Print ISSN 2319-2003 | Online ISSN 2279-0780

IJBCP International Journal of Basic & Clinical Pharmacology

doi: 10.5455/2319-2003.ijbcp20140401

Review Article

Montelukast: much more than an antiasthma drug

Ghada M. Suddek*

Department of Pharmacology and Toxicology, Faculty of Pharmacy, Mansoura University, Egypt

Received: 27 December 2013
Accepted: 02 February 2014

***Correspondence to:**
Ghada M. Suddek,
Email: ghmsuddek@yahoo.com

ABSTRACT

Montelukast (MK), a selective leukotriene D4 receptor antagonist, is used mainly to reduce eosinophilic inflammation in asthmatic patients. The primary objective of this mini-review is to describe novel additional targets for MK besides the lung and to highlight its antioxidant potential. Literature published between 2002 and 2013 was reviewed for significant antioxidant and anti-inflammatory properties of MK in various experimental models of inflammation rather than that in the airways of asthmatics. Evidence suggests the potential use of MK in many inflammatory diseases rather than asthma therapy.

Keywords: Montelukast, GIT, Liver, Brain, Kidney, Urinary bladder

INTRODUCTION

Leukotrienes (LTs), derivatives of arachidonic acid are synthesized in response to cell activation from membrane phospholipids. Cysteinyl leukotrienes (CysLTs), namely LTC4, LTD4, and LTE4, are potent proinflammatory lipid mediators produced from arachidonic acid through 5-lipoxygenase (5-LOX) pathway.[1]

They are mainly secreted by eosinophils, mast cells, monocytes, and macrophages, and play a crucial role in inflammation, bronchoconstriction, and airway remodeling of asthmatics.[2-5]

It has been reported that bioactive metabolites of LTs have a pivotal role in oxidative stress.[6] Montelukast (MK), the selective LTD4 receptor antagonist, is used mainly to reduce eosinophilic inflammation in asthmatic patients.[7,8] It is also effective in management of allergic rhinitis, chronic obstructive pulmonary disease and idiopathic pulmonary fibrosis.[5]

Moreover, MK was reported to have significant antioxidant properties in various experimental models of inflammation rather than that in the airways of asthmatic patients.

Accordingly, in the current mini review, MK was chosen as a candidate to review its effects in different experimental models of inflammation and oxidative stress.

MONTELUKAST AND GIT

CysLTs play a part in inflammatory reactions such as inflammatory bowel diseases. Results of Marusova et al.[9] demonstrated that MK prevented the stomach mucosa in rats from acute erosive gastritis model induced by aspirin. Serner et al.[10] found that MK has a gastroprotective effect against alendronate, a local irritant that causes inflammation through neutrophil infiltration and oxidative damage in gastric mucosa. It also possesses an anti-inflammatory effect on burn-induced gastrointestinal damage and protects against oxidative injury by a neutrophil-dependent mechanism.[11] In a similar way, MK exhibited a gastroprotective effect on indomethacin-induced ulceration which may be attributed to its ameliorating effect on oxidative damage and myeloperoxidase (MPO) activity.[12,13] It also has some potential to ameliorate mild experimental colitis induced by dextran in rats.[14] In water avoidance stress (WAS)-induced degeneration of rat gastric, ileal and colonic mucosa model,

MK supplementation attenuated inflammatory effects of WAS induction in GIT mucosa.[15] Muthuraman and Sood[16] attributed the antiulcerogenic effect of MK in pyloric ligation and water immersion stress-induced peptic ulcer to its antisecretory, antioxidative along with its antiapoptotic properties. In a trial to investigate the effects of MK on experimental rat colon anastomosis, the investigators found that MK causes impairment of wound healing without altering the anastomosis bursting pressure and reverses the oxidative damage of the colon anastomoses in rats.[17]

