

Montelukast: A Review of Articles on the Experimental Level

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ABSTRACT

Montelukast is an orally dosed drug (available as a film-coated tablet, chewable tablet, or oral granules) an antagonist of the cysteinyl leukotriene receptor is frequently used to treat asthma symptoms in both adults and children. This study aims to conduct a review of articles on the use of Montelukast on the experimental level. Due to the significant adverse effects of montelukast and the high prevalence of asthma in children, there is a warning by FDA regarding the use of this drug to stop this agent immediately if side effects occur. However, an intense and, at times, life-threatening withdrawal upon discontinuation of montelukast was reported including severe neuropsychiatric side effects including anxiety, depression, insomnia, suicidal thoughts and actions. Several studies with contradictory views were performed on the effect of Montelukast use on the animals. Montelukast has anti-inflammatory, antioxidant actions on several tissues.

Further research on how montelukast works and its effects on which organ, particularly on children, is incredibly important, given the enormous popularity and global distribution of this drug.

The present study analyzed the previous published case reports regarding montelukast induced adverse drug reactions. They included agitation, anxiety, depression, sleep disturbance, hallucinations, suicidal thinking and suicidality, tremor, dizziness, drowsiness, neuropathies and seizures. The immune system can be involved, in particular, cases of Churg-Strauss syndrome have been published. Furthermore, it can induce hypersensitivity reactions, including anaphylaxis and eosinophilic infiltration. In addition, hepatobiliary, pancreatic and uropoietic disorders have been observed. Some of these cases are characterized by severe prognosis (i.e. neurological deficit and fatal hepatotoxicity).

Keywords: Montelukast, review, rat .

مونتيلوكاست : مراجعة للمقالات على المستوى التجريبي

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الخلاصة

يستخدم بشكل متكرر أحد مضادات مستقبلات السيستينيل ليكوترين المعروفة باسم مونتيلوكاست (MTK) لعلاج أعراض الربو لدى كل من البالغين والأطفال. تهدف هذه الدراسة إلى إجراء مراجعة للمقالات حول استخدام مونتيلوكاست على المستوى التجريبي. بسبب الآثار الضارة الكبيرة لمونتيلوكاست والانتشار المرتفع للربو عند الأطفال ، هناك تحذير من إدارة الغذاء والدواء بشأن استخدام هذا الدواء لإيقاف هذا الدواء فوراً في حالة حدوث آثار جانبية. ومع ذلك ، تم الإبلاغ عن انسحاب مكثف ، وفي بعض الأحيان ، يهدد الحياة عند التوقف عن تناول المونتيلوكاست بما في ذلك الآثار الجانبية العصبية والنفسية الشديدة بما في ذلك القلق والاكتئاب والأرق والأفكار والأفعال الانتحارية. تم إجراء العديد من الدراسات ذات الآراء المتناقضة حول تأثير استخدام مونتيلوكاست على الحيوانات.

يعد إجراء مزيد من الأبحاث حول كيفية عمل مونتيلوكاست وتأثيراته على هذه الأعضاء ، خاصة على الأطفال ، أمراً مهماً للغاية ، نظراً للشعبية الهائلة والتوزيع العالمي لهذا الدواء.

الكلمات المفتاحية : مونتيلوكاست ، عرض مقالة ، الجرذان ، الكبد ، المخ .

INTRODUCTION

Montelukast sodium as a leukotriene receptor antagonist, is used to treat chronic asthma episodes, maintain asthma control, and alleviate the symptoms of seasonal allergies. that is used for the maintenance treatment of asthma, chronic asthma attacks and to relive symptoms of the seasonal allergies¹.

The food and drug administration (FDA) has granted approval for the oral medication montelukast for the treatment of chronic asthma as well as prophylaxis for the prevention of exercise-induced bronchoconstriction. It is available as a film-coated tablet, chewable tablet, or oral granules.^{2,3} Figure 1.³

