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Management of Epilepsy in Older People

Christine J Kilpatrick, Adrian J Lowe

ABSTRACT

Epilepsy is a relatively common disorder among older people, with the incidence increasing significantly with age. In Australia, epilepsy is a major cause of disability in the elderly and, in the context of an ageing population, it is of increasing importance as a public health issue. The aetiology of epilepsy in older people and the spectrum of epilepsy and seizure type differs from the younger population. Making the diagnosis of epilepsy in the elderly poses particular difficulties. There are multiple medications available for the management of seizures, a number of which have been introduced only within the last decade, and have not been systematically studied in older people. Age-related changes in metabolism, physiology, and pathology alter the pharmacokinetics of these medications, and these need to be taken into consideration when treating elderly patients with an antiepileptic drug. This article reviews the causes of seizures, issues regarding commencement of an antiepileptic drug, and age-related changes in pharmacokinetics of these medications.

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INTRODUCTION

Epilepsy is a chronic condition defined by repeated and intermittent seizures, caused by abnormal electrical activity within the brain. Of all the nervous system disorders, epilepsy is the largest cause of hospitalisations and expense in Australia.¹ For the year 1993 to 1994, epilepsy was estimated to affect over 62 000 Australians, and cost the health system in excess of \$157 million.¹

EPILEPSY IN THE ELDERLY

Epileptic seizures are the third most frequently identified neurological condition identified in the elderly, with only cerebrovascular disease and dementias being more common.² When plotted against age, the incidence of epilepsy has a distinctly U-shaped distribution, with children under 5 years and people over 60 years of age having an elevated risk of epilepsy. As can be seen in Figure 1, after the age of 60 the incidence of epilepsy increases rapidly, peaking in the 80-year-old age group.³ It should be noted that in the older age group the incidence of partial (focal) onset epilepsy outstrips that of general-

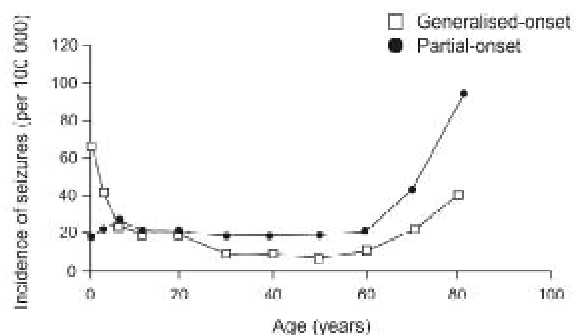


Figure 1. Age-specific incidence of generalised onset (squares) and partial onset (circles) epilepsies in Rochester, Minnesota, 1935–1984. Reproduced from Hauser et al. (1993) with permission.³

ised epilepsy. This figure also dispels the myth that epilepsy is predominantly a condition of childhood, showing the incidence of epilepsy is greater in the aged than in the youngest age group. Status epilepticus, which may be convulsive or non-convulsive, accounts for approximately 6% of all seizures in the aged, which is twice that found in the general population.⁴ This statistic is of real concern, as the mortality rate in elderly patients who experience status is between 30 and 40%, which is twice that of younger age groups.⁵ Due to the ever-ageing population, management of epilepsy in the elderly will increasingly become an important health issue in Australia.

Diagnosis

Delay in diagnosis of epileptic seizures in the elderly is not uncommon.⁶ In the elderly where dementia is common, and memory function is declining, obtaining a clear history of the seizure-like event from the patient can be very difficult. This increases the need for an accurate eyewitness account. Partial seizures may be misdiagnosed as non-specific confusional states. Non-convulsive status epilepticus may simply be interpreted as acute behavioural changes, dementia or delirium. As such, it can take some time following an initial epileptic seizure for a diagnosis to be made, and treatment to be commenced.

Conversely, care must be taken in making a diagnosis of epilepsy, as there is an extensive range of differential diagnoses to consider. Conditions that are common

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in the elderly that may be misdiagnosed as seizures include syncope due to cardiac arrhythmias, transient ischaemic attacks and transient global amnesia.

