

# A Brief Consideration of Cyanocobalamin and Pyridoxine HCl

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November 28, 2006

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## CYANOCOBALAMIN

**Abstract:** Oral cyanocobalamin is an effective, safe, and nontoxic form of B<sub>12</sub> that provides all relevant clinical benefit related to B<sub>12</sub> need. Methylcobalamin, while an effective oral form of B<sub>12</sub>, has not demonstrated superiority over cyanocobalamin and does not nearly have a similar breadth of research. **Cyanocobalamin and methylcobalamin are generally considered clinically equivalent.** Due to the long history of effective and safe clinical use, cyanocobalamin remains the predominant oral B<sub>12</sub> supplement worldwide.

Advocates of oral cyanocobalamin recognize its clinical efficacy and evidence-based safety profile as cyanocobalamin is the most commonly used form of B<sub>12</sub> in fortification, dietary supplements, and in the research literature.<sup>1</sup> Methylcobalamin supporters state its superiority as it is the primary circulatory form and acts as a methyl donor. Adenosylcobalamin, however, accounts for 70% of cobalamin stored in the liver—the major storage site for B<sub>12</sub>—while methylcobalamin accounts for only 1% to 3%.<sup>2</sup> It is also argued that cyanocobalamin is poorly converted into its active forms and releases cyanide into circulation—neither of these statements is supported by research.

### Research

Research findings have demonstrated that oral **cyanocobalamin is safe and easily and rapidly converted to both methylcobalamin and adenosylcobalamin during absorption and at the target cell,**<sup>3</sup> and does reverse B<sub>12</sub> deficiency signs and symptoms. Oral cyanocobalamin has a long history of use worldwide. In Sweden, oral high-dose cyanocobalamin is the major treatment form for B<sub>12</sub> deficiency and maintenance and has gained widespread popularity since its introduction in 1964. **More than one million patients and years of data** in Sweden support the use of oral cyanocobalamin to correct and prevent B<sub>12</sub> deficiency signs and symptoms and it is considered a standard of care for most patients.<sup>4</sup> In the absence of specific genetic concerns, oral cyanocobalamin is easily absorbed and converted to its active forms.<sup>2</sup> **Oral cyanocobalamin rapidly corrects plasma markers of B<sub>12</sub> deficiency at a standard daily dosage of 500 to 1,000 micrograms.**<sup>5</sup>

In virtually every aspect of B<sub>12</sub> activity oral cyanocobalamin has demonstrated benefits, including psychological, neurological, and hematological.<sup>6</sup>

### Homocysteine/Methylation

A key function of B<sub>12</sub> is its participation in methylation reactions. Foremost of these processes is the reduction of homocysteine. While methylcobalamin does participate in homocysteine reduction, it is secondary in significance to folic acid. Methylcobalamin receives its methyl group from folic acid (*methyltetrahydrofolate*).<sup>7</sup> The body “recycles” methyl groups and cobalamin. In the homocysteine cycle, as an example, cobalamin donates its methyl group and is then converted back to methylcobalamin, receiving a methyl group from 5-methyl-tetrahydrofolate. The primary methyl donor is folic acid along with other methyl donors, whereas cyanocobalamin provides the vitamin B<sub>12</sub> component for the cycle.<sup>1</sup> **In patients with end stage renal disease—a condition associated with hyperhomocysteinemia—cyanocobalamin was demonstrated to be equipotent in reducing plasma homocysteine levels in a comparison to hydroxycobalamin.**<sup>8</sup> In a 2001 study printed in *JAMA*, Tice et al. reported oral cyanocobalamin to be a cost-effective method of reducing plasma homocysteine levels in multiple population groups.<sup>9</sup>

## Cognition

B<sub>12</sub> deficiency has been associated with alterations in cognition in the elderly. There is a known connection between elevations in homocysteine and age-related cognitive decline. The relationship must certainly include deficiencies of both folic acid and B<sub>12</sub>.<sup>9</sup> Oral cyanocobalamin is capable of reducing serum methylmalonic acid concentrations—an indication of B<sub>12</sub> repletion. Therefore, increasing the intake of B<sub>12</sub> as cyanocobalamin may provide protection against cognitive decline in older populations.<sup>10</sup> Oral use of cyanocobalamin is associated with improvements in all parameters of B<sub>12</sub> deficiency, including cognitive issues.<sup>6</sup>

## Toxicity

No toxic effects of oral B<sub>12</sub> consumption have ever been reported at any level of intake.<sup>11</sup> In a 1991 JAMA report, Hatchcock and Troendle reported no concerns with the oral use of B<sub>12</sub>. Cyanide release from oral B<sub>12</sub> was said to be toxicologically insignificant.<sup>12</sup> The lack of reported B<sub>12</sub> toxicity is a testament to the effective and safe use of this oral compound.

