouped within several neuropsychological domains, including memory, attention/vigilance, language, cognitive speed, and motor speed, in addition to others. In some studies, the subjects were healthy volunteers, whereas in other studies, the subjects were patients with newly diagnosed epilepsy.

In considering the older AEDs, it has been shown that, in general, carbamazepine, phenytoin, and valproate all have a similar effect. Across studies, the negative cognitive effects of carbamazepine, phenytoin, and valproate were found to be worse than that of untreated seizures for approximately 50% of the administered tests. For approximately 1/3 of the variables measured, phenobarbital had a greater negative cognitive effect than phenytoin.

The newer AEDs seem to have less negative effect on cognition. Gabapentin was found to be superior to carbamazepine for 48% of the variables in healthy volunteers in a double-blind crossover study. Several groups have also shown an improvement in cognitive function in healthy volunteers and in newly diagnosed epileptic patients for lamotrigine as compared with carbamazepine. Levetiracetam showed a similar superiority as lamotrigine over carbamazepine. Oxcarbazepine, however, was found to be equal in effect to phenytoin.

Finally, within the second-generation AEDs, some drugs seem to have better cognitive effects than others. Healthy volunteers had improved cognitive scores for 50% of variables when gabapentin was compared with topiramate. In a comparison of lamotrigine and topiramate, it was found that approximately 80% of cognitive variables were improved under lamotrigine. When memory was assessed in recall tests in the studies just mentioned, it was found that lamotrigine and gabapentin had little negative effect on recall, whereas drugs such as carbamazepine and phenytoin had a much greater effect. Although polytherapy is effective at controlling seizures, it seems to greatly increase cognitive impairment.

The number of adverse events (including the measures of cognitive impairment described above) correlates well with decreasing quality-of-life scores. Avoiding AEDs associated with an increased risk of cognitive impairment would be an important first step in minimizing neuropsychiatric adverse events. Based on available evidence, several newer AEDs seem to be superior to older AEDs in terms of cognitive impairment. Secondly, it would benefit the patient to slowly titrate the dose. Achieving a minimum plasma level sufficient for seizure control would minimize cognitive impairment. This approach, however, requires establishing an outcomes measure that can be practically applied. Because polytherapy increases the risk of cognitive impairment, monotherapy is preferred whenever possible. Finally, drug interactions that exacerbate cognitive impairment should be avoided.

**ECONOMIC CONSIDERATIONS**

There are several factors that must be taken into account when considering cost. For example, in the absence of therapy, there is a risk of injuries caused by falls and uncontrolled movements that may lead to emergency department visits and/or hospitalizations. In addition, AEDs can produce clinically important adverse effects, including injuries. The newer AEDs are relatively costly; however, this will change as these drugs go off patent in the next few years. Because it is becoming clear that plasma levels can vary significantly, leading to increased adverse events or breakthrough seizures, monitoring and testing will be constant expenses. Perhaps the most unexpected cost, however, is the impact of certain AEDs on concomitant drug therapy. This effect is mediated by AEDs that induce drug-metabolizing enzymes. In a study of the effect of carbamazepine on simvastatin and simvastatin acid exposure, it was determined that carbamazepine significantly reduced the concentrations of the parent drug and the active metabolite by 75%. Thus, to administer both therapies simultaneously, the simvastatin dose would need to be increased 3-fold to 4-fold to achieve a therapeutic level. Similar interactions can occur when enzyme-inducing AEDs such as phenobarbital, primidone, phenytoin, and carbamazepine are started in patients taking other medications that are metabolized by the affected enzymes. The Table shows a set of examples of potential increase in drug costs resulting from these types of drug interactions.

**CONCLUSIONS**

AED therapy is common in the nursing home environment and requires significant monitoring. In theory, the elderly show certain physiological changes that can have dramatic effects on the pharmacokinetics of drugs. In practice, however, these changes are highly individual, making it difficult to generalize. The pharmacokinetic properties of AEDs differ in...
clinically important ways, requiring special attention to those that are variably absorbed, highly protein bound, or display nonlinear clearance. Adverse effects include toxic reactions and cognitive changes that can strongly affect the quality of life apart from seizure control. All AEDs appear to have some cognitive effects; however, these vary significantly from drug to drug. Recent clinical trials are favoring lamotrigine, levetiracetam, and gabapentin in this regard.

This is as important an issue in the elderly as it is in the younger population. Additionally, costs must be considered. Improved cognition and seizure control will require increased testing and monitoring. Drug dosing may need to be altered because of changes in metabolic enzymes. All of these factors must be balanced when tailoring AED therapy to optimize care for this patient population.

**REFERENCES**