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Are high doses of carbidopa a concern? A randomized clinical trial in Parkinson's disease

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Abstract

Background—Recommended doses of carbidopa are 75–200 mg/day. Higher doses could inhibit brain aromatic amino acid decarboxylase and reduce clinical effects.

Methods—We compared 4-week outpatient treatments with carbidopa 75 mg and 450 mg/day administered with levodopa on the subjects' normal schedule. After each treatment phase subjects had two 2-hour levodopa infusions. The first infusion examined the effects of carbidopa doses administered the preceding four weeks and the second infusion determined the acute effects of the two dosages of carbidopa. The antiparkinsonian effects and levodopa and carbidopa plasma concentrations were monitored during the infusions.

Results—Twelve subjects completed the study. Carbidopa concentrations were eight times higher after the high carbidopa phase. Area under the curve (AUC) for clinical ratings did not differ for the four levodopa infusions although AUC for plasma levodopa was modestly increased with 450 mg of carbidopa. Nine subjects reported the high carbidopa outpatient phase was associated with greater response to levodopa.

Conclusion—Doses of 450 mg/day of carbidopa did not reduce the responses to levodopa infusion, extending the safe range of carbidopa to 450 mg/day.

Keywords

Carbidopa; levodopa; Parkinson's disease

Introduction

Levodopa is always administered with a peripheral inhibitor of aromatic amino acid decarboxylase (AAAD), carbidopa or benserazide. Inhibition of AAAD decreases peripheral

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decarboxylation of levodopa to dopamine, reducing the dose of levodopa required for a clinical response by approximately 75% and diminishing peripheral side effects.[1–3] The minimum daily dose of carbidopa is thought to be 75 mg per day.[4] FDA approved drug information indicates that the daily dose of carbidopa should not exceed 200 mg because there is inadequate experience with higher doses.

What are the effects of higher-than-recommended doses of carbidopa? High doses of carbidopa could cross the blood-brain barrier, inhibit the conversion of levodopa to dopamine in the striatum and thereby reduce the clinical effectiveness of levodopa, as occurs in animals.[5–6] Arguably, this is more of an issue in PD because the blood brain barrier may be altered in PD.[7–10] On the other hand, higher doses of carbidopa may increase the bioavailability of levodopa[11–12] and thereby enhance the effects of levodopa.

To examine these issues, we compared the effects of acute and chronic low and high dose carbidopa on levodopa pharmacokinetics and clinical response.

Methods

A randomized, double-blind, crossover trial compared two 4-week outpatient treatment periods with levodopa administered with carbidopa 75 mg daily and with 450 mg daily. The primary outcome was the alteration of the response to two 2-hour levodopa infusions at the termination of each treatment phase. IND 102,294 was obtained for high dose carbidopa and the protocol was approved by the Oregon Health & Science University (OHSU) Institutional Review Board. Clincaltrials.gov identifier is NCT00745277.

Subjects

Men and women between the ages of 35 and 85 with a diagnosis of idiopathic PD as judged by history and physical exam were recruited.[13] Subjects had had idiopathic PD for at least 3 years; had motor fluctuations and were taking at least 600 mg levodopa/day. Atypical parkinsonism, hallucinations, dementia, and other significant medical illness were exclusions. A 15% improvement in finger tapping speed from “off” to “on” was required to qualify for the study.

Protocol

Subjects were randomized in blocks of four for order of low and high carbidopa phases. Subjects and study team were blinded to assignment. The initial dosages of levodopa, administered as 50 or 100 mg gelatin capsules, approximated the subjects’ prior dosages and were titrated to obtain a satisfactory clinical response. Subjects on sustained release levodopa were converted to immediate release levodopa before randomization. Other antiparkinsonian medications, including entacapone, were continued per their usual regimen. Carbidopa was administered three times daily at either 25 or 150 mg per dose using an A and B capsule containing carbidopa or placebo. The subjects’ reports of clinical effectiveness and levodopa dose adjustments between the first and second 4-week outpatient phases were secondary measures of the effectiveness of low and high dose carbidopa regimens.

