Lesson of the week

Syncope and falls due to timolol eye drops

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Beware of syncope and falls in patients using β blocker eye drops

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The prevalence of glaucoma increases with age.[1] Timolol, a non-selective β blocker, is the first line treatment. We present three cases from our falls clinic, in which we show that even a low dose of timolol eye drops may cause severe systemic adverse effects.

Case reports

Case 1

A 73 year old man was referred by his general practitioner because he had been unconscious for half an hour the previous day. His medical history consisted of a myocardial infarction, glaucoma, and insulin dependent diabetes mellitus. During the past few years, he had experienced four spells of dizziness with severe perspiration. These spells had been ascribed to hypoglycaemia, although low blood glucose values had never been detected. His medication consisted of insulin, acenocoumarol, alfuzosin, and timolol eye drops (0.5%, twice daily in both eyes). During his last dizzy spell, his blood glucose concentration had been 8 mmol/l. According to his wife, the patient had not experienced a convulsion, tongue biting, or urinary incontinence.

At referral to our clinic, the patient was alert and feeling well. Blood pressure was 142/90 mm Hg, with a regular pulse rate of 48 beats/min. There was no evidence of orthostatic hypotension. Further physical examination, including neurological examination, showed no abnormalities. Glycated haemoglobin (HbA_{1c}) was slightly increased—8.2% (reference range 4-6%); the glucose day curve showed values of 4.6-17.4 (3.5-11) mmol/l, with no hypoglycaemia. Electrocardiography showed sinus bradycardia of 41 beats/min, and 24 hour Holter monitoring showed a sinus rhythm of 69 beats/min and frequent episodes of bradycardia, with a minimum frequency of 43 beats/min, during which the patient experienced presyncopal symptoms, which he recognised as the dizzy spells mentioned before. His syncopal episodes were diagnosed as resulting from symptomatic bradycardia induced by timolol eye drops. After consultation with the ophthalmologist, the timolol eye drops were changed to latanoprost eye drops, a prostaglandin F2 analogue. Since then (a follow-up period of one and a half years), the patient has had no recurrence of syncope. A few weeks after the change in eye drops, a repeat Holter test showed a sinus rhythm of 80 beats/min, without bradycardia.

Case 2

A 73 year old woman complained of unexpected falls during the previous five years. Furthermore, she regularly had a feeling of lightheadedness and weakness in both arms. She had a five year history of glaucoma, for which she used latanoprost and timolol eye drops (0.5%, once daily in both eyes). Besides orthostatic hypotension, no other abnormalities were found at physical examination. Her supine blood pressure was 139/68 mm Hg, with a regular pulse rate of 58 beats/min; lowest blood pressure during three minutes of standing was 117/64 mm Hg, with a regular pulse rate of 66 beats/min. Electrocardiography showed sinus bradycardia of 53 beats/min. On tilt table testing, orthostatic hypotension was confirmed; supine blood pressure was 160/85 mm Hg, with a regular pulse rate of 58 beats/min, and lowest blood pressure during five minutes of standing 134/75 mm Hg, with a regular pulse rate of 62 beats/min. There was no vasovagal collapse or carotid sinus hypersensitivity. Her falls were diagnosed as resulting from orthostatic hypotension, induced by timolol eye drops. Because of this, and because of an insufficient reaction of the glaucoma to the eye drops, her ophthalmologist decided to perform eye surgery, after which her eye drops were stopped. Since then (a follow-up period of one year) she has not experienced any more falls, nor has she experienced any more episodes of lightheadedness or weakness in the arms. On repeat tilt table testing, orthostatic hypotension did not occur.

Case 3

A 74 year old man with a metastasised prostate carcinoma, essential hypertension, and glaucoma presented, having had weekly falls with loss of consciousness for two years. He also often felt lightheaded on standing up. His medication consisted of losartan, aspirin, latanoprost eye drops, and timolol eye drops (0.5%, twice daily in both eyes).

