Daily Inhibition of CYP3A4 alleviates the symptoms of Parkinson's disease

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Abstract
Levodopa is administered orally in Parkinson's disease therapy to generate dopamine in the brain to compensate for reduced production from lost dopaminergic cells. It is metabolized by several enzymes, in the intestines and the liver, some of which are inhibited by prescription drugs. Even so its half-life remains short (about 90 minutes), which leads to the on/off states well known to Parkinson patients. We explore the hypothesis that this short half-life is due to metabolism by the Cytochrome P450 enzyme, CYP3A4. We have carried out an n = 1 trial of the evolution of Parkinson's disease symptoms over a 50-day cycle of inhibition and non-inhibition of CYP3A4. It demonstrates that inhibiting CYP3A4 attenuates the symptoms of Parkinson's disease and improves the quality of life of patients, whereas short-term inhibition leads to worsening of the symptoms. This contrasting result is believed to be due to the long lead time required for the regeneration of CYP3A4.

Introduction

It is recognised that levodopa is metabolised by two specific enzymes, DDC and COMT. Drugs are regularly prescribed to inhibit these enzymes to improve the performance of levodopa for the treatment of Parkinson's disease. Even so, its bio-availability and short half-life in the blood remain problematic (Meiser *et al*, 2013 [1]. This suggests that a third enzyme becomes dominant when these two enzymes are inhibited. A likely candidate for this third enzyme is CYP3A4, the most potent drug-degrading enzyme of the Cytochrome P450 system which metabolizes more than 70% of all drugs. Supporting work for this hypothesis has been presented in previous work (A F Wright, 2019 [2]), so will only be briefly summarised here.

In this paper we test this hypothesis and publish the first results of an n = 1 study of systematic CYP3A4 inhibition for a Parkinson's patient treated with levodopa. The results demonstrate that CYP3A4 plays a major role in the metabolism of levodopa and is largely responsible for the short half-life of this drug when administered to Parkinson's disease patients.

About the metabolism of levodopa

Published experimental data on the metabolism of levodopa by CYP3A4 is scarce and inconclusive, possibly because of priority given to DDC and COMT enzymes for which inhibitors are regularly prescribed. Despite this, a combination of indirect indicators and anecdotal observations together suggest that CYP3A4 cannot be excluded as the cause of the low bio-availability and short persistence of levodopa.

Levodopa has two active active chemical sites that are known to be readily metabolised by CYP3A4 (R. Scott Obach, 2010 [3]. The phenol groups can be oxidized to quinones and the

amine group can be oxidised to an active nitroso group. Indeed, levodopa has also been shown to be a potent inhibitor of CYP3A4 in rat liver microsomes (R. Sultana & Md. Z. Sultan,2018 [4]), which implies strong binding mechanism between the two reactants and resultant inactivation of both substrate and enzyme.

R. Cacabelos [5] studied the variability of the pharmacokinetics of levodopa without DDC inhibition in patients graded according to variations in their genetic CYP 450 metabolic activity. Careful analysis of these results reveals a strong correlation between the degree of CYP3A4 activity of patients and the resultant dopamine blood concentrations. Poor CYP3A4 Metabolisers showed a much higher (x 6) dopamine blood concentration than Rapid CYP3A4 Metabolisers under the same conditions. These results suggest that CYP3A4 plays an active role in levodopa metabolism. There was no correlation for other CYP 450 enzymes. According to Cacabelos, levodopa is metabolized by many enzymes Cytochrome P450 including CYP3A4, but no direct experimental proof of this assertion was presented.

CYP3A4 is however the most potent CYP enzyme in the intestines and the liver. It offers a formidable barrier to any drug administered orally and metabolises more than 50% of all drugs (M F Paine *et al,* 2006 [6], D.G Bailey *et al,* 2013 [7]).