MONTELUKAST AND LIVER

In different models of liver oxidative injury, MK proved to protect against this injury. Sener et al. demonstrated that MK protects against burn-induced damage in remote organs of which liver is an important one through a neutrophil-dependent mechanism.[18] In another model, MK was found to possess an anti-inflammatory effect on sepsis-induced (through cecal ligation and puncture) hepatic and intestinal damage in rats.[19] In the studies of Daglar et al. and Ozkan et al.,[20,21] the anti-inflammatory and the inhibitory effect of MK on lipid peroxidation could account for its preventive effect on the liver and intestinal injury in hepatic ischemia/reperfusion (I/R) injury, which may occur in transplantation processes. MK was found to exhibit partial hepatoprotective effects on carbon tetrachloride-treated rats with less severe cellular lesions.[1] It also has an ameliorating effect on necroinflammatory liver injury and fibrogenesis in cholestasis rats.[22] MK reduced portal pressure in rat liver cirrhosis induced in rats either by bile duct ligation or thioacetamide application[23] and therefore, MK may be of therapeutic benefit in patients with portal hypertension. Furthermore, MK treatment after methotrexate application could reduce methotrexate-induced experimental liver damage possibly through reduction of malondialdehyde (MDA) and MPO levels as an antioxidant.[24]

MONTELUKAST AND BRAIN

In the study of Yu et al.,[25] they found that MK has a dose- and time-dependent neuroprotective effect on permanent focal cerebral ischemia in mice induced by middle cerebral artery occlusion. In addition, it protected mice and rats against chronic brain injury after focal cerebral ischemia, as judged by attenuated behavioral dysfunction, brain infarct volume, brain atrophy and neuron loss[26] supporting the therapeutic potential of CysLT(1) receptor antagonists. On the other hand, Hu et al. have reported that MK has not an effect on viability and ischemic-like injury in the primarily cultured rat cortical neurons induced by oxygen-glucose deprivation followed by reperfusion.[27] Biber et al. found that MK decreases blood-brain barrier permeability, but does not prevent edema formation in a rat model of traumatic brain injury-induced oxidative stress of the brain.[28] In 2010, Kalonia et al.[29] emphasized that MK has a protective effect against intrastriatal quinolinic acid/malonic acid-induced Huntington's like symptoms in rats confirming the therapeutic potential of LT receptor antagonists in different neurodegenerative disorders. MK strongly elevated neural stem and progenitor proliferation, while maintaining their differentiation fate and potential and thus the inhibition of the 5-LOX pathway might be potent candidates for future therapies employing neurogenesis to promote structural and functional improvement in neurodegeneration, neuropsychiatric disease and ageing.[30] In a rat model of cognitive dysfunction induced by intrahippocampally injection of kainic acid, MK potentiated the protective effect of rofecoxib (cyclooxygenase [COX-2] inhibitor) emphasizing the positive modulation of cysteinyl LT receptor inhibition on COX and LOX pathways in the control of the neuroinflammation.[31] MK alleviated central nervous system inflammatory cell infiltration and pathogenesis of experimental autoimmune encephalomyelitis indicating that it could be used to treat multiple sclerosis.[32]

MONTELUKAST AND KIDNEY

MK was reported to have a protective effect in different models of renal injury in experimental animals. In a model of renal I/R injury in rats, MK reversed I/R-induced oxidant responses, improved microscopic damage and renal function by inhibiting neutrophil infiltration, balancing oxidant-antioxidant status, and regulating the generation of inflammatory mediators.[33] The same protective effect of MK was observed in pyelonephritic rats in a model of *Escherichia coli*-induced oxidative injury and scarring in renal tissue suggesting a future role for LT CysLT1 receptor antagonists in the treatment of pyelonephritis.[34] Kidney and lung are the most protected tissues by MK in a rat model of cecal ligation and puncture-induced sepsis.[35] This could be due to the ability of MK to reduce inflammatory cytokines, such as TNF-α and IL-6, and ameliorate the negative alteration in the tissue levels of SOD, GSH, MPO, and LPO under these conditions. It was reported that MK ameliorated kidney function in chronic cyclosporine,[36] an acute cisplatin,[37] and acute amikacin-treated rats.[38] It was also able to prevent rhabdomyolysis-induced acute renal failure in rats.[39]

MONTELUKAST AND URINARY BLADDER

MK reduces urinary bladder dysfunction in different sets of models. In a model of I/R of rat urinary bladder, MK almost completely reversed the low contractile responses of rat urinary bladder to carbachol and prevented oxidative tissue damage following I/R.[40] Furthermore, it alleviated protamine sulfate-induced changes in rat urinary bladder through its anti-inflammatory effects.[41] In the study of Suddek, MK ameliorated urinary bladder sensitivity in cisplatin-induced renal dysfunction in rats by reducing the responses of isolated bladder rings to acetylcholine.[37]

