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The Effects of Zileuton and Montelukast in Reperfusion-Induced Arrhythmias in Anesthetized Rats☆

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ABSTRACT

Background: 5-Lipoxygenase is an enzyme involved in the synthesis of leukotriene eicosanoids from arachidonic acid. The therapeutic potential of zileuton, an inhibitor of 5-lipoxygenase, and montelukast, a cysteinyl leukotriene receptor antagonist, for the treatment of ischemia/reperfusion (I/R) injury of the heart has been proposed in a few studies. However, the effects of zileuton and montelukast on I/R-induced arrhythmias have not been determined.

Objective: We assessed the possible protective effects of zileuton and montelukast against I/R-induced arrhythmias.

Methods: Forty-five male Wistar albino rats were divided into 5 groups, each containing 9 rats. Group 1: control, Groups 2 and 3: rats treated with montelukast (10 and 30 mg/kg IP); and Groups 4 and 5: rats treated with zileuton (1 and 3 mg/kg IV) 15 minutes before the induction of ischemia. Ischemia and reperfusion were induced by occluding the left main coronary artery of anesthetized rats for 6 minutes followed by reopening the artery for 6 minutes.

Results: Both doses of zileuton decreased the mean [SE] arrhythmia score (zileuton 1 mg/kg: 1.4 [0.8]; zileuton 3 mg/kg: 1.3 [0.5] vs control: 2.9 [0.3]; $P < 0.05$), the duration of ventricular tachycardia, and the total length of arrhythmias, but montelukast was not effective to decrease the ventricular arrhythmias during the 6 minutes of reperfusion.

Conclusions: The results indicate for the first time that zileuton exerts an antiarrhythmic effect at different doses and that montelukast is not effective against I/R-induced arrhythmias. These results indicate that zileuton may be a candidate for drug treatment of I/R-induced arrhythmias.

Introduction

The initiation of reperfusion by thrombolysis or coronary angioplasty is a standard treatment for acute myocardial infarction.[1] Although the reinstitution of blood flow to the previously ischemic myocardium is the only way to save the myocardium from eventual necrosis, reperfusion often exacerbates myocardial damage and leads to life-threatening ventricular arrhythmias.[2] The mechanisms mediating ischemia/reperfusion (I/R)-induced arrhythmias are not well defined. However, oxidative stress, activated neutrophils, and calcium overload are considered the major factors associated with I/R-induced arrhythmias.[3–6]

Leukotrienes (LTs) are eicosanoids that are generated from arachidonic acid by 5-lipoxygenase (5-LO) via biochemical pathways.[7] LTs not only increase the severity of the inflammatory response but are also produced after cardiac injury; the level of LTB4 in particular is increased in rat myocardium after experimental myocardial infarction, and in patients with cardiac ischemia.[8,9] LTs induce the recruitment and activation of neutrophils and increase vascular permeability. The activated neutrophils transmigrate into ischemic tissue and release reactive oxygen species, proteases, elastase, myeloperoxidase, and various other mediators, all of which exacerbate inflammation and contribute to tissue injury.[10]

Zileuton is a selective inhibitor of 5-LO, and montelukast is a cysteinyl-LT (Cys-LT) receptor antogonist. Both compounds are currently being used to treat patients with asthma.[11] Both compounds have been shown to decrease the severity of I/R injury in various organs.[12–16] A recent clinical study[17] suggested that the use of montelukast decreases the risk for myocardial infarction and ischemic stroke. Only a few experimental studies have focused on the cardioprotective effects of zileuton and montelukast. Montelukast was found to be protective against isoproterenol-induced myocardial necrosis due to its ability to inhibit LT-induced inflammatuary responses.[18] Zileuton has also been shown to

