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Thiamin (B1) and Its Application in Patients with Critical Condition

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Abstract

Thiamin is an essential water-soluble nutrient that is naturally available in some foods and available as a supplement. This nutrient plays a vital role in metabolism, cell growth and development. The recommended daily intake of thiamin for adults is around 1.1–1.2 mg/day. Several studies have described that thiamin deficiency is commonly seen in critically ill patients, mainly sepsis. Thiamin deficiency reduces pyruvate access to the Krebs cycle, therefore, increases the production of lactate. The administration of thiamin in critically ill patients has been linked to better outcomes and depletion of mortality rate.

Keywords: thiamin, vitamin B1, sepsis, septic shock

1. Introduction

Thiamin is the first vitamin B discovered; thus, it is known as vitamin B1. This micronutrient is also known as aneurine. Thiamin is an essential micronutrient that is water-soluble and involved in aerobic metabolism. Humans' daily requirement of thiamin is highly dependent on food intake due to their inability to synthesise it endogenously. Some bacteria in the human intestine can produce thiamin. However, the amount is limited [1].

The chemical name for B1 is 3-[(4-amino-2-methyl-5-pyrimidine)methyl]-(2-hydroxy ethyl)-4-methylthiazolium. Thiamin originated from pyrimidine and thiazole ring substitution, combined with the methylene bridge (**Figure 1**) [2].

Figure 1.
Thiamin structure [2].

2. Pharmacokinetics and pharmacodynamics of thiamin

Thiamin works as a cofactor in citric acid cycles. Vitamin B1 reacts with adenosine triphosphate (ATP) to form an active form called thiamin pyrophosphate.

Thiamin is an essential cofactor for enzymes pyruvate dehydrogenase, alpha-ketoglutarate dehydrogenase, and transketolase. Pyruvate dehydrogenase enzymes are the main entrance to the Krebs cycle, catalysing oxidative decarboxylation of pyruvate to form acetyl-coenzyme A (acetyl-CoA). Without this enzyme, pyruvate would be converted to lactate. Alpha-ketoglutarate dehydrogenase catalyses the oxidative decarboxylation of alpha-ketoglutarate to succinyl-CoA to complete the Krebs cycle. Transketolase is an enzyme necessary for the pentose phosphate pathway and the production of nicotinamide adenine dinucleotide phosphate (NADPH). Thiamin is required in each of these three steps (**Figure 2**) [3, 4].

The mechanism of thiamin absorption in the body is still controversial. Some researchers argue that it is only absorbed from active transport mechanisms in the proximal small intestine. However, recent studies show that thiamin is also absorbed by passive diffusion [5]. Thiamin absorption by the intestine is mediated by a transport system and absorbed by cells in the liver, heart, and other various tissues from the blood, except neural fibres. In the nervous system, thiamin is transported from circulation blood towards cerebrospinal fluid across the blood–brain barrier [2, 6]. Vitamin B1 is rapidly absorbed and transformed through a

Figure 2.
Pathogenesis of cell death in deficiency thiamin [2, 16].

Figure 3.
Oral Thiamin concentration in blood [5].

phosphorylation process into an active coenzyme, thiamin pyrophosphate. Vitamin B1 is absorbed in the jejunum at low concentrations, involving the phosphorylation process through an active transport system. At high concentrations, absorption of vitamin B1 occurs by passive diffusion. The relative bioavailability of vitamin B1 is about 5.3%. A study by Smithline et al. (2012) shows oral thiamin concentration reaching the peak at 4 hours after consumption (**Figure 3**) [5].

Thiamin is widely distributed to almost all body tissues, including breast milk. Thiamin is not stored in the body. Thiamin transport occurs through the blood, both in erythrocytes and plasma. About 90–94% of vitamin B1 is bounded to protein [2].

Thiamin metabolism occurs in the liver and produces active metabolites, thiamin pyrophosphate, thiamin monophosphate, and thiamin triphosphate. Thiamin diphosphate is the primary active metabolite, which acts as a coenzyme in carbohydrate metabolism through transketolase reaction [2, 7].

Thiamin half-life ranges from 9 to 18 days on daily consumption, and the elimination or dephosphorylation process occurs in kidneys. This half-life appears to be variable and highly dose-dependent. One study showed that the half-life of thiamin is only about 6 hours at high doses (500-1500 mg). For intravenous administration, peak levels reached within 2–6 hours depending on doses [5]. If there is an excess of free-form vitamin B1, it will be excreted in the urine. In regular doses, it is secreted in the urine in unchanged form [2].

