NeuroResearch
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L-Cysteine intolerance
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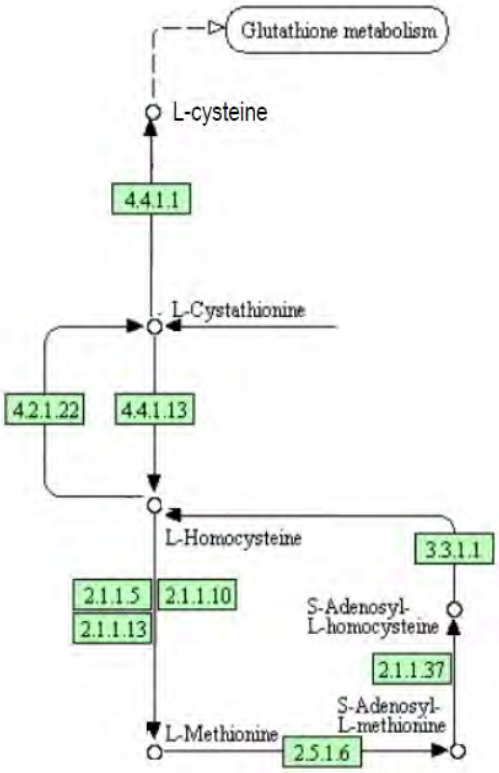
CysReplete induced heartburn



A common complaint is a GI discomfort after taking CysReplete. While the presenting complaint tends to focus on stomach upset, close questioning reveals that the discomfort is usually centering in the lower substernal region. The majority of these cases involve CysReplete adhering to the distal esophagus then dissolving. For some unknown reason, the L-cysteine irritates the esophagus but not the stomach lining.

Sitting slumped forward while taking pills is associated with induction of substernal burning by the pills. Proper management is to have the patient stand up straight, and tall then hold the CysReplete pills in their mouth with water for 20 to 30 seconds so that the exterior of the capsules start to liquify. The capsules should be swallowed with 16 ounces of water to ensure they dissolve in the stomach, not the distal esophagus.

If the patients have experienced several days of substernal burning (heartburn) following the capsule ingestion, discontinue the CysReplete for five days then restart making sure the patient is standing straight and talk with each dose of capsule ingested.

If repeated attempts reveal an inability to take six pills of CysReplete per day change the patients to L-methionine with selenium and homocysteine testing as discussed on the next page.

INFO@NEUROSUPPORT.COM
1150 88TH AVE W., DULUTH, MN
(218) 626-2220

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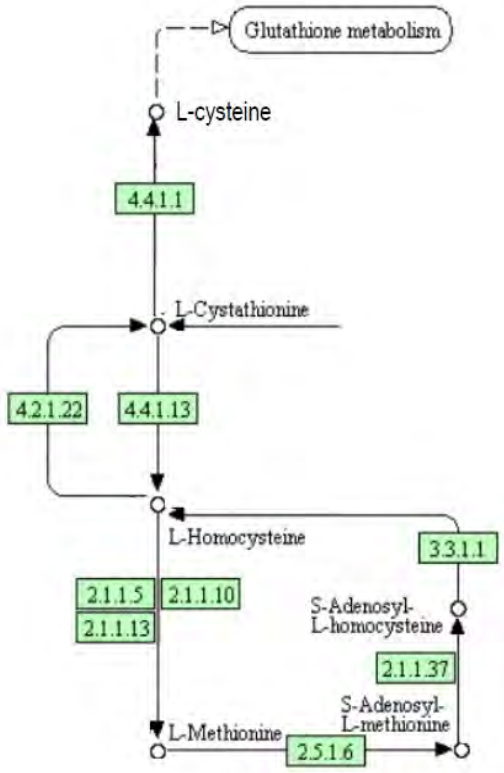
Homocysteine considerations

Abstract: If the patient is truly intolerant of L-cysteine switch to
-L-methionine 6,000 mg per day
-Selenium 400 mcg per day
-Obtain a serum homocysteine assay

If the homocysteine levels are elevated place start vitamin B6 600 mg per day for two months then repeat the test. Assume the patient does not have adequate gluathione coveratge if serum homocysteine concentrations are elevated.



For years some have pounded the drum that hyperhomocysteinemia requires vitamin B6, vitamin B12, and folate for proper care. The B12 and folate are a consideration with the metabolism of homocysteine to methionine. Both are associated with megaloblastic processes if deficient. The B12 and folate (or 5-MTHF) drum beats continue even in patients with no objective sign of megaloblastic process. The whole argument is moot because L-methionine is an essential amino acid. There are not significant amounts of L-methionine made in the system. The systemic level is dependent; on dietary sources. As you study the attached pathways, even though there are three enzymes capable of metabolizing homocysteine to methionine, the amount is not adequate to meet the needs of the system.

Homocysteine is also metabolized to cystathione and L-cysteine by the 4.2.1.22 and the 4.4.1.1 enzymes respectively. Both enzymes are vitamin B6 dependent (PLP-dependent) enzymes. Vitamin B6 binds to the enzyme body then becomes the active site of the enzyme. Metabolism of over 95% of the homocysteine is by this pathway. Of interest is the 4.4.1.13 enzyme which is a minor enzyme metabolizing cystathione to homocysteine, this too is a vitamin B6 dependent enzyme.

Physicians who have obtained extensive vitamin B6 assays from blood are aware that the results are generally not reproducible from one day to the next. Reported values can jump all over the place. We have taken the position if testing is not reproducible; it is not valid.

