



Benserazide-induced diarrhea – A retrospective clinical study

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ABSTRACT

Background: Although diarrhea has been reported as a side effect of L-3,4-dihydroxyphenylalanine (L-DOPA)/benserazide, it is largely unknown and unrecognized, presumably because it is very rare. There is almost no literature on benserazide-induced diarrhea (BID), no pharmacological explanation and, crucially, no treatment recommendation. This can lead to physicians misdiagnosing BID, for example as colitis, and initiating misguided and ultimately ineffective drug treatments. Or it can lead to erroneous assumptions about a general intolerance and subsequent discontinuation of L-DOPA medication – for lack of a better solution – at the high price of living with the recurring symptoms of Parkinson's disease. Thus, our study aims to fill these gaps, beginning with a treatment recommendation: A simple switch to L-DOPA/ carbidopa has proven to be an effective solution in virtually all cases of BID, usually leading to full remission within days. Finding a possible pharmacological explanation was the next objective of this study.

Methods: We retrospectively analyzed 50 case files of patients with BID, searching for patterns that could potentially explain this intolerance.

Results: The most frequent concomitant disease was hypertension, likely due to high average age. Beta-blockers and acetylsalicylic acid were the most frequent concomitant medications. Otherwise, no conspicuous pattern emerged in this seemingly rather heterogeneous sample.

Conclusions: Plasma protein binding (PPB) was suspected as a key difference between benserazide and carbidopa that might potentially explain why some patients can tolerate carbidopa but not benserazide. However, reports on PPB of carbidopa and benserazide vary wildly from one source to another, making definitive conclusions impossible.

1. Introduction

The prodrug L-3,4-dihydroxyphenylalanine (L-DOPA), a precursor of dopamine, is still regarded as the gold standard among current drug therapies for Parkinson's disease (PD), because dopamine cannot pass the blood–brain barrier. However, owing to decarboxylation and methylation, almost 99% of L-DOPA is metabolized in the peripheral tissue before it reaches the brain. This is prevented by combining L-DOPA with an inhibitor of the aromatic-L-amino-acid decarboxylase, such as carbidopa or benserazide, resulting in significantly higher cerebral bioavailability of L-DOPA, and therefore of dopamine. That way, the required doses of L-DOPA can be lowered drastically – thereby minimizing undesired side effects and significantly improving overall tolerance – while maintaining the same therapeutic effects [1].

Despite the administration of L-DOPA with the stated inhibitors, some patients are unable to tolerate L-DOPA, especially at the start of treatment, and may develop nausea, vomiting, or orthostatic

hypotension. These undesirable side effects are normally temporary and can be managed therapeutically, but lasting diarrhea is more complicated [2]. Decades of clinical experience have shown that this is a rare but reliable side effect specifically of L-DOPA/benserazide. We tentatively estimate that, out of the 2500 Parkinson patients we treat annually in our hospital, roughly 25–50 (1–2%) are suffering from benserazide-induced diarrhea (BID). We are confident in establishing this causal link between benserazide and diarrhea because a simple switch to L-DOPA/carbidopa has proven to be an effective solution in virtually all cases of BID, which is further evidenced by the time-frame: Diarrhea usually starts within hours or days after administration of benserazide, and likewise subsides completely within days or weeks after a switch to carbidopa. Patients establish this connection themselves in their complaints and may stop taking their L-DOPA medication altogether when diarrhea is so severe and exhausting in its daily impact that even the recurring symptoms of PD appear preferable in early stages of the disease. Needless to say, this is no solution at all,

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especially long-term. However, BID appears to be largely unknown, which is apparent in the medical histories of our patients with BID, who often receive extensive and invasive gastroenterological examinations with negative results, followed by ineffective drug treatments, suggesting a lack of knowledge among physicians about BID and the possibility of switching to carbidopa as a solution. This is paralleled in the literature; we could not find any reliable source describing BID specifically, which is why we cannot cite any prevalence rates, even though diarrhea is stated as a side effect in patient information leaflets of both carbidopa and benserazide products. We found only a single case file among all the patients we've treated in recent years where it was actually the other way around, that is, diarrhea started after administration of carbidopa and subsided after a switch to benserazide, suggesting a much higher prevalence of BID. But again, in the absence of studies examining diarrhea as a side effect of L-DOPA/carbidopa and benserazide respectively, we can only speculate in regards to the prevalence of BID compared to carbidopa-induced diarrhea at this point. Hence, the objective of this study was primarily to raise awareness of BID and stimulate further research. To that end, we collected and retrospectively analyzed the files of 50 cases of BID, whose clinical characteristics are presented below, searching for any discernible pattern in their commonalities that could shed some light on the biochemical underpinnings of this intolerance.