Resolving the question of the short half-life of levodopa

The short half-life of levodopa (~ 90 minutes) has serious consequences for Parkinson's disease patients since it induces important fluctuations in the dose on target that give rise to the well-known "on/off" states that seriously disorganise and degrade the quality-of-life of patients. Identifying the origin of its short half-life with the aim of finding a way to resolve it is therefore a strategic step on the path to improving the comfort and quality-of-life of Parkinson's disease patients.

In 2011, Dr R. Hutton, a chemist by profession and Parkinson's disease patient from Kent, England wrote about a chance observation concerning the impact of drinking a glass of grapefruit juice prior to taking his Parkinson medications and noted the considerable extension of his "On" time during the day from 2-3 hours to 6½ hours *(neurotalk.org/parkinson-s-disease)*. He repeated the process the following day and confirmed the result. It is well established that grapefruit juice is a potent inhibitor of CYP3A4 and although this was discussed at the time, his observation was not followed up, so an opportunity to investigate this further was missed.

The n = 1 trial described below, was specifically designed to resolve the question of whether CYP3A4 is a major player in the metabolism of levodopa by observing symptoms of a Parkinson's disease patient during a 4-phase cycle of CYP3A4: baseline stabilisation, inhibition, cessation of inhibition and resumption of inhibition. This trial forcefully demonstrates that CYP3A4 is critically involved in controlling the availability and persistence of levodopa. The results provided much more information than was initially expected and explain why intermittent inhibition aggravates symptoms whereas systematic inhibition improves the quality of life of the patients. These results now need to be confirmed by quantitative pharmacokinetics measurements comparing the relative importance of CYP3A4, COMT and DDC in the metabolism of levodopa.

The study involved noting the nature and intensity of the patient's Parkinson's symptoms over a cycle during which standard Parkinson's drugs were administered normally, whereas the CYP3A4

enzyme was alternatively inhibited or non-inhibited. The chosen inhibitor was that commonly used by pharmacologists to test for susceptibility to CYP3A4 inhibition, namely grapefruit juice. This fruit contains two very potent CYP3A4 inhibitors, bergamottin and 6',7' dihydroxy-bergamottin, in sufficient quantities to be an effective therapeutic agent. (S. Olguin-Reyes *et al*. 2012 [8]. It is also the most intensively researched food product due to its implication in drug-drug (or drug-food) interactions mediated by CYP3A4 (Lown K S, Bailey D G, *et al* 1997 [9].

One glass (250 ml) of grapefruit juice is proven to totally and irreversibly inhibit CYP3A4 in the intestine (J Kiani & S Z Imam, 2007 [10]. More than 24 hours (and up to 3 days) are required to fully restore enzyme activity after inhibition by grapefruit juice (D.G Bailey *et al,* 2013 [7]). When consumed on a daily basis, CYP3A4 activity in the liver has also been shown to be reduced over time, leading to slower clearance of drugs in the circulating system (M L Veronese *et al,* 2003 [11]).

An n = 1 study on the effects of grapefruit juice on Parkinson's symptoms

This study was carried out by a Person with Parkinson's (PwP), male, 77, diagnosed in April 2018. It was designed to identify as clearly as possible whether or not grapefruit juice (and by implication CYP3A4 inhibition) strongly affects Parkinson's symptoms by modifying the availability of levodopa in the blood. Care was taken to exclude the ingestion of any other potential CYP enzyme inhibitors in food supplements or medication (green tea extract, liquorice etc. (A. F. Wright 2018, [13])). The study comprised 4 distinct phases:

1) Stabilisation of symptoms on a standard levodopa dose, 2) Inhibition of CYP3A4 using a standard dose of grapefruit juice, 3) Sudden withdrawal of grapefruit juice, 4) Resumption of grapefruit juice. The evaluation of the symptoms was based on the subjects personal observations.

The stabilisation phase was rigorously carried out using a base dosage of 10/100mg Carbidopa/Levodopa 4 x daily. For the inhibition phase, CYP3A4 was inhibited by drinking one glass (250 ml) of grapefruit juice (Tropicana, pamplemousse rose) per day 30 minutes before taking the first dose of medication. Both of these phases lasted 21 days. The withdrawal of inhibition, by stopping the grapefruit juice was effective without any prior adjustment. This phase was planned to last 7 days, but had to be cut short to 4 days due to the severity of the symptoms experienced. During the whole period, the C/L levodopa dosing was not interrupted.