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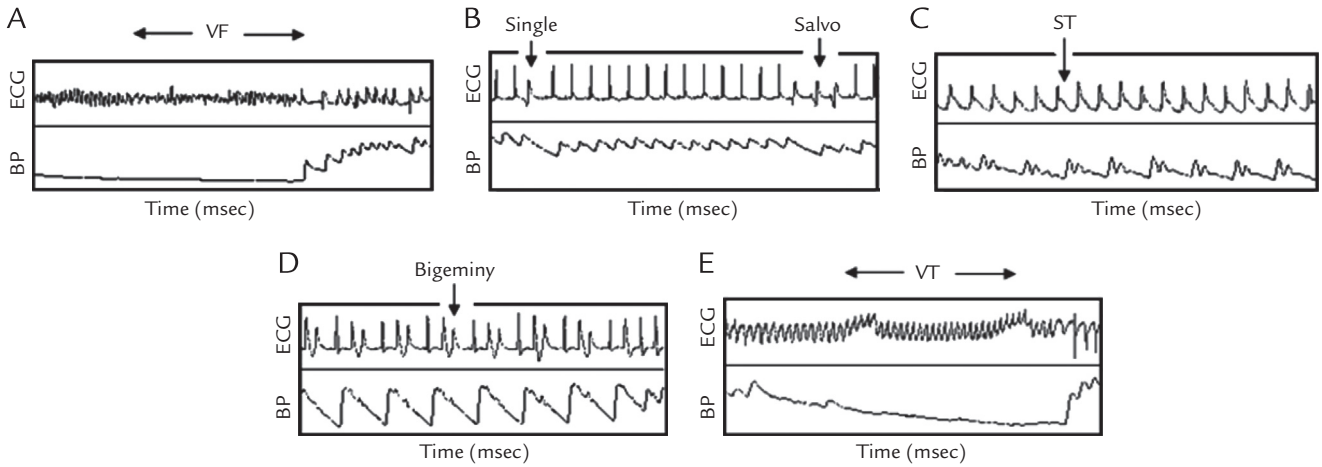

Figure 1. Original electrocardiogram and blood pressure recordings, from (A) a control anesthetized rat, (B) a zileuton 1 mg/kg treated rat, (C) a zileuton 3 mg/kg treated rat, (D) a montelukast 10 mg/kg treated rat, and (E) a montelukast 30 mg/kg treated rat. BP = blood pressure; ECG = electrocardiogram; single = single extrasystole; ST = ST segment elevation; VF = ventricular fibrillation; VT = ventricular tachycardia.

protect cardiomyocytes from hydrogen peroxide-induced cytotoxicity by activating protein kinase C.[19]

Because both zileuton and montelukast may have anti-inflamatory and antioxidant activities,[16,18] they may also decrease the duration of I/R-induced arrhythmias. To the best of this author's knowledge, the effects of zileuton and montelukast on I/R-induced arrhythmias have not been studied previously. Therefore, I aimed to investigate the possible antiarrhythmic effects of zileuton and montelukast.

Materials And Methods

Animals

A total of 45 male Wistar albino rats (5–6 months old weighing between 300 and 450 g) were used in the experiments. Animals were housed in individual cages in an animal room at a temperature of 22°C ($\pm$ 3°C) with 12-hour light/dark cycle and with free access to standart pellet food and water ad libitum. All experiments were performed in adherence to all of the guiding principles in the care and use of animals, together with the recommendation from the Declaration of Helsinki, and were approved by the Committee on Animal Research at Bülent Ecevit University, Zonguldak, Turkey.

Surgical procedures and hemodynamic measurements

Fundamental surgical procedures used in the study were described before by Bozdogan et al.[20] Briefly, animals were anaesthetized with thiopental sodium (85 mg/kg IP in a volume of 2 mL/kg) (Abbott, İstanbul, Turkey) and tracheotomy was used for artificial respiration. The left carotid artery was cannulated with polyethylene tubing (0.58 mm $\times$ 0.96 mm; Harvard Apparatus, Boston, Massachusetts) to record the arterial blood pressure with a blood pressure transducer (SS 13 L; Biopac Systems, Goleta, California). A standard limb lead I electrocardiogram (ECG) was recorded using subcutaneous needle electrodes. The chest was opened by left thoracotomy followed by sectioning of the fourth and fifth ribs. Artificial respiration was started immediately with room air using a volume of 1.5 mL/100 g body weight at a rate of 60 strokes/min to maintain carbon dioxide partial pressure at 18 to 24 mm Hg, partial oxygen pressure at 100 to 130 mm Hg, and pH at 7.4 (SAR 830; IITC Life Science, Woodland Hills, California).

After the pericardium was incised, the heart was eased out of the chest by gentle pressure on the rib cage. A 5/0 silk suture was placed around the arterial descendant branch of the left coronary artery approximately 2 mm from its origin. The heart was placed back into the chest cavity, attention was paid to proper reinflation of the lungs. The animal was allowed to recover for a stabilization period of 5 minutes. Any animal having arrhythmias or a sustained decrease in mean arterial blood pressure (MABP) below 70 mm Hg before ligation was discarded. A total of 4 animals were excluded from the evaluation on the basis of these criteria. After stabilization of blood pressure and heart rate (HR), coronary artery occlusion was applied for 6 minutes by tying a knot in the coronary artery vessel by making a bowknot. Then the silk was pulled through the bowknot so this knot was untied to permit reperfusion for 6 minutes.

