A DIFFICULT CASE

Fluctuations in Parkinson's disease

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Parkinson's disease is the most treatable of the neurodegenerative diseases, but the treatment tends to get more difficult with time. One problem is solved only for another to emerge. Even the greatest therapeutic enthusiast must admit to occasions where he or she reaches for the prescription pad with a faint feeling of foreboding.

Derek is a 58-year-old, well-educated and professional man, who has had Parkinson's disease for 15 years. He came to his local neurology clinic because he was no longer able to travel to the more distant specialist centre that had managed his illness over recent years. He was agitated and confused, and unable to give a coherent history. He spoke of frequent 'off periods'. He showed me his pills and claimed to be taking one or two cobeneldopa 25/100 mg and benzhexol 2 mg every waking hour and whenever he awoke at night, ropinirole 3 mg and baclofen 20 mg 'three or four times per day', and lithium carbonate 300 mg 'two or three times per day'. His wife made it clear that this was indeed the case. Subsequent correspondence with his previous neurologist confirmed that he had a long-standing tendency to escalate his therapy unilaterally. The baclofen and lithium had been introduced in more modest dosages in an attempt to control periods of dystonia (Quinn & Marsden 1986). The previous neurologist did not seem unduly upset that Derek was seeking help closer to home.

THE STORY

Derek was dishevelled and wildly dyskinetic. He had pressured speech and was hallucinating, holding conversations with people that I could not see. He was disorientated in time but it was not possible to make any detailed cognitive assessment. As far as I could tell, there were no cerebellar signs to suggest acute lithium poisoning.

I confiscated his lithium on safety grounds and persuaded his wife to co-operate with a programme to withdraw the benzhexol over the next 4 weeks. Anticholinergic drugs are of course the most potent provokers of confusion in Parkinson's disease. I explained to them that it is better to be lucid and stiff than confused and mobile.

He returned unannounced a fortnight later to explain that I was wrong. He was now taking about 10 mg of benzhexol per day and was much less confused. His cobeneldopa consumption had increased and he was even more agitated, dishevelled and dyskinetic. He was able to tell me that without the lithium his dystonia had become unbearable, with severe painful spasms in both legs whenever the cobeneldopa wore off.

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The next step was to see what he meant. There is no substitute for this. No matter how sophisticated the patient's understanding of Parkinson's disease and the language that we use to describe its phenomena, it is vital to make sure that you and the patient both use the same words to describe the same thing. Remember that admitting the patient to the ward will not necessarily help: you may transform a communication problem between you and the patient into one between you and the ward staff. You can sort it all out in clinic if your patients fluctuate reasonably rapidly and your clinics are, like mine, unreasonably long. Failing that, ask the family to video the different phases for you.

THE REAL PROBLEM?

So, Derek went to the waiting room and I continued the clinic until his dystonia began. It was immediately clear that his concept of dystonia was not the same as mine. He was certainly in a severe 'off' state, with profound bilateral bradykinesia and rigidity. He was very distressed, weeping and rocking slowly back and forth, rubbing his painful thighs. But there was no abnormality of posture, no spasm and no cramp. The problem was 'off period' pain.

Pain is a neglected feature of Parkinson's disease, and a major cause of impaired quality of life (Schrag *et al.* 2000). It is sometimes a presenting feature, with aching around the shoulders, where it seems to reflect muscle stiffness and usually resolves with the start of treatment. In established cases it sometimes reflects musculoskeletal complications such as a frozen shoulder. But often it is a diffuse, distal pain with no obvious cause, and with an unpleasant burning neuropathic character.

In Derek's case the pain was so unpleasant that he would go to almost any lengths to avoid an 'off' period, and this was why he over-medicated to such a dramatic extent. Again, this illustrates an obvious point about looking after patients who seem to be taking more medicine than is good for them. You need to understand their motives. The most common is a desire to avoid anxiety associated with the 'off' state. This can amount to an overwhelming feeling of doom. Much rarer is a desire to achieve the opposite, a feeling of intense well-being associated with the 'on' state, described as hedonistic homeostatic dysregulation by Andrew Lees and colleagues (Giavannoni *et al.* 2000).

AN ATTEMPTED SOLUTION

Derek and I agreed that he would continue to withdraw the benzhexol and try cabergoline instead of ropinirole to see if this would give him fewer and less intense 'off' periods. Changing from one agonist to another is always difficult, because there is no reliable conversion table to allow you to estimate the required dosage of the new drug. I have given up trying to make the transition gradually, which just seems to cause prolonged misery, and now make a straight swap to what I guess will be a slightly less effective dose, with instructions to titrate up rapidly until the desired effect is obtained. There have not been any useful trials to compare the efficacy and tolerability of the newer dopamine agonists. Having used them all, my impression is that cabergoline is preferred by most patients. This is partly because, with its very long half-life, it can be taken as a single night-time dose with few adverse effects. In a journal edited

by an evidence-based medicine enthusiast, I can scarcely mention my mere impression that it may also have a mild positive psychotropic effect. It is perhaps permissible to note that it can reverse levodopa-induced dyskinesia in parkinsonian monkeys (Hadj Tahar *et al*. 2000).