***Caution:** This was a single experiment carried out on a unique subject with early stage PD. The whole cycle took about 2 months and included periods which are now known to be highly disagreeable or intensely painful. For this reason it has not been repeated.*

***1) Stabilisation phase, no inhibition :** Parkinson's symptoms were stable as follows. Modest but constant left-hand tremor with regular pain in the left hand, left hand weakness, overnight left internal tremor with pain. Minor right hand pain, intermittent right foot pain. The subject complained of having a weak voice, low energy, limited concentration time with regular off times and fatigue, often requiring 1 – 2 hours sleep during the day. He also complained of regular vivid dreams and frequent urinary urgency, but was able to walk 2 hours on level ground or 1 hour uphill most days.*

2) Inhibition phase: *A considerable improvement in symptoms was observed after the first week and a sustained improvement thereafter. Except for occasional pain in the left hand, all other pain ceased. Tremor was considerably reduced and was absent for several hours a day. The subject's energy levels improved, and his voice became strong again (he was even told not to shout). Off periods were progressively eliminated and the occurrence of vivid dreams and urinary problems was considerably reduced. The subject was able to lead a normal life and travelled for several days during this period. He was able to work long hours and drive long distances without difficulty. After two weeks the C/L dosage was reduced to 3 x 300 mg/day for a few days with no negative effect. So far so good!*

3) Withdrawal phase: *The daily grapefruit juice was suddenly and totally stopped on day 1 of this phase, but the C/L was maintained as normal. No significant change was reported on the first day. On the second and third days, all symptoms progressively and significantly worsened. The subject reported that regular tremor returned with painful arms and hands, restless legs, vivid dreams and severe fatigue. Due to prolonged off periods and fatigue, afternoon sleep became essential.*

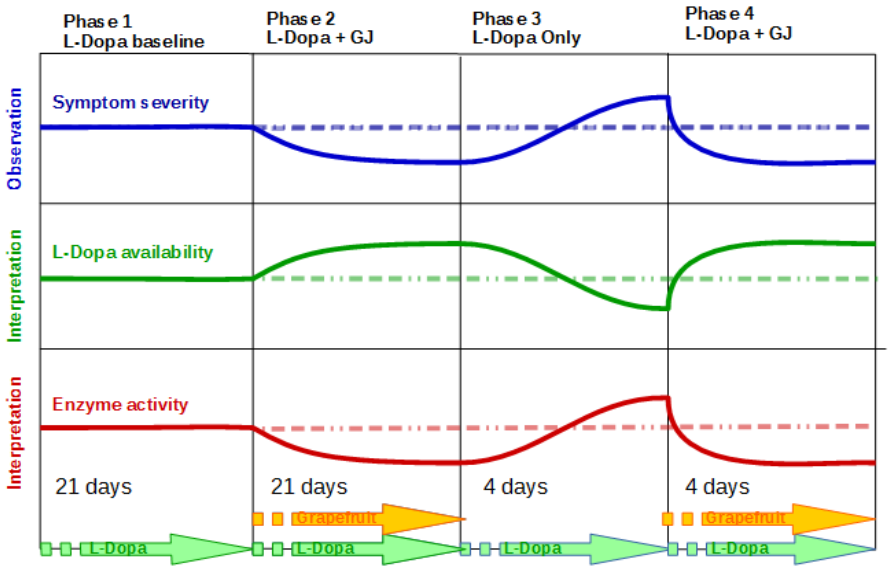

Figure 1, *Simplified schematic representation of symptom severity and possible interpretation in terms of levodopa availability and CYP3A4 enzyme activity.*

The fourth day *was described as intolerable. All Parkinson's symptoms returned with greater intensity than ever experienced before by the subject. He complained of intense hand, foot and leg pain along with crushingly painful fatigue. The C/L 10/100mg dose had no effect on any symptoms. This was described as his worst day since being diagnosed with Parkinson's disease.*

4) Resumption of Inhibition: *The intensity of the fatigue and pain persuaded the subject to terminate the withdrawal phase at the end of the fourth day by taking a single glass of grapefruit juice shortly before the evening C/L dose. In less than one hour pain and fatigue was reduced by more than 80% along with a significant reduction in all other symptoms. Over the next 3 days, symptom relief returned to the levels of phase 2 and remained stable.*

How can we interpret these observations ?