MONTELUKAST AND LUNG

Increased activation of alveolar macrophage, neutrophil and mast cell has been proven in cigarette smoking-related lung disorders (CSLD). MK may protect against active or passive smoking-induced lung injury and related disorders suggesting that some part of the pathogenesis of CSLD may be related to an enhanced LTs synthesis.[42] MK protects lung tissue from toxicity signs of paraquat in rats by balancing oxidant/antioxidant status, inhibiting neutrophil infiltration, and by regulating the generation of inflammatory mediators as evidenced by reversal of the elevated levels of serum TNF-alpha, and LDH induced by paraquat.[43] This study greatly recommends the usage of MK in management of paraquat toxicity. In a rat model of bleomycin-induced lung fibrosis, MK was effective in inhibiting further progression of lung fibrosis through inhibition of α- smooth muscle actin positive myofibroblasts.[44] MK may ameliorate lung injury in shocked rats by interfering with inflammatory (TNF-α and IL-6) and oxidative pathways, implicating the role of leukotrienes (LTB4, LTC4) in the pathogenesis of hemorrhagic shock-induced lung inflammation.[45] Furthermore, MK abrogates lipopolysaccharide-induced markers of liver injury and suppresses the release of inflammatory (TNF-alpha, IL-1β, MPO) and oxidative stress markers through its antioxidant properties and enhancement enzymatic antioxidant activities.[46]

MONTELUKAST AND HEART

MK is cardioprotective during myocardial injury in rats[50] by halting the LTs-induced inflammatory response and upregulating the eNOS expression as well as downregulating the iNOS expression. This may represent an approach to the treatment of myocardial ischemia with LT antagonists.[47]

MISCELLANEOUS

MK in arthritis

MK has an anti-inflammatory effect in sodium monourate-induced gouty arthritis in mice[48] and in collagen-induced arthritis in mice.[49]

MK in pancreatitis

MK reduced cerulean-induced pancreatic injury in rats suggesting that CysLTs may be involved in the pathogenesis of acute pancreatitis and that the CysLT receptor antagonist, MK, might be of therapeutic value for proinflammatory cytokines tumor necrosis factor α and interleukin 1β levels as well as Na, K-adenosine triphosphatase and MPO activities.

MK in seizures

MK markedly and dose dependently suppressed the development of kindled seizures as well as pilocarpine induced spontaneous recurrent seizures. Therefore, LTsD(4) may be implicated in the pathogenesis of seizures.[51]

Clinical application

Many published clinical trials, reviews, and case reports have demonstrated beneficial effects of LTRAs on other diseases commonly associated with asthma (rhinitis, chronic obstructive pulmonary disease, interstitial lung disease, exercise induced asthma, chronic urticaria, allergic fungal disease, nasal polyposis, paranasal sinus disease, and atopic dermatitis) as well as other diseases not connected to asthma (migraine, respiratory syncytial virus post bronchiolitis, systemic mastocytosis, cystic fibrosis, pancreatitis, vulvovaginal candidiasis, cancer, atherosclerosis, eosinophils cystitis, otitis media, capsular contracture, and eosinophilic gastrointestinal disorders).[52]

This short review delineates the future roles that MK may have in the management of many diseases rather than asthma such as inflammatory bowel diseases, pulmonary hypertension, multiple sclerosis, pyelonephritis, myocardial ischemia, gouty arthritis, acute pancreatitis, and epilepsy.