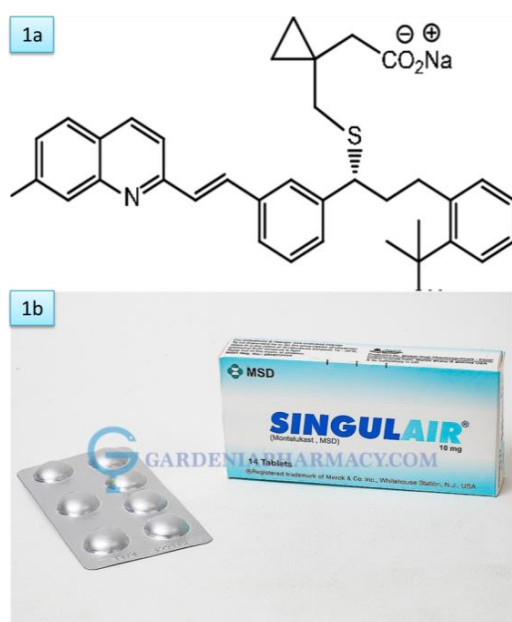


Figure 1a: Molecular structure of montelukast sodium (3), figure 1b: Picture of montelukast tablet (<https://wikikenko.com/product/zespira-film-coated-tablet/>).

Indication of Montelukast:

Singulair, a trade name for Montelukast manufactured by Merck, received the first US FDA approval for clinical usage in 1998.⁴ The drug belongs to the class of medications known as leukotriene receptor antagonists (LTRA)⁵⁻⁷. Although they have proven to be successful, certain LTRAs, like montelukast, are often used in step treatment for asthma in addition to or as a complement to inhaled corticosteroids or other medications was recommended⁵.

Montelukast is recommended for the prevention and long-term management of asthma in adults and children 12 months of age and older^{7,8}, the treatment of individuals aged 6 years and over for the prevention of exercise-induced

bronchoconstriction⁴, the reduction of seasonal allergic rhinitis symptoms in patients older than two years and perpetual allergic rhinitis symptoms in individuals older than six months.⁵ certain formulations such as montelukast tablets are approved by special regulatory agencies as the prevention and long-term asthma treatment⁸ and for the prevention of bronchoconstriction brought on by exercise in different ages⁹.

Moreover, when used for these purposes, montelukast is thought to be beneficial either alone or in combination with other drugs that are authorized for the maintenance treatment of chronic asthma⁹. For example, using montelukast and inhaled corticosteroids simultaneously can show synergistic effects to control asthma or allow for a reduction in the required dose of inhaled corticosteroids while still maintaining clinical stability¹⁰.

Montelukast an inhaled corticosteroid, or an inhaled corticosteroid mixed with a long-acting beta-agonist in individuals who still experience asthma symptoms¹¹.

Mechanism of action:

The leukotriene receptor antagonist montelukast (empirical formula C₃₅H₃₅CINNaO₃S) interacts with a high affinity to the cysteinyl leukotriene receptor for leukotrienes D₄ and E₄, that are included in the inflammatory process that may result in the signs and symptoms of asthma and allergic rhinitis, mast cells are one type of cell that excretes substances that are thought to cause these conditions. Figure 2¹²

Airway cells such as macrophages and smooth muscle cells contain leukotriene receptors. Without displaying any agonist activity, montelukast reduces the physiological consequences of leukotrienes (such as airway edema, smooth muscle contraction, and disruption of normal cellular activity) when attached to leukotriene receptors.

Leukotriene D₄-induced bronchoconstriction is significantly inhibited by low dosages of montelukast (5 mg) in asthmatics. Also, in a crossover study including 12 asthmatic patients, montelukast caused suppression of both early and late phase bronchoconstriction brought on by a challenge with an antigen^{13,14}.

Montelukast-treated asthmatics in controlled studies showed a 9%–15% reduction in the number of eosinophils in their peripheral blood compared to placebo-treated patients. Patients with seasonal allergic rhinitis who took montelukast experienced a 0.2% rise in eosinophil counts in peripheral blood as opposed to a 12.5% increase in those who took a placebo.¹²

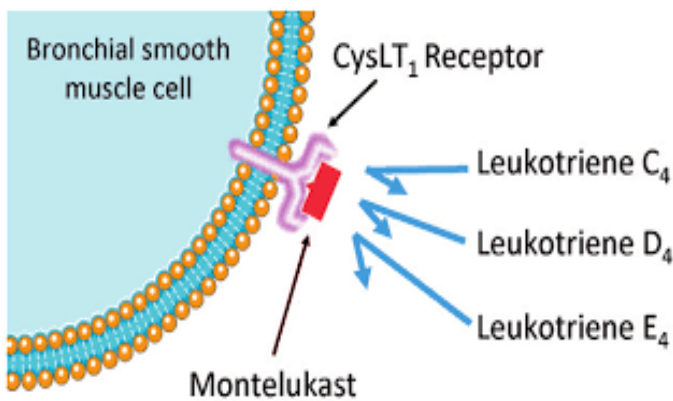


Figure 2. mechanism of action of montelukast¹⁴

Side Effects:

Childhood asthma is a prevalent illness, and in the past 20 years, its frequency has climbed from 8 to 23%.^{15,16} Due of the significant adverse effects of montelukast and the high prevalence of asthma in children, there is a warning by FDA regarding the use of this drug to stop this agent immediately if side effects occur^{17,18}. However, an intense and, at times, life-threatening withdrawal upon discontinuation of montelukast was reported including severe neuropsychiatric side effects including anxiety, depression, insomnia, suicidal thoughts and actions.

Long-term mental health injuries and neurological complications were recorded including cognitive, sensory, or motor deficits that may also manifest as emotional instability, significant behavioral dysregulation, and seizures in the most severe cases.^{19,20}

Main side effect of montelukast on the patients (tooth pain, exhaustion, fever, stuffy nose, sore throat, coughing, hoarseness, skin rash, mood swings, tremors, headache, stomach pain, heartburn, upset stomach, nausea, vomiting, and diarrhea.^{21,22}

Many researches on the neuropsychiatric consequences of leukotrienes were published throughout this decade, but the connection was indirect and the subject of debate^{23,24}.

However, there were FDA-led investigations concerning the risk that montelukast could cause neuropsychiatric side effects such as agitation, hallucinations, and suicidal thoughts in 2008–2009, those who utilized the medication's behavior and other characteristics²⁵, and even while the official montelukast prescribing material now mentions these kinds of side effects^{26,27}, Millions of prescriptions for the medication are still written each year, and it is now offered both as a generic and a brand-name medicine.

Drug Interactions:

Therapeutic doses of montelukast also have no clinically-significant effect on the pharmacokinetics of prednisone, prednisolone, terfenadine, digoxin, warfarin, and oral contraceptives (ethynyl oestradiol/norethindrone 35/1). Co-administration of phenobarbitone decreases by almost 40% the plasma concentration curve (AUC) for montelukast^{28,29}.

While taking montelukast sodium along with inducers of 3A4 such phenytoin, phenobarbitone, and rifampicin, care should be taken because montelukast is processed by cytochrome P450 3A4.^{30,31}

Metabolism and Excretion of Montelukast:

Montelukast is extensively oxidatively metabolized in the liver by the cytochrome P450 enzyme system, with the mono-oxidase CYP2C8 (72%), CYP3A4 (16%), and CYP2C9 (12%), Each contributing significantly. It is then eliminated in the bile^{32,33}

It doesn't stay in the bloodstream for very long. Its plasmic concentration peaks 2 to 4 hours after ingestion, and it is quickly eliminated. 2.7 to 5.5 hours is the average plasma half-life.³⁴

the montelukast's reported moderately high oral bioavailability allowed researchers to draw the conclusion that the majority of the radioactivity was eliminated through the bile. In order to determine montelukast's biliary metabolites, a second clinical research was carried out.

The recovery of radioactivity in bile was incomplete and ranged from 3 to 20% of the dose due to the collection method and the short sampling period. Radio-chromatographic and LC-MS/MS analysis of the bile revealed the presence of one main, numerous minor metabolites, as well as trace levels of the parent medication that had not changed³⁵.

Studies on the Effect of Montelukast on Various Animals' Organs:

Several studies with contradictory views were performed on the effect of Montelukast use on the experimental level as follows:

The Effect on the Respiratory System:

Montelukast demonstrated anti-inflammatory activities in numerous animal respiratory illness models. For instance, montelukast inhibited airway hyperresponsiveness and inflammation in an animal model of respiratory syncytial virus (RSV) produced bronchiolitis and suppresses vascular permeability of airway mucosa³⁶.

In two investigations on lung damage brought on by hemorrhagic shock, montelukast decreased IL-6 and TNF- levels.^{37,38} reduced serum levels of antibodies related to lung myositis, as well as the amount of total protein and bronchoalveolar lavage fluid, and lessened lung injury³⁹. Montelukast also reduced lung inflammation brought on by lipopolysaccharide in a model of acute respiratory distress syndrome.⁴⁰

In vitro nasal airway epithelial cells were exposed to montelukast, which inhibited the release of pro-inflammatory mediators such IL-8 and RANTES.⁴¹

Airway inflammation in asthmatics is linked to intravascular platelet activation, with platelets helping to activate and infiltrate T cells and eosinophils into the bronchial wall.^{42,43} Intriguingly, animal studies show that combining the antiplatelet medicine clopidogrel with the asthma therapy montelukast appears to reduce airway inflammation⁴⁴. Thrombosis and platelet aggregation are two significant outcomes brought on by SARS-CoV-2 infection^{45,46}.