Presenting these results in a simplified schematic manner (Figure 1) enables these observations to be checked against the hypothesis of the existence of a reversible 2-stage process. Namely that: 1) Grapefruit juice effectively inhibits CYP3A4. 2) Inhibition of CYP3A4 reduces levodopa metabolism, allows more of the drug to reach the circulating system and improves its persistence,

thus reducing PD symptoms. 3) Stopping grapefruit juice allows the CYP3A4 enzyme to be regenerated without restriction, reducing the availability and persistence of levodopa once again.

The top curve represents the global severity of the symptoms as witnessed by the patient, reduced to a single parameter. If we assume that the severity of symptoms correlates inversely with the average amount of levodopa in the blood, we can represent this progression (second curve) as the inverse of the top curve although the vertical scale could well be modified. Finally on the assumption that the level of levodopa is a consequence of CYP3A4 activity, we get the third curve which essentially follows the direction of movement of the first one, albeit with possible delays and changes of scale.

How do these results correlate with the original hypothesis?

1) For the first two phases, we observe that a glass of grapefruit juice, taken every day in combination with C/L had a significant and durable positive effect on the subject's Parkinson's symptoms and quality-of-life. It supports the hypothesis that systematically inhibiting CYP3A4 improves the delivery of levodopa and extends its duration in the circulating system.

2) Symptom improvement was progressive over a period of 8-10 days and stable thereafter, suggesting a progressive improvement of the delivery of levodopa or its use. This correlates with progressive CYP3A4 inhibition in the liver also. The total disappearance of "Off-times" is consistent with a more stable delivery of levodopa to the brain.

3) Symptom progression during the first three days of the grapefruit withdrawal phase was consistent with the time required for the regeneration of the CYP3A4 enzyme stock and consequent resumption of enzyme metabolism of levodopa.

4) The 4th day of (cold turkey) withdrawal, demonstrated that the rate of change and magnitude of enzyme expression, as measured by the symptoms, had moved into a new extreme level. The intensity and violence of the symptoms suggests that the level of levodopa in the blood was aggressively reduced, leading to a severe lack of dopamine in the brain in spite of continued levodopa medication. We can reasonably interpret this in terms of more intense CYP3A4 renewal occurring when the dynamic equilibrium between powerful inhibition and the strong biological forces for renewal, established over 21 days was suddenly destabilised by allowing the renewal process to proceed unchecked. Even though CYP3A4 inhibition had depressed its apparent activity to well below baseline, the dynamics of the renewal process clearly pushed the enzyme activity up to levels well above baseline in just 4 days. This result that is entirely consistent with the common and well-documented effect known as the "Withdrawal Rebound Effect" (M Teixeira, 2013 [13]). It further reinforces the hypothesis that CYP3A4 metabolism is indeed the major cause of the low bio-availability of levodopa. The mechanism of operation of this rebound effect, based on the reaction of the Pregnane X Receptor (PXR) to a high concentration of xenobiotics in the gut mucous, is given below.

5) The speed and magnitude of symptom relief produced by a single glass of grapefruit juice on day 4 suggests that the major source of the excessive CYP3A4 activity could still be deactivated by a single dose of enzyme inhibitor enabling levodopa medication to reach the blood and circulate almost immediately. This very rapid response suggests that the blockage caused by excessive CYP3A4 expression was essentially in the intestinal tract.