At the termination of the experiment, heparin (500 IU/kg) was given intravenously, and the heart was excised. The left coronary artery was retightened, and the heart was first perfused through the aorta with 10 mL isotonic sodium chloride solution, followed by 2 mL 96% ethanol for the demarcation of the occluded and nonoccluded myocardium.[20] The nonperfused area that remained red colored (ischemic risk zone) was cut along the epicardially visible border zone from the well-perfused area that seemed white in color (nonischemic myocardium mass). The wet weight of the ischemic risk zone and the total wet weight of ischemic risk zone and nonischemic myocardium mass were measured. The ischemic risk zone was expressed as the percentage of the total weight of the myocardium.

Successful occlusion of the coronary artery was judged visually by the development of pallor of the exposed myocardium, ST-segment elevation, increased R wave amplitude on ECG, decrement in MABP, and by the perfusion proved that the ligature was at an adequate place (ischemic risk zone must be $>$ 40%), whereas successful reperfusion was judged by the reversal of ischemia-induced ST-segment changes and the recovery of MABP. A total of 8 animals were excluded from the evaluation on the basis of these criteria.

Recording and arrhythmia analysis

ECG and arterial blood pressure were continuously monitored throughout the I/R periods (**Figure 1**) and data subsequently analysed using data acquisition system (MP35, Biopc System). HR and MABP were derived from these recordings immediately before the ligation, at 1 and 5 minutes of ligation, and at 5 minutes of

reperfusion. Arrhythmias were detected during the I/R periods and defined by following guidelines of the Lambeth Conventions[21] as ventricular tachycardia (VT); ventricular fibrillation (VF); and other types of arrhythmias, including single extrasystoles, bigeminy, and salvos (**Figure 1**). VT was defined as a run of 4 or more consecutive ventricular premature complex. VF was defined as a ventricular rhythm without a recognizable QRS complex, with changing signal morphology from cycle to cycle. The arrhythmic periods that included the time interval between the onset of arrhythmias and the end of the arrhythmias were measured for the reperfusion period and the length of arrhythmic attacts was also measured for both periods. The incidences of VF, VT, other types of arrhythmias, and mortality were quantified for the reperfusion period. An arrhythmia score was used to indicate the severity of arrhythmias based on the type and duration of arrhythmic episodes by giving a grade to each animal as follows: 0 = no arrhythmia; 1 = ≤10 seconds VT and/or other types of arrhythmias, no VF; 2 = 11 to 30 seconds VT and/or other types of arrhythmias, no VF; 3 = 31 to 90 seconds VT and/or other types of arrhythmias, no VF; 4 = 91 to 180 seconds VT and/or other types of arrhythmias and/or < 10 seconds reversible VF; 5 = ≥180 seconds VT and/or other types of arrhythmias and/or > 10 seconds reversible VF; and 6 = irreversible VF.[22]

Drug treatments and experimental groups

We obtained pure powder montelukast from Sanofi Company (Levent, İstanbul, Turkey) and purchased zileuton from Sigma Chemical Co (St. Louis, Missouri). Zileuton and montelukast were dissolved in 1% dimethyl sulfoxide (DMSO) and 0.9% saline solution, respectively. Drugs were applied in a volume of 100 μL/kg. The doses of zileuton and montelukast and their administration routes and timing used in this study are based on previous studies.[14–16,18] Zileuton was administrated through a femoral vein at a dose of 1 and 3 mg/kg. Montelukast was applied IP at a dose of 10 and 30 mg/kg.

The experimental protocol consisted of 5 separate groups:

- Control: 100 μL/kg, IV 1% DMSO, and IP 0.9% sodium chloride, 15 minutes before coronary ligation, respectively.
- Zileuton: IV 1 mg/100 μL/kg zileuton and 100 μL/kg IP 0.9% sodium chloride, 15 minutes before coronary artery ligation, respectively.
- Zileuton: IV 3 mg/100 μL/kg zileuton and 100 μL/kg IP 0.9% sodium chloride, 15 minutes before coronary artery ligation, respectively.
- Montelukast: IP 10 mg/100 μL/kg montelukast and 100 μL/kg IV 1% DMSO, 15 minutes before coronary artery ligation, respectively.
- Montelukast: IP 30 mg/100 μL/kg montelukast and 100 μL/kg IV 1% DMSO, 15 minutes before coronary artery ligation, respectively.