Investigation of a first seizure in the elderly should include serum electrolytes, electrocardiogram, electroencephalogram (EEG) and neuroimaging. Ideally patients should have brain magnetic resonance imaging which has been shown to be more useful than computerised tomography in the investigation of late onset seizures.⁷ Care must be taken when interpreting both EEG and neuroimaging results, so that normal age-related changes are not interpreted as the cause of seizures or a reflection of seizure activity.⁸ On rare occasions, video EEG monitoring may be needed to clarify the diagnosis.

Aetiology

The most common identified aetiology in elderly patients presenting with seizures is stroke. The incidence of cerebrovascular disease increases with age and this contributes to the sharp rise in prevalence of epilepsy after the age of 65 years. Approximately 7% of ischaemic and 15% of haemorrhagic cortical strokes are complicated by acute or early seizures (within 2 weeks of stroke onset),⁹ and approximately one-third of these patients develop late epilepsy. A further 10% of stroke patients without early seizures go on to develop late epilepsy.¹⁰

Other causes of seizures in the elderly include tumour, degenerative disorders such as Alzheimer's disease, head trauma, toxic/metabolic factors and drug-induced seizures.¹¹⁻¹⁶ Studies suggest that approximately 16% of all patients with Alzheimer's disease will go on to develop seizures.¹¹ Despite extensive investigations including neuroimaging, no cause can be identified in a significant proportion of elderly patients.^{13,15,17}

Seizure Type and Epilepsy Syndrome

There is a different distribution of seizure types and epilepsy syndromes in the elderly compared to younger patients. Primary generalised epilepsy is rarely diagnosed in the elderly and the majority of seizures are partial, either simple, complex or secondarily generalised.^{3,13,14,17} This is a reflection of the underlying causes in this patient population. Complex partial seizures are probably more common than appreciated with clinical features different to the more typical mesial temporal lobe complex partial seizures seen in younger patients.¹⁶ Status epilepticus, both convulsive and non-convulsive, is relatively common in the aged, with stroke being the most commonly identified cause.¹³

ANTIEPILEPTIC DRUG THERAPY

Decision to Commence Treatment

The decision to commence antiepileptic drug (AED) treatment should be based on a number of factors, including risk of seizure recurrence, consequences for the individual of further seizures, potential adverse effects of AEDs and ultimately, the patient's views.

Limited research has been conducted to determine the risk of seizure recurrence in the elderly following a first seizure. One study found that 68% of elderly patients who have a first seizure go on to develop epilepsy within the next year.¹⁸ This is higher than the rate of seizure recurrence reported in younger patients. However, other studies that included mixed age groups, repeatedly report that increased age does not predict higher

seizure recurrence.¹⁹⁻²¹ These studies did not include high numbers of older patients.

It should be noted that in a systematic review of 17 studies by Berg and Shinnar, patients who had an identifiable neurological abnormality were at higher risk of seizure recurrence (57% v. 32% for idiopathic patients).²⁰ As the proportion of patients who have an identifiable cause of seizure is greater in older groups than in younger patients, the risk of seizure recurrence following a single seizure is probably higher in the elderly.

The effects of seizures and epilepsy in the elderly are potentially more debilitating than in younger age groups. As with all patients experiencing a seizure, patients may sustain spinal or head injury, burns from various sources, or a motor vehicle accident.²² The risk of morbidity to a patient from a further seizure however is greater in this age group, as a fall is more likely to be associated with a fracture, and the post-ictal phase in the elderly is more prolonged than in younger patients. In addition, the development of seizures in the elderly is more likely to result in loss of confidence, leading to restricted social interactions, and a decline in quality of life. In addition to these issues, the relatively common adverse effects of drowsiness and somnolence associated with most AEDs, as well as other potential adverse effects, need to be considered when deciding whether or not to commence AED treatment.

