Clinical Medicine Journal
Vol. 1, No. 2, 2015, pp. 34-37
http://www.publicscienceframework.org/journal/cmj

How to Dose Carbidopa and Levodopa Extended-Release Capsules (Rytary)

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Abstract

Carbidopa and levodopa extended-release capsules (Rytary) are designed to provide benefit as quickly as carbidopa/levodopa immediate release (IR) and levodopa plasma concentrations are maintained for about 4 to 5 hours before declining. Dosages of Rytary are not interchangeable with other carbidopa/levodopa products and those wishing to prescribe Rytary must be familiar with its dosing. In clinical trials, patients on carbidopa/levodopda IR were converted to Rytary according to a dose conversion table followed by tiration according to clinical response and ended up on approximately twice the daily levodopa milligram dose. For levodopa naïve patients, the usual Rytary maintenance dose is 145 mg three times daily, although lower doses may suffice.

Keywords

Rytary, Levodopa, IPX066, Extended Release, Parkinson's Disease, Treatment

Received: March 22, 2015 / Accepted: April 6, 2015 / Published online: April 20, 2015

1. Introduction

Rytary is an extended-release formulation of carbidopa/levodopa. It consists of capsules that contain beads of carbidopa and levodopa that dissolve and are absorbed at different rates. Following administration, therapeutic levodopa levels are relatively rapidly achieved (similar to carbidopa/levodopa immediate release [IR]) and are maintained for 4-5 hours.

It is critically important to recognize that dosages of Rytary are not interchangeable with other carbidopa/levodopa products! Therefore, those wishing to prescribe Rytary must be familiar with its dosing and proper administration.

2. Dosage Strengths Available

Rytary contains carbidopa and levodopa in a 1:4 ratio. Available dosage strengths are extended-release capsules:

- 23.75 mg carbidopa and 95 mg levodopa: blue and white capsule imprinted with IPX066 on the capsule cap and 95 on the capsule body
- 36.25 mg carbidopa and 145 mg levodopa: blue and light blue capsule imprinted with IPX066 on the capsule cap and 145 on the capsule body
- 48.75 mg carbidopa and 195 mg levodopa: blue and yellow capsule imprinted with IPX066 on the capsule cap and 195 on the capsule body
- 61.25 mg carbidopa and 245 mg levodopa: blue capsule imprinted with IPX066 on the capsule cap and 245 on the capsule body

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Table 1. Conversion from carbidopa/levodopa immediate release to Rytary.

Total Daily Dosage of Levodopa in Carbidopa-Levodopa Immediate Release	Recommended Starting Dosage of Rytary	
	Total Daily Dosage of Levodopa in Rytary	Rytary Dosing Regimen
400 mg to 549 mg	855 mg	3 capsules Rytary 23.75 mg / 95 mg taken TID
550 mg to 749 mg	1140 mg	4 capsules Rytary 23.75 / 95 mg taken TID
750 mg to 949 mg	1305 mg	3 capsules Rytary 36.25 mg / 145 mg taken TID
950 mg to 1249 mg	1755 mg	3 capsules Rytary 48.75 mg / 195 mg taken TID
≥ 1250 mg	2340 mg or	4 capsules Rytary 48.75 mg / 195 mg taken TID or
	2205 mg	3 capsules Rytary 61.25 mg / 245 mg taken TID

[a]TID – three times a day

For dosing purposes, only the levodopa dosage usually needs to be considered and that is what will be discussed here unless otherwise indicated. The levodopa 95 mg, 145 mg, 195 mg, and 245 mg dosage capsules were developed to help avoid confusion with other oral carbidopa/levodopa products that contain levodopa in multiples of 50 milligrams (mg). IPX066 was the investigational name.

2.1. Dosing Conversion for Patients on Carbidopa/Levodopa Immediate Release

In clinical trials (1,2), patients on carbidopa/levodopda IR (Sinemet) were converted to Rytary according to a dosage conversion table that is provided above. This table is in the Rytary FDA approved label and is therefore considered the "official recommendation."

To use the table, one adds up the daily milligrams of levodopa the patient is currently taking and finds the appropriate line in the left hand column, identifies the appropriate total daily dosage of Rytary to switch to in the middle column on the same line, and implements a three times daily (TID) regimen as suggested in the third column of that same line. By way of example, if a patient is on carbidopa/levodopa IR 25/100, 1½ tablets 6 times a day, their total daily levodopa IR dosage is 900 mg and the table suggests an initial conversion to 3 capsules Rytary 36.25 mg / 145 mg taken TID, for a total daily Rytary levodopa dosage of 1305 mg. Further adjustments would be made based on the clinical response.