On examination, his blood pressure decreased from 145/95 mm Hg supine to 135/87 mm Hg on standing, at which point he recognised the prodromal symptoms of the syncope. Electrocardiography showed a sinus bradycardia of 43 beats/min. A tilt table test was performed; after three minutes there was a decrease in blood pressure from 167/103 mm Hg to 117/81 mm Hg, with a regular pulse rate of 68 beats/min and 62 beats/min respectively, and recognition of the prodromal symptoms. After 13 minutes of tilt table testing, blood pressure decreased to 89/74 mm Hg, with a regular pulse rate of 40/min, at which he fainted. The patient was diagnosed with systolic and diastolic orthostatic hypotension and vasovagal syncope induced by timolol eye drops. The sinus bradycardia seen in the electrocardiogram was not associated with the prodromal symptoms. In consultation with the ophthalmologist, the timolol eye drops were discontinued. At repeat tilt table testing, no abnormalities were found. During follow-up for one year the patient had no complaints and no further falls or lightheadedness.

Discussion

Timolol is a non-selective β adrenergic antagonist without intrinsic sympathicomimetic activity, which was first marketed in 1978. At least 80% of the administered drop drains through the nasolacrimal canal, where it is absorbed by the nasal mucosa. Thus it spreads systemically, and as there is no hepatic first

pass effect, the absorbed dose behaves like an intravenous drug dose.[2]

At first the only side effect mentioned was a minor decrease in heart rate.[3] By now, numerous adverse events of timolol eye drops have been reported. The cardiovascular adverse events that have been reported are arrhythmia (bradycardia and tachycardia), hypotension, orthostatic hypotension, angina pectoris, myocardial infarction, heart failure, and syncope.[3–6] A significant decrease in heart rate and exercise performance has been documented in a group of 20 young healthy volunteers, after a dose of two eye drops of timolol 0.5% twice daily, with no detectable plasma concentration[7]; the study also found a lengthening of the pre-ejection period, indicating a negative inotropic effect. In older patients, the capability to increase heart rate is very important as exercise capacity largely depends on it.[8]

As shown in case 3, orthostatic hypotension can be missed if tested on one occasion only. This may be explained by the fact that its presence varies during the day and between days. It is therefore useful to measure orthostatic hypotension at different occasions.[9] Moreover, a slight decrease in systemic blood pressure can have major cerebral effects when there is pre-existent cerebral morbidity. When cerebral morbidity is suspected, tests such as transcranial Doppler ultrasonography should be carried out, or decisions should be made empirically.[10]

Conclusion

Eye drops with β blocking action can have a strong and prolonged systemic effect, especially in older age groups. β blocker eye drops should be prescribed with caution in older patients and in patients with pre-existing cardiovascular morbidity.[11] If such patients present with syncope, a systemic adverse drug reaction should be considered.

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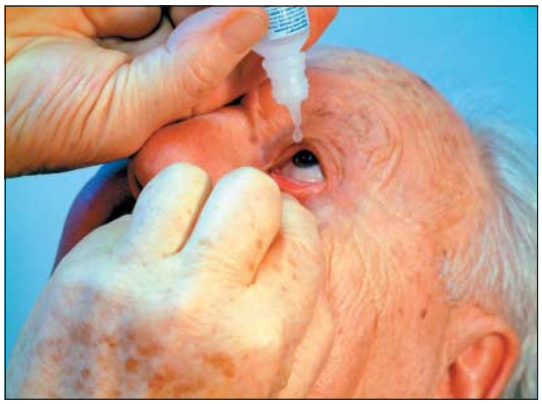

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β Blocker eye drops can cause severe systemic effects

