PRELIMINARY REPORT

Increased Plasma Tryptophan in HIV-Infected Patients Treated With Pharmacologic Doses of Nicotinamide

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OBJECTIVE: Decreased plasma tryptophan in persons infected with human immunodeficiency virus (HIV) was first reported over a decade ago, and this observation has since been confirmed by many groups. Before this study, only zidovudine (an antiviral medication) had been reported to reverse plasma tryptophan depletion in HIV-infected persons. Starting with the hypothesis that HIV induces a pellagralike state and that plasma tryptophan in HIV-infected patients is decreased as a known biochemical correlate of pellagra, we predicted that niacin therapy would reverse plasma tryptophan depletion as it does in pellagra.

METHODS: After receiving approval from the institutional review board, we treated HIV-infected patients for 2 mo with high-dose niacin in the form of oral nicotinamide.

RESULTS: There was an average 40% increase in plasma tryptophan ($P = 0.01$) in the four HIV-infected individuals who completed the 2-mo protocol. This finding was specific in that four other amino acids, which have been shown to have significant plasma concentration alterations during HIV infection (i.e., cystine, methionine, taurine, and lysine), showed no significant change with nicotinamide therapy.

CONCLUSIONS: There were no adverse side effects attributable to this treatment. The effects of high-dose nicotinamide treatment on morbidity or mortality in HIV-infected persons are yet to be determined. This report marks the first successful use of a vitamin to reverse this HIV-induced metabolic abnormality. *Nutrition* 2001;17:654–656. ©Elsevier Science Inc. 2001

KEY WORDS: tryptophan, human immunodeficiency virus, nicotinamide, niacin, pellagra, humans, metabolic

INTRODUCTION

Pellagra is the condition caused by niacin depletion. Some patients infected with human immunodeficiency virus (HIV) have been known to idiopathically develop one or more of the three major clinical findings of pellagra: dermatitis, diarrhea, and dementia. This observation previously led us to a series of in vitro studies showing that HIV infection leads to a decrease in intracellular nicotinamide adenine dinucleotide (NAD) and niacin in the form of nicotinamide can reverse this loss of NAD. We labeled this sequence of events "HIV-induced intracellular pellagra" because the NAD findings recapitulate those observed in pellagra.[1]

The reasons for decreased levels of plasma tryptophan in HIV-infected individuals has not been fully elucidated.[2] However, we noted that tryptophan depletion completes a pentad of findings (three clinical and two biochemical) associated with pellagra that also have been observed in HIV infection. Dermatitis, diarrhea, dementia, decreased intracellular NAD, and decreased plasma tryptophan are the five findings.[3] Tryptophan is decreased in pellagra due to the increased metabolic transformation of tryptophan into niacin in the absence of an alternative adequate niacin supply; the same cause and effect seems to be at work in HIV-infected persons.

We report the successful use of nicotinamide, a B-vitamin compound, to reverse this HIV-induced metabolic abnormality. Fuchs et. al.[4] reported that zidovudine (also known as AZT or ZDV) leads to increased levels of tryptophan in plasma and cerebrospinal fluid in HIV-infected individuals. Zidovudine is believed to exert its tryptophan effect as an indirect result of inhibition of the HIV reverse-transcriptase enzyme. In vitro data from our laboratory studies have suggested that nicotinamide exerts no measurable HIV reverse-transcriptase inhibition and therefore likely works through an alternative mechanism.[5]

Pharmacologic doses of nicotinamide in excess of 3 g/d have been used in other disease models, such as type I diabetes.[6] The existence of a body of literature on the safe use of high doses of nicotinamide allowed us to proceed with some confidence that these doses would be non-toxic, an expectation borne out in our small study group.

MATERIALS AND METHODS

Patients

The Institutional Review Board of the University of Pennsylvania reviewed and approved the protocol before the recruitment of

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TABLE I.

BASELINE CHARACTERISTICS OF PATIENTS TAKING NICOTINAMIDE

Patient	CD4 count	Antiretroviral (duration)	Tryptophan (daily intake)	Niacin (% RDA)
1	0	None	0.89 g	210
2	220	SQV/ZDV/DDI (3 y)	1.44 g	112
3	290	ZDV (2 y)	0.66 g	164
4	620	None	1.05 g	120

DDI, didanosine; RDA, recommended daily allowance; SQV, saquinavir; ZDV, ziduvidine.

TABLE II.