CAUTION. Please note that Parkinson's disease patients should not attempt to repeat this experiment without medical supervision. The health risks associated with sudden withdrawal of grapefruit juice have not been evaluated. Cessation of grapefruit juice after a long period of use in combination with levodopa should normally be carried out progressively over a timescale of several days. This rule was deliberately breached to explore its impact.

Discussion

The n = 1 study described above has provided a clear response to the question posed. There is little doubt that levodopa is strongly metabolised by the CYP3A4 enzyme. This does not exclude the possibility that other enzymes of the Cytochrome P450 system could also be involved. However, the magnitude of the effect of grapefruit juice on the symptoms of Parkinson's disease demonstrates that CYP3A4 is a major player in controlling the bio-availability of levodopa. Indeed its activity could be more important than that of COMT and comparable with that of DDC.

The kinetics of inhibition and induction of CYP3A4

The kinetics of CYP3A4 inhibition (destruction) and induction (regeneration) are quite different but are closely interrelated. Xenobiotics (drugs, toxins, metabolites from the breakdown of nutrients by gut microbiotics) in the intestinal tract are normally degraded by CYP enzymes and especially by CYP3A4. The expression of CYP3A4 is controlled by the nuclear receptor PXR (Pregnane X Receptor) (Moon & Gwak, 2015 [14]). PXR detects the presence of xenobiotics in the gut mucous and stimulates specific genes in the DNA of the enterocytes to increase or decrease expression of CYP3A4 (or other CYP enzymes) to ensure rapid metabolism of the xenobiotics. This process breaks down when certain xenobiotics, during the process of being metabolised, irreversibly inhibit and inactivate the enzyme. The reduction of enzyme activity enables more xenobiotics to pass through the gut membrane and into the blood. The increased quantity of xenobiotics immediately stimulates PXR to launch the regeneration of CYP3A4 in order to re-establish the equilibrium between enzyme and toxins. An imbalance arises because of the long lead time (24-48 hours) needed to regenerate the CYP3A4, compared to the very short time (minutes) required to inactivate it. This creates a temporal window of at least 24 hours when CYP3A4 activity is very low and xenobiotic flow through the gut membrane is high. During this period the high flow of xenobiotics constantly activates PXR to express more CYP3A4. The imbalance leads to a process of excessive production of CYP3A4, but with a 24-hour time lag between inhibition and the effective supply of new enzyme.

The quantity of CYP3A4 present at any one time therefore depends on the kinetics of the different processes, inhibition, and regeneration and the timing of events that modify these processes. In the absence of inhibitors, the CYP3A4 activity will increase or decrease as a function of the quantity of xenobiotic in the gut mucous, albeit with a significant delay to allow for the production new CYP3A4.

Potent inhibitors such as the furanocoumarins in grapefruit juice, rapidly inactivate most or all of the existing CYP3A4 in the gut in one pass, and simultaneously activate the regeneration process at t = 0, via PXR, a process that requires 24-48 hours. During this temporal window when CYP3A4 is inactivated, the quantity of levodopa passing through the gut wall at each dose will be

higher than when CYP3A4 is not inhibited. This exceptional state will stimulate the PXR receptors in the enterocytes to express more CYP3A4 to respond to this higher load. The process of expression of CYP3A4 will therefore be exceptionally high during this period, but the regenerated CYP3A4 will only become available some 24-48 hours later.

An isolated dose of inhibitor, or a cessation of inhibition will therefore create a severe modulation of enterocyte CYP3A4 activity, starting from near zero at t = 0, remaining low for 24 hours, but followed by a surge in regenerated CYP3A4 activity over the following days. Intermittent inhibition of CYP3A4 using grapefruit juice will therefore increase CYP3A4 expression starting from about 24 hours after inhibition is ceases and this may severely aggravate Parkinson's disease symptoms. In the absence of other factors, the intensity of the CYP3A4 surge is likely to be dependent on the dose of levodopa being ingested when this is the principle substance available to stimulate PXR during the inhibition window. Numerous cases of this affect have been reported.