Choice of Antiepileptic Drug

As with all patients with epilepsy, the choice of AED depends on seizure type and, where appropriate, epilepsy syndrome. Of the commonly used AEDs, carbamazepine and phenytoin are drugs of choice for partial epilepsy. Valproate is used in primary generalised epilepsy, although it has a broad spectrum of activity and may be used to prevent partial seizures. Some believe it is as effective as carbamazepine in this patient group. Phenobarbitone, although not usually recommended for elderly patients, may be useful in preventing partial or generalised seizures. Of the newer agents, both lamotrigine and topiramate have a broad spectrum of activity and are used as add-on therapies to prevent both partial and generalised seizures. Gabapentin, tiagabine and oxcarbazepine are used in the management of partial epilepsies. Vigabatrin is rarely used due to unacceptable adverse effects. With the exception of oxcarbazepine, these new AEDs are currently licensed as add-on therapy only.

These newer AEDs, however, have not been extensively studied in the elderly and their role in the management of this population is yet to be determined. Given the different spectrum of epilepsies and the potential differences in pharmacokinetics of the drugs in the elderly, trials of the newer AEDs in this patient group are needed.

If a first line drug fails to control seizures, either another first line drug could be tried or a second line AED should be added.

Pharmacokinetics

Age-related physiological changes need to be considered when choosing therapy. These changes result in alterations in pharmacokinetics and pharmacodynamics of AEDs, which in turn alter drug absorption, distribution, biotransformation and elimination.²³

Alterations in protein binding are common in the elderly and have a significant impact on highly protein bound AEDs such as phenytoin and valproate. Reduced protein binding in the elderly may be due to an age-related reduction in albumin synthesis,²⁴ liver or renal disease, malnutrition or interaction with other highly protein bound drugs.

Impaired renal and hepatic function is common in the elderly and influences hepatic metabolism of drugs and renal excretion of parent drug and their metabolites. The exponential increase in serum concentration of phenytoin with increasing dose occurs earlier in the elderly compared with younger individuals.²⁵

There is an increase in the ratio of fat:lean body mass in the elderly with a decline in total body water resulting in an increased distribution volume for lipid soluble drugs such as carbamazepine, phenytoin and phenobarbitone. The half-life and action of these drugs can increase in elderly patients, as they accumulate in adipose tissue, elevating the risk of adverse effects.²⁶

These changes have the potential to alter AED pharmacokinetics.²⁷ In addition, the elderly are often taking multiple drugs, increasing the chance of drug interactions. Given the potential changes in pharmacokinetics, plasma levels of AEDs should be monitored more closely.

The ideal therapy in the elderly would meet the following criteria: once or twice daily dosing, simple dose implementation, no enzyme inducing properties, few or no interactions with other drugs, low protein binding, minimal cognitive adverse effects and linear pharmacokinetics. Each of the AEDs will now be discussed in light of these ideals.

Carbamazepine

Carbamazepine undergoes hepatic metabolism and the metabolites are eliminated through the kidney, hence in the elderly, who often have impaired renal and hepatic function, the clearance of this drug is reduced and the required daily dose is lower. Carbamazepine autoinduction is less in the elderly but the propensity of carbamazepine to induce the metabolism of other drugs results in drug interactions. Skin rash, a relatively common adverse effect of carbamazepine, is more common in the elderly.²⁸ The drug is not highly protein bound and hence age-related reduction in serum albumin does not influence drug clearance and interpretation of total plasma concentrations. Carbamazepine is associated with hyponatraemia, particularly in the elderly.

Sodium Valproate

Sodium valproate, although probably not as effective as carbamazepine or phenytoin in the management of partial seizures, is often used in the elderly as it is less likely to be associated with the side effect of sedation. The drug is highly protein bound and hence may interact with other highly protein bound drugs such as phenytoin. The drug is not a hepatic metabolic enzyme inducer, limiting its interaction with other drugs.

Phenobarbitone

This drug is now less commonly used and rarely introduced in the elderly. Often elderly patients, however, with longstanding epilepsy will have been established on phenobarbitone many years ago and in this situation the drug should be continued. Withdrawal seizures are

a significant problem in patients of all ages. The elderly may be particularly susceptible to the behavioural and cognitive adverse effects of this drug.

