Cognitive Vitality Reports® are reports written by neuroscientists at the Alzheimer's Drug Discovery Foundation (ADDF). These scientific reports include analysis of drugs, drugs-in-development, drug targets, supplements, nutraceuticals, food/drink, non-pharmacologic interventions, and risk factors. Neuroscientists evaluate the potential benefit (or harm) for brain health, as well as for age-related health concerns that can affect brain health (e.g., cardiovascular diseases, cancers, diabetes/metabolic syndrome). In addition, these reports include evaluation of safety data, from clinical trials if available, and from preclinical models.

Etifoxine

Evidence Summary

Etifoxine may be beneficial for peripheral nerve injury, but there is little evidence it will be beneficial in Alzheimer's disease.

Neuroprotective Benefit: Etifoxine is hypothesized to be beneficial in Alzheimer's because it increases allopregnanolone and other neurosteroids; however, brain concentrations of allopregnanolone do not increase to the extent that has been beneficial in other mouse studies.

Aging and related health concerns: N/A

Safety: Etifoxine has been in clinical use for more than 30 years and has a more favorable safety profile than benzodiazepines, but safety for chronic use is uncertain.

What is it?

Etifoxine is a benzoxazine derivative with anxiolytic and anti-convulsant properties prescribed in Europe since 1979. Similar to benzodiazepines, it binds to the $GABA_A$ and TSPO receptors; however, it binds to a different site on the $GABA_A$ receptor and lacks the benzodiazepine side-effects such as dependence, anterograde amnesia, sedation, and impaired psychomotor performance. Its binding to the mitochondrial membrane bound TSPO ligand facilitates the transport of cholesterol into the mitochondria and thus increases the production of neurosteroids such as progesterone, pregnenolone, and allopregnanolone. The increase of the neurosteroids, therefore, may provide neuroprotection and anti-inflammatory properties.

Neuroprotective Benefit: Etifoxine is hypothesized to be beneficial in Alzheimer's because it increases allopregnanolone and other neurosteroids; however, brain concentrations of allopregnanolone do not increase to the extent that has been beneficial in other mouse studies.

Types of Evidence:

- Two clinical trials (one for anxiety and another with cognitive outcomes)
- Multiple preclinical studies in neurodegenerative diseases

Etifoxine was approved for use in Europe in 1979; however, none of the original papers are available. With regards to its anxiolytic effects, one RCT compared the efficacy of etifoxine (50mg 3x per day) to lorazepam in 189 patients with adjustment disorders and anxiety over 28 days. Etifoxine was deemed non-inferior to lorazepam for the treatment of anxiety. In addition, more patients responded to etifoxine than lorazepam and fewer patients' anxiety rebounded 7 days after treatment was stopped (Nguyen et al, 2006). In 48 healthy subjects, acute ingestion of 50mg or 100mg etifoxine did not impair vigilance, psychomotor performance, or free recall compared to placebo (Micallef et al, 2001).

TSPO expression is increased in the brain of Alzheimer's patients (in fact TSPO is a PET target used as a marker of neuroinflammation), but no studies have examined whether etifoxine prevents or slows the progression of Alzheimer's disease. The interest in the use of etifoxine for neurodegenerative diseases stems from its ability to increase the expression of neurosteroids, such as allopregnanolone (see separate CognitiveVitality Report), in the brain and the ability of other TSPO ligands, such as Ro5-4864, to attenuate and reverse pathology in Alzheimer's mouse models (Barron et al, 2013). Despite the lack of studies in Alzheimer's disease, etifoxine does provide benefits in a number of mouse models of neuronal insults.