Funding: No funding sources
Conflict of interest: None declared
Ethical approval: Not required

REFERENCES

1. Cuciureanu M, Căruntu ID, Păduraru O, Stoica B, Jerca L, Crauciuc E, et al. The protective effect of montelukast sodium on carbon tetrachloride induced hepatopathy in rat. Prostaglandins Other Lipid Mediat. 2009;88:82-8.
2. Samuelsson B. Leukotrienes: Mediators of immediate hypersensitivity reactions and inflammation. Science. 1983;220:568-75.
3. Busse WW, McGill KA, Horwitz RJ. Leukotriene pathway inhibitors in asthma and chronic obstructive pulmonary disease. Clin Exp Allergy. 1999;29 Suppl 2:110-5.
4. Peters-Golden M. Do anti-leukotriene agents inhibit asthmatic inflammation? Clin Exp Allergy. 2003;33:721-5.
5. Rubin P, Mollison KW. Pharmacotherapy of diseases mediated by 5-lipoxygenase pathway eicosanoids. Prostaglandins Other Lipid Mediat. 2007;83:188-97.
6. Sener G, Sakarcan A, Sehirli O, Ekşioğlu-Demiralp E, Sener E, Ercan F, et al. Chronic renal failure induced multiple-organ injury in rats is alleviated by the selective CysLT1 receptor antagonist montelukast. Prostaglandins Other Lipid Mediat. 2007;83:257-67.
7. Aharony D. Pharmacology of leukotriene receptor antagonists. Am J Respir Crit Care Med. 1998;157: S214-9.
8. O'Byrne PM. Asthma treatment: antileukotriene drugs. Can Respir J. 1998;5:64A-70.
9. Marusova IB, Vlasov TD, Marusov IV, Panchenko AV. Potential gastroprotective effect of a CysLT1 receptor blocker sodium montelukast in aspirin-induced lesions of the rat stomach mucosa. Eksp Klin Farmakol. 2002;65:16-8.
10. Sener G, Kapucu C, Cetinel S, Cikler E, Ayanoğlu-