Phenytoin

Phenytoin, commonly used in the elderly,¹⁷ is highly protein bound (90%). When the plasma level is requested, the total concentration i.e. the bound and unbound level is reported. Only the unbound drug however, is biologically active. In the elderly, with reduced serum albumin, a higher proportion of the total drug concentration is unbound or free and hence biologically active. This needs to be taken into consideration when interpreting total plasma concentrations. When ordering phenytoin levels, if available, the unbound level should be requested.

Due to a declining rate of metabolism with increasing age, it is estimated that elderly patients require only 79% of the phenytoin dose administered to younger adults to achieve seizure control.²⁹ As noted above, the exponential increase of phenytoin plasma levels with increased dose occurs earlier in the elderly, and studies have shown that increasing an elderly patient's phenytoin dose by 10%, can induce a 67% increase in serum concentration.²⁹ Therefore, care must be taken when increasing phenytoin dose to avoid symptoms of toxicity, which include ataxia, dizziness and cognitive effects. Phenytoin has the advantage of once daily administration and can be given intravenously. Like many other AEDs phenytoin is an enzyme inducer, which increases the risk of drug interactions.

Lamotrigine

Lamotrigine, one of the newer AEDs, has a number of advantages. It does not induce liver enzymes, hence limiting its interaction with other drugs, clearance is not altered by renal impairment, the drug is not highly protein bound, it has little cognitive effects and has a broad spectrum of effect. However, the introduction of this drug involves a complex regimen to avoid adverse effects (rash), which is difficult for the elderly patient to achieve. The drug has been shown to be as effective and better tolerated than carbamazepine in treatment of partial seizures in the elderly.²⁸

Gabapentin

Gabapentin, another new AED, is not protein bound, is not metabolised, does not interact with other drugs, has relatively few cognitive effects if introduced slowly, and hence has the potential to be a useful AED in the elderly population. The drug however, has not been extensively studied in this age group.

Topiramate

Topiramate has the advantage of not being highly protein bound, has minimal enzyme inducing properties, a long half-life so it can be given twice daily and a broad spectrum of efficacy. The drug however has relatively common cognitive adverse effects and has not been extensively studied in the elderly.

Tiagabine

Tiagabine is highly protein bound and has a short half-life. Although it has been shown to be useful in the treatment of partial epilepsies, it has not been systematically studied in the elderly. The relatively common adverse

effect of somnolence may limit its use in this age group.

Oxcarbazepine

Oxcarbazepine has been recently introduced in Australia as an effective monotherapy or add-on therapy in the management of partial seizures and generalised tonic-clonic seizures. The drug is rapidly metabolised in the liver to its active metabolite (MHD, 10-monohydroxy-derivative). Oxcarbazepine, and its metabolite, are moderately bound to albumin. Impaired renal function, as commonly occurs in the elderly, reduces the clearance of the drug, and correspondingly, a decrease in dose is recommended. This drug's adverse effect profile is similar to carbamazepine, although rash is less common.

Vigabatrin

This drug, although effective in the management of partial seizures, is now rarely introduced due to the common adverse effect of visual field constriction.

Treatment of Status Epilepticus in Older People

Status epilepticus is treated in a manner similar to younger patients. Initial control with intravenous benzodiazepines is appropriate followed by intravenous phenytoin. Fosphenytoin has been advocated, as it can be given at a much faster rate than intravenous phenytoin and is associated with fewer local cutaneous reactions.^{15,30} Fosphenytoin however is no longer available in Australia.

Adverse Effects of AED Therapy

All AEDs potentially have adverse effects. It is recommended that the adverse effects profile of each AED be considered for the specific patient who is about to commence therapy, in terms of their other current medications and co-morbidities. It is beyond the scope of this paper to discuss all the adverse effects of AED therapy. However, three adverse effects, osteoporosis, ataxia and somnolence, are of particular importance to the elderly population.

