Neurol Sci (2009) 30:87–92
DOI 10.1007/s10072-009-0033-y

REVIEW ARTICLE

Drugs with anticholinergic properties: cognitive and neuropsychiatric side-effects in elderly patients

Iacopo Cancelli · Massimiliano Beltrame · Gian Luigi Gigli · Mariarosaria Valente

Received: 27 January 2009 / Accepted: 29 January 2009 / Published online: 20 February 2009

Abstract Drug consumption in older people is usually high and many prescribed medications have unsuspected anticholinergic (ACH) (Table 1) properties. Drug induced ACH side-effects are particularly severe in aging brain and even more in demented patients. This review will focus on the association between ACH drug intake and the risk of developing central nervous system side-effects in elderly people. The threat of developing cognitive impairment, psychosis and delirium will be particularly analyzed.

Keywords Elderly patients · Anticholinergic drugs · Side effects

Introduction

Prevention of drug-related problems is a key issue in the aged [1]. Aging is characterized by an increased likelihood of illness and by a disproportionate amount of self-administered and prescribed medications. In USA, people aged over 65 years consume 30% of prescription- and 40% of over-the-counter remedies, despite they consist of only 13% of the population [2]. In UK, elderly people use 45% of all prescription drugs even if they include only 18% of the residents [3]. The amount of drug intake further increases when we consider nursing home residents: 97% of elderly inpatients receive at least one drug prescription within one year [4].

Polypharmacy increases the risk of anticholinergic (ACH) drug intake in the elderly. More than 600 drugs have some ACH activity [5] and 14 of the 25 most commonly prescribed drugs for older adults have detectable ACH effects [6] (see Table 1). Blazer et al. [7] found that nearly 60% of nursing-home residents and 23% of elderly people living in the community received one or more drugs with ACH activity. In France, 13.7% of elderly subjects were taking at least one drug with ACH activity [8]. In Italy, 40% of a community-dwelling sample of subjects aged 80 years or more were using drugs with ACH properties [9]. To note, Alzheimer's disease (AD) patients make use of ACH medications even more than elderly who are not demented [10].

This huge utilization of drugs with ACH properties is amazing: elderly people, especially those affected by dementia, are known to be more sensitive to ACH side-effects [1, 11]. This predisposition has been associated to an increased permeability of the blood-brain barrier, to a deficient drug metabolism/elimination and to an age-related deficit in central cholinergic transmission [12]. The use of multiple drugs further increases the probability and severity of ACH adverse events [12]: in fact combinations of drugs may cause ACH side-effects even in a setting in which a single ACH drug may not [12].

In the elderly, drugs with ACH activity are potentially responsible for several peripheral and CNS adverse effects [12]. However, the morbidity and management issues associated with unwanted ACH activity are underestimated and frequently overlooked [13]. ACH side-effects are often viewed as "unavoidable" or they are attributed to the aging process itself [14]. Failure to identify ACH side-effects

I. Cancelli · G. L. Gigli · M. Valente
Department of Neurology, Santa Maria Della Misericordia University Hospital, Udine, Italy

M. Beltrame · G. L. Gigli (✉) · M. Valente
DPMSC, University of Udine Medical School, Piazza Santa Maria Della Misericordia, 33100 Udine, Italy
e-mail: gigli@uniud.it

Table 1 Drugs with definitive or probable ACH effects

ATC classification	Drugs
Alimentary tract and metabolism	Atropine, belladonna alkaloids, cimetidine, clidinium bromide, dicyclomine, dicycloverine, dimenhydrinate, diphenoxylate, hyoscyamine, loperamide, methscopolamine bromide, octatropine methylbromide, otilonium bromide, pirenzepine, propantheline, ranitidine
Blood and blood forming organs	Dipyridamole, warfarin
Cardiovascular system	Digoxin, disopyramide, furosemide, isosorbide dinitrate, nifedipine, quinidine
Genito-urinary system and sex hormones	Flavoxate, oxybutynin, tolterodine
Systemic hormonal preparations, excl. sex hormones and insulins	Prednisolone
Musculo-skeletal system	Carisoprodol, chlorzoxazone, cyclobenzaprine, metaxalone, methocarbamol, orphenadrine, pancuronium
Nervous system	Alprazolam, amitriptyline, amoxapine, benztropine, biperiden, chlordiazepoxide, chlorpromazine, clomipramine, clozapine, desipramine, diazepam, doxepin, duloxetine, ethopropazine, fluphenazine, flurazepam, glutethimide, hydroxyzine, imipramine, maprotiline, mesoridazine, nortriptyline, olanzapine, orphenadrine, oxazepam, paroxetine, perphenazine, pethidine, phenobarbital, pimozide, prochlorperazine, procyclidine, promazine, protriptyline, thioridazine, thiothixene, trihexyphenidyl, trimethobenzamide, trimipramine
Respiratory system	Brompheniramine, clemastine, codeine, cyclizine, cyproheptadine, desloratadine, dexchlorpheniramine, diphenhydramine, doxylamine, fexofenadine, ipratropium bromide, loratadine, meclozine, mepyramine, promethazine, pyrilamine, theophylline, tripelennamine, triprolidine
Sensory organs	Cyclopentolate, homatropine, hyoscine, tropicamide

