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The Role of Montelukast in Traumatic Brain Injury and Brain Ischemia

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Abstract

Introduction: Montelukast has a fundamental role in the management of respiratory disorders including asthma and allergic rhinitis. We reviewed literature to determine the role of Montelukast in Traumatic Brain Injury and Brain Ischemia.

Methods: Articles reported from 1950 to present and identified through PubMed, Cochrane, and Google Scholar were searched on the use of Montelukast in traumatic brain injury and ischemia.

Results: Montelukast is a Cysteinyl leukotriene receptor-1 antagonist. Cysteinyl leukotriene receptors have a dynamic biphasic response to appear on the surface of brain, as it increases 3-24 hours and then 7 days after brain trauma and ischemia. Montelukast plays an important role in neuroprotection and anti-apoptotic pathway by antagonizing these receptors. Its unique mechanism of action is evident by halting lipid peroxidation, neutrophil accumulation and pro inflammatory cytokine release, thereby, preventing metabolic crisis and stabilizing the blood brain barrier. However, almost all these studies are carried out in experimental model. Therefore, there is an urgent need to confirm the use of this drug in patients with TBI and ischemia.

Conclusion: In recent years, in addition to Montelukast effects in respiratory disorders, several studies have presented evidence suggesting its potential to have a neuroprotective effect in traumatic brain injury and ischemia. Therefore, further clinical trials might help in determining the efficacy, safety and role of Montelukast in traumatic brain injury and ischemia.

Keywords: Montelukast; Traumatic brain injury; Ischemia; Intracranial hypertension; Cysteinyl Leukotriene receptor

Abbreviations: TBI: Traumatic Brain Injury; ICP: Intracranial Pressure; CPP: Cerebral Perfusion Pressure

Introduction

Traumatic Brain Injury (TBI) is a 'silent epidemic' and the leading cause of mortality and morbidity worldwide. Due to significant external impact to the brain, there is alteration in the normal cerebrovascular physiology. This leads to increase in Intracranial Pressure (ICP), reduction in Cerebral Perfusion Pressure (CPP), and ultimately brain edema [1,2]. There exists controversial literature regarding the time course of disruption of Blood Brain Barrier (BBB) following TBI and ischemia; with some studies suggesting it to be short-lived [3] while other suggest it to be following a biphasic course, with 3-6 hours as early-phase disruption followed by further BBB disruption in 1-3 days after injury [4]. Recent therapeutic strategies focus upon stabilization of BBB, thus decreasing intracellular brain edema.

Montelukast is a Cysteinyl-Leukotriene Receptor-1 Inhibitor. It has a documented role in allergic rhinitis and asthma, however, there exist literature for its role in treating neurological conditions like Alzheimer's, Multiple Sclerosis, Epilepsy [3-9]. In addition, preclinical studies suggest that it might be useful in TBI by stabilizing BBB4. Its unique mechanism of action is evident by halting the inflammatory cascade following TBI that involves lipid peroxidation, neutrophil accumulation and pro inflammatory cytokine release [9]. Thus, it has a role in neuroprotection and anti-apoptotic pathway. The use of Montelukast for the management of BBB stabilization and reduction of brain edema secondary to trauma and ischemia is largely the result of experimental evidences and small clinical trials. Our review article is the first to determine the efficacy of Montelukast in Traumatic Brain Injury and brain ischemia.

Methods

We applied stringent inclusion criteria, selecting articles (experimental or non-experimental) describing role of

Montelukast in neurological conditions especially in reducing brain edema and stabilizing the blood brain barrier. Articles on role of Montelukast in non-neurological symptoms (asthma, allergic rhinitis, gastrointestinal tract) were excluded. We used the following MeSH headings Montelukast or traumatic brain injury or brain ischemia. We did not define any limitation in language. Articles published between 1950 and the present were searched. The following databases were reviewed: Cochrane Library, PubMed and Google Scholar. This has been indicated in the Figure 1 To avoid publication bias, we reviewed abstracts from European and American traumatic brain injury meetings, looking at the unpublished articles on Montelukast in TBI and ischemia.