Osteoporosis is widespread in aged populations. The risk of seizures causing fractures in such patients is increased, making seizure control a greater priority. Chronic use of phenytoin and carbamazepine has been repeatedly linked to poor bone density measures.^{31,32} Therefore the risk of osteomalacia and osteoporosis is increased. The use of an AED by elderly women has been associated with an increased risk of hip fracture by two to three times that of age-matched controls.³³ This finding may however, be due to the increased risk of falls due to seizures associated with epilepsy. Osteomalacia in these patients is most likely mediated by the negative effect of AEDs on vitamin D metabolism. As a precaution, it has been suggested that elderly patients on phenytoin or carbamazepine should be given a combination of vitamin D and calcium, and bone density should be monitored.³²

Ataxia is an adverse effect of a number of AEDs, which takes on greater significance in the elderly. Ataxia is particularly common with phenytoin toxicity, but may be associated with all of the AEDs, even at therapeutic concentrations.³⁴

The elderly are probably more susceptible to the adverse effects of sedation and somnolence and this is a common problem with many of the AEDs. Of the first

line AEDs, somnolence is more prominent with phenytoin, carbamazepine and phenobarbitone.

Decision to Stop Treatment

If the patient has been seizure free for at least three years, particularly if epileptiform activity has disappeared from the EEG, the possibility of ceasing antiepileptic drug therapy could be considered. If the patient has had multiple seizures prior to commencing treatment, or the epilepsy has been difficult to control, a more conservative approach is recommended, and medication should be continued longer term. It is always difficult to know whether a patient is seizure free because they are taking effective treatment or the condition has resolved. If medication is to be withdrawn, this should be done gradually over several months and even more slowly for barbiturates.

CONCLUSIONS

Epilepsy in the elderly is a significant health problem. The spectrum of seizure and epilepsy types is different to the younger population as are the aetiologies of the seizure disorder. Age-related physiological changes potentially alter drug pharmacokinetics and these need to be taken into consideration when treating elderly patients with AEDs. Given epilepsy is more common in the elderly than younger age groups, and the range of seizure types and the drug pharmacokinetics differ, there is a need for drug trials in this specific population.

Competing interests: None declared

References

1. Australia's Health 2000: the seventh biennial health report of the Australian Institute of Health and Welfare. Canberra: Australian Institute of Health and Welfare; 2000.
2. Kramer G. Epilepsy in the elderly: some clinical and pharmacotherapeutic aspects. *Epilepsia* 2001; 42 (suppl. 3): 55-9.
3. Hauser WA, Annegers JF, Kurland LT. Incidence of epilepsy and unprovoked seizures in Rochester, Minnesota: 1935-1984. *Epilepsia* 1993; 34: 453-68.
4. Ettinger AB, Shinnar S. New-onset seizures in an elderly hospitalized population. *Neurology* 1993; 43 (3 Pt 1): 489-92.
5. DeLorenzo RL. Clinical and epidemiologic study of status epilepticus in the elderly. In: Rowan AJ, Ramsay RE, editors. *Seizures and epilepsy in the elderly*. Newton: Butterworth-Heinemann; 1997. p. 191-206.
6. Tallis R. Epilepsy in old age. *Lancet* 1990; 336 (8710): 295-6.
7. Kilpatrick CJ, Tress BM, O'Donnell C, Rossiter SC, Hopper JL. Magnetic resonance imaging and late-onset epilepsy. *Epilepsia* 1991; 32: 358-64.
8. Sirven JI. Epilepsy in older adults: causes, consequences and treatment. *J Am Geriatr Soc* 1998; 46: 1291-301.
9. Kilpatrick CJ, Davis SM, Tress BM, Rossiter SC, Hopper JL, Vandendriesen ML. Epileptic seizures in acute stroke. *Arch Neurol* 1990; 47: 157-60.
10. Kilpatrick CJ, Davis SM, Hopper JL, Rossiter SC. Early seizures after acute stroke. Risk of late seizures. *Arch Neurol* 1992; 49: 509-11.
11. Romanelli MF, Morris JC, Ashkin K, Coben LA. Advanced Alzheimer's disease is a risk factor for late-onset seizures. *Arch Neurol* 1990; 47: 847-50.
12. Loiseau J, Loiseau P, Duche B, Guyot M, Dartigues JF, Aublet B. A survey of epileptic disorders in southwest France: seizures in elderly patients. *Ann Neurol* 1990; 27: 232-7.
13. Sung CY, Chu NS. Epileptic seizures in elderly people: aetiology and seizure type. *Age Ageing* 1990; 19: 25-30.
14. Hauser WA. Seizure disorders: the changes with age. *Epilepsia* 1992; 33 (suppl. 4): S6-14.
15. Thomas RJ. Seizures and epilepsy in the elderly. *Arch Intern Med* 1997; 157: 605-17.
16. DeToledo JC. Changing presentation of seizures with aging: clinical and etiological factors. *Gerontology* 1999; 45: 329-35.
17. Scheuer ML, Cohen J. Seizures and epilepsy in the elderly. *Neurol Clin* 1993; 11: 787-804.
18. Luhdorf K, Jensen LK, Plesner AM. Epilepsy in the elderly: prognosis. *Acta Neurol Scand* 1986; 74: 409-15.
19. Hopkins A, Garman A, Clarke C. The first seizure in adult life. Value of

