

Levetiracetam as a Neuroprotective agent against Alcohol Induced Cognitive Disorders: Review of Literature

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Abstract

Background: Chronic alcohol use could lead to withdrawal, delirium and dementia. Alcohol related delirium include delirium tremens, hepatic encephalopathy and Wernicke's Encephalopathy (WE). Alcohol related dementia include Korsakoff Syndrome (KS). Studies support benefit of anti-epileptics in alcohol withdrawal. There is limited data on their role in alcohol related cognitive disorders. Levetiracetam (LEV) is used for the treatment of seizure disorders. Studies have suggested neuroprotective properties for LEV. The purpose of this review is to discuss the possible use of LEV in alcohol related cognitive disorders.

Methods: PubMed database and relevant publication reference were reviewed. Search terms were: Levetiracetam, Neuroprotection, Piracetam, alcohol induced Cognitive Disorders, Wernicke's encephalopathy, Korsakoff syndrome.

Results: We identified several studies supporting evidence for LEV helping alcohol withdrawal, offering neuroprotection. We identified 2 studies supporting Piracetam's efficacy in alcohol related cognitive problems. Piracetam is related to LEV. One study identified alcohol withdrawal patients who were on LEV had shortened Intensive Care Unit (ICU) stay and decreased time mechanically ventilated.

Conclusion: LEV may be the first medication that could cover all complications of alcohol dependence, especially in chronic users who are at risk of cognitive impairment. Could LEV treat WE along with thiamine and other measures?. Could it prevent or delay the progression of WE to KS?. For KS pt, could it decrease the severity?. Prospective studies are needed to see if LEV works in decreasing the cognitive impairment in Wernicke-korsakoff syndrome through neuroprotection.

Keywords: Chronic alcoholism; Dementia; Anti-epileptics

Introduction

Chronic alcohol use could lead to withdrawal, delirium and dementia. Alcohol related delirium include delirium tremens, hepatic encephalopathy and Wernicke's Encephalopathy (WE). Alcohol related dementia include Korsakoff Syndrome (KS). Studies support benefit of anti-epileptics in alcohol withdrawal. There is limited data on their role in alcohol related cognitive disorders. Levetiracetam (LEV) is used for the treatment of seizure disorders. Studies have suggested neuroprotective properties for LEV. The purpose of this review is to discuss the possible use of LEV in alcohol related cognitive disorders.

Alcohol Withdrawal Syndrome (AWS) include alcohol hallucinosis, alcohol withdrawal, seizures, delirium tremens, hepatic encephalopathy and Wernicke-Korsokoff Syndrome (WKS) [1]. Benzodiazepines are the treatment of choice for alcohol withdrawal [2]. Anticonvulsants are well tolerated in alcohol withdrawal and are increasingly being used for alcohol withdrawal [3,4]. WKS comprises both WE and KS. WKS is accompanied by neurological and cognitive problems [5]. Not all patients present with the classic signs and many cases are not properly diagnosed. Intravenous (IV) thiamine and high serum levels of thiamine restore cognitive function [5]. Thiamine is the treatment of choice for Wernicke encephalopathy [6]. Memory and learning are affected in KS, they have anterograde and retrograde amnesia, and lack of insight. Many patients require life-long residential support [7]. Early recognition of WE and treatment prevents development of KS [7].

Methods

PubMed database and relevant publication reference were reviewed. Search terms were: Levetiracetam, Neuroprotection, Piracetam, alcohol induced Cognitive Disorders, Wernicke's encephalopathy, Korsakoff syndrome.

Results

We identified several studies supporting evidence for LEV helping alcohol withdrawal, offering neuroprotection. We identified 2 studies supporting Piracetam's efficacy in alcohol related cognitive problems. Piracetam is related to LEV. One study identified alcohol withdrawal patients who were on LEV had shortened Intensive Care Unit (ICU) stay and decreased time mechanically ventilated.

Discussion

Racetams are cognitive enhancing drugs, such as piracetam, also called nootropics. Levetiracetam (LEV) has similar structural features as piracetam, and it has anti-epileptic activity. Many studies report LEV exhibiting neuroprotective effects, anti-inflammatory, anti-oxidative, and anti-apoptotic effects and elevated learning abilities [8]. LEV has been found to be beneficial for treating other conditions like dyskinesia, dystonia and myoclonus, [9,10]. It also could work in treating bipolar disorder [11].