In a rat model of traumatic brain injury, 7 days of etifoxine treatment attenuated sensorimotor deficits, reduced neuroinflammation, and reduced the production of neuro-inflammatory cytokines (Simon-O'Brien et al, 2016). In a mouse model of ischemia, etifoxine decreased infarct volume, improved neurological outcomes, and decreased the expression of pro-inflammatory cytokines (TNFα, IL-6, IL-1β). Ischemia increased the expression of TSPO in the microglia, and depletion of microglia prior to ischemia diminished the effects of etifoxine, suggesting it provided benefit by reducing microglia inflammation (Li et al, 2017). The same group also tested etifoxine in two mouse models of intracerebral hemorrhage, finding similar results (i.e. decreased lesion volume and inflammation, dependent on the presence of microglia) (Li et al, 2017). Etifoxine was also efficacious in models of multiple sclerosis; interestingly, however, in one study it did not increase brain levels of progesterone or allopregnenolone in female rats (the other studies did not measure allopregnanolone levels) (Ravikumar et al, 2016; Daugherty et al, 2013).

Etifoxine is also beneficial for peripheral nerve repair and regeneration in models of nerve injury. In a rat model of sciatic nerve injury, etifoxine improved nerve regeneration, myelination, functional recovery and nerve conduction, possibly due to an increased expression of NGF, GDNF and VEGF (Zhou et al, 2014). In a cryo-lesion injury model, etifoxine increased axonal regeneration, decreased the infiltration of activated macrophages, decreased TNFα, and improved functional recovery (Girard et al, 2008). In a rat model of mononeuropathy, etifoxine suppressed neuropathic pain symptoms (Aouad et al, 2014).

Pharmacokinetics

Etifoxine's reported benefits are due to its ability to increase the production of neurosteriods in the brain. Contrary to the results of Ravikumar et al (2016) (the MS model where neurosteroid levels did not increase); a single IP injection of etifoxine (50mg/kg) increased brain levels of progesterone, pregnenolone, and allopregnenolone in the brain of male rats. Brain allopregenolone levels increased to 1ng/g after one hour (Liere et al, 2017). In another pharmacodynamics study, a single injection of etifoxine into male rats increased brain allopregnenolone levels to 0.72ng/g after 30 minutes (Verleye et al, 2005). Intermittent treatment of allopregnenolone in mouse models of Alzheimer's disease was efficacious when brain levels reached at least 15ng/g. Additionally, continuous treatment of allopregnenolone at lower doses increased Alzheimer's pathology (Irwin and Brinton, 2014). Therefore, it does not seem likely that treatment with etifoxine will sufficiently increase brain levels of allopregnenolone and chronic treatment may exacerbate pathology. Whether etifoxine is beneficial for Alzheimer's disease through some other mechanism is unclear.

Safety: Etifoxine has been in clinical use for more than 30 years and has a more favorable safety profile than benzodiazepines, but safety for chronic use is uncertain.

Etifoxine was safer than lorazepam over a 28-day period with the most common side effect being drowsiness (25% of patients). There was little other information on drug-related side effects (Nguyen et al, 2006). A recent French pharmacovigilance survey reported some adverse side-effects, primarily dermatological in nature, but these side effects are rare and the authors concluded that etifoxine is a safer alternative to benzodiazepines (Cottin et al, 2015). Etifoxine has been used for more than 30 years, although there are few published human studies. Etifoxine is contraindicated in individuals with severe liver or kidney impairment and it not recommended for greater than 12 weeks (Choi and Kim, 2015).

Drug Interactions:
Etifoxine is not listed on drugs.com and there are no reports of drug interactions. Theoretically, it could have similar interactions as benzodiazepines such as benzodiazepines themselves, opioids, alcohol, or other drugs that produce drowsiness.

Sources and dosing:
Etifoxine not available in the United States but can be purchased with prescription in a number of countries under the brand name Stesam. Typical dose is 50mg three times per day.

Research underway:
There is no clinical research underway for the use of etifoxine in humans or on NIH Reporter.

Search terms:
Pubmed:

- Etifoxine

Websites visited for Etifoxine:

- Clinicaltrials.gov
- Treato.com
- DrugAge (0)
- Geroprotectors (0)
- Drugs.com

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