3. Sources

Thiamin cannot be produced indigenously in the human body. Therefore, we rely on dietary intake [8]. The sources of thiamin include fortified flours, whole grain cereals, meat (pork, beef or poultry), eggs, dried beans, soybeans and nuts. Nevertheless, polished rice, fats, processed flours, dairy products and vegetables are not reliable sources to satisfy the daily requirements of thiamin [9]. Significant losses of thiamin happen when the food is cooked or undergone other heating processes. Polyphenolic compounds in tea and coffee may inactivate thiamin;

therefore, their consumption must be in moderation. Similarly, uncooked fish and shellfish contain thiaminases that inactivate and break down thiamin [9, 10].

4. Intake and novel applications

4.1 Recommended daily intake of thiamin

Recommended daily thiamin intake in healthy adult men is 1.2 mg/day, while adult women are 1.1 mg/day. For children aged 1–8 years, recommended intake of vitamin B1 ranges from 0.5 to 0.6 mg/day and for ages 9–13 years, it starts from 0.9 mg/day (**Table 1**) [5]. Thiamin is water-soluble across the placenta. Its requirements increase during pregnancy. Pregnancy also increases the risk of thiamin deficiency when prolonged nausea and vomiting (including hyperemesis gravidarum). The dose of parenteral nutritional supplements is 6 mg/day. The parenteral form can be given by intramuscular (IM) or intravenous (IV) injection. Administration of thiamin intravenously can be given as much as 100 mg over 5 minutes [11].

4.2 Side effects of thiamin

Adverse reactions to thiamin administration have been reported as reactions at the injection site, but their frequency is unknown. Other side effects can be diaphoresis, pruritus, skin sclerosis (at the injection site after IM administration), urticaria, nausea, bleeding (in the digestive tract). For hypersensitivity side effects, reported anaphylaxis (after IV administration), angioedema, hypersensitivity reactions (following IV administration). Side effects of intravenous thiamin are rarely reported. A prospective study by Wrenn in 989 samples given thiamin 100 mg IV found adverse reactions in the form of minor reactions, which were transient local irritation in 1.1% and pruritus in 0.0093% of patients. Thiamin hydrochloride can be given intravenously without problems. An intradermal test dose before administration is not required unless the patient had a previous allergic reaction [12]. Local side effects for larger doses can be minimised by slow administration into a larger and more proximal vein. Thiamin should be administered before parenteral glucose solutions to prevent Thiamin deposition as a symptom of acute thiamin deficiency in malnourished patients [11].

Patients by age	mg per day
Infant and children	
Newborn to 6 months	0.3
6 months–1 year	0.4
1–3	0.7
4–6 years	0.9
7–10 years	1.0
Teens and adults	
Men	1.2–1.5
Women	1.0–1.1
Pregnant women	1.5
Breastfeeding women	1.6

Table 1.
Recommended dietary allowance (RDA) of thiamin [2].

Alcohol consumption can interfere with intestinal absorption of vitamin B₁, and chronic alcoholism leads to *Wernicke-Korsakoff syndrome* (WKS) [2]. Intoxication may occur with ingestion of more than 3000 mg thiamin in the long term. Based on animal research, thiamin lethal dose/LD₅₀ are 8224 mg/kg, while the LD₅₀ in rats are 3710 mg/kg [13]. Sporadic anaphylactic reactions have been reported. Some researchers suggest that intravenous thiamin should be administered in a resuscitation facility. However, due to the life-threatening nature of WKS, EFNS (European Federation of Neurological Society) guidelines recommend starting treatment immediately, even in the absence of facilities for resuscitation [14].

4.3 Thiamin and brain metabolism

Thiamin has an essential role in brain metabolism. Nerve cells use glucose as the primary fuel in producing energy. Glucose reaches brain tissue by diffusion across the blood–brain barrier. Around 30% of glucose absorbed by the brain undergoes complete oxidation through the Krebs cycle [15]. Various mechanisms contribute to selective brain lesions observed in WKS and thiamin deficiency. Recent evidence of early microglial activation and increased production of free radicals suggests that oxidative stress processes play a vital role in brain cell death associated with thiamin deficiency. Recent studies in animal models of WKS demonstrated changes in thiamin-dependent enzymes in the brain and suggested that changes in these enzyme activities may result in neuronal death, characteristic of this syndrome [16].