A steady, but reduced state of CYP3A4 expression can therefore only be achieved with regular and systematic inhibition of CYP3A4 to establish a balance between inactivation and regeneration mediated by PXR. To take into account the kinetics of the opposing processes, a constant dose of inhibitor must be administered every 24 hours. The results obtained in the n = 1 trial are entirely consistent with this mechanism. However, with constant dosing, symptom control on days 3 and 4 was modest but rose to a high and stable level over 7-10 days.

We can hypothesise that under conditions of continuous inhibition of CYP3A4, the levodopa drug dose required to deliver an adequate supply to the brain for good symptom control should be less than when CYP3A4 is not inhibited. There are advantages to finding the minimum dose required under these conditions. The first is to reduce the peak serum concentration to avoid dyskinesia caused by a peak over-supply of dopamine in the brain. The second is to slow the regeneration rate of CYP3A4 after inhibition which could be dependent on the levodopa concentration passing through the enterocytes. Lowering the levodopa dose to the minimum necessary is therefore a win-win situation. In the weeks following the n=1 trial, the minimum dose of levodopa needed by the subject was found to be about 150 mg/day (2 x 75 mg), compared to 400 mg/day when CYP3A4 was not inhibited. This provided very extended periods (up to 12 hours) almost symptom-free and is still improving. No work has yet been done to establish the minimum useful dose of grapefruit juice for long-term use.

Diet may also be a factor in CYP3A4 inhibition

Dietary polyphenols have been shown to interact with CYP3A4 and modify its expression and activity (Basheer & Kerem, 2015 [15]). The term polyphenols covers a vast array of substances found in foods that include phenolic acids, flavonoids, stilbenes, lignans and tannins. The food sources are common; coffee, nuts, vinegar, grapes, red wine, whole cereals, green vegetables, celery, parsley, broccoli, apples, strawberries, citrus fruits, soya beans, onions and berries etc. These are all foods that are necessary for a healthy diet and raises questions concerning potential drug-food interactions. Eating a healthy diet automatically implies inhibiting CYP3A4 and this may impact on the efficacy of some drugs. Avoiding it is neither possible nor desirable.

On average, humans ingest about 1000 mg of polyphenols per day, but this varies considerably depending on local diet. The Vietnamese diet provides only about 600 mg, whereas the

Mediterranean diet provides between 2000 and 3000 mg per day. Polyphenols are widely accepted to be health promoting. This is attributed to their antioxidant properties through free-radical scavenging and iron-chelating activity. CYP3A4 inhibition by polyphenols may be less potent than the furanocoumarins in grapefruit juice, but they are ingested in much greater quantities (20 mg of furanocoumarins in a glass of grapefruit juice, compared to 2000 mg of polyphenols in the Mediterranean diet).

Combining this information with our understanding of the kinetics of CYP3A4 inhibition and regeneration, we can now see how diet could also have an effect on the bio-availability of levodopa. With prior knowledge of the kinetics of CYP3A4 inhibition and regeneration, it may now be possible to identify the causes. We can however hypothesise that varying the daily dose of polyphenols through a mix of a healthy diet, rich in fruit, nuts and vegetables one day, and an unhealthy diet on other days is likely to be a bad choice for Parkinson's disease patients..

A healthy diet rich in polyphenols, will partially inhibit CYP3A4 on day 1, but will also programme a surge in CYP3A4 expression on days 2, 3 and 4. If the healthy diet is continued on days 2, 3 and 4, then CYP3A4 inhibition will continue and the patient will feel the benefits. If on the other hand, the patient adopts a diet low in polyphenols for more than 2 days, CYP3A4 regeneration will continue unchecked during this period. Days 2, 3 and 4 will then be bad days. One of the difficulties of Parkinson's disease is having unpredictable good days and bad days. Many people think that diet is the cause, but making sense of daily diet history has always been difficult. Understanding the kinetics of CYP3A4 inhibition and regeneration may help to identify the causes of good and bad days. Choosing to eat a healthy diet is known to be beneficial, but for Parkinson's disease patients, eating a healthy diet everyday could be particularly helpful.

