Eye drop psychosis in Parkinson’s disease: a cautionary tale

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Anticholinergic agents are used in a number of conditions ranging from overactive bladder and bradycardia to travel sickness but side-effects such as hallucinations, impaired memory and restlessness are increasingly recognised, though still under-reported in clinical practice. In Parkinson’s disease anticholinergics such as atropine are recommended by NICE for the management of excessive drooling. Dr Ferris et al. present such a case where commencing sublingual atropine drops caused a patient to develop hyperactive delirium and psychosis. They also discuss the subsequent clinical management steps.

Parkinson’s disease (PD) is a progressive neurodegenerative disorder with an estimated UK prevalence of 145,519.1 It is characterised by loss of dopaminergic neurones from the substantia nigra and typically presents in older adults. It is diagnosed clinically based on the UK Parkinson’s Disease Brain Bank diagnostic criteria2 including the classical features of bradykinesia with rigidity, resting tremor or postural instability; but the disease can present with a range of features, which can be challenging to manage.

Hypersalivation is a non-motor feature of PD that can cause skin damage and significant psychological distress. NICE guidelines advise initial non-pharmacological management before trialling drugs such as glycopyrronium or botulinum toxin injections. Atropine can also be used but only if the ‘risk of cognitive adverse effects is thought to be minimal’, and ideally via the topical route, to reduce the risk of adverse events.3

Atropine is a competitive inhibitor of the muscarinic acetylcholine receptor.4 When used in hypersalivation it blocks the effects of acetylcholine released from the glossopharyngeal and facial nerves supplying the salivary glands to reduce the amount of saliva produced (Figure 1). This is an off-licence use, usually given as 1% atropine eye drops administered sublingually.

Presentation
The patient was a 75-year-old gentleman who has suffered from PD for 16 years. He was taking Stalevo (levodopa, carbidopa and entacapone) 100/25/200 one tablet three times a day, pramipexole modified release (dopamine agonist) 2.62mg per day and rasagiline (monoamine oxidase inhibitor) 1mg per day. His motor symptoms were well controlled and he remained fully independent in his activities of daily living but felt his drooling was severely affecting his quality of life. Conservative self-management strategies had made little difference, and he had been unable to tolerate glycopyrronium. After extensive discussions of the risks and benefits the patient was commenced on atropine eye drops 10mg/ml 0.5ml sublingually once daily, off-licence.

After two doses the patient collided with a stationary car when...
driving home; he was not injured. As the day progressed he became dysarthric and his gait became more unsteady culminating in a number of falls. He was admitted to hospital.

On examination he was disoriented, with an Abbreviated Mental Test 4 (AMT-4) score of 3/4 (previously normal) and classical but mild parkinsonian signs of bradykinesia, tremor and cogwheeling. His power, reflexes sensation and co-ordination were normal and other systems examinations were unremarkable. Baseline investigations including inflammatory markers, ECG, CT head and urine dip were all within normal range.

The patient was admitted for observation and the atropine was stopped. Over the next 12 hours he became more confused and aggressive; he developed vivid auditory and visual hallucinations and exhibited paranoia, accusing patients of stealing from him. All conservative de-escalation strategies failed to calm him and he required intramuscular sedation for his own and other patient’s safety. He received supportive care and his rasagiline was stopped, his Stalevo switched to Madopar and pramipexole weaned down and stopped over 10 days to reduce the dopaminergic drive that may have been worsening his symptoms. Forty eight hours later the patient settled on cessation of the offending medications, but it is unknown whether this has increased his risk of future cognitive impairment or Parkinson’s dementia, or whether this florid reaction is a prodromal clinical feature of already inevitable future dementia. No specific guidance exists on what cognitive assessments or monitoring should be used following an episode of delirium or psychosis but the patient, as with all patients in the movement disorder clinic, will have annual cognitive screening tests in the form of clock drawing test and Montreal Cognitive Assessments (MOCA). His last MOCA performed following his discharge from hospital was 26/30 so there is no objective evidence of cognitive impairment currently.

