

Translated from ***Rev Prescrire*** **June 2011; 31 (332): 434**

Syncope with cholinesterase inhibitors

● Adverse effects of cholinesterase inhibitors used in Alzheimer's disease include cardiac disorders (bradycardia, conduction disorders) that can cause malaise and syncope.

● A cohort study compared 20 000 patients who received a cholinesterase inhibitor for dementia with a control group of untreated dementia patients. Cholinesterase inhibitor therapy was associated with statistically significant increases in hospitalisations for syncope or bradycardia, pacemaker insertion, and hip fracture.

● In practice, cholinesterase inhibitors have little more than a placebo effect and do not justify exposing patients to these risks.

RevPrescrire **2011; 31 (332): 434**

Three cholinesterase inhibitors, *donepezil*, *galantamine* and *rivastigmine*, are widely used as symptomatic treatment for Alzheimer's disease (1-3). Yet their efficacy is minimal and transient, and none of these drugs has been shown to prevent disease progression (1).

Bradycardia with syncope. The adverse effects of these drugs include cardiac disorders (bradycardia and conduction disorders) that can cause malaise and syncope. The risk is increased by coadministration of drugs that reduce their elimination or provoke the same adverse effects (**a**)(3).

The risks of bradycardia and syncope associated with cholinesterase inhibitors were expected on the basis of their pharmacological properties and confirmed by pharmacovigilance studies (4). A 2009 case-control study showed that the risk of bradycardia in patients receiving cholinesterase inhibitors was not adequately taken into account: more than half of the patients treated with these drugs who were admitted to hospital for bradycardia were retreated with the same drug class after discharge (5,6).

Hospitalisation, pacemaker insertion, fractures. A Canadian cohort study conducted from April 2002 through March 2004 analysed data concerning 19 803 patients aged at least 66 years who had received *donepezil*, *galantamine* or *rivastigmine* for dementia, and 61 499 untreated controls with dementia (7). There was a statistically significant increase in hospitalisation for syncope among patients who received a cholinesterase inhibitor (31.5 versus 18.6 events per 1000 person-years; adjusted relative risk 1.76; 95% confidence interval (95% CI) 1.57 to 1.98), as well as hospitalisation for bradycardia (6.9 versus 4.4 per 1000 person-years; adjusted relative risk 1.69; 95% CI: 1.32 to 2.15) (7).

Serious consequences of syncope and bradycardia were more frequent in the patients who received a cholinesterase inhibitor, in terms of pacemaker insertion (4.7 versus 3.3 per 1000 person-years; adjusted relative risk 1.49; 95% CI: 1.12 to 2.00) and hip fracture (22.4 versus 19.8 per 1000 person-years; adjusted relative risk 1.18; 95% CI 1.04 to 1.34) (7).

In practice: avoid cholinesterase inhibitors. The minimal benefits of cholinesterase inhibitors, beyond a placebo effect, do not justify exposing patients to the risk of syncope and bradycardia, and their consequences (pacemaker insertion, hip fracture). These drugs should simply be avoided and the emphasis placed on non-drug management, however difficult.

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a- Cholinesterase inhibitors carry a risk of pharmacokinetic interactions due to a reduction in their elimination: donepezil and galantamine are metabolised by cytochrome P 450 isoenzymes CYP 3A4 and CYP 2D6, creating a high potential for interactions with inhibitors of these isoenzymes. Pharmacodynamic interactions include additive heart-rate-lowering effects during combination with other heart-rate-lowering drugs (ref 3). In patients treated with cholinesterase inhibitors, concomitant neuroleptic therapy increases the risk of death, cardiac arrhythmias, etc. (ref 8).

Selected references from Prescrire's literature search.

1- Prescrire Editorial Staff "Anticholinesterases in Alzheimer's disease: a modest effect on moderately severe disease" *Prescrire Int* 2003; **12** (68): 230-231.
2- "Donepezil", "Galantamine", "Rivastigmine". In: "Martindale The Complete Drug Reference" The Pharmaceutical Press, London. www.medicinescomplete.com accessed 22 December 2010: 20 pages in total.
3- Prescrire Rédaction "12-5-2. Patients sous anticholinestérasique" *Rev Prescrire* 2010; **30** (326 suppl. interactions médicamenteuses).
4- Prescrire Rédaction "Syncopes et inhibiteurs de la cholinestérase" *Rev Prescrire* 2003; **23** (245): 836.
5- Prescrire Editorial Staff "Bradycardia due to cholinesterase inhibitors: identify adverse effects and take them into account" *Prescrire Int* 2011; **20** (115): 95.
6- Park-Wyllie LY et al. "Cholinesterase inhibitors and hospitalization for bradycardia: a population-based study" *Plos Medicine* 2009; **6** (9) e1000157.doi:10.1371/journal.pmed.1000157: 9 pages.
7- Gill SS et al. "Syncope and its consequences in patients with dementia receiving cholinesterase inhibitors" *Arch Intern Med* 2009; **169** (9): 867-873.
8- Prescrire Rédaction "12-5-5. Patients sous neuroleptique" *Rev Prescrire* 2010; **30** (326 suppl. interactions médicamenteuses).

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