At the end of each 4-week treatment phase, subjects were admitted to the research unit for two days to evaluate their response to 2-hour levodopa infusions at 1 mg/kg/hr. Antiparkinsonian medications were held from 10 PM till 2 PM the following day.

The first 2-hour levodopa infusion was accompanied by 25 mg carbidopa orally before (8 AM), during (10 AM) and after (12 PM) the infusion to determine if the carbidopa dosage during the 4-week outpatient treatment phase affected the response to the infusion. The

infusion on the second day used the dosage of carbidopa employed the four weeks preceding the admission tested the acute effects of low and high dosages of carbidopa on the clinical effects of the 2-hour levodopa infusion. After the first inpatient stay, subjects crossed over to the other carbidopa dosage for 4 weeks followed by another identical inpatient admission.

Parkinsonism, measured by finger tapping speed, was the primary outcome. Walking speed, tremor scores and dyskinesia scores were secondary outcomes.[14] These measures were collected at 30–60 minute intervals from one hour before starting the levodopa infusion to three hours after stopping the infusion.[14] Adverse events reported by subjects during inpatient and outpatient phases were recorded.

Plasma samples for levodopa and carbidopa assays were collected at the times of clinical scoring. Levodopa and carbidopa were measured by liquid chromatography tandem mass spectrometry. Plasma samples of one subject were inadvertently thawed so pharmacokinetic results are available from eleven subjects.

Area under the curve (AUC) for the clinical scores and plasma concentrations of levodopa was calculated by the trapezoid rule between the beginning of the levodopa infusion to three hours after completion of the 2-hour levodopa infusion. The AUC for carbidopa also included the hour before the infusion when the first oral carbidopa was administered. The AUCs for the clinical scores and the plasma levodopa and carbidopa levels for the four infusions were compared by ANOVA with repeated measures and pair-wise comparisons made with Student-Newman-Keuls tests.

Results

Seventeen subjects entered the study. Three did not meet screening criteria. Fourteen subjects were randomized. One subject withdrew before starting experimental medications and the second withdrew during the first phase due to mania [Supplemental Figure 1]. Twelve subjects, four women and eight men, completed the study. Average age was 63 +/− 6 (SD) years, duration of disease was 8 +/− 4 years and duration of levodopa therapy was 7 +/− 3 years. The average motor UPDRS “off” was 30 +/− 14 and “on” was 15 +/−11. The average levodopa equivalents were 1354 +/− 588.[15] [Supplemental Table 1].

The primary outcome was the effect of the two carbidopa regimens on the responses to the 2-hour levodopa infusions. The first day examined the possibility that carbidopa accumulated in brain with four weeks of high dose carbidopa and would reduce the effect of the infused levodopa. The AUCs of the clinical measures immediately following four weeks of treatment with 75 or 450 mg of carbidopa per day did not differ. This observation indicated that there was no decrease in central decarboxylase activity with 450 mg carbidopa per day [Table and Supplemental Figure 2].

The 2-hour levodopa infusion on the second day compared the acute effects of high and low dose carbidopa. There were no differences between the clinical responses whether the 2-hour levodopa infusion was administered with 75 or 450 mg of carbidopa [Table]. This observation indicated that the 14–17% increase in levodopa AUC with 450 mg carbidopa, described below, was clinically unimportant.

Despite no changes in clinical responses to levodopa infusions, during the outpatient phases when levodopa was administered orally, eleven subjects reported different clinical effects during the two phases. Examining the response to switching from low to high carbidopa and vice versa, nine subjects described changes in dyskinesia, “off” time or need to alter levodopa doses that suggested 450 mg/day of carbidopa augmented levodopa effects more than 75 mg of carbidopa (NS by Fisher Exact test).

The time-levodopa concentration profiles were similar for the four levodopa infusions [Supplemental Figure 3] but the AUCs for levodopa differed [Table]. The levodopa AUC for the day that carbidopa 450 mg was administered during the infusion was 14–17% greater than the two infusions that followed the 75 mg/day outpatient phase..