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LEV is a promising agent in the therapy of alcohol withdrawal syndrome [12,13]. LEV has been reported to treat alcohol withdrawal and reduce craving for alcohol [14,15]. LEV's ability to limit the progression of alcohol related cognitive disorders need to be explored. In their retrospective study of LEV for alcohol withdrawal syndrome in hospitalized patients, Youland KM et al found that LEV group had shorter stay in intensive unit care and they spent less time mechanically ventilated [16]. Changes in cognitive functions has been reported in epileptic patients maintained on LEV [17-22]. LEV showed neuroprotective effects in a neonatal rat model hypoxic-ischemic brain injury [23]. Piracetam and LEV, are pyrrolidone derivatives and share similar chemical structures [24]. Piracetam has neuroprotective effect and is effective in the treatment of cognitive disorders of cerebrovascular and traumatic origins [25]. Piracetam was found to be beneficial for cognitive functions in alcoholic patients. [26,27] and it can offer protection in alcohol-induced stress [28]. In their double-blind study of Piracetam study on 27 alcoholics, Buranji et al assessed cognitive function on inpatients who were admitted to hospital with acute withdrawal syndrome. Piracetam group demonstrated good perceptual organization, visual motor coordination, abstract reasoning, psychomotor speed and attention capacity [26].

The closest study conducted yet was by Barnas C et al. They conducted placebo controlled Piracetam study on alcohol organic mental disorder comparing two doses (high and low dose) in the treatment of organic mental disorder of chronic alcohol dependent patients. Psychological testing to assess cognitive impairment was done on days 0, 7, 14, 28 and 42. Significant improvement in cognition was observed in the high Piracetam dose group [27].

Wernicke-Korsakoff syndrome related brain damage include an excitotoxic component [29,30] and oxidative stress [31]. LEV has neuroprotective role and exhibits antioxidant action against the brain damage induced by excitotoxicity [32]. LEV has antioxidant properties and protect against oxidative stress [33]. LEV can improve cognitive performance by inhibiting A β -induced vesicular glutamate release from astrocytes [34]. In an animal study that evaluated oxidative stress and neurodegenerative conditions in the brain following Thiamine deficiency, increase in lipid peroxidation led to neuronal loss and oxidative stress and neurodegenerative conditions [35]. LEV reduces lipid peroxidation and hippocampal oxidative stress [36]. Kainate receptor system is implicated in neuronal loss in pyrithiamine-induced thiamine deficiency [37]. LEV exhibits neuro-protective effects against kainic acid induced brain toxicity by inhibition of lipid peroxidation [38].

LEV has non-hepatic metabolism and primary renal excretion and because of this mechanism, it has low drug-drug interaction. This is important because many alcoholics have hepatic encephalopathy as an end stage complication [39]. Common side effects of LEV include somnolence; headache; asthenia; accidental injury; dizziness; infection; Psychiatric side effects include personality disorder; nervousness; depression; aggression; agitation [40]. The behavioral side effects are more common in children and in patients with a prior history of behavioral problems [41,42].

Conclusion

Alcohol related complications are broader including alcohol withdrawal seizures, delirium tremens, WE and korsakoff dementia. Benzodiazepines work for withdrawal. Anti-epileptics are emerging as adjuncts for withdrawal and also to decrease craving, Medications to decrease craving approved by FDA are acomprosate and naltrexone.

Thiamine is used to treat WE. There is no cure at this time for Korsakoff dementia. Progression from WE to korsakoff needs to be prevented. LEV, an anti-epileptic medication is reported to work for alcohol withdrawal and decrease alcohol craving. It has neuroprotective benefits. Piracetam which shares similar chemical structures to LEV was found to be beneficial for cognitive functions in alcoholic patients.

LEV may be the first medication that could cover all complications of alcohol dependence, especially in chronic users who are at risk of cognitive impairment. Prospective study is needed to confirm this. Nervous system damage lead to neuronal death. Drugs already available could confer neuroprotection. Could LEV treat WE along with thiamine and other measures? Could it prevent or delay the progression of WE to KS? For KS patients, could it decrease the severity?

As mentioned above, alcohol withdrawal patients who were on LEV had shorter Intensive Care Unit (ICU) stay and decreased time mechanically ventilated. Typically, cognitive related complication like delirium tremens and WE are common in alcohol withdrawal patients admitted to intensive care unit. Is LEV playing a positive role by alcohol withdrawal patients leaving ICU sooner? Prospective studies are needed to see if LEV works in decreasing the cognitive impairment in Wernicke-korsakoff syndrome through neuroprotection.

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