A Medline search (1946–24/4/2018) was conducted for ‘atropine’ and ‘delirium or psychosis’ and 64 potential papers were identified. Papers were then reviewed by title and abstract and excluded if irrelevant, no English translation was available or they described paediatric cases. Seven other similar cases of delirium/psychosis in adults thought to be induced by atropine were selected and are summarised in Table 1.

Four cases were from patients receiving atropine eye drops for ophthalmic conditions, one received nebulised atropine for bronchospasm, one patient received it intravenously as part of a general anaesthetic and one patient received atropine in combination with hyoscine through a variety of routes in a smoking cessation clinic.

In all the cases described the symptoms tended to begin insidiously with unsteadiness and disorientation, quickly progressing to agitation, irritability, hallucinations and paranoia, with one patient also exhibiting both suicidal and homicidal ideation.

The timing of onset of symptoms was not always clear but tended to be within a few hours to a few days of commencing treatment and resolved promptly after stopping the atropine administration. Treatment other than supportive care was only given in three cases, and only two of these required sedation. One case was given physostigmine (an anticholinesterase inhibitor) to counteract the effect of atropine by blocking the enzymatic breakdown of the acetylcholine in the synapse or neuromuscular junction potentiating its effect on the receptors. In the patient receiving the physostigmine symptoms of delirium and agitation resolved almost immediately after administration. Kortabarria (1990) also used the physostigmine as part of an atropine challenge in a patient whose symptoms were initially induced by cyclogepic eye drops but had spontaneously resolved. She was given a further challenge of atropine sulphate along with other anticholinergics to reproduce her symptoms, followed by physostigmine, which reversed them; this challenge...
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Case notes

Test supports the association between atropine drops and the neuropsychiatric syndromes observed.

Anticholinergic burden
It is interesting to note that some of the most florid reactions were seen in patients receiving more than one anticholinergic agent and the concept of cumulative anticholinergic burden has been increasingly reported in the literature and is thought to be a strong predictor of cognitive and physical impairments. A number of rating scales are available to quantify the anticholinergic effects of a range of medications but these have a relatively weak evidence base and are compiled largely from expert opinion. A systematic review in 2015...
considered a number of rating scales and identified two randomised control trials demonstrating a relationship between increasing anticholinergic burden and adverse outcomes, and a number of cohort studies that also supported the relationship between increasing use of drugs with anticholinergic activity and cognitive side-effects, including cognitive impairment, confusion and delirium. The most validated tool appeared to be the Anticholinergic Cognitive Burden Scale, which has been shown in a number of studies to predict cognitive impairment in older people. But there is no overall standardised rating scale, or even consensus on which drugs should be classified as having anticholinergic activity, and although NICE guidance on dementia advises minimising patients anticholinergic burden it is also unable to recommend an appropriate tool to aid clinicians due to insufficient evidence.

A number of studies have specifically identified an association between the use of anticholinergics and delirium and several others highlight a link between anticholinergic use and worsening cognitive test scores. This may suggest a possible link between their use and subsequent development of dementia, however, longitudinal studies of this have not been conclusive and the mechanism for this is not fully understood but may be related to cell death caused by reduced cholinergic input. A study by Risacher et al. (2016) again found that patients using medication with anticholinergic effects had poorer cognitive performance, including immediate recall and executive function, but also identified reduced glucose metabolism in the hippocampus on PET scanning and greater brain atrophy and volume loss on MRI. These findings go some way to suggest a biological basis for some of the clinical effects of the medication but the underlying cellular mechanism is still not clear.

Conclusion
In the patient described atropine was given for a relatively benign symptom of hypersalivation, but the drug caused significant psychomotor side-effects, the consequences of which could have been serious both medically, cognitively and legally given his car accident. As presented here, atropine and other medications with anticholinergic effects are recognised to cause a range of adverse effects, including confusion, agitation, delirium and, in severe cases, psychosis. The authors would advise all clinicians to carefully consider the perceived risks and benefits before commencing anticholinergic medication, as well as considering how this may have a cumulative effect with other drugs the patient is already taking; use of an anticholinergic burden score may be helpful. When additional medications are necessary we advocate the use of the minimum dosage of anticholinergic to achieve therapeutic effect for the shortest possible time while limiting polypharmacy where practical.

Declaration of interest
No conflicts of interest were declared.

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