Carbidopa concentrations measured the evening of admission to the research unit were higher after the 450 mg/day carbidopa phase, 439 +/− 384 (SD) versus 52 +/− 33 after the 75 mg/day phase ($p = 0.001$) indicating compliance with the protocol. AUCs for carbidopa concentrations differed for the four infusions, with the 450 mg of carbidopa administered during the infusions leading to higher carbidopa levels than the three infusions with 75 mg of carbidopa administered during the infusions. In addition, the carbidopa concentrations were higher for the first infusion after the 450 mg/day outpatient phase because of higher concentrations of carbidopa carried over from the outpatient phase [Table and Supplemental Figure 3].

Adverse events for the 75 and 450 mg/day carbidopa phases were dominated by levodopa effects [Supplemental Table 2]. Pain, as manifest by GERD, back injuries and sciatica, was present during the low dose carbidopa phase, possibly representing relative under-treatment of parkinsonism.

Discussion

The most important result of this study is that higher doses of carbidopa do not detract from the therapeutic effects of levodopa. The concern that higher doses of carbidopa might enter the brain is not supported by these results for doses of carbidopa up to 450 mg/day. Our results are consistent with the clinical impression that doses of carbidopa above 200 mg/day are not a problem and with the effects of large doses of carbidopa in marmosets.[16]

Do higher doses of carbidopa improve response? The 10% increase in AUC for levodopa after the 2-hour infusion following the 450 mg/day carbidopa outpatient phase and the 17% increase when 450 mg of carbidopa was administered with the levodopa infusion were relatively small increases and unlikely to be detectable by clinical response. A 27% increase in AUC of oral levodopa when mean carbidopa was increased from 145 mg/day to 290 mg/day did not alter clinical response.[12] Nevertheless, we have to reconcile the observations that the levodopa effects appeared to be augmented in the majority of subjects during the 450 mg/day carbidopa outpatient phase with the lack of effect of carbidopa on the clinical response to the infusions. Bioavailability of oral levodopa is increased with higher doses of carbidopa.[11–12] However, a large portion of the levodopa-sparing effect of carbidopa is from inhibition of first pass metabolism.[17–19] Thus we may have missed any benefit from high dose carbidopa because first pass metabolism was avoided with levodopa infusions.

In conclusion, our results extend the safe range of carbidopa from 75 to 200 mg/day to 75 to 450 mg/day.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table

Areas Under the Curve (AUCs) for Clinical and Pharmacokinetic Measures (Mean ± SD)

MEASURE	Levodopa Infusions on Day 1 Following 4 weeks of Carbidopa[1]		Levodopa Infusions on Day 2 Concomitant Carbidopa		p[2]
	75 mg/day	450 mg/day	75 mg	450 mg	
Tapping (taps/min) 0900–1400	141 ± 103	145 ± 123	141 ± 131	201 ± 214	0.336
Walking (seconds) 0900–1400	27 ± 66	30 ± 90	36 ± 90	37 ± 114	0.526
Tremor (score)0900–1400	2.6 ± 5.9	1.2 ± 2.2	1.1 ± 1.2	1.4 ± 3.4	0.789
Dyskinesia (score) 0900–1400	27 ± 28	23 ± 23	23 ± 19	23 ± 23	0.733
Levodopa (μg/ml) 0900–1400	5.38 ± 1.38	5.91 ± 1.64	5.23 ± 1.23	6.13 ± 1.45[3]	0.014
Carbidopa (μg/ml) 0800–1400	0.55 ± 0.29	0.75 ± 0.41[3]	0.47 ± 0.23	3.58 ± 1.56[4]	0.001

[1] Carbidopa 25 mg was administered at 8 AM, 10 AM and 12 PM during the infusions

[2] One way ANOVA with repeated measures

[3] Different from infusions following carbidopa 75 mg/day in outpatient phase

[4] Different from all infusions using 75 mg carbidopa