Urinary assays such as the xanthurenic acid test which established the US Recommended Daily Allowance (USRDA) in 1943 at about 2 mg per day is also of concern. The test does not recognize the impact of renal processing by transporters on outcomes. It appears that in patients who have induced vitamin B6 deficiency by carbidopa, the xanthurenic acid results still indicate only a 2 mg deficit.

While we do not believe blood and urine assays of vitamin B6 are valid, consider the following. The primary force driving elevated homocysteine levels is vitamin B6 deficiency. Homocysteine levels are like the canary in the coal mine warning something is wrong. In this case, elevated homocysteine is a direct indicator of vitamin B6 functional status, not a disease.

The approach we have developed is to place the patient with hyperhomocysteinemia on 600 mg of vitamin B6 per day for two months then recheck the homocysteine level. If at two months levels are too high continue the vitamin B6 at 600 mg per day with monthly lab assays until homocysteine levels have returned to normal. Do not address folate or B12 unless megaloblastic processes are present.

For patients that do not tolerate L-cysteine (which is rare), the recommended daily dose is L-methionine 6,000 mg per day with selenium 400 mcg per day. With the initiation of L-methionine, obtain a homocysteine assay. Giving L-methionine to patients with vitamin B6 deficiency as verified by elevated homocysteine levels will greatly exacerbate hyperhomocysteinemia.

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THIOLS: GLUTATHIONE, L-CYSTEINE AND NAC

For the management of thiol related relative nutritional deficiency ™*

In 1998, NeuroResearch developed clinical data that statistically verified that the optimal daily L-cysteine dose for all adults is 4,500 mg.[1*]

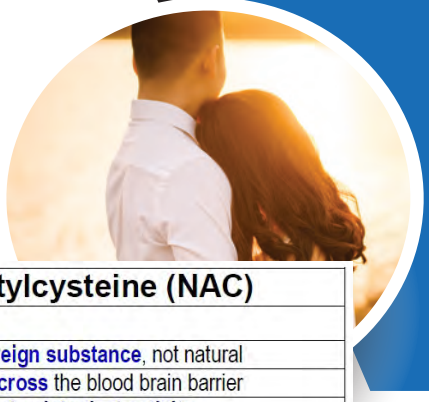
The concentrations of the seven thiols rise and fall in unison, provided enough vitamin B6 exists. Any of the seven thiols can serve as a thiol precursor.*

Based on molecular equivalent dosing the right column below indicates the monthly cost of each thiol. There is no source for the listed pricing. The price listed represents an average from three sources.*

Sulfur Moiety	Molecular Weight	Molecular Weight Equivalency Factor	Sulfur molecule milligram equivalent to 4,500 mg of L-cysteine	Monthly cost sulfur molecular equivalent to 4,500 mg L-cysteine per day
L-cysteine	121.16 gr/mol	1.000	4,500 mg	$30.31
N-acetyl-L-cysteine (NAC, not a nutrient)	163.19 gr/mol	1.3469	6,061.05 mg	$70.40
L-methionine	149.21 gr/mol	1.2315	5,541.75 mg	$111.65
S-adenosylmethionine (SAMe)	398.44 gr/mol	3.2885	14,798.25 mg	$1,479.52
Glutathione (Oral)	307.32 gr/mol	2.5365	11,414.25 mg	$1,776.06
Glutathione (Rectal)	307.32 gr/mol	2.5365	11,414.25 mg	$5,022.27
Glutathione (IV)	307.32 gr/mol	2.5365	11,414.25 mg	$10,786.47

THIS APPROACH:
When deficient serotonin or dopamine concentrations exist on an optimal diet, a relative nutritional deficiency of the naturally occurring aromatic amino acids or cofactors is always present. ™

NAC and glutathione do not cross the blood brain barrier. NAC has no direct physiologic activity. It must be metabolized to L-cysteine to become physiologically active. NAC is also metabolized to N-acetylcystine and N-diacetylcystine. If equal amounts of these two other metabolites occur when NAC is metabolized to L-cysteine, then 18,000 mg of NAC needs to be administered to equal systemic equivalent of 4,500 mg L-cysteine.*



L-cysteine	Glutathione	N-acetylcysteine (NAC)
L-cysteine **occurs naturally** in the system	Glutathione **occurs naturally** in the system	NAC is **foreign substance**, not natural
Crosses the blood brain barrier	**Does not cross** the blood brain barrier	**Does not cross** the blood brain barrier
Physiologically active	**Physiologically active**	**No direct physiological activity**
Is a thiol	**Is a thiol**	**Is not a thiol**
Rate limiting step in glutathione synthesis	**Synthesis limited** by L-cysteine availability	**Does not directly** affect glutathione
Is **a nutrient**	Is a **nutrient**	Is **not a nutrient** (a drug)
No known anaphylaxis	**No known anaphylaxis**	May induce **anaphylactoid reactions**
No asthmatic deaths known	**No asthmatic deaths** known	May induce **asthmatic deaths**
No rash reactions associated	**No rash reactions** associated	**Known urticaria flushing and pruritus**
No contraindications known	**No contraindications known**	**Contraindicated** in some patients

A comparison of L-cysteine, glutathione, and N-acetylcysteine (NAC)

[1] Hinz, M. et. al Relative nutritional deficiencies associated with centrally acting monoamines International Journal of General Medicine 2012:5 413–430