Investigation on the solubility of a Levodopa/Carbidopa tablet (isicom®) – Overcome early morning Akinesia more rapidly

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Abstract
Objective: The investigated levodopa/carbidopa formulation is beside tablet formulation also licensed for the administration as a suspension. The solubility behaviour and the onset of effect on early morning akinesia were investigated.

Results: The different formulations showed no significant differences in relation to efficacy, duration of action and side effects. Both tablets in dissolved form had a rapid and good solubility behaviour and showed a markedly more rapid onset of action.

Conclusion: To simplify levodopa therapy, it is therefore in principle possible to treat patients stabilized on therapy with levodopa in dissolved form as a kick start dose while retaining their basic stabilizing therapy.

Key words
levodopa - carbidopa – solubility – akinesia – onset – effect

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Introduction
Since it was first introduced in 1967, levodopa has remained the most effective drug in the therapy of idiopathic Parkinson’s syndrome (IPS) [1]. In approx. 80 – 90% of all IPS patients, clinical signs and symptoms improve by more than 50% [2]. Early use of levodopa also results in an increase in life expectancy. While mortality in untreated patients is increased by a factor of 3, early administration of levodopa reduces mortality 1.3-fold [3]. At therapeutic concentrations, levodopa is free of direct toxicity [4]. Some studies even demonstrated trophic effects on dopaminergic neurones.

Besides the standard levodopa drugs (regular release levodopa) also other pharmaceutical formulations with delayed (sustained release) or accelerated (fast release) levodopa release are available. As early as 1980, there have been reports of continuous administration of levodopa in liquid form in cases of severe “on-off” phenomenon. In 1996, the first soluble fast release product to contain the decarboxylase inhibitor benserazide was licensed in Germany. It has been acknowledged for some time that the investigated levodopa/carbidopa tablet also dissolves very well and rapidly in water. There have been indications of this in the literature since 2002 [5].

There are some possible problems in levodopa long-term therapy. Various efforts to supply changed pharmaceutical formulations are based on the fact that, despite efficient therapy, the advance of the disease pro-
cess cannot be stopped. In addition, what is known as the Long-Term Dopa Syndrome (LTDS) develops after about 5 to 10 years. This term is used to describe the increasing fluctuations in drug action accompanied by dyskinesia and dystonia. In the psychopathological field, levodopa induced psychosis is a potential complication of drug therapy.

As well as the benefits of the sustained release drugs, in clinical practice it is especially the dispersion of levodopa tablets that acquires particular significance. Rapid control of distressing “off” phases is of real importance for the quality of life of Parkinson’s patients. In this context, interest is focused in particular on the most rapid possible control of early morning akinesia.

**Rapid onset of action**

The absorption of levodopa from fast release drugs into the blood is more rapid due to shorter gastric retention time. Therefore also a more rapid onset of action from fast release drugs is observed. The measurably shorter onset of action (on latency) recommends rapidly soluble levodopa for patients with delayed response as the first levodopa administration of the day. Prolonged wearing off can also be effectively shortened by administration of soluble levodopa. In patients with protein akinesia, administration of levodopa before the main meals also appears to be beneficial. For the patients, this option means increased reliability in therapy and a resulting increase in certainty when dealing with the disease as well as more independence in daily planning.

**Dysphagia**

In dysphagia soluble levodopa tablets can simplify therapy. The absorption of active substance is improved, and the bioavailability is better. Compared to levodopa capsules or solid tablets, the presentation of levodopa in dispersible form offers advantages in the therapy of Parkinson’s patients with dysphagia. Occasionally, tablet residues are still present in the oral cavity of this kind of patient for some time after taking the medication, from which it can be inferred that absorption of the active substance is inadequate. The dry mouth that frequently prevails in Parkinson’s patients increases the difficulty with the act of swallowing. Pre-psychotic or psychotic patients tend to refuse to take medication or consciously leave tablets in the oral cavity. In this case, an oral solution offers an ideal and safe route of administration. If patients are already fed via a feeding tube, dissolving the tablets before administration via the tube can also improve availability. It is then no longer necessary to grind up the tablets.

**Levodopa test**

The levodopa test is a valuable diagnostic aid. Use of soluble and thus rapid acting levodopa has proved itself in diagnostic applications as well. In the course of the levodopa test, after appropriate preparation with domperidone, up to 200 mg levodopa in liquid form can be administered as a single dose to test in the subsequent observation phase how extrapyramidal signs and symptoms respond to specific medication with levodopa. The apomorphine test, routinely used to date, can be restricted to a minimum as a result of this option.

**Peri-operative management**

Also in peri-operative management solved levodopa plays a role. The literature contains an increasing number of reports on the practical application of levodopa dissolved in water, which is administered intra-operatively via a nasogastric tube [6]. Table 1 gives an overview on the indications for solved levodopa.

**Patients and methods**

In an observational study, we considered the question whether levodopa/carbidopa in dissolved form (4:1 ratio, isicom®) shows a rapid onset of action similar to that of levodopa/benserazid (4:1 ratio, Madopar® LT). We studied 20 patients admitted for treatment diagnosed with Parkinson’s disease at Hoehn and Yahr stage II–III in the “on” phase, who clearly responded to levodopa therapy and who regularly experienced motor fluctuations of the wearing off type in the early morning despite optimum

### Table 1: Indications for administration of soluble levodopa

- Dysphagia
- Early morning akinesia
- Postprandial akinesia
- Loss of drug action associated with the “off” phase
- “Off” dystonia
- Delayed “on”
- Problems with absorption of levodopa
- Tube feeding
- Levodopa test
- Intra-operative enteral levodopa administration
therapy (Table 2 shows the demographic data). The levodopa dose and residual concomitant medication were kept stable during the observational study. The pre-existing combined therapy was administered on the morning of the study to create study conditions similar to those of clinical practice. The study was performed with an open design and without a placebo-control group. The following parameters were measured: 1. "On" latency; 2. "On" duration; 3. Effects on motor function; 4. Dyskinesia severity. Clinical evaluation of efficacy on motor function was performed using the UPDRS III motor score. Dyskinesia severity was assessed with sub-score IV, 33. The study parameters were documented over a study period of three hours after taking medication.

Results

The "on" latency period on the levodopa/carbidopa tablet (isicom®) in dissolved form was significantly shorter at 27.3 ± 9.8 minutes (p<0.0001) compared to nondissolved tablet (37.5±12.0 min.). There was no significant difference from dissolved levodopa/benserazid tablet (26.5 ± 10.1 minutes). Mean duration of the "on" period, improvement in motor score and dyskinesia severity did not differ significantly between the different forms of administration.

In a way that is consistent with the literature [7-9], our study also showed a statistically significant and clinically relevant shortening of "on" latency when the dissolved presentations of levodopa/carbidopa tablet were used, without an increase in dyskinesia and at the same time with good efficacy on motor function.

Conclusion

The data collected permit us to conclude that administration of levodopa drugs in dissolved form represents a valuable therapeutic alternative in the therapy of early morning akinesia because of their markedly more rapid onset of action. The levodopa/carbidopa drug shows good solubility behaviour and is comparable in its action to a soluble levodopa/benserazid tablet in the indication of early morning akinesia. Patients treated with levodopa/carbidopa as basic stabilizing therapy can, for this reason, be treated with dissolved levodopa/carbidopa tablets as kick start dose. The benefits are two-fold: the therapeutic regimen is simplified and the possible interactions between the various DDCI (DOPA decarboxylase inhibitor) drugs are reduced, which is particularly important, bearing in mind that today additional COMT (catechol-O-methyl transferase) inhibitor therapy may be given.

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Literature

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