Sulbutiamine

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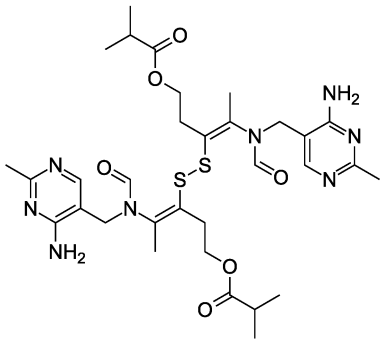


Systematic (IUPAC) name	
-methyl-pyrimidin-5-yl)methyl-formyl-amino]-3-[2-[(4-amino-2-methyl-pyrimidin-5-yl)methyl-formyl-amino]-5-(2-methylpropanoyloxy)pent-2-en-3-yl]disulfan 2-methylpropanoate	
Clinical data	
	?
	?
	Oral
Pharmacokinetic data	
	5 hours
	Renal
Identifiers	
	3286-46-2 [1]
	A11 DA02 [2]
	CID 71124 [3]
	16736830 [4] ✓
	42NCM1BW43 [5] ✗
	D01319 [6] ✓
	Arcalion, bisibuthiamine, enerion, youvitan
Chemical data	
	$C_{32}H_{46}N_8O_6S_2$
	702.89 g/mol
	eMolecules [7] & PubChem [8]

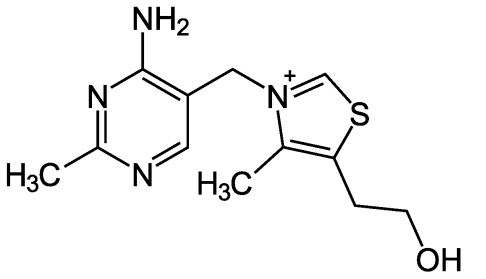
✗ **(what is this?) (verify)** **[9]**

Sulbutiamine (brand name: **Arcalion**) is a synthetic derivative of thiamine (vitamin B_1). As a dimer of two modified thiamine molecules, it is a lipophilic compound that crosses the blood-brain barrier more readily than thiamine and increases the levels of thiamine and thiamine phosphate esters in the brain.[10] Sulbutiamine was

discovered in Japan in an effort to develop more useful thiamine derivatives since it was hoped that increasing the lipophilicity of thiamine would result in better pharmacokinetic properties.[11]

Although its clinical efficacy is uncertain,[12] it is the only compound used to treat asthenia that is known to selectively target the areas that are involved in the condition.[13] In addition to its use as a treatment for chronic fatigue, sulbutiamine also appears to improve memory and erectile dysfunction. At therapeutic dosages, it has few reported adverse effects, though it may interfere with the therapeutic outcome of bipolar disorder.[14] It is available for over-the-counter sale as a nutritional supplement.

History



Thiamine

The history of sulbutiamine is closely tied to the study of thiamine in Japan. A deficiency of thiamine causes a nervous system disorder called beriberi.[15] Until the twentieth century, beriberi was prevalent in Japan and other Asian countries due to the widespread dependence on white rice as a staple food. The relationship between beriberi and diet was first noted by a navy surgeon named Takaki Kanehiro.[16] Additional work resulted in the discovery of thiamine, which was isolated in 1926 and synthesized in 1936. The establishment of a Vitamin B Research Committee in Japan led to additional scientific investigation into the properties of thiamine and its derivatives.[16]

The first lipophilic thiamine derivative to be discovered was allithiamine, which was isolated from garlic (*Allium sativum*) in 1951.[17] Allithiamine is an allyl disulfide derivative. After the discovery of allithiamine, several additional derivatives were synthesized with the hope that they would have better pharmacokinetic properties than thiamine. Thiamine is unable to diffuse across plasma membranes because it has a positively charged thiazole moiety. Instead, it must be transported across plasma membranes by high affinity carriers, and the rate of transport is low.[18] Sulbutiamine overcomes the poor oral bioavailability of thiamine because it is highly lipophilic. It is not clear when sulbutiamine was first synthesized, but the earliest reference to it in the literature is from 1973.[19]

Therapeutic uses

Asthenia

Sulbutiamine is indicated for the treatment of asthenia. Asthenia is a condition of chronic fatigue that is cerebral rather than neuromuscular in origin.[20] Several studies have shown that sulbutiamine is effective at relieving the symptoms of asthenia. In a study of 1772 patients with an infectious disease and asthenic symptoms, sulbutiamine was administered in addition to specific anti-infective treatment for 15 days.[21] The number of patients with complete resolution of all asthenic symptoms was 916. Another study showed that sulbutiamine is effective at relieving asthenia in patients after mild craniocerebral trauma.[22] Nevertheless, the clinical efficacy of sulbutiamine is uncertain. In a study of postinfectious chronic fatigue patients, sulbutiamine did not demonstrate sustained benefits over the placebo, which raises doubts about its clinical efficacy.[12] However, the authors of that study suggest that additional research is needed to evalulate the potential usefulness of sulbutiamine in the treatment of chronic fatigue.

