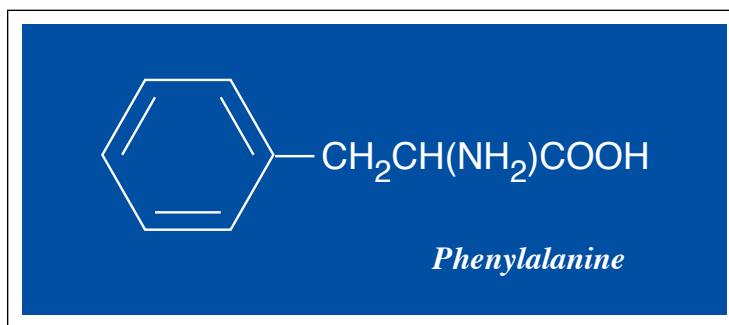


DL-Phenylalanine

Introduction

Phenylalanine is a biologically essential amino acid that acts as a precursor to tyrosine and the catecholamines (epinephrine, norepinephrine, dopamine, and tyramine), and is a constituent of many central nervous system neuropeptides. Normal dietary levels of phenylalanine are approximately 1-2 grams daily.¹ As a clinically important amino acid, phenylalanine has been used to treat endogenous depression² and attention deficit disorder,³ and as a potentiator of opiate analgesia in chronic pain.⁴



Biochemistry

Phenylalanine not needed for tissue synthesis is converted to tyrosine via phenyl-alanine hydroxylase, an oxygenase enzyme that requires the presence of oxygen and tetrahydrobiopterin (part

of the folic acid molecule). The reaction is irreversible, making phenylalanine an essential amino acid and tyrosine a non-essential one.¹ The conversion of phenylalanine to tyrosine is an efficient process; over 95 percent of ingested phenylalanine is converted to tyrosine.¹ When given in a fasting state, phenylalanine can supply 70 percent of the tyrosine appearing in the plasma.⁵ Phenylalanine is a precursor to the catecholamines and is also present in several active brain neuropeptides, including somatostatin, vasopressin, melanotropin, ACTH, substance P, enkephalin, angiotensin II, and cholecystokinin.⁶

In phenylketonuria (PKU), an inborn error of metabolism, either phenylalanine hydroxylase or the cofactor tetrahydrobiopterin are absent. This prevents the production of tyrosine, depresses levels of serotonin in the plasma, and elevates blood and urine levels of phenylalanine.⁷ The metabolites of phenylalanine are believed to be responsible for the symptoms of altered mental capacity in children with PKU. Those with untreated PKU have severe retardation and very low IQs. Symptoms include hyperactivity, aggression, convulsions and tremors, light pigmentation, and abnormal posture or gait patterns. Although severe PKU is usually picked up in infancy, mild PKU may not be diagnosed at an early age.⁸

Pharmacokinetics

Phenylalanine is the only amino acid besides methionine in which both isomers, the D- and L-forms, are equally absorbed, due to efficient enzymatic conversion between the isomers. The synthetic isomer (D- form) appears to be absorbed rapidly in humans and converted into the L-form.⁹

Mechanisms of Action

A metabolic end-product of phenylalanine, phenylethylamine (PEA), is metabolized by monoamine oxidase type B to phenylacetic acid (PAA).¹⁰ Tricyclic antidepressants and MAO inhibitors increase PEA levels in the brain.¹¹ PEA is believed to have amphetamine-like properties, and urine levels have been found to be reduced in patients with depression.¹² Using it as a diagnostic tool, Sabelli found significantly lower levels of PEA in plasma and urine in depressed subjects, compared with normal controls. Treatment with phenylalanine improved mood in 78 percent of depressed subjects.¹²

Phenylalanine has been shown to inhibit enkephalinase and increase levels of met-enkephalin in the brain, producing opiate-mediated analgesia.¹³ Enkephalinase-inhibitors are unique analgesia-producing agents that do not show tolerance or dependence. No signs of withdrawal are evident in animal studies when large doses (250-400 mg per kg) are used for long periods of time.¹³

Clinical Indications

Endogenous Depression

Multiple studies indicate a possible role for DL-phenylalanine in the treatment of depression. In an open, uncontrolled trial, 75-200 mg of DL-phenylalanine was administered to 20 patients suffering from endogenous depression. Assessment tools included psychometric testing, including the Hamilton Depression Scale, and psychiatric assessment. At the end of the trial (20 days), 60 percent of patients were asymptomatic and 20 percent were significantly improved and able to be discharged from care.¹⁴