Statistical analysis

For the statistical analysis of the survival rate and the incidence of arrhythmias, Fisher exact test was employed. The other paremeters were expressed as mean [SE] and all comparisons between the control and drug treated groups were made using a 1-way analysis of variance and Dunnett's post hoc test. Preocclusion and postocclusion MABP and HR values were also compared using a 1-way analysis of variance and Dunnett post hoc test. Changes were considered significant at $P < 0.05$.

Table I
Mean [SE] arterial blood pressure (MABP) and heart rate (HR) during 6 minutes of ischemia and reperfusion.

Time	Control	Zileuton (1 mg/kg)	Zileuton (3 mg/kg)	Montelukast (10 mg/kg)	Montelukast (30 mg/kg)
MABP (mm Hg)					
0 (Basal)	82 [3]	84 [3]	95 [4]	96 [7]	80 [4]
1 (Ligation 1 min)	57 [6]*	52 [7]*	73 [7]*	75 [10]*	62 [5]*
5 (Ligation 5 min)	53 [6]*	58 [10]*	90 [6]	79 [10]*	60 [7]*
11 (Reperfusion 5 min)	83 [5]	86 [4]	94 [7]	95 [10]	70 [4]
HR					
0 (Basal)	393 [20]	372 [18]	395 [8]	400 [18]	398 [14]
1 (Ligation 1 min)	390 [25]	368 [22]	387 [7]	404 [20]	389 [12]
5 (Ligation 5 min)	401 [21]	387 [17]	384 [12]	400 [18]	401 [18]
11 (Reperfusion 5 min)	404 [10]	387 [17]	394 [10]	390 [19]	390 [16]

*$P < 0.05$ versus basal values.

Results

All groups exhibited a characteristic decrease in MABP upon the occlusion of the coronary artery ($P < 0.05$). MABP showed a moderate recovery in the late phase of ischemia. However, the MABP recovered earlier in the zileuton-treated (3 mg/kg) group and approached the basal value during the fifth. minute of ligation in this group. Following reperfusion, MABP increased gradually and approached the basal value observed before ligation. None of the drug treatments had any significant effect on HR at any time point **(Table I)**. The MABP, HR, and the percentage of the ischemic risk zone was not different between the drug-treated groups and the control group (see **Table I** and **Table II**).

The ligation of coronary arteries resulted in the generation of arrhythmias, occurring as the other types of arrhythmias, including single extrasystoles, bigeminy, and salvos (**Figure 1**). Drug treatments did not affect the duration of other types of arrhythmias during 6 minutes of ligation. Neither control nor drug-treated groups experienced any VF and VT (data not shown).

In all groups, reperfusion-induced arrhythmias started within 0 to 20 seconds of the reperfusion period. With regard to the incidence of VF, VT, other types of arrhythmias, and mortality, there

Table II
The effects of drug treatments on the incidence of arrhythmias during 6 minutes of reperfusion.

Group	Dose (mg/kg)	n*	Zone at risk (% of total)	Mortality n†/%	Incidence of arrhythmias (n‡/%)		
					VF	VT	Other
			Mean [SE]				
Control	-	7	46 [2]	0/0	3/43	7/100	7/100
Zileuton	1	7	44 [4]	0/0	0/0	3/43	7/100
Zileuton	3	7	52 [3]	0/0	0/0	2/29§	5/71
Montelukast	10	6	44 [1]	0/0	1/17	3/50	6/100
Montelukast	30	6	49 [2]	0/0	0/0	5/83	6/100

Other = other types of arrhythmias; VF = ventricular fibrillation; VT = ventricular tachycardia.

*The number of animals just before the reperfusion.
†The number of dead animals after 6 min of reperfusion.
‡The number of animals experienced arrhythmia.
§$P < 0.05$ compared with control.

Table III
The effect of drug treatments on the duration of arrhythmias during 6 minutes of reperfusion.