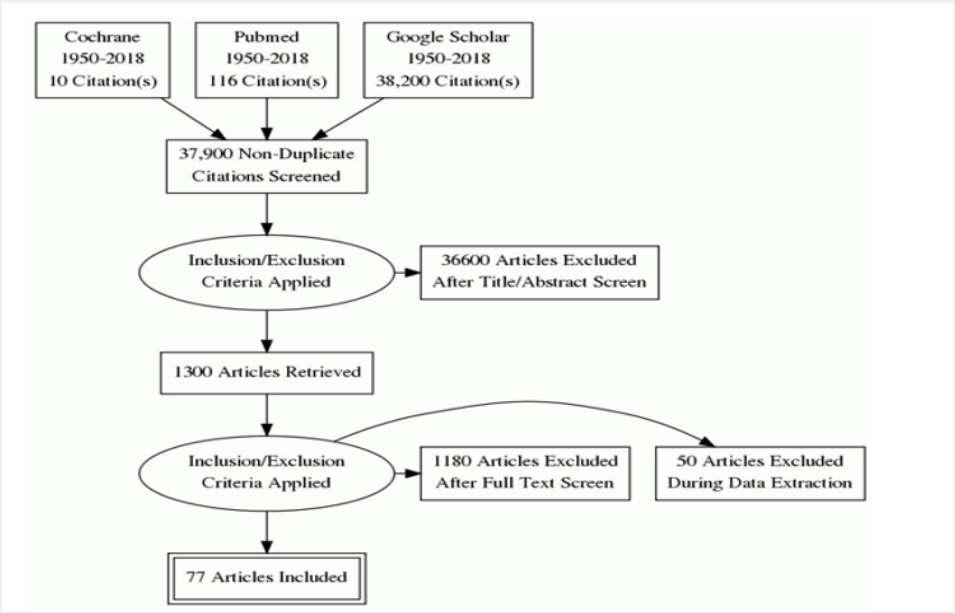

Figure 1

Study selection and data extraction

Primary research question: Does Montelukast play role in Traumatic Brain Injury and brain ischemia. Therefore, we reviewed all the articles including pre-clinical trials using Montelukast in TBI and ischemia, and determined the dose, timing and clinical outcome. 2 articles were included in which the ischemia was induced by occlusion of middle cerebral artery leading to brain edema; thus, to determine the role of Montelukast in reducing brain edema. The reviewer was not blind to the author's name and institutions, journals of publication, or study results.

Results

After primary impact to the brain (trauma or ischemia), secondary brain damage occurs due to multiple factors including the activation of inflammatory pathway [10,11]. Various Cysteinyl leukotrienes (LTC4, LTD4, LTE4) are produced [12-14] which causes release of reactive oxygen species [15] that are involved in phospholipid breakdown [16], ultimately increasing the membrane permeability [17]. This lay the foundation of disruption of blood brain barrier. Primary BBB damage [18,19] occurs due to shearing of the endothelium of blood vessels as a result of direct head trauma. However, abnormal brain activity, inflammation, astrocyte dysfunction and metabolic disturbances in response to brain injury and ischemia leads to Secondary BBB disruption [20].

During several pathological conditions (ischemia [20-22] traumatic brain injury [23]), there is increase expression of CysLTRs on the surface of brain. CysLTR-1 expression is localized in microvascular endothelial cells [24], in glial cells (namely astrocytes and microglia [25-27]) and in various other kinds of neuronal cells [21,26]. On the other hand, the CysLTR-2 is expressed in many regions of human brain such as hypothalamus, thalamus, putamen, pituitary, and medulla [28], astrocytes [25] and vascular smooth muscle cells [23]. It is also observed in neurons and glial-appearing cells [23] after brain trauma and in brain tumors. Microglial cells play a neuroprotective role [29,30] but over activation causes release of inflammatory mediators (cytokines and nitric oxide) [31,32] leading to detrimental effects [33,34] including neuronal injury [35-39]. Montelukast has CysLTR-1 receptor dependent and independent effects.

Montelukast dependent effect occurs by directly acting upon its receptor (CysLTR-1) and decreasing inflammation [20,40,41] and astrocyte proliferation [27,42]. It has several independent effects of its receptor including indirectly inhibiting GPR17 [43-49] and P2 Y receptor [50-52] thus reducing neuronal injury after ischemia [53-56]. It is found to reverse the cognitive deficit in Alzheimer's disease by inhibiting the inflammatory and apoptotic

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response to Aβ1-4 [6,25,57,58]. In addition, in Multiple sclerosis 7 and Epilepsy [8,9,59] it inhibits the chemotaxis of inflammatory mediators and leukocyte infiltration, thus preventing against demyelination and seizures [60,61] respectively. Montelukast is extensively metabolized.

In vitro studies using human liver microsomes indicated the cytochromes P450 3A4 and 2C9 involved in the metabolism of Montelukast. The plasma clearance of Montelukast averages 45ml/min in healthy adults. The mean plasma half-life of Montelukast ranged from 2.7 to 5.5 hours in healthy young adults [62]. The patients with memory loss and dementia showed improvement in memory function using 20mg orally upon arising and then 20mg every 2-3 hours for a total of 4 doses [63].

Common side effects associated with Montelukast include diarrhea, nausea, vomiting, mild rashes, asymptomatic elevation in liver enzymes, and fever. Uncommon side effects include fatigue, malaise, behavioral changes, paresthesia and seizures, muscle cramps, and nosebleed. Rare but serious side effects include severe behavioral changes, angioedema, erythema multiforme, and liver problems [64]. Although clinical trials revealed an increased risk of insomnia, post marketing surveillance showed that this drug is associated with increased risk of suicidal behavior and other side effect such as agitation, aggression, anxiousness, dream abnormalities and hallucinations, depression, irritability, restlessness, and tremor [64].