It's interesting to note that CysLTs appear to have an impact on platelet function in the setting of allergen-induced airway inflammation⁴⁷. Platelets express CysLT1R and CysLT2R⁴⁸, and mouse platelets have demonstrated that LTC₄ activates platelets⁴⁹. These findings imply that CysLTs may be involved in platelet activation, and that the use of CysLT1R antagonists, such montelukast, may be helpful in the management of inflammatory conditions, especially when combined with clopidogrel^{50,51}.

The Effect on the Nervous System:

In AD animal models, montelukast reverses the effects of -amyloid-induced neurotoxicity and CysLT1R expression, which results in a decrease in pro-inflammatory factors and proteins linked to apoptosis^{52,53}. Montelukast has also been investigated in relation to aging, where its good impact on microglial activation was once more observed. More intriguingly, however, was an increase in hippocampus neurogenesis, which shows that the medication may be able to restore neural circuitries⁵⁴.

In a mouse model of Lewy-body dementia based on -synuclein, montelukast therapy was demonstrated to lower -synuclein burden and restore memory⁵⁵.

Based on the theory that montelukast can cure cognitive impairment, a case study from 2017 demonstrated encouraging subjective improvements in memory and other dementia-related symptoms⁵⁶.

On the other hand, Eriksson et al. (2018) found negative effects on the developing brain of a mouse both acute and 2-week administrations of montelukast inhibited cellular proliferation and

maturation in the hippocampus of the intact juvenile mouse brain. However, these mice were sacrificed before sexual and brain maturation. We do not know what a brain treated with montelukast looks like when it reaches adulthood¹⁷. Further research on how montelukast works and its effects on the brain, particularly on children's brains, is incredibly important, given the enormous popularity and global distribution of this drug.¹⁸

In the context of traumatic brain injury (TBI), when inflammation and disruption of the blood-brain barrier occur after a traumatic event, an increase in CysLTs and CysLT receptors has been investigated⁵⁷.

In order to lessen the long-term neurological damage brought on by neuro-inflammation following a TBI, the use of montelukast has been suggested.

Conclusion: In animal models, where effects on symptoms and disease biomarkers have been observed, montelukast has demonstrated promising effects on neuroinflammation in a number of neurodegenerative disorders.

The Effect on the Liver:

Montelukast may have an impact on liver damage in experimental obstructive jaundice through its additional anti-inflammatory and antioxidant actions.

Many different cell types, including epithelial cells, fibroblasts, myoblasts, smooth muscle cells, basophils, eosinophils, neutrophils, macrophages, and lymphocytes, create leukotrienes (LTs), bioactive proinflammatory chemicals, through the 5-lipoxygenase pathway from arachidonic acid⁵⁸.

In the synthesis and metabolism of LTs, the liver is crucial. Studies on humans have revealed that CysLTs play a role in the etiology of a number of disorders, including liver cirrhosis, hepatitis B, bile duct blockage, and hepatitis. Moreover, experimental findings show that liver injuries caused by alcoholism, CCl₄ exposure, LPS exposure, hepatic ischemia/reperfusion injury, liver cirrhosis, and liver allograft rejection result in increased CysLTs production⁵⁹.

CysLTs have recently been identified as potential cholestasis mediators. They may generate hepatic edema by increasing vascular permeability in the microcirculation, which in turn causes cholestasis because of an increased resistance to bile flow.

The CysLTs in guinea pigs cause plasma extravasation near the bile ducts. Leukotriene D₄ (LTD₄) and prostaglandin E₂'s synergistic activity has a comparable effect in rats (PGE₂). Leukotriene C₄ (LTC₄) promotes bile salt excretion at low dosages but has a cholestatic impact at high levels in the isolated rat liver⁶⁰.

The detrimental effects of obstructive jaundice on liver histology were lessened by montelukast.

