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Bradycardia due to cholinesterase inhibitors: identify adverse effects and take them into account

Abstract

● **The cholinesterase inhibitors *donepezil*, *rivastigmine* and *galantamine* have a modest and transient benefit in Alzheimer's disease. Their known adverse effects include bradycardia.**

● **A Canadian case-control study conducted between 2003 and 2008 showed a statistically significant increase in the risk of hospitalisation for bradycardia among patients who had been taking a cholinesterase inhibitor for less than 3 months, compared with patients who had stopped taking a cholinesterase inhibitor more than 6 months previously.**

● **After hospital discharge, more than half of these patients were again prescribed a cholinesterase inhibitor, and 4% of them were re-admitted for bradycardia.**

● **In practice, when an adverse effect has been identified and treated, this information must be shared and taken into account by all those involved in the patient's subsequent management.**

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The cholinesterase inhibitors *donepezil, rivastigmine* and *galantamine* have only limited and transient symptomatic effect in Alzheimer's disease (1,2).

These drugs can cause cardiac disorders, including bradycardia, malaise and syncope, as well as conduction disorders, sometimes amplified by drug-drug interactions (3-5).

A Canadian team has examined hospitalisations for bradycardia among patients treated with cholinesterase inhibitors (6). The results show that this known adverse effect is not adequately taken into account, especially after hospital discharge.

A Canadian case-control study. A case-control study was conducted in the province of Ontario. It focused on patients at least 67 years of age who had been hospitalised for bradycardia between 1 January 2003 and 31 March 2008 after taking a cholinesterase inhibitor during the 9 months preceding hospitalisation (6). For each "case" (a patient hospitalised for bradycardia), the authors recruited 3 matched controls (patients hospitalised without bradycardia) (6).

Among the 161 patients hospitalised for bradycardia, 22 had stopped taking cholinesterase inhibitors at least 6 months previously and 139 had taken a cholinesterase inhibitor during the 3 months prior to admission. Among the 466 controls (patients hospitalised for another reason), 117 had stopped taking cholinesterase inhibitors at least 6 months previously and 349 had taken a cholinesterase inhibitor during the 3 months prior to admission.

Mean age was 83 years and 51% of the patients were women (6).

Hospitalisation for bradycardia twice as frequent in patients having recently started cholinesterase inhibitor therapy. A statistically significant increase in the risk of hospitalisation for bradycardia was found among patients who had taken a cholinesterase inhibitor less than 3 months prior to admission compared to patients who had stopped taking cholinesterase inhibitors at least 6 months preceding hospitalisation (adjusted odds ratio 2.13, 95% confidence interval (CI) 1.29-3.51, p=0.003) (**a**)(6).

A similar level of risk was found in the subgroups of patients with a history of heart disease (odds ratio 2.25; 95% CI 1.18-4.28; p=0.014) or patients treated with other heart-rate-lowering drugs (odds ratio 2.34; 95% CI 1.16-4.71; p=0.017) (**b**)(6).

Among the 161 patients hospitalised for bradycardia, 17 (11%) received a pacemaker and 6 (4%) died in hospital (6).

A known but neglected adverse effect. After hospital discharge, more than half of patients (78 out of the 138 patients, after excluding those who received a pacemaker or died) were again prescribed a cholinesterase inhibitor. Three of them (4%) were again hospitalised for bradycardia within the 3 months following hospital discharge (6).

In practice: identify adverse effects and take them into account. Bradycardia is a predictable adverse effect associated with cholinesterase inhibitors and is therefore, to some extent, avoidable. Rechallenge entails a risk of recurrence.

When an adverse effect has been identified and treated, this information must be shared and taken into account by all those involved in the patient's subsequent management (7).

a- The odds ratio is the ratio of the odds of an event occurring in one group to the odds of it occurring in another group. Calculation of the relative risk is inappropriate in case-control studies, while the odds ratio, under certain conditions, provides a good estimate of the relative risk of the event of interest (ref 8).

b- Digoxin, drugs with a betablocking effect, and calcium channel blockers such as verapamil and diltiazem (ref 6).

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- "Dementia". In: "Martindale The Complete Drug Reference" The Pharmaceutical Press, London. www.medicinescomplete.com accessed 28 December 2009: 9 pages.

3- Prescrire Editorial Staff "Anti-Alzheimer drugs: life-threatening adverse effects" *Prescrire Int* 2007; **16** (87): 16.

4- Prescrire Rédaction "Syncopes et inhibiteurs de la cholinestérase" *Rev Prescrire* 2003; **23** (245): 836.

5- Prescrire Rédaction "12-5. Patients ayant une maladie d'Alzheimer" *Rev Prescrire* 2010; **30** (326 suppl. interactions médicamenteuses).

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- Prescrire Rédaction "Effets indésirables médicamenteux négligés en cours d'hospitalisation" *Rev Prescrire* 2007; **27** (289): 833.

8- Prescrire Rédaction "Rapport de cotes: une estimation du risque relatif, sous certaines conditions" *Rev Prescrire* 2008; **28** (298): 626-629.