A reminder about enzyme inhibition and drug-drug interactions

The pharmaceutical industry is rightly very concerned about enzymes and enzyme inhibition due to their role in drug-drug interactions (DDI), (D.G Bailey *et al,* 2013 [7]. In the vast majority of these cases, the link between the two drugs is in their reaction to the CYP3A4 enzyme whose role is to oxidise toxins before they enter the blood. When this enzyme is fully active, many drugs are partially metabolised by it, so that only part of the administered dose reaches the blood stream. This is taken into account when fixing the drug dose recommendations. Problems arise when one drug or food supplement (unintentionally) inhibits CYP3A4. It can lead to higher concentrations of a second drug reaching the blood, potentially causing a serious overdose situation.

Enzyme inhibition is widely used as a pharmaceutical tool to improve the bio-availability of drugs, but is ideally restricted to those enzymes which have a specific action on a single target drug. Specifically inhibiting such an enzyme then has little or no effect on other molecules. This is not the case for CYP3A4 which is a broad spectrum enzyme that metabolises more than 50% of all drugs to some degree. Inhibiting CYP3A4 therefore has wide-ranging consequences for a vast array of drugs which are sensitive to it. For this reason, CYP3A4 inhibitors are only rarely developed to improve the bio-availability of drugs or to simplify drug schedules (J. Krauß, & F. Bracher, 2018 [16]), but are more commonly avoided due to "Risk of DDI" (Bonhert *et al*, 2010 [17]. By virtue its ability to inhibit CYP3A4, grapefruit juice has all the characteristics to induce drug-drug interactions. Before drinking grapefruit juice, it is therefore vital to seek medical advice to ensure that patients are not taking other drugs that could lead to dangerous overdose situations.

What are the current options for Parkinson's patients ?

We have demonstrated that the low bio-availability and short half-life of levodopa is strongly affected by metabolism by the CYP3A4 enzyme. Inhibiting this enzyme can very significantly improve the efficacy and persistence of the drug, thus offering greater comfort and quality-of-life to Parkinson's disease patients.

Inhibiting CYP3A4 will not however be possible for all Parkinson's patients because of the serious risk of DDIs. Those using other drugs for conditions unrelated to PD must seek medical advice to avoid such risks.

Grapefruit juice is a proven inhibitor of CYP3A4, but to use it to enhance the performances of levodopa will be controversial. Grapefruit juice also inhibits other Cytochrome P450 enzymes which further increases the risk of DDIs. Any protocol for the use of grapefruit juice to inhibit CYP3A4 must take into account the kinetics of the inhibition and regeneration processes mediated by PXR. Regular and systematic dosing is essential. Intermittent inhibition of CYP3A4 is counter-productive and will aggravate Parkinson's disease symptoms.

A properly dosed CYP3A4 inhibitor, prescribed by medical professionals under controlled conditions to avoid CYP3A4 fluctuations and minimize the safety risk with respect to other drugs would be the preferred solution. In its favour, there are no safety issues with grapefruit for people in good health and who are not otherwise medicated. In addition, grapefruit contains flavonoids which have anti-inflammatory and free-radical scavenging properties which may also be beneficial for Parkinson's disease patients in the long term.

WARNING

Anyone with Parkinson's disease considering drinking grapefruit juice on a regular basis should first discuss the matter with their doctor and consult in detail the article by D.G. Bailey [7] on grapefruit-induced drug-drug interactions.