Groups	Dose (mg/kg)	n	Arrhythmia score	Arrhythmic period (sec)	Length of arrhythmias (sec)			
					VF	VT	Other	Total
					Mean [SE]			
Control	-	7	2.9 [0.3]	133 [19]	2 [1]	35 [13]	11 [2]	48 [14]
Zileuton	1	7	1.4 [0.8]*	124 [44]	0	7 [7]*	8 [8]	16 [10]*
Zileuton	3	7	1.3 [0.5]*	34 [17]*	0	5 [2]*	3 [3]*	8 [4]*
Montelukast	10	6	1.8 [0.5]	104 [41]	1 [1]	11 [7]	9 [2]	20 [10]
Montelukast	30	6	2.0 [0.0]	101 [13]	0	10 [4]	12 [3]	22 [4]

Other = other types of arrhythmias; VF = ventricular fibrillation; VT = ventricular tachycardia.
*$P < 0.05$ compared with control.

was no significant difference among groups. Only exception was the higher dose of zileuton group (3 mg/kg) in which the incidence of VT significantly decreased compared with control (Table II).

Both doses of zileuton (1 and 3 mg/kg) reduced the arrhythmia [SE] scores, the duration of VT, and the total length of arrhythmias during the 6 minutes of reperfusion (arrhythmia scores: zileuton 1 mg/kg, 1.4 [0.8]; zileuton 3 mg/kg, 1.3 [0.5] vs control, 2.9 [0.3]; $P < 0.05$) (see Table III and Figure 2). Treatment with 3 mg/kg zileuton but not 1 mg/kg zileuton, decreased the mean [SE] duration of arrhythmic periods and other types of arrhythmias (length of arrhythmic period(s): zileuton 3 mg/kg 34 [17] vs control, 133 [19]; $P < 0.05$) (Table III). Both doses of Montelukast (10 and 30 mg/kg) did not significantly decrease the duration of any type of arrhythmias (see Table III and Figure 3).

Discussion

Because leukotriene production increases in patients with cardiac ischemia,[9] we assumed that the inhibition of LTs would suppress ventricular arrhythmias following ischemia and reperfusion. Although zileuton, a 5-LO inhibitor, and montelukast, a Cys-LT receptor antagonist, are currently in use as effective antiasthma agents,[11] their potential clinical usefulness in preventing reperfusion-induced arrhythmias has not been clarified.

My study demonstrated that zileuton pretreatment at doses of 1 and 3 mg/kg suppressed reperfusion-induced arrhythmias in an in vivo anesthetized rat model. To the best of our knowledge, this is the first report of the effect of zileuton on reperfusion-induced ventricular arrhythmias. This finding is in line with the results of a recent clinical study[23] in which zileuton treatment decreased the number of tachycardia events in patients with permanent atrial fibrillation.

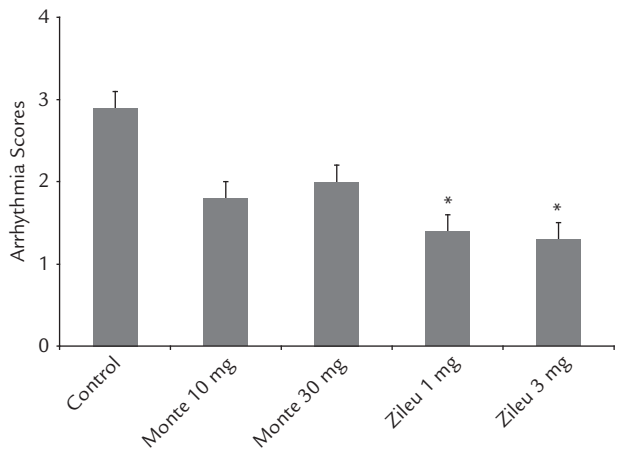

Figure 2. The effect of drug treatments on the arrhythmia score during 6 minutes of reperfusion. Values are means [SD]. *$P < 0.05$ compared with control.

Zileuton has been shown to possess tissue-protective effects in nerve and testicular tissues.[12,13] This effect was suggested to be the result of its anti-inflammatory and antioxidant effects. The excess LTs produced in ischemic myocardial tissue activate neutrophils, which promote oxidative stress and the development of intracellular ionized calcium overload.[24] Intracellular ionized calcium overload and oxidative stress are considered the major factors that lead to ventricular arrhythmias in reperfused myocardium.[25,26] Therefore, in my study, zileuton may have suppressed reperfusion-induced arrhythmias by decreasing LT production and reducing the number of activated neutrophils, which suppressed oxidative stress and intracellular ionized calcium overload. Likewise, the dual inhibition of lipoxygenase (LO) and cyclooxygenase (COX) by BW755C has been proposed to be protective against digoxin-induced arrhythmias.[27]

In a recent study, another LO inhibitor, baicalein, was found to suppress reperfusion arrhythmias in an in vivo rat coronary ligation model.[28] The results of that study suggest that reperfusion arrhythmias originate from mitochondrial depolarization, which is mediated by LO and reactive oxygen species release. In my study, the antiarrhythmic effect of zileuton may also be attributed to the inhibition of mitochondrial membrane depolarization, which is mediated by its inhibitory action on 5-LO.