It is very important to tell patients that this is just a suggested starting point and in patients who are experiencing motor fluctuations on carbidopa/levodopa IR further adjustments are likely to be required. In clinical trials (2), approximately 60% of patients converted from carbidopa/levodopa IR to Rytary ultimately required higher daily Rytary dosages than suggested by the table and 16% required lower daily Rytary dosages. Many patients, especially those who are more advanced and more sensitive to changes in levodopa dosage will notice a difference within a day or two (or even with the first dose), so clinicians must have a plan in place for the patient to be able to provide feedback and be prepared to make changes quickly if the patient is very under-dosed (parkinsonian) or over-dosed (dyskinetic).

Overall, patients with motor fluctuations tended to require about twice the daily levodopa mg dosage from Rytary as from carbidopa/levodopa IR (2). There are two reasons for this. First, Rytary is only 75% bioavailable (based on concentration area under the curve [AUC]) compared to carbidopa/levodopa IR (1). Second, more levodopa is required to fill in the levodopa troughs created by carbidopa/levodopa IR and to smooth the clinical response.

An alternative approach to dosing is to utilize a conversion formula based on knowledge of the pharmacokinetics of Rytary. In converting patients with motor fluctuations from carbidopa/levodopa IR to Rytary, one would like to match the serum levodopa maximum concentration (Cmax) to provide the same level of antiparkinsonian benefit during ON time, without increasing dyskinesia. Because the Cmax of Rytary is approximately 30% of carbidopa/levodopa IR (1), one should administer approximately three times the levodopa mg dosage of carbidopa/levodopa IR for an individual dose. Because the Rytary total daily levodopa dosage is expected to be about twice that of carbidopa/levodopa IR (2), it follows that if you are administering approximately three times as much for an individual dose, you would only have to administer it two thirds (2/3) as often. Thus, for the example of a patient taking carbidopa/levodopa IR 25/100, 1½ tablet 6 times a day, one can apply the formula of 3 times the individual dose (3 x 150 mg = 450 mg) administered 2/3 as often to derive an initial starting regimen of 3 capsules Rytary 36.25 mg / 145 mg taken four times daily (QID) for a total daily Rytary levodopa dosage of 1740 mg. Note that the formula approach often leads to a higher daily Rytary levodopa starting dosage than does the table. The formula is more likely to provide an initial dosage conversion that is close to the patient's final dosage, but is less conservative, especially for patients with dyskinesia or other levodopa-associated side effects. The table is more conservative, but upward dosage titration will be required more often.

As with titration of other levodopa products, if a single dose

does not provide a good ON response, that dose should be increased. If a dose is not lasting until the next dose "kicks in," the inter-dose interval should be shortened. The dosing frequency may be changed from three times a day up to a usual maximum of five times a day if more frequent dosing is needed and if tolerated. Some patients may even require more frequent dosing. Too frequent dosing for an individual patient may lead to dyskinesias or other adverse dopaminergic side effects. In clinical trials of Rytary in patients with motor fluctuations, the usual administration frequency was three or four times per day. The usual maximum recommended daily dosage of Rytary is 612.5 mg / 2450 mg.

Clinical experience suggests that for more advanced patients who are sensitive to small changes in levodopa dosage, a strategy of only switching over the first dose of the day (morning dose) as the initial step in going to a full day Rytary regimen may be helpful. Patients who are sensitive to small levodopa changes may not tolerate a complete switch to Rytary easily. These patients are those who have substantial motor fluctuations on levodopa IR, with deep OFF periods in which they are very parkinsonian and have a very short duration of benefit from levodopa IR (typically less than 3 hours). Many also have dyskinesia. If such patients are switched to a full day Rytary regimen that is too low they will be very parkinsonian through the day and will not to tolerate it. If they are switched to a full day Ryatry regimen that is too high, they may have troublesome dyskinesia through the day and will not tolerate it. Unless dosing changes are instituted right away, they are likely to stop Ryatry and return to their previous levodopa regimen. A useful alternative strategy for such patients is to initially find the right Rytary dosage for the first morning dose while the patient remains on his current levodopa schedule the rest of the day. Once the correct Rytary morning dose is identified, a second Rytary dose can be introduced to provide benefit as the first dose wears off. This process can then be continued until the full day is covered by Rytary.

Consider a patient who is taking carbidopa/levodopa IR 25/100 2 tablets 7 times a day at 2½ hour intervals who reports she is quite slow when OFF and has at least some dyskinesia during most of her ON time. In this case, one could consider the strategy of first finding the best Rytary morning dose. She currently takes 200 mg of levodopa IR as her first daily dose, so to match that Cmax, one might switch to approximately 600 mg of Rytary. The patient can be told to take 3 capsules of Rytary 195 mg as her first morning dose and when that begins to wear off, she can resume her usual schedule of levodopa IR 200 mg every 2½ hours. However, if this morning Rytary dosage is insufficient to provide an ON response, she can resume her prior levodopa IR schedule beginning about 4 hours after taking the Rytary dose and she can stay on levodopa IR until she can try a higher Rytary morning dosage. If the initial morning Rytary dose causes excessive dyskinesia, she should wait until the Rytary dose begins to wear off and then she can resume her levodopa IR regimen and stay on it until she can try a lower Rytary morning dosage. Once a morning dosage of Rytary is found that provides a good ON response, the same dosage can then be given for the second dose of the day, to start working when the first dose wears off. Thus, if she reports that the initial morning dose of 3 capsules of Rytary 195 mg takes about a half hour to kick in and starts to wear off about 4½ hours after her first, she should be instructed to take a second dose of 3 capsules of Rytary 195 mg 4 hours after the first dose. The remainder of the day would still be covered by levodopa IR. The inter-dose interval, and possibly the dosage of the second Rytary dose may then have to be adjusted with the goal of optimizing the clinical response through the first two Rytary doses of the day. This process is then repeated to add additional Rytary doses until the full day is covered by Rytary and levodopa IR is no longer required.