CHANGES IS PLASMA TRYPTOPHAN LEVELS (μMOL/L) IN PATIENTS TAKING 3 G OF NICOTINAMIDE DAILY FOR 2 MO

Patient	Days of treatment	Baseline plasma tryptophan	Final plasma tryptophan	Change in plasma tryptophan
1	57	31.1	52.9	+70.1%
2	61	53.4	82.3	+54.1%
3	63	62.0	75.1	+21.1%
4	60	51.0	66.5	+30.4%

patients for this study. The patients were recruited from the Immunodeficiency Clinic at the University of Pennsylvania if they expressed interest in participating and met the eligibility criteria of having confirmed HIV infection and being on no antiretroviral medications or a stable antiretroviral regimen for at least 3 mo.

Diet Survey

A registered dietitian performed a baseline diet survey and determined the prestudy dietary niacin equivalents for each participant by with the Food Processor program.

Clinical Monitoring

None of the patients recruited for the study had baseline wasting syndrome, dermatitis, diarrhea, or dementia; it was planned that these clinical measures would be monitored if present during the study.

Nicotinamide

Tablets containing 500 mg of nicotinamide were purchased from Rugby Laboratories, Inc. (Norcross, GA, USA) and dispensed with instructions to take two tablets three times a day.

Routine Laboratory Testing

Serum chemistries, complete blood counts, and CD4 and CD8 lymphocyte counts were performed on all patients at baseline and at the completion of their participation.

Quantification of Plasma Amino Acids

SSA deproteinization and high-performance liquid chromatography were used to quantify amino acids.[7]

Statistical Methods

The significance of differences between pre- and posttreatment values were assessed with a paired *t* test.

RESULTS

Baseline characteristics of the four patients who completed the trial are listed in Table I and show that niacin effect was tested across a range of immune statuses (CD4 counts ranging from 0 to 620). There was a wide range of baseline dietary niacin intake, although none of the patients had baseline niacin intakes exceeding 325% of the recommended daily allowance associated with the survival benefit in the study by Tang et al.[8] We found no significant changes in CD4 counts pre- and posttreatment and did not test HIV viral load.

Of the five amino acids that Hortin et al.[7] found to be significantly altered in HIV-infected patients, application of the paired *t* test resulted in a significant *P* value only for tryptophan ($P = 0.0112$; Table II). Comparison of pre- and posttreatment plasma levels for cystine ($P = 0.901$), methionine ($P = 0.531$), taurine ($P = 0.873$), and lysine ($P = 0.208$) showed no significant changes.

Seven patients who were enrolled did not complete the study, two because of recurrent medical problems (i.e., recurrent abdominal pain and recurrent transfusion requirement) and five because of non-adherence to the regimen of six pills per day. None of the 11 enrollees had side effects attributable to the niacin therapy.

DISCUSSION

Previous studies have shown that alterations in plasma tryptophan inversely correlate with markers of inflammation (e.g., neopterin) and oxidative metabolites of tryptophan (e.g., kynurenine).[9] The conclusion of other investigators, that plasma tryptophan is diminished in HIV-infected individuals because of interferon-γ–induced indoleamine-2,3-dioxygenase, provides the potential mechanism for diminished tryptophan.[10] Our hypothesis, that tryptophan is diminished due to the shunting of tryptophan to niacin along the oxidative pathway in response to HIV-induced intracellular pellagra, suggests the potential homeostatic strategy. These two concepts are easily integrated.

The prognostic implications of increased plasma tryptophan are unclear.[11] However, tryptophan is essential to the synthesis of protein, serotonin, niacin, and NAD; whereas tryptophan, serotonin, and NAD are diminished in HIV-infected persons, serum niacin concentrations are elevated.[12] Elevated serum niacin levels in the presence of depleted tryptophan, serotonin, and NAD suggest that maintaining niacin levels is a metabolic priority in HIV-infected individuals.

This is the first report in which niacin in the form of nicotinamide was used prospectively to reverse a HIV-induced in vivo phenomena. Our use of high-dose oral niacin (150 times the recommended daily allowance) in HIV-infected individuals was well tolerated and had a significant effect on plasma tryptophan levels. These findings and those of prospective epidemiologic studies showing a survival benefit to daily niacin doses simply exceeding 3.25 times the recommended daily allowance[8] and in vitro data showing HIV inhibition with niacin[5] suggest significant potential benefit with the use of this compound by HIV-infected individuals. The optimal dose is unclear. We are currently engaged in ongoing attempts to test the clinical use of pharmacologic doses of nicotinamide in HIV-infected persons; these studies will measure multiple metabolites in addition to amino acids (e.g., serum

niacin and quinolinic acid) and markers of inflammation (e.g., neopterin) and test serum HIV viral load.

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