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References

1) J. Meiser, D. Weindl & K. Hiller,
Complexity of dopamine metabolism.
Cell Commun Signal. 2013 May 17;11(1):34
https://www.ncbi.nlm.nih.gov/pubmed/23683503

2) A F Wright,
The Metabolism of L-Dopa – Why are Cytochrome P450 Enzymes being ignored.
https://www.researchgate.net/publication/331648033_The_Metabolism_of_L-Dopa_-_why_are_Cytochrome_P450_Enzymes_Being_Ignored

3) R. Scott Obach
Enzyme Inhibition and Inactivation: Cytochrome P450 Enzymes
Enzyme Inhibition in Drug Discovery and Development: The Good and the Bad, p 243-264, Wiley, 2010. Editors: Chuang Lu, Albert P. Li

4) R. Sultana & Md. Z. Sultan
In vitro Effect of Withania somnifera, Mucuna pruriens and Pausinystalia johimbe on Hepatic Cytochrome P450 in Rat. *Bangladesh Pharmaceutical Journal*, *21*(2), 118-122.
https://doi.org/10.3329/bpj.v21i2.37922

5) Ramon Cacabelos
Parkinson's Disease: From Pathogenesis to Pharmacogenomics
Int J Mol Sci. 2017 Mar; 18(3): 551.
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5372567/#B17-ijms-18-00551

6) Paine MF, Hart HL, Ludington SS, Haining RL, Rettie AE, Zeldin DC.
The human intestinal cytochrome P450 "pie". - NCBI – NIH
https://www.ncbi.nlm.nih.gov/pubmed/16467132
Drug Metab Dispos. 2006 May;34(5):880-6. Epub 2006 Feb 7.

7) D.G. Bailey, G. Dresser & J.M.O Arnold.
Grapefruit–medication interactions: Forbidden fruit or avoidable consequences?
CMAJ. 2013 Mar 5; 185(4): 309–316.
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3589309/

8) S.Olguín-Reyes R.Camacho-Carranza, S.Hernández-Ojeda, M.Elinos-Baez *et al*
Bergamottin is a competitive inhibitor of CYP1A1 and is antimutagenic in the Ames test : Food and Chemical Toxicology, Volume 50, Issue 9, September 2012, Pages 3094-3099

9) Lown KS, Bailey DG, Fontana RJ, et al. Grapefruit juice increases felodipine oral availability in humans by decreasing intestinal CYP3A protein expression. J Clin Invest 1997;99:2545–53
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC508096/

10) Jawad Kiani & Sadar Z Imam
Medicinal importance of grapefruit juice and its interaction with various drugs.
Nutr J. 2007; 6: 33. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2147024/

11) M.L. Veronese, L.P. Gillen, J.P. Burke, E.P. Dorval, W.W. Hauck, F. Pequignot, S.A. Waldman & H.E. Greenberg
Exposure-dependent inhibition of intestinal and hepatic CYP3A4
J. Clin Pharmacol. 2003 Aug;43(8):831-9.
https://www.ncbi.nlm.nih.gov/pubmed/12953340

12) A F Wright
The role of Cytochrome P450 enzyme inhibitors in herbal treatments of Parkinson's Disease
https://www.researchgate.net/publication/330683781_The_role_of_Cytochrome_P450_enzyme_inhibitors_in_herbal_treatments_of_Parkinson's_Disease

13) M Teixeira
Rebound effects of modern drugs: serious adverse events unknown by health professionals
Rev. Assoc. Med. Bras. vol.59 no.6 São Paulo Nov./Dec. 2013

14) J Y Moon & H S Gwak
The Role of the Nuclear Pregnane Receptor in Drug Metabolism and its Clinical Response.
Receptors and Clinical Investigation, 2; e; 996, 2015
https://www.smartscitech.com/index.php/rci/article/view/996/pdf_128

15) L Basheer & Z Kerem.
Interactions between CYP3A4 and Dietary Polyphenols
Oxidative Medecine and Cellular Longevity, volume 2015 Article ID 854015
https://www.ncbi.nlm.nih.gov/pubmed/26180597

16) J. Krauß & F. Bracher
Pharmacokinetic Enhancers (Boosters)-Escort for Drugs against Degrading Enzymes and Beyond
Sci Pharm. 2018; 86(4)

17) T. Bonhert & L-S Gan
The Role of Drug Metabolism in Drug Discovery
Enzyme Inhibition in Drug Discovery and Development: The Good and the Bad, pp 91-176, Wiley, 2010. Editors: Chuang Lu, Albert P. Li