Although the exact mechanism of the bile salt-induced damage has not been determined, endotoxemia, changes in the mitochondrial permeability transition, inflammatory cell infiltration, accumulation of hydrophobic bile acids, and the harmful effects of oxygen free radicals are potential factors that may be to blame.^{61,62}

According to studies, the liver and plasma MDA levels are affected by montelukast, which is thought to lessen tissue damage and lipid peroxidation. Montelukast decreased tissue MPO activity, which could be interpreted as resulting in less neutrophil infiltration and tissue damage.

It is clear that montelukast has antioxidant qualities, which may contribute to some of the positive effects it has on liver damage Sener et al.⁶³ demonstrated that montelukast protects against oxidative damage following heat injury using a neutrophil-dependent mechanism Steib et al.⁶⁴ claimed that a 10-day course of treatment with montelukast significantly decreased basal portal pressure and attenuated the Kupffer cell-dependent rise in portal pressure. These findings led them to conclude that montelukast may have therapeutic value for people who have portal hypertension and hepatic fibrosis in cholestatic rats⁶⁵.

By its various separate modes of action, montelukast can be utilized to treat various organ problems. In the experimental obstructive jaundice model, montelukast had a considerable hepatoprotective effect, which can be attributed to its anti-inflammatory and antioxidant properties. To determine the precise mechanism of montelukast's hepatoprotective action, however, more research is required. Gideroglu et al.⁶⁶ Montelukast sodium's impact on neutrophil infiltration and flap survival was examined. In the montelukast-treated rat group, flap survival was improved, and this finding was connected to reduced neutrophil infiltration and a balance in the oxidant-antioxidant activity status.

The Effect on the Kidneys:

Tugtepe et al.⁶⁷ The results showed that montelukast inhibited neutrophil infiltration, balanced the oxidant-antioxidant status, and controlled the production of inflammatory mediators in the kidney tissue of pyelonephritic rats. Coskun et al.⁶⁸ In a rat model of cecal ligation and puncture-induced sepsis, the effects of montelukast on antioxidant enzymes and proinflammatory cytokines on the heart, liver, lungs, and kidneys were examined. The dose-dependent attenuation or reduction of MPO in lung, liver, heart, and kidney tissues as well as the reduction of lipid peroxide (LPO) in all of these

tissues with the exception of kidney tissue were notable effects of montelukast. Montelukast was most effective in protecting the lung tissue when sepsis was present.

Montelukast provides preventive benefits against various organ harm brought on by chronic renal failure⁶⁹. They explained this by the fact that montelukast can prevent neutrophil infiltration and apoptosis. Additionally, they proposed that montelukast controls the production of proinflammatory mediators and balances the oxidant-antioxidant status. In a different investigation, it was discovered that montelukast reduced microscopic damage and enhanced kidney functioning by reversing ischemia reperfusion-induced oxidative reactions⁷⁰.

Studies have shown that lipid peroxidation, an autocatalytic mechanism that results in the oxidative degradation of cellular membranes, is connected to IR in the kidney⁷¹. The amount of the intracellular antioxidant glutathione, which would otherwise be damaged when neutralizing free radicals, remained unaffected as montelukast lessened the oxidative damage on cellular structures. The antioxidant pool is thus further strengthened by the action of montelukast, suggesting that the anti-oxidative impact of montelukast on lipid peroxidation does not require the consumption of tissue GSH stores. Additionally, montelukast therapy also corrected the IR-induced decrease in total antioxidant capacity⁷².

Montelukast has a protective effect against both the reperfusion damage that results from the treatment of blockage that results in increased renal blood flow and the renal damage caused by unilateral ureteral obstruction.

Montelukast, which functions as a CysLT1 receptor antagonist, has been found to have neuroprotective and antiapoptotic effects in an IRI mouse model. These benefits are linked to the reduction of neutrophil accumulation, lipid peroxidation, and the release of pro-inflammatory cytokines⁷³ have demonstrated that montelukast can lessen tissue damage, neutrophil infiltration, and inflammation in the spinal cord.

The Effect on the Intestine:

In a histological analysis of Erdem et al, Montelukast (2 mg/kg) acts against the Rats' intestinal mucosal ischemia and reperfusion injury caused intestinal mucosal damage and apoptosis , Also, direct cytoprotective effects in the intestine with the suppression of caspase pathways, harm to the liver and kidneys, as well as systemic anti-inflammatory mechanisms with the control of IL-6 and TNF- production⁷⁴.

CONCLUSION

According to the results of this study, montelukast showed a significant effect on the body organs, which might be due to its antioxidant and anti-inflammatory activities.

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Conflict of Interest Statement

None

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