Memory

Several studies have shown that sulbutiamine improves memory through the potentiation of cholinergic, dopaminergic, and glutamatergic transmission. When sulbutiamine is administered to mice, they perform better on operant conditioning tests[23] and object recognition tests.[24] Sulbutiamine also reduces the amnesiac effects of dizocilpine and improves memory in schizophrenics.[24] More recently, sulbutiamine has been shown to improve everyday activities in patients suffering from early-stage and moderate Alzheimer's disease when used in conjunction with an acetylcholinesterase inhibitor.[25] In a randomized double-blind study of Alzheimer's disease patients, the combination of sulbutiamine and donepezil improved episodic memory and daylife activities better than the combination of donepezil and a placebo.

Erectile dysfunction

According to one recent study, sulbutiamine is effective for the treatment of psychogenic erectile dysfunction.[26] Twenty patients with psychogenic erectile dysfunction received sulbutiamine for thirty days. After the treatment was over, erectile function improved in sixteen of the patients.

Availability

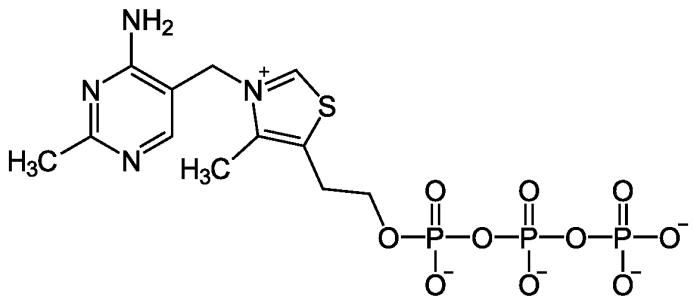
Sulbutiamine is available in several forms. Arcalion is supplied in 200 mg tablets, and generic sulbutiamine is supplied in tablets, capsules, and powder. The proper therapeutic dosage has been reported to be 12.5 mg/kg,[24] which corresponds to 850 mg for a 68 kg (150 lb) person. However, it should be noted that dosage recommendations vary. The manufacturer of Arcalion, for example, recommends no more than 600 mg per day.

Adverse effects

Sulbutiamine has few reported adverse effects at therapeutic dosages. According to the manufacturer of Arcalion, a mild skin allergy may occur. A mild agitation has also been observed in elderly patients. There is only one published report where the chronic overuse of sulbutiamine caused complications.[14] A patient with bipolar disorder was prescribed sulbutiamine because he was complaining of a lack of energy. He found the medication helpful and began taking 2 g per day, which was far more than he was prescribed. Subsequently, he stopped taking his other prescription medications and insisted that sulbutiamine was the only medication that helped him. The authors of the report conclude that sulbutiamine has the potential to interfere with the therapeutic outcome of bipolar disorder although this was an indirect effect since the patient's suspension of his other medications ultimately caused the issue with his treatment.

Mechanism of action

Sulbutiamine is a lipophilic molecule that crosses the blood-brain barrier more easily than thiamine. Its metabolism in the brain leads to an increase in the levels of thiamine and thiamine phosphate esters.[10] [27] While the exact mechanism of action of sulbutiamine is unknown, it is thought to occur through the upregulation of the reticular activating system, which is the center of arousal and motivation in the



Thiamine triphosphate

brain.[13] The administration of sulbutiamine potentiates cholinergic activity in the hippocampus.[23] It also potentiates glutamatergic activity in the prefrontal cortex through a reduction in the density of kainate glutamate receptors, which may occur in response to a modulation of intrasynaptic glutamate.[28] The facilitation of central glutamatergic transmission is a likely explanation for the ability of sulbutiamine to improve memory.[29] [30] [31] [32] In addition to its action on cholinergic and glutamatergic transmission, the administration of sulbutiamine reduces the release of dopamine in the prefrontal cortex, which increases the density of D_1 dopamine receptors through a compensatory mechanism.[28] The modulation of dopaminergic transmission may also contribute to the ability of sulbutiamine to improve memory.[33] [34] [35] A possible explanation for the pharmacodynamics of sulbutiamine is the increased availability of thiamine triphosphate (ThTP). Although the full physiological role of ThTP is unknown, it is an integral component of synpatosomal membranes,[36] participates in the phosphorylation of proteins,[37] and activates chloride channels that have a large unit conductance.[38] The activation of chloride channels by ThTP may be involved in the modulation of receptor binding.

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- Serdia Pharmaceuticals (http://www.serdiapharma.com/about/arcalion.asp)

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