IS CDS A CONCEPT OF RELEVANCE TO PD? (YES)

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There is evidence to indicate that the physiological release of dopamine in the striatum is relatively constant, with short duration peaks in response to reward type stimuli. The loss of dopaminergic neurons and dopamine receptor stimulation results in the typical features of Parkinson's disease (PD). Once the clinical features PD of are expressed, they are present in perpetuity unless temporarily reversed in part by dopaminergic therapy i.e. PD is a '24/7' disease.

The concept of continuous dopaminergic stimulation (CDS) has simple practical and more complex theoretical implications for the PD patient.

The motor symptoms of PD, particularly the bradykinesia and rigidity, are well treated by dopaminergic drugs in the great majority of sufferers. However, insufficient dopaminergic stimulation as a consequence of inadequate dopamine replacement or advancing disease will see the re-emergence of these motor symptoms. This is seen with levodopa where the clinical response is prolonged in the early phase of the disease but progressively shortens with advancing neurodegeneration in combination with the effects of short half-life stimulation of dopamine receptors. The latter effect was observed in the early PD patients given 600mg/day in the ELLDOPA study. Thus, longer acting drugs are required to maintain dopamine replacement and suppress motoric symptoms.

The failure to provide 24-hour dopaminergic replacement by CDS can lead to problems at night as well as during the day. Sleep disruption is a common feature of PD and has multiple causes and consequences. One particularly important symptom is that of nocturnal akinesia. This can be associated with pain, poor sleep, difficulties with sphincter control and day time somnolence due to fragmented sleep. Effective nocturnal replacement of dopamine therefore improves these aspects and the early morning dystonia and off-periods.

The more theoretical aspect of CDS relates to the notion that more continuous, as opposed to episodic, dopamine receptor stimulation will reduce the risk for motor complications – particularly dyskinesias, and may also be used to treat established dyskinesias. There is abundant evidence that short duration and intermittent stimulation of the dopamine receptors can induce dyskinesias. It is acknowledged that this is not the only cause of dyskinesias, for instance progressive denervation and patient age are also important factors. The MPTP primate model demonstrated that pre- and post-synaptic changes could be induced by levodopa therapy and these could be reversed by continuous infusion of the same drug. Furthermore, long-acting dopamine agonists were at much lower risk of inducing dyskinesias in this model than short-acting dopamine agonists. These observations indicated that it was not the drug that was so critical but rather the method of delivery.
From the MPTP model came the hypothesis that dopamine agonists with a long half-life e.g. ropinirole, pramipexole would have a lower rate of dyskinesias induction than levodopa. Several dopamine agonist trials have confirmed this effect. It is important to acknowledge that this property may be a consequence not only of the duration of effect of the drug, but other benefits specific to agonists, or alternatively other adverse properties of levodopa.

Established dyskinesias can be reduced or eradicated by continuous infusion therapies. Thus levodopa induced motor complications can be effectively managed by a levodopa jejunal infusion, again emphasising that it is not the drug but its method of delivery which is so important. Similar beneficial effects are seen with lisuride or apomorphine infusions. What is of particular interest is that the plasma concentrations of levodopa infusions are substantially greater than the peak levels reached with intermittent oral dosing, and the there are no deep troughs with infusions, in contrast to the oral delivery. This has lead to the concept that it is the troughs rather than the peaks of levodopa plasma levels that are important in contributing to dyskinesias.

The practical and hypothetical benefits of CDS have driven an important aspect of drug development: the 24-hour delivery of dopamine stimulation. This has evolved from infusion therapies through transcutaneous patches and once-a-day dopamine agonists to long acting inhibition of dopamine breakdown with MAOB inhibitors and the improved delivery of levodopa with COMT inhibition either as combined therapy or as bimodal timed treatment. These strategies have improved motor control in PD patients and reduced the risk for motor complications.

References

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