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PERSPECTIVES

Parkinson's disease: carbidopa, nausea, and dyskinesia

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Abstract: When L-dopa use began in the early 1960s for the treatment of Parkinson's disease, nausea and reversible dyskinesias were experienced as continuing side effects. Carbidopa or benserazide was added to L-dopa in 1975 solely to control nausea. Subsequent to the increasing use of carbidopa has been the recognition of irreversible dyskinesias, which have automatically been attributed to L-dopa. The research into the etiology of these phenomena has identified the causative agent of the irreversible dyskinesias as carbidopa, not L-dopa. The mechanism of action of the carbidopa and benserazide causes irreversible binding and inactivation of vitamin B_6 throughout the body. The consequences of this action are enormous, interfering with over 300 enzyme and protein functions. This has the ability to induce previously undocumented profound antihistamine dyskinesias, which have been wrongly attributed to L-dopa and may be perceived as irreversible if proper corrective action is not taken.

Keywords: vitamin B_6, PLP, irreversible, pyridoxal 5'-phosphate

Introduction

Serotonin, dopamine, norepinephrine, and epinephrine are centrally acting monoamines. The immediate amino acid precursor of serotonin is 5-hydroxytryptophan (5-HTP); L-3,4-dihydroxyphenylalanine (L-dopa) is the immediate amino acid precursor of dopamine. The aromatic L-amino acid decarboxylase (AADC; EC 4.1.1.28) enzyme catalyzes the synthesis of serotonin, dopamine, and histamine.[1,2]

Side effects may position L-dopa as one of the last drugs administered, despite the fact that it has the highest efficacy in the treatment of Parkinson's disease.[3] Two prominent L-dopa side effects are nausea and dyskinesias. Carbidopa is listed as a decarboxylase inhibitor and is sold in the US. It is administered in combination with L-dopa to alleviate nausea.[4] It irreversibly binds to and permanently deactivates pyridoxal 5′-phosphate (PLP) and PLP-dependent enzymes and depletes PLP reserve pools.[5] The first documentation of novel carbidopa-induced dyskinesias was in 2012.[1] Research into the phenomenon led to the formulation of the hypothesis that if significant depletion of histamine induces dyskinesias, then carbidopa is capable of inducing dyskinesias, which if not managed properly may be perceived as irreversible.

Benserazide is a decarboxylase inhibitor sold outside of the US. The term "benserazide" refers to the drug or its metabolite trihydroxybenzylhydrazine. No efficacy claims have been approved by the US Food and Drug Administration (FDA) for carbidopa or benserazide.[6] Their only indication is management of L-dopa-induced nausea, a side effect.[4,6] Double-blind studies are used to demonstrate efficacy, but are not appropriate for developing comprehensive side-effect profiles. Fatal events, which

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can occur at a rate of one in 10,000, may not be observed during a limited-population and limited-duration study.

Endogenous versus competitive inhibition

The endogenous state relating to serotonin and dopamine exists when no amino acid precursors are taken, or when inadequate or improperly balanced precursors are administered. Competitive inhibition is the interaction of serotonin and dopamine that may occur in synthesis, transport, and metabolism only when adequate and properly balanced amounts of serotonin and dopamine amino acid precursors are administered simultaneously. Organic cation-transporter type 2 functional status analysis verifies the existence of the serotonin/dopamine competitive inhibition state under the apical regulatory supersystem model. When competitive inhibition under this system exists, changes to either serotonin or dopamine concentrations individually will affect both serotonin and dopamine concentrations in a predictable manner.[1,7–16]

Relative nutritional deficiency

A relative nutritional deficiency (RND) exists when optimal nutrient intake cannot meet system needs. Parkinson's disease may induce many RNDs associated with depletions of serotonin, dopamine, norepinephrine, epinephrine, thiols (homocysteine, L-methionine, *S*-adenosyl-L-methionine, *S*-adenosyl-homocysteine, cystathione, L-cysteine, and glutathione), L-tyrosine, and L-tryptophan.[1,7,17,18–23]

L-dopa may induce depletions of serotonin, thiols, L-tyrosine, and L-tryptophan, resulting in RNDs (Figure 1).[1,7] Carbidopa may induce depletions of peripheral serotonin, dopamine, norepinephrine, and epinephrine, along with system-wide depletion of niacin and vitamin B_6, resulting in multiple system RNDs. Over 300 enzymes and proteins require vitamin B_6 for normal function.[1,7,24–29]

Drug/nutrient perspective

A nutrient is any substance that facilitates normal system function. A drug is any substance that induces abnormal system function. A nutrient may become a drug. A drug may not become a nutrient. When the nutrient 5-HTP is administered as a single agent, dopamine depletion may occur. If dopamine depletion is induced, 5-HTP is no longer functioning as a nutrient; it is a drug.[1,7–22] When L-dopa is administered as a single agent, it may deplete serotonin, and would then be considered a drug, not a nutrient.[1,7,30–34]

L-dopa-induced nausea

The only indication for carbidopa and benserazide is control of nausea resulting from improper L-dopa administration. The enzyme L-aromatic amino acid decarboxylase (AADC) catalyzes the synthesis of serotonin and dopamine by metabolizing 5-HTP and L-dopa, respectively. Through irreversible inhibition of AADC, carbidopa or benserazide compromises peripheral synthesis of serotonin and dopamine. This drug-induced inhibition of peripheral metabolism of L-dopa by AADC leaves more L-dopa unmetabolized and available to freely cross the blood–brain barrier into the central nervous system. As a result, when carbidopa or benserazide is administered, lower L-dopa daily intake values are required to achieve the same central nervous system results.[4,6]

It is documented that 5-HTP controls L-dopa-induced nausea, utilizing the same basic chemical mechanism as carbidopa and benserazide: AADC inhibition. Carbidopa and benserazide inhibition is irreversible while 5-HTP inhibition is reversible. The use of 5-HTP is superior, since under proper administration it is a nutrient that does not deplete systems or induce abnormal system functions when properly administered.[1,7,35–37]

If the goal of administering 5-HTP for the control of L-dopa-induced nausea is to have it function as a nutrient, this is not merely a simple substitution. It requires concomitant

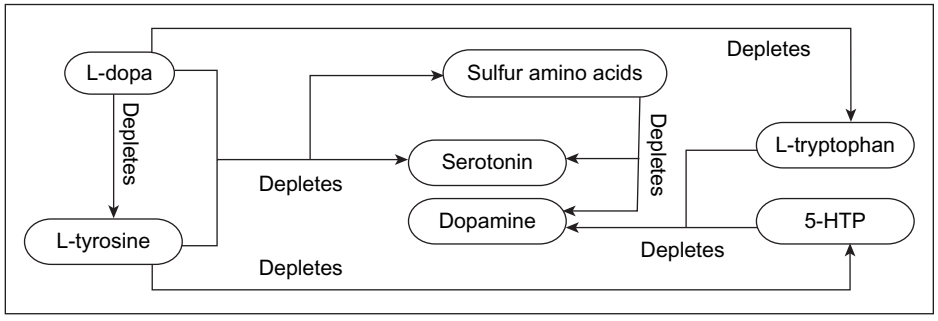

Figure 1 Administering any of the illustrated components in a dominant manner will facilitate the associated depletion.
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Abbreviation: HTP, hydroxytryptophan.