Discussion

Brain was considered to be immunologically privileged site, but several literatures exist against this notion. After TBI and brain ischemia, the inflammatory response begins within hours and last several days to weeks [65]. As a result of disruption of BBB, there is transmigration of leukocytes, which results in activation of the resident cells of CNS (such as microglia and astrocytes) to possess the immunological function. This infiltration of immune cells and activated resident cells, subsequently leads to increased intrathecal production of cytokines [65]. There exists a vicious cycle as release of chemokines, adhesion molecules, and pro-inflammatory cytokines released from activated microglia [66], further mediate the migration of peripheral immune cells and activation of resident CNS cells, which ultimately contribute to an overall increase in the blood brain permeability [67]. In response to activation of glial cells, modulation of synaptic transmission and plasticity occurs, [68,69] which ultimately leads to seizures due to neuronal network re organization, hyper synchronicity and hyper excitability [70].

Excessive inflammatory response is associated with the poor clinical outcome; therefore, prevention of inflammation is prudent therapeutic strategy. Besides, the protection against post traumatic epilepsy could be obtained by decreasing the activation of astrocytes. Cysteinyl leukotrienes receptors are increased on the surface of neurons and glial producing cells (astrocytes and glial cells) following brain trauma and ischemia. Neuroprotective and anti-apoptotic role of Montelukast is evident by inhibiting the lipid peroxidation, neutrophil accumulation and pro inflammatory cytokine release [71], eventually reducing the blood brain permeability [72]. Stabilization of the BBB after TBI and ischemia could be a promising strategy to limit neuronal inflammation, secondary brain damage and acute neurodegeneration [73].

Cysteinyl leukotriene receptors has a dynamic biphasic response to appear on the surface of brain, as it increases 3-24 hours and then 7 days after brain trauma and ischemia [32]. In a fluid percussion model of traumatic brain injury to the rats [74], the levels of cysteine leukotrienes were elevated after fluid percussion injury with a maximal formation 1 hour after injury. Using immunohistochemical analyses, they found increased expression of CysLT1 on microvascular endothelial cells along with increased expression neurons and glial-appearing cells in gray and white matter after traumatic brain injury and brain ischemia [24]. Montelukast has a dose and time-dependent neuroprotective effect [75]. This was determined in an experimental model in mice by occluding the Middle Cerebral Artery (MCAO). Montelukast was injected intraperitoneally either as multiple doses (once a day for 3 days and 30 mins before MCAO) or as a single dose (at 30 min before, 30 min after, or 1 hour after MCAO). It was found that Montelukast single dose given within 30 minutes of ischemia reduced the brain edema and infarct volume, however, there was no effect on neurological deficit. Similarly, in another experiment [25] it was found that Montelukast (0.1 mg/kg) attenuated behavioral dysfunction, brain infarct volume, brain atrophy and neuron loss in mice after transient focal cerebral ischemia induced by Middle Cerebral Artery Occlusion. Therefore, Montelukast decreases the intracellular edema and hence, reduces the intracranial pressure as evident by the experimental model. Montelukast down regulates the migration of LTD4-induced astrocyte migration by inhibiting TGF-beta 1, thus prevent inflammatory response and abnormal synaptic activity 39. Thus, it can help in preventing the seizures activity.

Our study has several limitations. Firstly, there is a possibility of selection and publication bias since one reviewer carried out this process. Therefore, he might be influenced by positive trials only. However, we tried to limit such bias by reviewing all articles including the unpublished literature as well. Second, almost all articles were experimental models conducted on animals, therefore, it makes it difficult to imply on human beings as well. Finally, the results cannot be generalized to all forms of traumatic brain injury since the article limited to severe traumatic brain injury.

Conclusion

Montelukast as Cysteinyl leukotrienes Receptor-1 antagonist has a clear role in the pathophysiological conditions such as

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asthma, allergic rhinitis and other nasal allergies. Besides, its role has been implicated in a number of inflammatory conditions including cardiovascular and gastrointestinal diseases [76] However, its role in the treatment of cerebral disorders is still evolving [5-8]. With the experimental clinical trials, there is consistent reduction in the blood brain permeability and inflammatory responses following the administration of Montelukast without any reported adverse events.

The mechanism of action of Montelukast in reducing the BBB and ICP is not fully understood. But it seems that it's due to its effect on the inflammatory mediators that protects the neurons and stabilizes the blood brain barrier by acting upon the endothelial cells. Although there is lack of convincing data regarding its use in traumatic brain injury, but it appears that Montelukast will attenuate the secondary brain damage by inhibiting the inflammatory mediators. Data regarding the best route of administration is also lacking although the oral route would appear to be ideal [77]. Therefore, further clinical studies in form of Randomized Clinical Trials are suggested to determine the efficacy, safety and role of Montelukast in TBI.

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Contributor Ship

Maher Saqqur and Ashfaq Shuaib.

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