Thiamin is needed as an enzyme cofactor essential for brain metabolism, and around 80% of total thiamin is in the neural tissues [10, 17]. In addition to its co-enzymatic function in metabolism, thiamin also has a structural role [18, 19]. Thiamin affects membrane structure and function, including axoplasmic, mitochondrial, and synaptosomal membranes, which act against agent-induced cytotoxicity and improve membrane location [20, 21]. Thiamin also intervenes in synaptic transmission and plays a role in cell differentiation, synapse formation, axonal growth, and myogenesis [2].

4.4 Thiamin as a novel treatment for sepsis

Thiamin deficiency is common in critically ill patients and correlated with increased mortality in some cases. In addition, its levels are depleted throughout the illness, and administration of thiamin during critical illness can improve organ dysfunction [22]. Predisposing factors to thiamin deficiency result from several associated problems associated with nutritional disorders and other accompanying diseases. Several conditions can reduce thiamin levels, such as impaired carbohydrate metabolism, increased metabolic requirements for parenteral or enteral nutrition, diuretics, and haemodiafiltration. Several studies have found the presence of thiamin deficiency in critically ill patients. Thiamin deficiency is associated with poor prognostic outcomes [23].

A cohort study in Australia with 129 patients found no association between plasma thiamin concentrations with systemic inflammation and mortality in critically ill patients. In addition, it also shows that level of thiamin intake in patients who had not received its supplementation before ICU admission did not differ between patients who died and those who survived, 264 compared 268 nanomol/L (normal value: 190–400 nanomol/L). Besides that, only a weak correlation was found between thiamin levels and disease severity index. A study had investigated the correlation of thiamin, APACHE II, SOFA score, maximum SOFA score, SOFA delta (DSOFA), and CRP. However, the correlation is not statistically significant [24].

Thiamin deficiency can also be observed in septic shock patients, occurring in 8.5–72% depending on the cutoff value used to determine thiamin deficiency [4, 22, 25, 26]. Lack of thiamin reduces pyruvate access to the Krebs cycle, increasing lactate production as it converts metabolism to anaerobic [23].

A prospective observational study examined the association between thiamin levels and lactic acidosis in 30 septic shock patients and found no correlation between these variables. However, after excluding patients with abnormal liver function, a significant negative correlation was found between thiamin concentrations and lactic acidosis ($r = -0.53$, $P = 0.01$). This finding implies a potential relationship between thiamin levels and lactic acidosis in septic shock patients with normal liver function. Thus, by reducing pyruvate dehydrogenase complex activity, thiamin deficiency contributes to an increase in lactic acid in septic patients [26].

Parenteral administration of thiamin 250 mg once daily for 3–5 consecutive days is recommended to treat thiamin deficiency. Slow intravenous administration of thiamin diluted in isotonic NaCl or 5% dextrose is also safe. However, there is no consensus on the optimal daily dose of thiamin, its formulation, and duration of treatment [14]. The half-life of unphosphorylated thiamin blood is 96 hours. Therefore, two or three daily doses can achieve better concentrations in the brain than a single daily dose. In patients who do not consume alcohol, a daily intravenous dose of 100 or 200 mg is sufficient to meet thiamin requirements. However, alcoholic patients with WKS may require doses as high as 500 mg three times daily [14].

A clinical trial of *ascorbic acid and Thiamin effect in septic shock* (ATESS) conducted in South Korea compare outcomes of a combination of ascorbic acid (IV 50 mg/kg, maximum dose per dose of 3 g) and thiamin (200 mg) every 12 hours for two days with placebo groups on 111 subjects. The results showed no significant differences in SOFA scores and organ function but found an increase in serum levels of vitamin C and thiamin [27].

This finding is in contrast to another clinical study in 94 patients who received a combination of 1500 mg of vitamin C IV q6, 200 mg of thiamin IV q12 for four days or until discharge from ICU, and 50 mg of hydrocortisone IV q6 (with the optional alternative of 50 mg bolus, followed by continuous infusion of 200 mg in 24 hours) for four days. Thiamine administration had significantly reduced the progression of organ dysfunction and mortality in patients with severe sepsis and septic shock. However, the research design had weaknesses include small study size, pre-and post-study design, single-centre, absence of blinding, and presence of three simultaneous interventions limiting the generalizability of the conclusion. Although it can help invent new hypotheses in future, this study is still not strong enough to produce a change in clinical practice [22].

5. Conclusion

Thiamin plays a vital role in cell metabolism. The administration of thiamin supplementation should be considered adjunctive therapy in critically ill patients as it may improve their outcomes. Further research should be developed to determine the optimal dosage and timing to achieve the maximum effect.

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