ATC anatomical therapeutics classification system [59]; adapted from references [12, 53, 56–58]

may lead physicians to use other drugs to treat symptoms, rather than to quit the ACH drugs.

Recent studies suggested a possible relationship between ACH drug intake and neuropsychiatric side-effects, such as cognitive impairment [8, 15–18], psychosis [19, 20] and delirium [21–25].

Our review will focus on these specific items, which are, in our opinion, extremely important for the management of elderly patients.

Cognitive impairment

Anticholinergic drugs are a biologically plausible cause of cognitive impairment in elderly people. Age related cognitive impairment has been associated with a progressive cholinergic deficit [26], and several experimental and clinical studies have demonstrated the detrimental effect of ACH drugs on cognition [12, 27].

In young subjects, scopolamine induces a pattern of cognitive deficits similar to that occurring in aging [28]. In elderly subjects, scopolamine induces or exacerbates the preexisting cognitive impairment [29]. Mulsant et al. [30] evaluated the association between serum ACH activity (SAA) and cognitive performance in a random sample of 201 old adults. They found that high SAA levels, at or above the sample's 90th percentile, were significantly linked to poor performance at the mini mental state exam (MMSE).

So far, three cross-sectional population-based studies have investigated the effect of ACH drug intake on cognition [8, 15, 16]. Lechevallier-Michel et al. [8] studied the association between use of ACH drugs and cognitive performance in a study sample composed of people aged 70 and above. Dementia and institutionalization were exclusion criteria and cognitive status was assessed by the MMSE [31] and the Benton Visual Retention Test [32]. The authors found an association between use of ACH drugs and low cognitive performance. The association remained significant even after the results were statistically adjusted for age, gender, educational level, number of drugs taken and use of psychotropic drugs [8]. Similar results were found in a successive study involving 932 moderately to severely disabled women aged 65 years or more [15]. Similar to the study by Lechevallier-Michel et al. [8], dementia and institutionalization were exclusion criteria and cognitive status was assessed by MMSE. The results confirmed the presence of a link between ACH drug intake and low MMSE scores [15]. Recently, our group conducted a cross-sectional population-based study to evaluate the association between ACH drugs and cognitive impairment [16]. The sample study consisted of 750 subjects aged 65 years or older. Differently from the two studies mentioned above [8, 15], we did not consider dementia and institutionalization as exclusion criteria. We did so in order to evaluate the association between the ACH drug intake and cognitive deterioration in the general population, which includes demented and institutionalized

subjects as well. We employed the MMSE [31] and the Global Deterioration Scale [33] to evaluate the cognitive impairment and we classified the patients in ACH drug users and non-ACH drug users: we found that approximately 20% of the study subjects were ACH drug users and that they were more likely to have cognitive impairment than those using non-ACH drugs. The association remained significant even after adjusting the results by adding sex, total number of drugs taken, use of nervous system drugs, and use of cardiovascular drugs as covariates to the multivariate model.

To our knowledge, just two longitudinal studies have been carried out to assess the link between ACH drug intake and cognitive impairment, but they did not achieve a definitive result [17, 18]. Ancelin et al. [17] found that ACH drug intake was associated with a non-degenerative cognitive impairment but suggested that it was unlikely linked to an increased risk of dementia. The small sample size and the low rate of conversion to dementia in the group of ACH-drug users may not have had sufficient power for dementia incidence rate comparison [34]. Bottigi et al. [18] found no significant differences between ACH-drug users and the non ACH-drug users, after adjusting for age and education. However, the authors themselves suggest considering their results as preliminary, because their study was a non random prospective study with an unequal number ACH-drug users and non ACH-drug users.