Dülger G. Gastroprotective effect of leukotriene receptor blocker montelukast in alendronate-induced lesions of the rat gastric mucosa. Prostaglandins Leukot Essent Fatty Acids. 2005;72:1-11.
11. Kabasakal L, Sener G, Cetinel S, Contuk G, Gedik N, Yeğen BC. Burn-induced oxidative injury of the gut is ameliorated by the leukotriene receptor blocker montelukast. Prostaglandins Leukot Essent Fatty Acids. 2005;72:431-40.
12. Dengiz GO, Odabasoglu F, Halici Z, Cadirci E, Suleyman H. Gastroprotective and antioxidant effects of montelukast on indomethacin-induced gastric ulcer in rats. J Pharmacol Sci. 2007;105:94-102.
13. Cuciureanu M, Căruntu ID, Kuchar M, Nechifor M. The influence of leukotriene receptors' antagonists on experimentally induced ulcer in rats. Rev Med Chir Soc Med Nat Iasi. 2008;112:750-6.
14. Holma R, Salmenperä P, Virtanen I, Vapaatalo H, Korpela R. Prophylactic potential of montelukast against mild colitis induced by dextran sulphate sodium in rats. J Physiol Pharmacol. 2007;58:455-67.
15. Ersoy Y, Cikler E, Cetinel S, Sener G, Ercan F. Leukotriene D4 receptor antagonist montelukast alleviates water avoidance stress-induced degeneration of the gastrointestinal mucosa. Prostaglandins Leukot Essent Fatty Acids. 2008;78:189-97.
16. Muthuraman A, Sood S. Antisecretory, antioxidative and antiapoptotic effects of montelukast on pyloric ligation and water immersion stress induced peptic ulcer in rat. Prostaglandins Leukot Essent Fatty Acids. 2010;83:55-60.
17. Canbay E, Agachan B, Ozturk T, Giris M, Asoglu O, Balik E, et al. Dual inhibition of wound healing and oxidative process by montelukast in experimental colon anastomoses. Surg Innov. 2010;17:248-55.
18. Sener G, Kabasakal L, Cetinel S, Contuk G, Gedik N, Yeğen BC. Leukotriene receptor blocker montelukast protects against burn-induced oxidative injury of the skin and remote organs. Burns. 2005;31:587-96.
19. Sener G, Sehirli O, Cetinel S, Ercan F, Yüksel M, Gedik N, et al. Amelioration of sepsis-induced hepatic and ileal injury in rats by the leukotriene receptor blocker montelukast. Prostaglandins Leukot Essent Fatty Acids. 2005;73:453-62.
20. Daglar G, Karaca T, Yuksek YN, Gozalan U, Akbiyik F, Sokmensuer C, et al. Effect of montelukast and MK-886 on hepatic ischemia-reperfusion injury in rats. J Surg Res. 2009;153:31-8.
21. Ozkan E, Yardimci S, Dulundu E, Topaloğlu U, Sehirli O, Ercan F, et al. Protective potential of montelukast against hepatic ischemia/reperfusion injury in rats. J Surg Res. 2010;159:588-94.
22. El-Swefy S, Hassanen SI. Improvement of hepatic fibrosis by leukotriene inhibition in cholestatic rats. Ann Hepatol. 2009;8:41-9.
23. Steib CJ, Bilzer M, Op den Winkel M, Pfeiler S, Hartmann AC, Hennenberg M, et al. Treatment with the leukotriene inhibitor montelukast for 10 days attenuates portal hypertension in rat liver cirrhosis. Hepatology. 2010;51:2086-96.
24. Kose E, Sapmaz HI, Sarihan E, Vardi N, Turkoz Y, Ekinci N. Beneficial effects of montelukast against methotrexate-induced liver toxicity: a biochemical and histological study. Scientific World Journal 2012;2012:987508.
25. Yu GL, Wei EQ, Zhang SH, Xu HM, Chu LS, Zhang WP, et al. Montelukast, a cysteinyl leukotriene receptor-1 antagonist, dose- and time-dependently protects against focal cerebral ischemia in mice. Pharmacology 2005;73:31-40.
26. Zhao R, Shi WZ, Zhang YM, Fang SH, Wei EQ. Montelukast, a cysteinyl leukotriene receptor-1 antagonist, attenuates chronic brain injury after focal cerebral ischaemia in mice and rats. J Pharm Pharmacol. 2011;63:550-7.
27. Hu X, Ge QF, Zhang WP, Wei EQ. Effects of cysteinyl receptor agonist and antagonists on rat primary cortical neurons. Zhejiang Da Xue Xue Bao Yi Xue Ban. 2007;36:117-22.
28. Biber N, Toklu HZ, Solakoglu S, Gultomruk M, Hakan T, Berkman Z, et al. Cysteinyl-leukotriene receptor antagonist montelukast decreases blood-brain barrier permeability but does not prevent oedema formation in traumatic brain injury. Brain Inj. 2009;23:577-84.
29. Kalonia H, Kumar P, Kumar A, Nehru B. Protective effect of montelukast against quinolinic acid/malonic acid induced neurotoxicity: possible behavioral, biochemical, mitochondrial and tumor necrosis factor-α level alterations in rats. Neuroscience 2010;171:284-99.
30. Huber C, Marschallinger J, Tempfer H, Furtner T, Couillard-Despres S, Bauer HC, et al. Inhibition of leukotriene receptors boosts neural progenitor proliferation. Cell Physiol Biochem. 2011;28:793-804.
31. Kumar A, Prakash A, Pahwa D, Mishra J. Montelukast potentiates the protective effect of rofecoxib against kainic acid-induced cognitive dysfunction in rats. Pharmacol Biochem Behav. 2012;103:43-52.
32. Wang L, Du C, Lv J, Wei W, Cui Y, Xie X. Antiasthmatic drugs targeting the cysteinyl leukotriene receptor 1 alleviate central nervous system inflammatory cell infiltration and pathogenesis of experimental autoimmune encephalomyelitis. J Immunol. 2011;187:2336-45.
33. Sener G, Sehirli O, Velioğlu-Oğünç A, Cetinel S, Gedik N, Caner M, et al. Montelukast protects against renal ischemia/reperfusion injury in rats. Pharmacol Res. 2006;54:65-71.
34. Tuğtepe H, Sener G, Cetinel S, Velioğlu-Oğünç A, Yeğen BC. Oxidative renal damage in pyelonephritic rats is ameliorated by montelukast, a selective leukotriene CysLT1 receptor antagonist. Eur J Pharmacol. 2007;557:69-75.
35. Coskun AK, Yigiter M, Oral A, Odabasoglu F, Halici Z, Mentes O, et al. The effects of montelukast on antioxidant enzymes and proinflammatory cytokines on the heart, liver, lungs, and kidneys in a rat model of cecal ligation and puncture-induced sepsis. Scientific World Journal 2011;11:1341-56.
36. Atakan A, Arikan H, Macunluoglu B, Tuglular S, Ulfer G, Cakalagaoglu F, et al. Renal protective effects of leukotriene receptor blockers in an experimental model of cyclosporine nephrotoxicity. Transplant Proc. 2008;40:279-84.
37. Suddek GM. Montelukast ameliorates kidney function and urinary bladder sensitivity in experimentally induced renal dysfunction in rats. Fundam Clin Pharmacol. 2013;27:186-91.
38. Kose E, Beytur A, Dogan Z, Ekincioglu Z, Vardi N, Cinar K, et al. The effects of montelukast against amikacin-induced acute renal damage. Eur Rev Med Pharmacol Sci. 2012;16:503-11.
39. Helmy MM, El-Gowelli HM. Montelukast abrogates rhabdomyolysis-induced acute renal failure via rectifying detrimental changes in antioxidant profile and systemic cytokines and apoptotic factors production. Eur J Pharmacol. 2012;683:294-300.
40. Sener G, Sehirli O, Toklu H, Ercan F, Alican I. Montelukast reduces ischaemia/reperfusion-induced bladder dysfunction and oxidant damage in the rat. J Pharm Pharmacol. 2007;59:837-42.
41. Çetinel S, Çanıllıoğlu YE, Çikler E, Sener G, Ercan F.