Other small trials with doses of 50-200 mg DL-phenylalanine reported significant symptom improvement within 13-15 days. Unfortunately, these studies lacked objective diagnostic criteria or depression rating scales.^{15,16} In a large trial, 455 patients with depression were given up to 400 mg per day of D-phenylalanine for 2-6 months. Individuals with a diagnosis of endogenous depression showed the most improvement; after 15 days, 73 percent were asymptomatic and 23 percent had significant improvement. In a group of patients with reactive depression, 53 percent recovered and 23 percent had significant improvement of their symptoms. There was no significant effect on patients who had been diagnosed with depression after age 50.²

In two double-blind studies comparing equal doses of imipramine to either 100 mg D-phenylalanine or 150-200 mg DL-phenylalanine, improvement in psychometric testing and clinical improvement after 30 days were similar, with the majority of patients improving on either therapy.^{2,17}

There are many unanswered questions about the use of phenylalanine in depression. One study using 600 mg D-phenylalanine for one month in 10 depressed individuals had no effect.¹⁸ It is suggested this and other early studies used inadequate dosage levels, and that up to 6 grams DL-phenylalanine may be necessary to normalize PEA levels in treating endogenous depression.¹⁹

A more recent study attempted using an individualized dosing system of L-phenylalanine with a steady dose of 100 mg pyridoxine in 40 patients with either unipolar or bipolar depression.¹² The authors found maximum dosing levels for symptom alleviation were as high as 14 grams L-phenylalanine daily. In this trial, patients were given 500 mg twice daily as a baseline dose, which was increased by 500 mg daily until therapeutic effects occurred. Complete recovery occurred in 11 patients, and partial recovery in 20. L-phenylalanine reduced suicidal ideation, fatigue, and anhedonia (lack of ability to experience pleasure), and increased self-esteem. Sleep and appetite were not changed, but patients were allowed to continue benzodiazepines for sleep if needed.

An individualized combination trial with 5 mg selegiline (Deprenyl), 100 mg pyridoxine, and 2-6 grams L-phenylalanine was utilized in 10 patients with prior drug-resistant major depressive disorder.²⁰ L-phenylalanine dosages were increased daily as needed for symptom reduction. Nine of 10 patients experienced mood elevation within hours of taking L-phenylalanine, and six viewed their depression as having terminated within two to three days of starting the regimen. Global Assessment Scale scores were significantly lowered after three days of treatment and remained low on continued treatment for six weeks.

Chronic Pain

In an open study, 78 chronic pain patients were given 750-1,000 mg D-phenylalanine daily. Responses occurred in 50 percent of the study population after one week.⁴ In a double-blind, crossover study, 21 patients with chronic intractable pain were given 250 mg D-phenylalanine per day for two weeks; improvement was evident in 30 percent.²¹ A small, open study of ten patients with lumbosacral pain receiving 1,000 mg D-phenylalanine resulted in significant improvements in pain relief and analgesic use.²²

D-phenylalanine has also been used to potentiate acupuncture anesthesia, both in those who were non-responsive and to raise pain thresholds in those who were already responding. The doses used ranged between 2-4 grams.^{4,23}

Attention Deficit Disorder

In the only double-blind, crossover study published in this area, dosages of up to 1,200 mg of DL-phenylalanine were used in 19 adults with attention deficit disorder.³ After 14 days, a significant difference in mood and mood lability was observed in the treatment group. After two to three months, however, those who had improved on the DL-phenylalanine became tolerant to the effect and did not respond to higher doses.

Drug-Nutrient Interactions

Phenylalanine has been shown to compete with levodopa for transport across the blood-brain barrier.²⁴

Phenylalanine is a precursor to the catecholamines epinephrine, norepinephrine, dopamine, and tyramine. Theoretically, caution is warranted with the concomitant use of monoamine-oxidase inhibitors and phenylalanine.²⁵

Side Effects and Toxicity

LD-50 of D-phenylalanine in mice is more than 10 g/kg. Murine studies of 1 mg/kg body weight per day for six months resulted in no tissue toxicity.¹³ Short-term stimulant-type side effects have been reported, including elevation of blood pressure, headache, irritability, aggressiveness, and insomnia. Long-term side effects have not been studied.²⁶

Dosage

Dosages vary with the condition; depression responding to intake of 1-14 g daily, and pain management doses ranging from 1-4 g daily.

Warnings and Contraindications

Supplementation of phenylalanine should be avoided in PKU. Phenylalanine can interfere with the absorption and efficacy of levodopa.²⁴ Contraindications for the use of phenylalanine with schizophrenic patients has also been suggested.²⁷

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