Derek did report some improvement on cabergoline 4 mg *nocte*. His sleep improved considerably and he became more relaxed. Unfortunately he still had several painful 'off' periods each day and was adamant that only levodopa relieved his pain. He was very reluctant to consider any strategy that involved its reduction, despite his continuing severe dyskinesia. As a compromise, he agreed to try amantadine. In retrospect it seems surprising that we have only recently recognised the role of amantadine in treating dyskinesia (Verhagen Metman *et al*. 1998). A dose of 100 mg on waking and again at midday will often have an appreciable effect, although doses of up to 300 mg b.d. may be required. The discovery of this effect has been one of the most important pharmacological advances in treating Parkinson's disease of recent years (although not as helpful as the development of Parkinson's disease nurse specialists).

BUT NOW HALLUCINATIONS AND CONFUSION

In Derek's case, amantadine 100 mg b.d. suppressed his dyskinesia very substantially, but unfortunately this only encouraged him to take even more cobeneldopa. Worse still, florid visual hallucinations returned and he began to express the view that I was trying to kill him. The liaison psychiatrist charitably interpreted this as a paranoid delusion, but I was starting to feel that the patient had a point. His family were unable to cope with the return of agitated, restless behaviour and his demands for regular leg massage for his pain. They called out the family doctor who sent him to hospital as an emergency, voluntary, medical admission.

As a general rule, admitting people with Parkinson's disease to hospital to rationalise their therapy is a disappointing exercise. They don't get their pills at the time that you or they want, and they sit around doing nothing and so cannot tell you if the new regime is working. In Derek's case it was, however, an opportunity to make radical changes under conditions of relative safety. I stopped the last of the benzhexol and withdrew the baclofen in case they were contributing to the psychosis, and rationed his levodopa to cobeneldopa 25/100 mg every three hours. The visual hallucinations rapidly resolved but the paranoid delusions became more systematised. He could not tolerate a reduction in amantadine or cabergoline. The time had come for an antipsychotic drug.

There are two main options here. In patients whose psychosis is a manifestation of early dementia the cholinesterase inhibitors can be gratifyingly effective. The large randomised, controlled trial by McKeith *et al*. (2000) convincingly demonstrated this for rivastigmine in patients with dementia with Lewy bodies. This study did not include patients with Parkinson's disease before the onset of dementia, but smaller open studies and (can I get this past the Editor?) personal experience suggests that rivastigmine – and indeed donepezil and galantamine – are also useful in this situation. This is not surpris-

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ing, given that the pathology of dementia in Parkinson's disease is usually indistinguishable from that of dementia with Lewy bodies.

However, I was not convinced that Derek's psychosis was due to dementia and I was concerned that rivastigmine might aggravate his agitation. I chose the second option of an atypical neuroleptic (see 'Management of the neuropsychiatric and cognitive symptoms of Parkinson's disease, p.94). Again the choice of drug must take place in the absence of useful evidence in relation to comparative efficacy, and is mainly based on anecdotal experience of adverse effects. Mindful of the propensity of sulpiride and risperidone to cause motor deterioration, the risk of confusion associated with olanzapine, and the haematological complexities of clozapine, I started Derek on quetiapine. This is, in my view, a relatively low-potency antipsychotic that only helps in Parkinson's disease when given in large doses. In Derek's case his psychosis resolved when he reached a dose of 200 mg b.d.; there were no significant adverse effects.

THE FINAL SOLUTION

He was now lucid again, but still experiencing excruciating 'off' periods when his strictly-controlled cobeneldopa dosages wore off. I felt that adding selegeline would risk further psychosis and that entacapone would probably not achieve sufficient prolongation of 'on' time to be worthwhile. I was reluctant to embark on apomorphine injections for fear that his use of them would escalate out of control like the previous therapies.

The solution came from the Parkinson's disease nurse specialist, who sat with him during an 'off' period. She discovered that with the cabergoline therapy his 'off' periods were no longer intense or painful, and that Derek's distress was actually arising from the *anticipation* of 'off-period' pain. In consultation with the liaison psychiatrist, we decided to treat this as a kind of phobia, with cognitive behavioural therapy and the selective serotonin reuptake inhibitor (SSRI) citalopram 20 mg daily.

One year later, Derek still fluctuates, but copes with the distress this causes. He is enjoying an independent life again. He has not developed cognitive impairment. His levodopa, amantadine and cabergoline consumption have remained stable and he has been able to withdraw the quetiapine without a return of psychosis; he remains on the SSRI. For the moment we are both able to resist the temptation to tinker further.

PRACTICE POINTS

- Make sure that you and the patient are using the same words to describe the same things by actually observing what the patient means by 'off' periods, dystonia and so on. This can often be done during a clinic and does not necessarily require admission to hospital
- Pain is an under-recognised symptom in Parkinson's disease and a major determinant of quality of life.
- Fluctuations are complex: clarify the nature of the problem that you are trying to treat by observing it if you can.
- Amantadine is a useful treatment for levodopa-induced dyskinesia.
- Cabergoline is a long-acting dopamine agonist, which improves night-time control and may reduce the intensity of off-period motor symptoms.
- Anxiety related to 'off' periods can be treated with SSRIs or cognitive behavioural therapy or both.
- Parkinson's disease nurse specialists play a major role, in part because they spend so much more time listening to patients than neurologists.

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