Randomized prospective studies are certainly needed to further assess to which extent ACH drug intake deteriorates cognition in elderly. Nevertheless, the data we have at the moment strongly suggest that ACH drug intake may be a risk factor for cognitive impairment and, perhaps, for dementia too in the elderly population.

Psychosis

Several reasons exist to presume that ACH drugs may induce psychotic symptoms in the elderly and particularly in demented patients.

Cumming et al. [35] revisited the cholinergic hypothesis and highlighted the involvement of the central cholinergic system in the onset of behavioral and psychological symptoms in AD. In AD patients, psychosis correlates with metabolic and perfusion abnormalities in the frontal and temporal cortex, where the cholinergic deficit is more marked [35] and with an increased muscarinic M2 receptor binding in the same cortical areas [36]. On the other hand, acetylcholinesterase inhibitors (aCh-i), such as metrifonate and physostigmine, decrease the occurrence of hallucinations and delusions in AD patients [37].

A cholinergic deficit may induce psychosis in disorders other than AD: it has been suggested that an impaired cholinergic transmission could induce psychotic symptoms in schizophrenia through a weakening of the "sensory gating"—the brain's ability to inhibit repetitive and irrelevant incoming sensory stimuli—[38]. From this point of view, delusions and hallucinations may be considered within the frame of a specific central cholinergic deficiency syndrome, the core feature of which consists in an impairment of the fundamental cognitive functions devoted to detect, select, discriminate, and process sensory inputs [39]. Following these suggestions, we performed a study to evaluate whether a sensory gating deficit could be present in AD and whether this sensory gating deficit could be linked to the cholinergic transmission and to the onset of psychotic symptoms [40]. However, even if we found a sensory gating deficit in AD patients, we were not able to find a correlation neither between the sensory gating deficit and the cholinergic transmission nor between the sensory gating deficit and the occurrence of psychosis [40].

Several authors have suggested a causal link between ACH drug intake and psychotic symptoms. For instance, psychotic disorders have been reported to occur in patients taking oxybutynin [41] and complex visual hallucinations have been reported to occur in subjects undergoing antidepressant therapy, probably because of a decreased anticholinergic/serotoninergic ratio [20]. Other evidences come from a study by our group that was performed in AD patients to evaluate the relationship between ACH intake and psychosis occurrence [19]. The study sample comprised 230 patients with probable AD according to the NINCDS-ADRDA criteria. The patients were categorized as ACH drug users and non-ACH drugs users. Occurrence of behavioral symptoms was assessed by means of the Neuropsychiatric Inventory [42] and diagnosis of psychosis was made according to the criteria proposed by Jeste and Finkel [43]. Use of ACH drugs was significantly linked to the occurrence of psychosis and the frequency of psychosis increased along with the number of ACH drugs taken, which suggests a dose-related effect. These results remained significant even after we adjusted our data for the following confounding variables: age, sex, educational level, MMSE score, disease period of dementia, number of non ACH drugs, and use of aCh-i.

So far, evidences arising from literature do not allow us to state that ACH are an ascertained cause of psychosis in elderly subject and a prospective randomized trial is not available to draw decisive conclusions. However, it is reasonable to suggest that ACH drugs should be regarded as potential risk factors for the onset of psychotic symptoms in elderly patients, especially in those who are demented.

Delirium

Delirium is a relatively common disorder—especially in older people with physical illness—it has a high morbidity and mortality and is often under-recognized and under-treated [44].

Identifying risk factors for delirium, especially modifiable ones, is of great importance for the effective prevention of this condition. In recent decades, an increasing number of studies have examined the risk factors that might predispose, precipitate or perpetuate development and progression of delirium [45, 46]. Despite considerable methodological differences, most studies have found that ACH drugs may be a common risk factor for precipitating delirium in susceptible patients [47, 48]. Indeed, the association between ACH drug intake and delirium has a high biological plausibility, as suggested both by the theory that a central cholinergic deficit is to blame for delirium onset [21, 49] and by the evidence that a clinical correlation exists between SAA and delirium [22, 23]. At the moment, the most widely accepted theory is that delirium represents the clinical manifestation of a diffuse imbalance of cerebral neurotransmission [50]. Probably, several neurotransmitters such as serotonine, noradrenaline, dopamine, and γ-aminobutyric acid (GABA) are involved in the pathogenesis of delirium [51] and any drug interfering with neurotransmission may therefore facilitate delirium onset. However, Gibson et al. [52] suggested that the impaired cholinergic neurotransmission represents the final common pathway for the development of delirium.

