A case of melancholic depression induced by β-blocker antiglaucoma agents

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Clinical record

A man in his 70s was prescribed DuoTrav eye drops (Alcon Inc; combined prostaglandin analogue [travoprost] and β-blocker [timolol]) for worsening glaucoma. (He had previously been treated with latanoprost.)

Within 2–3 days, he felt depressed and described "a black cloud descending over [him]". His symptoms included tiredness, poor concentration, sleep disturbance, and loss of libido and appetite. Normally fit and active, with a zest for life and a good sense of humour, he struggled to get up in the mornings and lost interest in socialising. His general practitioner prescribed venlafaxine (75 mg, then 150 mg) for the depression. Subsequently, DuoTrav therapy was stopped and a combination of travoprost, brimonidine tartrate and brinzolamide started. A month later, his sleep and appetite were considerably improved and he rated himself as 70% better.

Eleven years previously, he had suffered an episode of major depression with melancholic features after his initial diagnosis of glaucoma, for which he was prescribed the β-blocker betaxolol.[1] At that time, his symptoms had been worse and of longer standing, requiring hospitalisation and electroconvulsive therapy (ECT). He had recovered slowly, while continuing to experience lethargy and a heavy head. Only several months later, when the episode of depression was linked to the initiation of betaxolol and the β-blocker was stopped, did he fully recover. Within 48 hours of ceasing betaxolol therapy, he felt more energetic, alert and alive.

The patient had been treated once before with ECT when he experienced his first depressive episode, at the age of 50 years, associated with severe work-related stress. Both subsequent episodes of depression were seemingly unrelated to stressors or life events. ◆

The most common medical treatments for glaucoma in Australia are prostaglandin analogues. However, β-blockers still comprise a substantial proportion of all prescriptions, either alone or in combination. Despite their topical administration, β-blockers are absorbed from the eye through the conjunctival epithelium, lacrimal channels, nasal mucosa and gastrointestinal tract into the systemic circulation. Although only small amounts are absorbed, concentrations may be sufficient to cause systemic β-adrenergic receptor-mediated effects, including slowing of heart rate, lowering of blood pressure and non-response to bronchodilators. Central effects such as depression have also been reported.

The literature investigating a causal relationship between β-blockers and depression is controversial. An evidence-based review concluded that depression was an uncommon side effect of treatment with β-blockers and usually occurred only in the presence of a pre-existing condition.[2] Randomised controlled studies of β-blockers in cardiovascular disease found the incidence of depressive symptoms was similar in β-blocker- and placebo-treated groups.[3] However, a review of 24 case reports[4] showed a temporal relationship between the use of β-blockers and depression in more than half the cases.

If there is a close temporal relationship between the commencement of a new treatment and the development of symptoms, the symptoms are considered likely to have been caused by the medication. In the initial case that we reported on this patient,[1] depressive symptoms began within days after the diagnosis of glaucoma and commencement of betaxolol treatment. The patient's symptoms only fully remitted when the drug was stopped, providing further evidence of a causative relationship. The case we report here describes recurrence of depression after the introduction of another β-blocker, timolol, and again cessation of symptoms when treatment was stopped. The recurrence of the syndrome following a re-challenge further strengthens the argument for a causal relationship. (The travoprost component of the medication was unlikely to have been the cause of the depression.)

It is possible that the onset of the disorder occurred coincidentally with the introduction of the medication (though such an event is unlikely to have occurred twice) or was caused by the underlying illness for which the new medication was prescribed. In the only study we could find of ophthalmological patients with depression with and without glaucoma, no association was shown between depression and glaucoma.[5]

Glaucoma is mostly a disease of older people, a group prone to developing depressive illness. Depression is often dismissed in older people as a normal reaction to ageing, loss or chronic illness. However, it is treatable, with a very good prognosis. Older patients are frequently taking multiple medicines and may develop depressive symptoms as a side effect. The purpose of this case presentation is to emphasise that even a drug that is administered topically, such as antiglaucoma eye drops, is absorbed systemically and can potentially cause adverse effects elsewhere, including centrally.

There are credible theoretical reasons why β-blockers may cause depression: the number of β_1 receptors is increased in the brains of suicide victims and chronically stressed animals, and antidepressants cause down-regulation of β_1 receptors. The fact that only a few patients develop depression after taking β-blockers may be due to genetic differences. It is possible that poor metabolisers of the enzyme cytochrome P450 2D6 will be exposed to higher systemic concentrations of β-blockers than those who are normal or fast metabolisers.[6,7] To our knowledge, there have been no

Lessons from practice

- Ophthalmic β-blockers are absorbed systemically and may cause central side effects.
- Depression is an occasional adverse effect of β-blockers, including those used for glaucoma.
- Ophthalmic β-blockers should be avoided in patients who have a history of clinical depression.
- When depression evolves soon after commencing β-blocker treatment, serious consideration should be given to changing the medication, as the β-blocker may be the causative agent. ◆

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studies of depression in relation to β-adrenergic receptor gene polymorphisms, although associations have been found between these polymorphisms and haemodynamic effects after administration of betaxolol and timolol.[8]

Variability between individuals in the time course, affinity and extent of receptor occupation may also be relevant. Vuori and Kaila[9] found substantial β_1 and β_2 blockade in plasma for up to 12 hours after administration of topical timolol. Thus, 12-hour dosage intervals could lead to substantial systemic blockade and could explain the reported systemic side effects.

Our report adds to the evidence that depression is an occasional adverse consequence of treatment with β-blockers, including topical antiglaucoma agents. Development of depression is a serious consequence. Discontinuation of a β-blocker may relieve symptoms, but specific antidepressant treatment may also be needed. As there are alternative antiglaucoma medications, it is prudent not to prescribe β-blockers for patients who have a history of depressive illness. If depression develops after commencement of a β-blocker antiglaucoma agent, an alternative medication should be substituted if possible.

Competing interests

Isaac Schweitzer and Chee Ng have received grant money, travel support and honoraria for talks from Pfizer.

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