2. Methods

We gathered case files of 50 patients who received inpatient treatment at the Gertrudis-Clinic Biskirchen from 2010 to 2015. Cases were included when the effects in question were very distinctly observable: the development of diarrhea shortly after administration of benserazide, as well as complete remission after a switch to carbidopa. Naturally, this means that correlation of benserazide administration and diarrhea was 100% in this sample, as was the remission rate after administration of carbidopa. Exclusion criteria were any variables that could otherwise explain or contribute to the development of diarrhea, particularly certain drugs (e.g., laxatives) and diagnoses (e.g., irritable bowel syndrome), notable changes in diet during the stay in our hospital etc., even food intolerances (e.g., gluten or lactose). This was to make sure that the onset of diarrhea could be pinpointed as a consequence of benserazide administration. Otherwise, no distinction was made between medical history, a diagnosis leading to hospitalization, or an undesirable side effect that developed during inpatient treatment.

All patients were being treated with L-DOPA/carbidopa at the time of data collection. The average dose was 550 mg (100–1250 mg) and was well tolerated.

Since this was a retrospective analysis of case files, we are unable to specify diarrhea in any way, because it is not common for our patients to give detailed accounts of the consistency or frequency of their stool passages. It is also not common for our physicians to inquire further details if source and solution of a problem are known, as was the case with these 50 patients with BID – they were very clear-cut – hence their inclusion our analysis. Thus, no standardized measures or definitions could be applied, because the descriptions of diarrhea in these reports were vague at best.

Clinical data from the selected files were gathered for analysis. The period from the initial diagnosis to the year of inpatient treatment was defined as the disease duration for the purpose of the evaluation. We recorded age, sex and prognostic subtypes of Parkinson's disease (tremor-dominant, akinetic-rigid type or equivalence type). Specifying the latter is common practice in Germany and stated in the official guidelines [3]. However, this might not be the case in other countries or the terminology may vary. For example, Rajput et al. [4] refer to them as tremor-dominant, akinetic-rigid and mixed subtypes, which is why a short definition seems warranted. The Tremor-dominant sub-

type is marked by early, typically unilateral onset, slow progression and retained cognitive skills; minimal akinesia and rigor; possibly coexisting essential tremor. The akinetic-rigid subtype is marked by bradykinesia, accelerated progression, dementia and worse long-term prognosis; tremor is minimal or nonexistent. The defining feature of the equivalence/mixed-subtype is that bradykinesia, rigor and tremor are mostly equally pronounced [5]. Furthermore, we recorded the degree of severity of the disease at the time of inpatient treatment as evaluated using the Hoehn & Yahr rating scale and the extent of motor impairment based on the total Unified Parkinson's Disease Rating Scale (UPDRS), both taken in the "on" state, as is routine in our hospital. Finally, comorbidities and medications were recorded in the active substance groups.

3. Results

Diarrhea developed in all patients after L-DOPA/benserazide was administered and subsided after a switch to carbidopa. A major limitation of this retrospective analysis is the inability to accurately describe the diarrhea induced by benserazide, let alone document its progression reliably, which makes it impossible to address important questions or, for example, correlate the severity of diarrhea with doses of benserazide. Future prospective studies are sorely needed for a detailed examination of the consistency of stool passages and the progression of diarrhea.

In general, diarrhea is defined as three or more stool passages per 24 h, or water content of 75% or more, or weight of 250 g or more per stool passage [6]. Diarrhea is defined as acute if it lasts up to two weeks or chronic if it lasts longer than that. Severity levels are defined as follows: mild (no physical impairments), moderate (impairment of everyday activities) and severe (significant physical impairments). We can't comment on the frequency or consistency of stool passages due to the study design. What we can say though, is that almost all patients (46 of 50) reported that they stopped taking their L-DOPA altogether within a maximum of four weeks after the development of diarrhea. It is therefore safe to assume that diarrhea induced by benserazide is at least moderate and likely severe, if it outweighs even the symptoms of PD. They also reported that diarrhea started within hours or days after administration of benserazide, without concomitant symptoms like nausea. It is therefore safe to assume that BID is acute, with an average incubation time of roughly 4 days after administration of benserazide. We can confirm these reports from our experience; if treatment with benserazide or a switch to carbidopa is initiated during the stay in our hospital, the effects in question (development/remission of diarrhea) are usually observable within the hospitalization period (i.e., 2–4 weeks). Of course, diarrhea can also become chronic if treatment with benserazide is continued regardless. Only four patients continued the treatment, and their general condition and locomotion consecutively deteriorated because of the significantly reduced absorption of L-DOPA.