- clinical features, electroencephalography, and computerised tomographic scanning in prediction of seizure recurrence. *Lancet* 1988; 1 (8588): 721-6.
20. Berg AT, Shinnar S. The risk of seizure recurrence following a first unprovoked seizure: a quantitative review. *Neurology* 1991; 41: 965-72.
21. Lindsten H, Stenlund H, Forsgren L. Seizure recurrence in adults after a newly diagnosed unprovoked epileptic seizure. *Acta Neurol Scand* 2001; 104: 202-7.
22. Perucca E, Beghi E, Dulac O, Shorvon S, Tomson T. Assessing risk to benefit ratio in antiepileptic drug therapy. *Epilepsy Res* 2000; 41: 107-39.
23. Scharf S, Christophidis N. Pharmacokinetics and pharmacodynamics in the elderly. *Aust J Hosp Pharm* 1991; 21: 198-202.
24. Gareri P, Gravina T, Ferreri G, De Sarro G. Treatment of epilepsy in the elderly. *Prog Neurobiol* 1999; 58: 389-407.
25. Rowan AJ. Reflections on the treatment of seizures in the elderly population. *Neurology* 1998; 51 (5 suppl. 4): S28-33.
26. Greenblatt DJ, Sellers EM, Shader RI. Drug therapy: drug disposition in old age. *N Engl J Med* 1982; 306: 1081-8.
27. Cloyd JC, Lackner TE, Leppik IE. Antiepileptics in the elderly. Pharmacoepidemiology and pharmacokinetics. *Arch Fam Med* 1994; 3: 589-98.
28. Brodie MJ, Overstall PW, Giorgi L. Multicentre, double-blind, randomised comparison between lamotrigine and carbamazepine in elderly patients with newly diagnosed epilepsy. The UK Lamotrigine Elderly Study Group. *Epilepsy Res* 1999; 37: 81-7.
29. Bauer LA, Blouin RA. Age and phenytoin kinetics in adult epileptics. *Clin Pharmacol Ther* 1982; 31: 301-4.
30. O'Brien TJ, Cascino GD, So EL, Hanna DR. Incidence and clinical consequence of the purple glove syndrome in patients receiving intravenous phenytoin. *Neurology* 1998; 51: 1034-9.
31. Feldkamp J, Becker A, Witte OW, Scharff D, Scherbaum WA. Long-term anticonvulsant therapy leads to low bone mineral density—evidence for direct drug effects of phenytoin and carbamazepine on human osteoblast-like cells. *Exp Clin Endocrinol & Diabetes* 2000; 108: 37-43.
32. Ray JG, Adachi JR. Anticonvulsants and bone disease: a systematic overview of their association and possible preventive strategies. *Can J Clin Pharmacol* 1998; 5: 217-23.
33. Cummings SR, Nevitt MC, Browner WS, Stone K, Fox KM, Ensrud KE, et al. Risk factors for hip fracture in white women. Study of Osteoporotic Fractures Research Group. *N Engl J Med* 1995; 332: 767-73.
34. Bourdet SV, Gidal BE, Alldredge BK. Pharmacologic management of epilepsy in the elderly. *J Am Pharm Assoc* 2001; 41: 421-36.

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