

CAN LEVODOPA DELIVERY BE IMPROVED? (NO)

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Still 40 years after its introduction in the early 1970-ies, L-dopa remains the most effective symptomatic therapy against the Parkinson (PD) symptomatology. L-dopa does, however, have a major weakness, being its pharmacokinetic properties, mainly its very short half-life (1,5h). Together with the fact that L-dopa is resorbed first in the proximal part of the small intestine and thereby becomes dependent of an irregular gastric emptying, this results in often strongly fluctuating plasma concentrations under peroral therapy. This in turn results in strong fluctuations of dopamine concentration also in the brain and at the synaptic cleft. This stands in contrast to the normal physiological situation, where the dopaminergic stimulation is more continuous. The non-continuous dopaminergic tonus is thought to be a major reason behind the development of motor fluctuations and dyskinesias.

This problem has, however, now been solved. Through the continuous delivery of an L-dopa/carbidopa gel directly down in the proximal jejunum with the the help of a portable pump system and tubing running through a PEG, the plasma L-dopa concentrations can be kept very stable. Several studies on L-dopa plasma levels have demonstrated that LCIG treatment results in a highly significant stabilization of plasma concentrations compared to peroral therapy. PET data have verified that this also results in more constant dopaminergic stimulation on the receptor level. This in turn leads to significant improvement in patients with motor complications, both concerning "off"-fluctuations and dyskinesias. Further more several non-motor symptoms improve.

It is difficult to believe that any other delivery method will be able to produce a significantly more stable dopaminergic stimulation compared to LCIG. It is my belief that LCIG will remain the golden standard for many years to come. There might of course be technical improvements of this therapy, with smaller and more sophisticated pumps, better infusion equipment etc, but the basic principles for this therapy will remain.

It is sometimes argued that the physiological stimulation is not totally constant, but varies depending on time of day and type of activity among other things. The variations according to time of day can be simulated by a clock in the pump and a time-dependent pump speed. The short-term changes in dopaminergic tonus will probably be impossible to simulate with any type of L-dopa delivery.

Several research groups and pharmaceutical companies work with other moods of L-dopa delivery, for example transdermal, subcutaneous and more long-acting peroral preparations. It seems likely that the more long-acting peroral preparations will come on the market. This treatment does produce a more continuous dopaminergic stimulation. Compared to LCIG the plasma concentrations are, however, clearly less stable. Apart from this, there is at this time no major break-through to be expected concerning alternative moods of L-dopa delivery.

Transplantation of dopaminergic cells and inducing more dopamine production with gene therapy represent more sophisticated ways of raising the dopaminergic tonus in the brain. The main mechanism of effect is probably again that the dopaminergic stimulation becomes more continuous. If these methods can result in even more physiological dopamine release remains unclear. A difference to LCIG is that the effect of these methods is more localized in the brain compared to LCIG. If this is an advantage or even a disadvantage remains to be investigated.

As shown above there are several interesting developments ongoing concerning alternative methods for L-dopa/dopamine replacement. In my opinion there are, however, good reasons to believe that LCIG will remain the most effective way of substituting L-dopa, at least for the next 5-10 years to come.