Patient characteristics, prognostic subtypes and degree of severity of Parkinson's disease are shown in Table 1. Overall, this is a rather typical sample, in that it is representative of the patient population in our hospital in general. In other words, it is quite inconspicuous in terms of a specific pattern that could potentially explain BID.

Parkinson's-associated comorbidities are shown in Table 2, other more general comorbidities are shown in Table 3. Those were recorded only if treated with drug therapy, in order to identify possible drug interactions with benserazide that may promote BID, for example through an additive pharmacokinetic effect. The frequency of diagnoses, therefore, tends to reflect the acceptance of drug treatment both by the patients as well as the treating physicians. This is the only explanation for the low number of polyneuropathies, which, in our experience, are likely to develop frequently rather than rarely in patients with Parkinson's disease. The most striking feature is the high percent-

Table 1
Patient data.

Characteristics	N	Minimum	Maximum	Mean (M)	Standard Deviation (SD)
Age (years)	50	47	88	74.08	6.627
Weight (kg)	50	49	117	77.28	16.850
Height (cm)	50	151	192	168.14	10.323
Age at start of treatment	50	42	83	67.12	8.393
Disease duration (years)	50	1	20	6.96	4.576
Prognostic subtypes		Prevalence (n)		Percent (%)	
Akinetic-rigid type		26		52,0	
Equivalence/mixed type		23		46,0	
Tremor-dominant type		1		2,0	
Total		50		100,0	
HY ¹ -Stages and Severity		Prevalence (n)		Percent (%) UPDRS ²	
HY I		0		0,0	
HY II		3		6,0	
HY III		20		40,0	
HY IV		22		44,0	
HY V		5		10,0	
Total		50		100,0	

¹ Hoehn and Yahr (HY).

² Unified Parkinson's Disease Rating Scale (UPDRS).

Table 2
Parkinson's-associated comorbidities.

Comorbidity	Frequency (n)	Percentage (%)
Depression	21	42.0
Organic hallucinosis	12	24.0
Parkinson's dementia	8	16.0
Urinary incontinence	8	16.0
Obstipation	8	16.0
Orthostatic hypotension	6	12.0
REM ¹ -sleep behavior disorder	4	8.0
Insomnia	4	8.0
Mild cognitive impairment	2	4.0

¹ Rapid eye movement.

Table 3
Other comorbidities.

Comorbidity	Frequency (n)	Percentage (%)
Arterial hypertension	41	82.1
Vascular encephalopathy	13	26.0
Chronic pain syndrome	12	24.0
Hypothyroidism	12	24.0
Hyperlipidemia	11	22.0
Diabetes mellitus	11	22.0
Reflux esophagitis	7	14.0
Peripheral edema	7	14.0
Hyperuricemia	6	12.0
Coronary heart disease	6	12.0
Folic acid deficiency	6	12.0
Osteoporosis	5	10.0
Gastritis	5	10.0
Polyneuropathy	4	8.0
Prostatic hyperplasia	4	8.0
Chronic obstructive bronchitis	2	4.0
Atrial fibrillation	2	4.0
Renal insufficiency	2	4.0
Colitis ¹	2	4.0
Epilepsy	1	2.0

¹ These were actually cases of BID, misdiagnosed as Colitis; see Results.

age of patients with hypertension. This is probably attributable to the mean age in the sample and corresponds to the prevalence in the general population: 85.7% of women and 88.4% of men aged higher than 70 years have hypertension [7]. An extensive gastroenterological diagnostic investigation, including colonoscopy, and the diagnosis of lymphocytic colitis and initiation of mesalazine therapy had been performed in two patients before coming to our hospital. However, diarrhea persisted nevertheless, which is why we suspected BID, discontinued benserazide and administered carbidopa. This led to a full remission of diarrhea during the stay in our hospital already, meaning that these were actually cases of BID misdiagnosed as colitis, hence their inclusion in this study. This again highlights the issue that BID is largely unknown and how this can lead to false diagnosis and inadequate treatment. The drug therapy for "colitis" was ineffective and superfluous, and could be discontinued before discharge.

Medications are shown in Table 4. The active substance groups were summarized when different products were used in a small number of cases. A conspicuous frequency could only be determined for beta-blockers and acetylsalicylic acid.