So far, research findings are still controversial, but most published studies considered ACH drug use to be a precipitating factor [24, 53]. Some studies found a significant association between use of ACH drugs and delirium [21, 25], whereas others did not [48, 49]. Several reasons may underlie this discrepancy. First, individual studies used different measures of ACH drug exposure, including SAA [23, 25], aggregate risk scores of ACH potency [54, 55], or number and dose of ACH drugs using different classifications [22, 48, 49]. Second, the effect of ACH medications on delirium may be confounded by other risk factors, such as dementia, age, or comorbid conditions. Third, patients with dementia showed delirium symptoms with doses of ACH drugs at which non-demented controls did not, suggesting that dementia may predispose patients to ACH drug induced delirium [11].

In conclusion, ACH drugs seems to be a highly plausible risk factors for delirium in elderly patients. Dementia, polipharmacy, and multiple comorbidity further increase the predisposition of elderly patients to develop ACH drug induced delirium.

Conclusions

The elderly frequently use ACH drugs and they are expected to be particularly sensitive to central ACH side-effects. Although further studies are needed to unequivocally prove the link, ACH drugs are strongly suspected to have negative effects on cognition as well as on behavior in older persons.

Cautious attitude suggests that physicians should be aware of ACH properties of drugs frequently prescribed in the elderly and that they should avoid ACH drugs, or at least, they should replace them with drugs that have less ACH properties. Attention should be paid, especially in those patients who are supposed to be particularly prone to ACH drug side-effects because of dementia, polipharmacy, and burden of comorbidities.

Two last considerations should be made: to date, to our knowledge, no complete and updated list of ACH drugs is available in literature. In Table 1 we tried to report a reliable list of drugs with probable or possible ACH properties. However, it should be remembered that our list is a combination of previously published lists among which there is no full overlap. A consensus on a complete and updated list of ACH drugs is needed both for clinical and research purposes.

Second, we are aware that the best approach to characterizing the issue addressed by this article would have been a systematic review of the evidence-based literature on ACH drug use in elderly. Unfortunately this approach was impossible due to the lack of controlled studies. In fact, most of the scientific papers concerning this topic are observational studies, case series, case reports, or expert opinion. This is primarily due to the fact that there is in general a lack of controlled studies in the older adults, particularly in those over 75 years and having comorbidities [1]. Moreover, drugs with ACH properties are quite numerous; they are used in several different clinical conditions and are supposed to cause ACH sides effects, particularly when used in combination. This, in our opinion, makes it difficult to design and perform a controlled study.

References

1. Fick DM, Cooper JW, Wade WE et al (2003) Updating the Beers criteria for potentially inappropriate use in older adults. Arch Intern Med 163:2716–2724
2. Salom IL, Davis K (1995) Prescribing for older patients: how to avoid toxic drug reactions. Geriatrics 50:37–40
3. Royal College of Physicians (1997) Medication for elderly people. RCP, London
4. Furniss L, Burns A, Craig SK et al (2000) Effects of a pharmacist's medication in nursing and residential homes. Br J Psychiatry 176:563–567