In my study, the administration of zileuton at a dose of 3 mg/kg resulted in the earlier recovery of baseline MABP. This result indicates that zileuton may have a protective effect on ischemic myocardium. Likewise, it has recently been demonstrated that zileuton protects cardiomyocytes from hydrogen peroxide-induced cytotoxicity.[29] In this study, it was suggested that pharmacologic inhibition of 5-LO by zileuton leads a shunt from the 5-LO pathway to COX-2 and the protective effect of zileuton was suggested to depend on a signaling pathway that involves the induction of COX-2 mediated through the protein kinase C delta-dependent activation of extracellular-signal-regulated kinases 1/2 and protein kinase B. In this study, zileuton may also have exhibited a cardioprotective effect via the activation of this type of pathway. Similarly, the protein kinase C and extracellular-signal-regulated kinases 1/2-dependent signaling pathway may also mediate the mitochondrial ATP-sensitive potassium channel (mitoK_{ATP}) activation,[30] which has recently been demonstrated to decrease I/R-induced arrhythmias in anesthetized rats.[31] Therefore, in my study, zileuton may also have activated mitoK_{ATP} channels to suppress arrhythmias. In previous studies, the activation of mito-K_{ATP} channels has been shown to mediate the antiarrhythmic effects of estrogen and oxytocin.[32,33]

The doses of montelukast, a higher dose (30 mg/kg) and a lower dose (10 mg/kg) used in our study have previously been reported

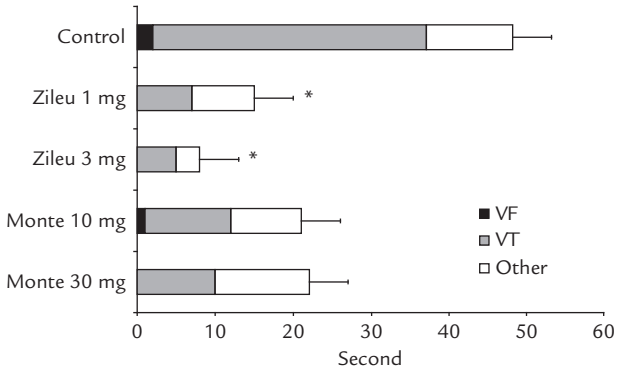

Figure 3. The effect of drug treatments on the total length of arrhythmias during 6 minutes of reperfusion. Values represent means [SE]. Other = other types of arrhythmias; VF = ventricular fibrillation; VT = ventricular tachycardia. $^{*}P < 0.05$ compared with control.

to decrease myocardial injury in the rat model of isoproterenol-induced necrosis.[18] Altough we found that neither dose of montelukast was effective in preventing I/R-induced arrhythmias, it nonsignificantly decreased the duration of VT and the total length of arrhythmias during the reperfusion. The doses of montelukast higher than 30 mg/kg might be effective against I/R-induced arrhythmias.

The different effects of zileuton and montelukast treatments can be explained by the different action mechanisms of these compounds. Zileuton inhibits the production of both LTB4 and Cys-LTs by inhibiting the 5-LO enzyme, whereas montelukast antagonizes the effects of Cys-LTs (LTD4 and the secondary ligands LTC4 and LTE4) by selectively blocking the Cys-LT1 receptor on target cells.[34] These results suggest that metabolites of 5-LO (especially LTB4) may contribute to I/R-induced arrhythmias. The effectiveness of montelukast may also indicate that the underlying antiarrhythmic effect of zileuton is dependent on possible non-specific effects, such as protein kinase C activation and the inhibition of mitochondrial depolarization, rather than the LT pathway.

Limitations

Further studies are needed to examine if treatment with zileuton immediately postischemia, but before reperfusion, is effective against I/R-induced arrhythmias to test applicability of these results to human beings.

Conclusions

My study clearly demonstrated for the first time that zileuton suppresses reperfusion-induced arrhythmias. Zileuton, which is currently used for the treatment of asthma, may also be a candidate for the treatment of reperfusion-induced arrhythmias. However, further studies should be conducted to determine the mechanism underlying its antiarrhythmic activity and to investigate the applicability of these results to human beings.

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Conflicts of Interest

The author has indicated that there is no conflict of interest regarding the content of this article.

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