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1 Weih LM, van Newkirk MR, McCarty CA, Taylor HR. Age-specific causes of bilateral visual impairment. *Arch Ophthalmol* 2000;118:264-9.
2 Shell JW. Pharmacokinetics of topically applied ophthalmic drugs. *Surv Ophthalmol* 1982;26:207-18.
3 Nelson WL, Fraunfelder FT, Sills JM, Arrowamith JB, Kutisky JN. Adverse respiratory and cardiovascular events attributed to timolol ophthalmic solution, 1978-1985. *Am J Ophthalmol* 1986;102:606-11.
4 Everitt DE, Avorn J. Systemic effects of medications used to treat glaucoma. *Ann Intern Med* 1990;112:120-5.
5 Novack GD, O'Donnell MJ, Molloy DW. New glaucoma medications in the geriatric population: efficacy and safety. *J Am Geriatr Soc* 2002;50:956-62.
6 Lesar TS. Drug review: comparison of ophthalmic beta-blocking agents. *Clin Pharm* 1987;6:451-63.
7 Leier CV, Baker ND, Weber PA. Cardiovascular effects of ophthalmic timolol. *Ann Intern Med* 1986;104:197-9.
8 Higginbotham MB, Morris KG, Williams RS, McHale PA, Coleman RE, Cobb FR. Relation of stroke volume during submaximal and maximal upright exercise in normal man. *Circ Res* 1986;58:281-91.
9 Weiss A, Grossman E, Beloosesky Y, Grinblat J. Orthostatic hypotension in an acute geriatric ward; is it a consistent finding? *Arch Intern Med* 2002:162:2369-74.
10 Grubb BP, Samoil D, Kosinski D, Wolfe D, Brewster P, Elliott L, et al. Cerebral syncope: loss of consciousness associated with cerebral vasoconstriction in the absence of systemic hypotension. *Pacing Clin Electrophysiol* 1998;21:652-8.
11 Van der Zanden JA, Valuck RJ, Bunch CL, Perlman JI, Anderson C, Wortman GI. Systemic adverse effects of ophthalmic β-blockers. *Ann Pharmacother* 2001;35:1633-7.

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Spellbound by CO_2

We have observed various spellings of words to describe carbon dioxide blood concentrations at scientific meetings, in textbooks, and in the published scientific literature (that is, with the suffix "capnia," "capnoea," or "capnea"). According to *Dorland's Illustrated Medical Dictionary* and the *Oxford English Dictionary*, the correct suffix describing CO_2 levels is "capnia," derived from the Greek noun for smoke (kapnos). In contrast, the suffix "capnoea" (we suspect) has been incorrectly derived from the Greek verb to breathe (pnoia), the absence of which (apnoea), by coincidence, leads to hypercapnia.

To explore this definitively, we searched for the words "hypercapnea," "hypercapnoea," "hypercapnia," "hypocapnea," "hypocapnoea," and "hypocapnia" on the websites of a series of general medical and specialty respiratory journals. Our hypothesis was that the spelling of words describing blood CO_2 concentrations would be more accurate in respiratory journals than non-specialty journals.

Our initial search via Medline and PubMed of all scientific journals yielded a 2.3% error rate in the spelling of either hypocapnia or hypercapnia (87/3800 and 244/10 538 citations respectively). We then examined the electronic records of the major respiratory journals: the misspelling rates were 3.8% (22/585) in the *American Journal of Respiratory and Critical Care Medicine*, 5.8% (32/549) in *Chest*, 2.8% (2/212) in the *European Respiratory Journal*, 2.4 % (4/169) in *Thorax*, and 5.6% (2/36) in *Respirology*—an overall average of 4.1%. In the general medical journals the error rates were 4.8% (3/62) in the *New England Journal of Medicine*, 5.1% (3/59) in the *Lancet*, 4.2% (1/24) in *Annals of Internal Medicine*, 2.4% (1/42) in the *BMJ*, and 3.3% (1/30) in *JAMA*—an average of 4.0%.

It may be time for the medical profession to wake up from the apnoeic world, look through the smoky haze, and initiate the correct spelling of CO_2 disorders in future presentations and published scientific documents.

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