5. Tollefson GD, Montagne-Clouse J, Lancaster SP (1999) The relationship of serum anticholinergic activity to mental status performance in an elderly nursing home population. J Neuropsychiatry Clin Neurosci 3:314–319
6. Tune L, Carr S, Hoag E et al (1992) Anticholinergic effects of drugs commonly prescribed for the elderly: potential means for assessing risk of delirium. Am J Psychiatry 149:1393–1394
7. Blazer DG, Federspiel CF, Ray WA et al (1983) The risk of anticholinergic toxicity in the elderly: a study of prescribing practices in two populations. J Gerontol 38:31–35
8. Lechevallier-Michel N, Molimard M, Dartigues JF et al (2005) Drugs with anticholinergic properties and cognitive performance in the elderly: results from the PAQUID Study. Br J Clin Pharmacol 59:143–151
9. Landi F, Russo A, Liperoti R et al (2007) Anticholinergic drugs and physical function among frail elderly population. Clin Pharmacol Ther 81:235–241
10. Roe CM, Anderson MJ, Pharm D et al (2002) Use of anticholinergic medications by older adults with dementia. JAGS 50:836–842
11. Sunderland T, Tariot PN, Cohen RM et al (1987) Anticholinergic sensivity in patients with dementia of Alzheimer's type and age-matched controls. Arch Gen Psychiatry 44:418–426
12. Mintzer J, Burns A (2000) Anticholinergic side-effects of drugs in elderly people. J R Soc Med 93:457–462
13. Feinberg M (1993) The problems of anticholinergic adverse effects in older patients. Drugs Aging 3:335–348
14. Tune LE (2001) Anticholinergic effects of medication in elderly people. J Clin Psychiatry 62(suppl 21):11–14
15. Cao YJ, Mager DE, Simonsick EM et al. (2008) Physical and cognitive performance and burden of anticholinergics, sedatives and ACE inhibitors in older women. Clin Pharmacol Ther 83:422–429
16. Cancelli I, Gigli GL, Piani A et al (2008) Drugs with anticholinergic properties as a risk factor for cognitive impairment in elderly people. J Clin Psychopharmacol 28(6):654–659
17. Ancelin ML, Artero S, Portet F et al (2006) Non degenerative mild cognitive impairment in elderly people and use of anticholinergic drugs: longitudinal cohort study. BMJ 332:455–459
18. Bottigi KA, Salazar JC, Yu L et al (2006) Long-term cognitive impact of anticholinergic medications in older adults. Am J Geriatr Psychiatry 14:980–984
19. Cancelli I, Valentinis L, Merlino G et al (2008) Drugs with anticholinergic properties as a risk factor for psychosis in patients affected by Alzheimer's disease. Clin Pharmacol Ther 84:63–68
20. Cancelli I, Marcon G, Balestrieri M (2004) Factors associated with complex visual hallucinations during antidepressant treatment. Hum Psychopharmacol 19:577–584
21. Trzepacz PT (1996) Anticholinergic model for delirium. Semin Clin Neuropsychiatry 1:294–303
22. Flacker JM, Cummings V, Mach JR et al (1998) The association of serum anticholinergic activity with delirium in elderly medical patients. Am J Geriatr Psychiatry 6:31–41
23. Mach JR, Dysken MW, Kuskowski M et al (1995) Serum anticholinergic activity in hospitalized older persons with delirium: a preliminary study. J Am Geriatr Soc 43:491–495
24. Han L, McCusker J, Cole M et al (2001) Use of medications with anticholinergic effect predicts clinical severity of delirium symptoms in older medical inpatients. Arch Intern Med 161: 1099–1105
25. Tune LE, Bylsma FW (1991) Benzodiazepine-induced and anticholinergic-induced delirium in elderly. Int Psychogeriatr 3: 397–408
26. Bartus RT, Dean RL, Beer B et al (1982) The cholinergic hypothesis of geriatric memory dysfunction. Science 217: 408–414
27. Moore AR, O'Keeffe ST (1999) Drug-induced cognitive impairment in the elderly. Drugs Aging 15:15–28
28. Flicker C, Serby M, Ferris SH (1990) Scopolamine effects on memory, language, visual-spatial praxis and psychomotor speed. Psychopharmacology 100:243–250
29. Ray PG, Meador KJ, Loring DW et al (1992) Central anticholinergic hypersensitivity in aging. J Geriatr Psychiatry Neurol 5:72–77
30. Mulsant BH, Pollock BG, Kirshner M et al (2003) Serum anticholinergic activity in a community-dwelling sample of older adults: relationship with cognitive performance. Arch Gen Psychiatry 60:198–203
31. Folstein MF, Folstein SE, McHug PH (1975) Mini-mental state: a practical method for grading the cognitive state of patients for the clinician. J Psychiatr Res 12:189–198
32. Benton A (1965) Applications Cliniques et Expèrimentales. Centre de Psychologie Appliquèe. Manuel pour l'Application du Test de Rètention Visuelle, Paris
33. Reisberg B, Ferris SH, De Leon MJ et al (1982) The global deterioration scale for assessment of primary degenerative dementia. Am J Psychiatry 139:1136–1139
34. Doraiswamy PM, Husain MM (2006) Anticholinergic drugs and elderly people: a no brainer? Lancet Neurol 5:379–380
35. Cummings JL, Back C (1998) The cholinergic hypothesis of neuropsychiatric symptoms in Alzheimer's disease. Am J Geriatr Psychiatry 6:S64–S78
36. Lai MK (2001) Psychosis of Alzheimer's disease is associated with elevated muscarinic M2 receptor binding in the cortex. Neurology 57:805–811
37. Wynn ZA, Cummings JL (2004) Cholinesterase inhibitor therapies and neuropsychiatric manifestations of Alzheimer's disease. Dement Geriatr Cogn Disord 17:100–108
38. Adler LE, Olincy A, Waldo M et al (1998) Schizophrenia, sensory gating and nicotinic receptors. Schizophr Bull 24:189–202
39. Lemstra AW, Eikelenboom P, Van Gool WA (2003) The cholinergic deficiency syndrome and its therapeutic implications. Gerontology 49:55–60
40. Cancelli I, Cadore IP, Merlino G et al (2006) Sensory gating deficit assessed by P50/Pb middle latency event related potential in Alzheimer's disease. J Clin Neurophysiol 23:421–425
41. Murat G, Murat P, Unal S (2006) Psychotic disorder induced by oxybutynin: presentation of two cases. Clin Drug Invest 26:603–606
42. Cummings JL, Mega M, Gray K et al (1994) The neuropsychiatric inventory: comprehensive assessment of psychopathology in dementia. Neurology 44:2308–2314
43. Jeste DV, Finkel SI (2000) Psychosis of Alzheimer's disease and related dementias. Diagnostic criteria for a distinct syndrome. Am J Geriatr Psychiatry 8:29–34
44. Fleminger S (2002) Remembering delirium. Br J Psychiatry 180:4–5
45. Elie M, Cole M, Primeau FJ et al (1998) Delirium risk factors in elderly hospitalized patients. J Gen Intern Med 13:204–212
46. Inouye SK, Charpentier PA (1996) Precipitating factors for delirium in hospitalized elderly patients: predictive model and interrelationship with baseline vulnerability. JAMA 275:852–857
47. Francis J, Martin D, Kapoor W (1990) A prospective study of delirium in hospitalized elderly. JAMA 263:1097–1101
48. Schor JD, Levkoff SE, Lapsitz LA et al (1992) Risk factors for delirium in hospitalized elderly. JAMA 267:827–831
49. Lipowski ZJ (1990) Delirium: acute confusion state. Oxford University Press Inc, New York
50. Lindesay J, Macdonald A, Starke I (1990) Delirium in the elderly. Oxford University Press, Oxford
51. Ross CA (1991) CNS arousal system: possible role in delirium. Int Psychogeriatr 3:353–371