Leukotriene D4 receptor antagonist montelukast alleviates protamine sulphate-induced changes in rat urinary bladder. BJU Int. 2011;107:1320-5.
42. Yüksel H, Ozbilgin K, Coskun S, Tuglu I. Protective effect of leukotriene receptor antagonist montelukast on smoking-induced lung injury in Wistar rats. Acta Med Okayama. 2003;57:13-9.
43. Ahmed AA. Protective effect of montelukast on paraquat-induced lung toxicity in rats. Biosci Trends. 2009;3:63-72.
44. Shaker OG, Sourour DA. Effect of leukotriene receptor antagonists on lung fibrosis in rats. J Appl Toxicol. 2011;31:678-84.
45. Al-Amran FG, Hadi NR, Hashim AM. Cysteinyl leukotriene receptor antagonist montelukast ameliorates acute lung injury following haemorrhagic shock in rats. Eur J Cardiothorac Surg. 2013;43:421-7.
46. Mohamadin AM, Elberry AA, Elkablawy MA, Gawad HS, Al-Abbasi FA. Montelukast, a leukotriene receptor antagonist abrogates lipopolysaccharide-induced toxicity and oxidative stress in rat liver. Pathophysiology 2011;18:235-42.
47. Chen S, Jin G, Shan J, Zhang M, Men Q, Xu L. Cardioprotective effect and influence on NOS expression of Montelukast sodium in rats. Yao Xue Xue Bao. 2003;38:821-5.
48. Ponce L, Arjona M, Blanco G, Alvarez S, Arcila E, Ortega A, et al. The effect of montelukast in a model of gouty arthritis induced by sodium monourate crystals. Invest Clin. 2011;52:15-22.
49. Shiota N, Shimoura K, Okunishi H. Pathophysiological role of mast cells in collagen-induced arthritis: study with a cysteinyl leukotriene receptor antagonist, montelukast. Eur J Pharmacol. 2006;548:158-66.
50. Ozkan E, Akyüz C, Sehirli AO, Topaloğlu U, Ercan F, Sener G. Montelukast, a selective cysteinyl leukotriene receptor 1 antagonist, reduces cerulein-induced pancreatic injury in rats. Pancreas 2010;39:1041-6.
51. Rehni AK, Singh TG. Modulation of leukotriene D4 attenuates the development of seizures in mice. Prostaglandins Leukot Essent Fatty Acids. 2011;85:97-106.
52. Riccioni G, Bucciarelli T, Mancini B, Di Ilio C, D'Orazio N. Antileukotriene drugs: clinical application, effectiveness and safety. Curr Med Chem. 2007;14:1966-77.

doi: 10.5455/2319-2003.ijbcp20140401
Cite this article as: Suddek GM. Montelukast: Much more than an antiasthma drug. Int J Basic Clin Pharmacol 2014;3:255-9.