2.2. Dosing Conversion for Patients on Carbidopa/Levodopa Controlled Release or Entacapone

There are no published studies to guide conversion of carbidopa/levodopa controlled release (CR) to Rytary. Since carbidopa/levodopa CR is approximately 70% bioavailable (by AUC) compared to carbidopa/levodopa IR, a reasonable approach would be to start with a Rytary dosage conversion that is approximately 30% lower than a similar dosage conversion from carbidopa/levodopa IR. Thus, for a patient who is taking carbidopa/levodopa CR 25/100, 1 tablet QID, rather than switching to 3 Rytary 23.75mg / 95 mg capsules TID as suggested by the table, a reasonable initial Rytary regimen might be Rytary 23.75 mg / 95 mg 2 capsules TID in light of the lower bioavailability of carbidaop/levodopa CR.

Conversely, since entacapone sends more levodopa to the brain, patients on carbidopa/levodopa IR plus entacapone will likely need a higher dosage of Rytary when converted (and entacapone discontinued). In a clinical trial of patients with motor fluctuations comparing carbidopa/levodopa IR plus entacapone to Rytary (3), the median daily dosage of carbidopa/levodopa IR (administered with entacapone) was 600 mg and the median daily dosage of Rytary was 1495 mg, suggesting a conversion ratio of approximately 2.5 (representing a 25% increase over the conversion from IR without entacapone). Thus, a patient who is taking carbidopa/levodopa IR 25/100, 1 tablet 6 times per day with entacapone 200 mg 6 times per day, might be switched to approximately 1500 mg Rytary per day (600 mg x 2.5),

possibly using a regimen of 1 Rytary 195 mg plus 1 Rytary 145 mg QID for a total Rytary levodopa dosage of 1360 mg per day (without entacapone).

2.3. Dosing in Patients Naïve to Levodopa Therapy

The "official" recommended starting dosage for Rytary in levodopa-naïve patients according to the label is 23.75 mg / 95 mg taken orally three times daily for the first 3 days. On the fourth day of treatment, the dosage of Rytary may be increased to 36.25 mg / 145 mg taken three times a day. Further increases can be undertaken as per the clinical response.

In the clinical trial evaluating Rytary in early PD (4) all dosages tested were effective compared to placebo, but the 145 mg TID dose, which was the lowest dosage tested, provided good efficacy with fewer side effects than higher Rytary dosages. Although the 95 mg TID dosage was not tested for efficacy in clinical trials, it carries strong appeal as a dosage that is likely to be well tolerated, and one can evaluate clinically for an individual patient whether it is sufficient or if a higher dosage is required. Less frequent dosing such as 95 mg BID has not been tested but might be sufficient in some patients with early disease.

2.4. Effect of Food

As with carbidopa/levodopa IR, Rytary can be taken with or without food. One gets the quickest and most consistent (initial) absorption taking it away from food, but if a patient experiences nausea, taking it with carbohydrate may reduce the nausea. Protein can reduce absorption, but whether this is clinically relevant depends on how sensitive to small dose changes the patient is. Interestingly, high fat meals delay absorption and reduce the amount absorbed, but can potentially lengthen the duration of benefit. Although this has not yet been studied, one might take Rytary at bedtime with a high fat snack such as ice cream, in an effort to extend benefit into the night as long as possible.

2.5. Other Information

Patients who have difficulty swallowing intact capsules, can carefully open the Rytary capsule and sprinkle the entire contents on a small amount of applesauce (1 to 2 tablespoons), and consume it immediately.

3. Conclusion

Compared to levodopa IR, Rytary is approximately 70% bioavailable by AUC and 30% bioavailable by Cmax. Patients with fluctuations on carbidopa/levodopa IR can be converted according to the dosage conversion table provided in the label, followed by titration according to clinical response. Those on carbidopa/levodopa CR can be converted to a dosage that is approximately 30% lower than provided in the table and those on carbidopa/levodopa IR plus entacapone can be converted to a dosage that is approximately 25% higher. It is critical to inform patients that the initial regimen is just a starting dosage and subsequent adjustments based on clinical response are highly likely. Patients naïve to levodopa can be initiated on Rytary 95 mg TID and increased to 145 mg TID if necessary.

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