52. Gibson GE, Blass JP, Hm Huang et al (1991) The cellular basis of delirium and its relevance to age-related disorder including Alzheimer's disease. Int Psychogeriatr 3:373–395
53. Tune LE, Egeli S (1999) Acetylcholine and delirium. Dement Geriatr Cogn Disord 10:342–344
54. Dening TR, Berrios GE (1990) Wilson's disease: a longitudinal study of psychiatric symptoms. Biol Psychiatry 28:255–265
55. Gilley DW, Wilson RS, Bennett DA et al (1991) Cessation of driving and unsafe motor vehicle operation by dementia patients. Arch Intern Med 151:941–946
56. WHO Collaborating centre for drug statistics methodology. Anatomical therapeutics chemical classification system. Available at http://www.whocc.no/atcddd/
57. Ness J, Hoth A, Barnett MJ et al (2006) Anticholinergic medications in community-dwelling older veterans: prevalence of anticholinergic symptoms, symptoms burden, and drug events. Am J Geriatr Pharmacother 4:42–51
58. Rudd KM, Raehl C, Bond CA et al (2005) Methods for assessing drug-related anticholinergic activity. Pharmacotherapy 25:1592–1601
59. Carnahan RM, Lund BC, Perry PJ et al (2004) The concurrent use of anticholinergics and cholinesterase inhibitors: rare events or common practice? JAGS 52:2082–2087