4. Discussion

All patients got well after being treated with L-DOPA/carbidopa. What are the differences between benserazide and carbidopa? The maximum plasma concentration of L-DOPA is reached more quickly with benserazide (tmax) and is also higher (Cmax), but falls off more quickly compared to carbidopa [8]. Both substances occur extracerebrally particularly in the bacterial flora of the intestine, the intestinal mucous membrane and the liver. Both substances stimulate the release of prolactin in the anterior lobe of the pituitary gland, resulting in hyperprolactinemia, and inhibit aromatic-L-amino-acid decarboxylase, which requires pyridoxine as a coenzyme. The inhibiting effect of carbidopa appears to be weaker in comparison to benserazide though [9,10]. In addition, benserazide influences the metabolism of this neurotransmitter through the inhibition of biogenic serotonin synthesis [11]. Furthermore, increased thyroid-stimulating hormone levels have been reported for benserazide, but not for carbidopa [12]. Genetic factors contributing to metabolic dispositions are also likely to play a role, since BID is a relatively rare side effect, but we could not find any sources for that.

Table 4
Medication (recorded only if taken by five or more patients).

Medication	Frequency (n)	Percentage (%)
Beta-blockers	20	40.0
Acetylsalicylic acid (100 mg)	19	38.0
Pramipexole	13	26.0
Amantadine sulphate	10	20.0
L-Thyroxine	10	20.0
Mirtazapine	10	20.0
Proton pump inhibitors	9	18.0
Benzodiazepines	8	16.0
SSRIs ¹	8	16.0
Statins	8	16.0
Torasemide	8	16.0
Clonazepam	8	16.0
ACE ² inhibitors	7	14.0
Metformin	7	14.0
Quetiapine	7	14.0
Rivastigmine	7	14.0
Sartanes	7	14.0
Allopurinol	6	12.0
Folic acid	6	12.0
Gabapentin	5	10.0
Piribedil	5	10.0

¹ Selective serotonin reuptake inhibitors.

² Angiotensin-converting enzyme.

Beta-blockers (40%) and acetylsalicylic acid (38%) were the most frequent concomitant medications in our study. Acetylsalicylic acid is a pharmaceutical with a high plasma protein binding (PPB) capacity (66%–98% salicylic acid). A high PPB capacity can influence pharmacokinetics in a variety of ways, for example, phenytoin levels can be increased [13]. As the two most frequently prescribed beta-blockers in this study have low PPB, interaction via PPB was not suspected here. The PPB of L-DOPA itself is negligible owing to its short half-life [14]. We could not find specific information regarding the PPB of benserazide. However, an interaction with warfarin (90%) via PPB was verified in a pharmacological investigation [15]. An interaction with another drug with high PPB is therefore hypothetically possible. Drugs with high PPB include acetylsalicylic acid and propranolol. The average age of patients in the cohort was higher than 70 years. A decrease in the production of plasma proteins can be assumed at this age. The percentage of unbound serum albumin is reduced by 10%, the percentage of unbound active substances with high PPB is increased, which may result in higher toxicity of drugs with high PPB [16].

This is assuming that PPB of benserazide is relatively higher than that of carbidopa, which is reported to be rather low with 36% by common (German) databanks [17,18]. However, we actually found conflicting information on PPB of both benserazide and carbidopa from various sources, for example, PubChem reports 0% for benserazide and 76% for carbidopa [19], which just emphasizes the need for more research into this area. Future studies could shed light on this discrepancy and evaluate these assumptions.

Beyond that though, we are quite limited in what we can say in regards to a possible biochemical basis for BID, because perhaps the most striking feature of this sample is its heterogeneity. This is undoubtedly in no small part due to the sample size as a major limitation, since this was, in truth, more of a modest side project of the authors rather than an actual study with sufficient resources and the capacity to allow for large-scale, in-depth examinations and standardized procedures.

5. Conclusion

The objective of this study was primarily to raise awareness of BID, which is still largely unknown. We could find only a single a review about drug-induced diarrhea where benserazide was mentioned [8]. However, the article does not go into detail in regards to the cause of this side effect, potential interactions of substances or even whether diarrhea is a side effect specific to benserazide. In this absence of information, patients suffering from BID find themselves in this predicament all too often where they have to choose between diarrhea as a perpetual burden, or discontinuing L-DOPA and living with the ever deteriorating symptoms of PD – both choices are unacceptable – and completely avoidable, because there is another solution. We want to raise awareness of the possibility of switching to carbidopa as a primary course of action in cases of inconclusive diarrhea, which is always worth a try since it should normally have no notable drawbacks

compared to benserazide. We hope that our study, despite its many limitations, is at least helpful in that regard and in stimulating further research.

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CRedit authorship contribution statement

Ilona Csoti: Conceptualization, Methodology, Data curation, Writing - original draft. **Natalia Koleva-Alazeh:** Data curation, Investigation, Writing - review & editing.

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