Continuous dopaminergic stimulation reduces the risk of motor complications in animal models of Parkinson's disease

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Introduction

Since its introduction into clinical medicine more than 30 years ago, levodopa has remained the standard of care for patients with Parkinson's disease (PD). Nevertheless, despite the substantial benefits associated with its initial administration, a satisfactory level of motor function can generally not be maintained. Most parkinsonian patients eventually develop intractable adverse effects, especially motor response complications (MRC), that increasingly compromise their response to dopaminomimetic therapy. The intact nigrostriatal system largely operates tonically but in late stage disease, postsynaptic dopaminergic receptors become increasingly exposed to intermittent and thus nonphysiologic stimulation as a consequence of standard dopaminomimetic therapy. As a result, reactive changes take place in striatal dopaminoceptive neurons that contribute to the pathogenesis of the motor complication syndrome. Mounting preclinical and clinical evidence suggests that the relatively continuous administration of dopaminomimetic therapy can not only palliate these motor complications but also delay or even prevent their appearance. To determine whether delivery of dopaminomimetics in a more continuous and thus more physiological manner can prevent MRC, we examined the effects of intermittent versus more continuous drug delivery in MPTP parkinsonian primates and 6-OHDA hemiparkinsonian rats.

Continuous vs intermittent treatments

The effect of intermittent versus continuous levodopa administration on the motor response duration in **rats** were examined by measuring the duration of rotation and the dose-response slope produced by levodopa injection on days 1 and 21 following initiation of the levodopa treatment. For duration measurement, rats were placed in a rotometer and given an acute levodopa injection (20 mg/kg with 5 mg/kg benserazide, i.p.). For dose-response slope evaluation, the total number of rotation was measured for each animal following acute levodopa injections at 12.5, 25.0, 50.0, and 100 mg/kg levodopa doses on four consecutive days (i.e. levodopa days 1-4 [Levodopa Day 1] and levodopa days 21-24 [Levodopa Day 21]). Continuous treatments were given by administering 8 mg/kg of levodopa six times a day for a total of 48 mg/kg per day. Intermittent treatments consisted of twice-daily injections of 24 mg/kg levodopa.
A subcutaneously implantable polymeric matrix (ethylene-vinyl acetate, **EVA**) has been developed for the sustained systemic delivery of drugs.

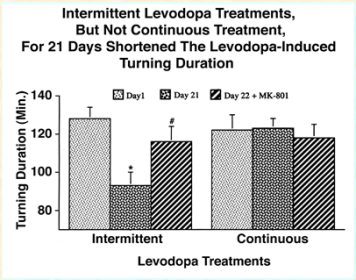
80-100 mg apomorphine / rod
2.6cm L x 2.4mm D

We implanted four MPTP-lesioned, L-DOPA-naive cynomolgus **primates** with three subcutaneous polymeric (ethylene-vinyl acetate, EVA) rods (each containing 80-100 mg apomorphine) to provide sustained systemic delivery of the drug. Three additional MPTP-lesioned primates received once daily injections of 0.2 mg/kg apomorphine.

Results in the rat model

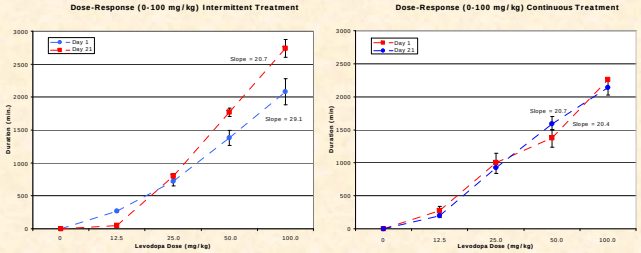
Ameliorative Effect of Continuous Levodopa Administration on Motor Response Duration

Levodopa, given intermittently (i.e., twice daily for 21 days), attenuated the duration of the motor response to levodopa injection, but, when given more continuously, did not produce response shortening. On day 23 of levodopa treatment, the administration of MK-801 (0.1 mg/kg, i.p) to intermittent levodopa group, but not to continuous group, completely normalized the response shortening induced by the chronic levodopa therapy ($p<0.01$).



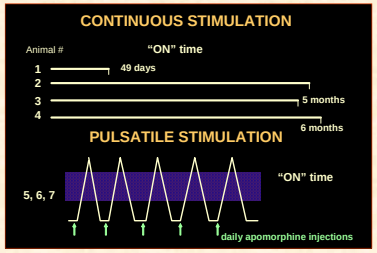
Effect of Continuous and Intermittent levodopa on Dose-Response Slope of Levodopa-Induced Rotation

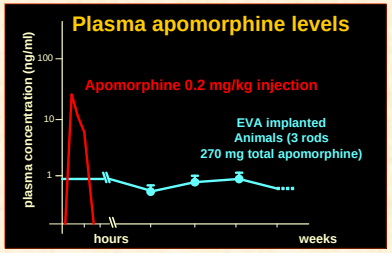
Rats with unilateral 6-OHDA lesion of the nigrostriatal pathway were treated for 21 days with levodopa (~48 mg/kg per day, i.p.) by either continuous or twice-daily injection. Following twice-daily levodopa treatments for 21 days, rotational response to an increasing doses of levodopa (12.5-100 mg/kg) over 4 days showed a markedly elevated dose-response slope in the intermittent levodopa group. However, the rotational dose-response slope in the continuous levodopa group was not altered by more continuous levodopa treatment for 21days.

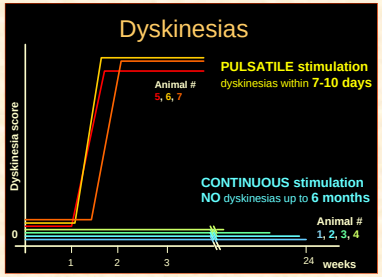


Results in the monkey model

After 8.3 days (range 7-10) of daily apomorphine injection, all animals in the pulsatile injection group developed dyskinesias whereas none of the continuous delivery-EVA implanted animals developed dyskinesias (up to six months). All animals in the pulsatile stimulation group were ON for approximately 90 minutes after each apomorphine injection; all EVA-implanted animals were continuously ON within 1 day after implantation and maintained for up to 6 months. The ON state induced by continuous apomorphine delivery was clinically similar to that induced by injection of apomorphine.







For the first time we were able to show that continuous stimulation of striatal dopaminergic receptors by the use of EVA implants prevents the onset of motor complications such as dyskinesias for the treatment period. The use of these EVA implants appeared to be safe and well tolerated in these animals. Based on these highly favorable results, a study of these implants in parkinsonian patients is warranted. If the clinical results prove as positive as those observed in the animal model, parkinsonian patients may be substantially benefited.