

Benserazide-induced Diarrhoea – an unknown phenomenon?

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Abstract

In today's drug therapy of Parkinson's Disease, levodopa is still considered the gold standard of therapy, and nearly every affected patient is treated with this dopamine pro-drug during the course of the disease. A discontinuation of the treatment on account of intolerable side effects would have serious consequences for the affected patient. For this reason, every physician who treats patients with L-DOPA should know that the occurrence of diarrhoea as a side effect of the treatment with L-DOPA/DDCI (DOPA-decarboxylase inhibitor) can be controlled easily and quickly by changing the decarboxylase inhibitor.

Introduction

In today's drug therapy of Parkinson's Disease, the pro-drug L-DOPA (L-3,4-Dihydroxyphenylalanine) is still considered the gold standard of therapy, and nearly every affected Parkinson's patient is treated with this blood-brain barrier pro-drug of dopamine. In order to prevent a premature break-

down of L-DOPA to dopamine before the drug reaches the sub-arachnoid spaces and to reduce peripheral side effects, it is administered together with an inhibitor of the aromatic L-amino acid decarboxylase which is effective in the peripheral tissue - carbidopa or benserazide - at a ratio of 4:1 or 10:1. The intelligent use of the interaction between L-DOPA and DDCI results in a significantly higher central bioavailability of L-DOPA and thus also of dopamine, which in turn leads to a significantly improved tolerability of L-DOPA preparations [1]. Despite administering L-DOPA with the inhibitors of the peripheral decarboxylase indicated above, there are always patients who do not tolerate the administration of L-DOPA, in particular at the beginning of the treatment, and who react with nausea, vomiting or orthostatic hypotension. The additional administration of domperidone is recommended in these cases. On the other hand, the occurrence of diarrhoea, which would be amplified by domperidone, is more complicated.

In everyday clinical practice, there is a significantly higher incidence of diarrhoea under L-DOPA/benserazide compared to L-DOPA/carbidopa. Managing this undesired side effect is very simple. By switching from a benserazide-containing preparation to a carbidopa-containing L-DOPA (e.g. isicom®) formulation at a ratio of 1:1, the diarrhoea disappears completely within just a few days. Against the backdrop of this information we suspect that this side effect is particular to benserazide. However, this phenomenon of „benserazide-induced diarrhoea“ seems to be largely unknown.

As an example, we present the case of a patient who developed benserazide-induced diarrhoea and was admitted to our hospital with the admission diagnosis "L-Dopa intolerance".

Key words

Parkinson, DOPA-decarboxylase inhibitor, Benserazide, diarrhea, carbidopa

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Case report

Medical history

In mid-June of 2010 the 80-year-old patient first noticed a tremor of the right arm under tension, as well as a deceleration of all movements. She found it more difficult to carry out tasks requiring fine motor skills, and her gait became increasingly slow. These symptoms were attributed to Parkinson's Syndrome by a neurologist. The treatment with L-DOPA/benserazide which was initiated was well tolerated by the patient at first, and led to a noticeable improvement of the reported symptoms.

6 weeks later, when the daily dose of L-DOPA/benserazide was at 300/75 mg, the patient visited her neurologist again on account of persistent diarrhoea. A previous examination of the stool for pathogenic micro-organisms had produced negative results; a colonoscopy produced macroscopically normal findings. The symptomatics disappeared once the L-DOPA/benserazide preparation was discontinued. Under the suspicion of being a side effect of the dopaminergic medication, the decision was made against a subsequent L-DOPA substitution therapy, after which a distinct worsening of locomotive function and of the tremor developed.

The patient's medical history of complicating additional diseases and conditions included arterial hypertension, hyperuricaemia, coronary heart disease as well as hyperthyroidism following a strumectomy. Medication included anti-hypertension drugs (candesartan / hydrochlorothiazide, atenolol, amlodipine, xipamide), thyroid gland hormones (L-thyroxin), coagulation inhibitors (acetylsalicylic acid), uricostatic drugs (allopurinol), muscle relaxants (tolperisone) and antidepressants (mirtazapine).

At the time of admission there was no Parkinson-specific drug therapy of the patient. „L-DOPA intolerance“ had been noted on the admission documents.

Findings of physical examination

During the clinical examination the patient was in a good nutritional and overall condition (160 cm, 72 kg), blood pressure 120/60 mm Hg, heart rate 68 bpm. The auscultation of the heart and lungs was unremarkable. There was an untreated, right-sided, hypokinetic-rigid stage III Parkinson's Syndrome according to the Hoehn and Yahr scale.

Clinical chemical examinations

There was no evidence of a malabsorption in the clinical chemistry. There was a slight increase in creatinine with 1.56 mg/dL (0.6-0.8), urea with 74 mg/dL (10-50) as well as cholesterol with 230 mg/dL (under 200).

Treatment and course

Under the suspicion of a benserazide-induced diarrhoea, treatment with an L-DOPA preparation was again initiated, however this time in combination with carbidopa (isicom[®], Desitin Arzneimittel GmbH, Hamburg, Germany). The dosage was increased gradually until a daily dose of 300/75 mg L-DOPA/carbidopa was reached. Due to persistent early-morning akinesia, we combined the standard formulation with a delayed-release L-DOPA/carbidopa preparation taken at night (100/25 mg). Once again, there was a significant improvement in locomotion as well as a satisfactory decrease of the tremor.

Discussion

There is mention of levodopa-benserazide in a review article about drug-induced diarrhoea written by Abraham and Sellin

[2]; levodopa-carbidopa, on the other hand, is not mentioned. However, the exact cause of this side effect, in relation to this combination of active substances, is not commented on. The article also lacks a statement as to whether this is a side effect specific to benserazide, or whether the combination levodopa-carbidopa can be considered a possible cause.

Despite extensive diagnostics we were unable to associate the diarrhoea with a specific aetiology for any of our patients. We assume this side effect is a benserazide-induced, unspecific side effect of the drug which subsides rapidly and completely as soon as the benserazide-containing levodopa preparation is discontinued.

What are the differences between benserazide and carbidopa? The maximum plasma concentration of levodopa is reached faster under benserazide (t_{max}) and is also higher (C_{max}), but also drops faster when compared to carbidopa [3]. Both substances are found outside of the cerebral hemispheres, in particular in the intestinal bacterial flora, the intestinal mucous membrane and in the liver. Both substances stimulate the release of prolactin in the anterior lobe of the pituitary gland, resulting in hyperprolactinaemia, and lead to an extracerebral inhibition of the aromatic L-amino acid decarboxylase, which requires pyridoxine as a coenzyme. However, when compared to benserazide, inhibition appears to be incomplete [4] and weaker under carbidopa than under benserazide [5]. In addition, by inhibiting the biogenic synthesis of serotonin, benserazide influences the metabolism of this neurotransmitter [6]. An increase in the TSH value is described under benserazide, but not under carbidopa [7]. Furthermore, given the irregularity of the incidence, genetic metabolic conditions appear to play a

role in triggering this undesired side effect of the drug.

Conclusion

The treatment with an L-DOPA/benserazide preparation can trigger unspecific diarrhoea as a side effect. However, this should not lead to the assumption of an L-DOPA intolerance of the patient or to a subsequent discontinuation of a treatment with L-DOPA, but should be followed by a change of DDCI. In the case of sensitive patients or to prevent this side effect from occurring in the first place it may be useful to initiate treatment with an L-DOPA/carbidopa preparation instead. Discontinuing the treatment is always associated with a worsening of the Parkinson's symptoms and thus also of the patient's quality of life.

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