## Conclusion

With the above in consideration, it should be evident that cyanocobalamin is a safe and effective solution for any concern related to B<sub>12</sub> deficiency.

## PYRIDOXINE HCL

*Abstract: Recently it has been suggested that the preferred form of B<sub>6</sub> supplementation is the “active” form pyridoxal-5-phosphate (P5P). Generally, research does not support the preferential use of P5P over the oral dietary supplementation standard, pyridoxine HCl.*

Vitamin B<sub>6</sub> is a collective term that includes various forms of B<sub>6</sub> including pyridoxine, pyridoxal, pyridoxamine, pyridoxine 5'-phosphate, pyridoxal 5'-phosphate, and pyridoxamine 5'-phosphate. The term vitamin B<sub>6</sub> primarily refers only to pyridoxine.<sup>13</sup> Pyridoxine HCl is the major form of B<sub>6</sub> used in supplementation and generally fulfills all known B<sub>6</sub> needs.

## Phosphorylated B Vitamins

The primary "active" phosphorylated B vitamin is B<sub>6</sub> as pyridoxal-5-phosphate (P5P). While P5P is the major circulating form of B<sub>6</sub>, there is a lack of evidence to support the substantive intact oral absorption of P5P. It is generally considered that P5P is broken down (hydrolyzed) via intestinal alkaline phosphatase prior to absorption. The majority of oral B<sub>6</sub> exits the intestine in a nonphosphorylated form.<sup>14,15</sup> Oral pyridoxine HCl, on the other hand, is readily absorbed via a nonsaturable, passive diffusion process.

## B<sub>6</sub> Metabolism

Following absorption, nonphosphorylated B<sub>6</sub> is transported to the liver where it is *then* converted to P5P and enters circulation. The liver and not the GI tract is the major organ responsible to supply P5P to the target tissues. P5P in circulation is bound to serum albumin.

It is demonstrated that those with chronic illness exhibit low hepatic and serum P5P levels with the suggestion that this is the result of decreased hepatic synthesis. Oral P5P is then recommended as the preferred form of supplemental B<sub>6</sub>. Research demonstrates that those with poor liver function, including cirrhotics, are actually quite capable of synthesizing P5P and the use of standard pyridoxine HCl restores plasma P5P to a normal level.<sup>16</sup> In those with chronic disease, rheumatoid arthritis, inflammatory diseases, and in smokers, as examples, decreased hepatic P5P is more associated with increased degradation of P5P (related to inflammatory cytokine stimulation) versus a lack of hepatic synthesis. Oral supplementation with pyridoxine HCl in individuals with chronic hepatic or systemic disease states is capable of restoring serum P5P levels to normal.<sup>17</sup> Beneficial results with P5P are reported primarily with intravenous (IV) P5P and not oral; therefore bypassing the potential for intestinal breakdown/hydrolysis. Few studies have taken place on the benefits of oral P5P. Generally, these have occurred in only a limited patient group, at high oral dose, or following IV usage.<sup>18</sup>

## Target Cells

B<sub>6</sub> passes thru hepatic circulation and is endogenously converted to P5P prior to being active in the body. As in the gut, albumin-bound serum P5P does not enter the target cell intact. Circulating P5P is once again broken down (dephosphorylated/hydrolyzed) extracellularly prior to entering the target cell.<sup>15</sup> Therefore, pyridoxal enters the cell as the primary form of B<sub>6</sub> and not P5P.<sup>19,20</sup> The metabolic fate of serum P5P is hydrolysis to pyridoxal followed by uptake into extrahepatic tissues.<sup>21</sup> Pyridoxine is actively taken up by red blood cells (RBC) and converted to pyridoxal-5-phosphate and then to pyridoxal. RBC P5P is not released back into circulation. Pyridoxal-5-phosphate is also not taken up intact into RBCs whereas pyridoxine is rapidly taken up, converted to pyridoxal and released into plasma, and likely delivered directly to the target cells.<sup>22</sup>

## CONCLUSION

In summary, current literature indicates that both oral cyanocobalamin and pyridoxine HCl are well-researched forms of oral supplementation and are also clinically effective—easily dealing with their respective nutrient deficiencies.

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