The present invention is directed to methods of treating and/or ameliorating muscular dystrophy and/or treating cardiomyopathy in muscular dystrophy patients by administration of a therapeutically effective amount of a thromboxane A2 receptor antagonist.
(A) Vehicle-treated DKO – 10 weeks

Fig. 1A

(B) Ifetroban-treated DKO – 10 weeks

Fig. 1B
FIGURE 2

Plasma cTNI in dSG KO males, 3 months

- vehicle
- ifetroban

ng/mL plasma cTNI

WT  dSG KO
FIGURE 4

Male dSG KO echoes at 3 months

p=0.018

p=0.015

WT

dSG KO-veh

dSG KO-if

Fract short  Eject fract  Cardiac output (in mL/min)
FIGURE 5

Spontaneous exercise
6 month males

avg km/day

WT  dSG+veh  dSG+ife
FIGURE 6

dSG 6 mo males

avg hang time (mins)

WT  dSG-veh  dSG-ife

p=0.526
FIGURE 8

Males-6mo longest hang time

<table>
<thead>
<tr>
<th></th>
<th>WT</th>
<th>dSG-veh</th>
<th>dSG-ife</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>3</td>
<td>5</td>
<td>3</td>
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</tbody>
</table>

longest hang time (mins)
Fig. 14A

dSG KO: Survival of males

- vehicle (n=8)
- ifetroban (n=9)

Fig. 14B

dSG KO: Survival of females

- vehicle (n=13)
- ifetroban (n=11)
COMPOSITIONS AND METHODS OF TREATING MUSCULAR DYSTROPHY WITH THROMBOXANE-A2 RECEPTOR ANTAGONISTS

[0001] This invention was made with government support under grant numbers R01HL095797 and P01HL108500 awarded by the National Institutes of Health. The government has certain rights in the invention.

FIELD OF THE INVENTION

[0002] The present invention is related to the use of thromboxane A2 receptor antagonists (e.g., etrobrotan) in the treatment of muscular dystrophy in mammals, e.g., humans, and pharmaceutical compositions for the same comprising thromboxane A2 receptor antagonists (e.g., etrobrotan) in an effective amount to treat these diseases.

BACKGROUND OF THE INVENTION

[0003] Muscular Dystrophy (MD) is a group of 30+ diseases that causes progressive weakness and loss of muscle mass due to mutations in dystrophin, a protein needed to form healthy muscle. Duchenne MD (DMD) comprises half of MD; affects 1 in 3,500 boys and 1/2 have no family history. Onset is between ages 2 and 3 and progresses rapidly. Becker MD (BMD) is the 2nd most common form of MD; 1 in 30,000 boys; BMD is milder and slowly progresses compared to DMD; symptoms may not be seen until teens, mid-20s or later. Limb-Girdle MD (LGMD) can affect as many as 1 in 14,500 and causes weakness and wasting of the muscles in the proximal arms and legs.

[0004] Complications of muscular dystrophy include inability to walk, breathing problems, scoliosis, cardiac myopathy and swallowing problems. There is no cure. Treatment to-date is to manage symptoms or slow progression.

[0005] Delta-sarcoglycan (DSG) is a transmembrane glycoprotein which forms as a complex, the dystrophin-associated glycoprotein complex (DGC). The DGC plays a central role in maintaining integrity of the cell membrane by linking the extracellular matrix (“ECM”); a substance containing collagen, elastin, proteoglycans, glycosaminoglycans, and fluid, produced by cells and in which the cells are embedded and cytoskeleton (the inner structural elements, or backbone, of a cell). It consists of microtubules and various filaments that spread out through the cytoplasm, providing both structural support and a means of transport within the cell.

[0006] In both skeletal and cardiac muscle, the DGC consists of dystrophin, the syntrophins, a- and b-sarcoglycan (a-, b-, DSG), and sarcospan (SSP).

[0007] Mutations in the dystrophin gene lead to high incidence of cardiac myopathy in DMD and BMD. Mutations in sarcoglycans within DGC are responsible for Limb-Girdle MD and associated with cardiac myopathy. A major function of dystrophin is to strengthen the sarcoclemma by cross-linking the ECM with the cytoskeleton. Urotropin and a2b1 integrin fulfill the same function. Dystrophin works to connect sarcoclemma to cytoplasmic actin cytoskeleton. Dysfunction produces membrane instability, elevated [Ca2+]L and disrupted NO signaling. a- and b-SSG form a core necessary for delivery/retention of other SG to the membrane.

[0008] Patients with mutations in DSG (e.g., patients suffering from muscular dystrophy) present with cardiac myopathy.

[0009] Absence of dystrophin in Duchenne muscular dystrophy (DMD) causes progressive breakdown of muscle cells. In the heart, loss of dystrophin leads to abnormally increased intracellular calcium, degradation of contractile proteins, fibrosis, and myocardial death. With advances in respiratory support, cardiomypathy is now a primary cause of death amongst DMD patients. DM D patients develop an insidious decline in cardiac function leading to heart failure and can also develop arrhythmias, with the potential for sudden cardiac death, even with minimal decrease in cardiac function by physical symptoms or echocardiography. Because of this, cardiac magnetic resonance (CMR) is useful for detection of early cardiac involvement in DMD patients. Increased myocardial fibrosis and expanded extracellular volume in CMR predicts left ventricular (LV) dysfunction, and are associated with an increased risk of arrhythmia and hospitalization for heart failure or death.

[0010] While less severely affected than skeletal and cardiac muscle, intestinal smooth muscle function can also be altered by atrophy and fibrosis. In DMD patients, particularly when wheelchair-bound, this can lead to poor gut motility, gastroesophageal reflux, and chronic constipation, which negatively affect patient quality of life. More critically, the possible complications of dilation, fecal impaction, or intestinal pseudo-obstruction can be life-threatening.


[0012] Fibrosis is the formation of excess fibrous connective tissue in an organ or tissue in a reparative or reactive process. This can be a reactive, benign, or pathological state,
and physiologically acts to deposit connective tissue, which can obliterate the architecture and function of the underlying organ or tissue. Fibrosis can be used to describe the pathological state of excess deposition of fibrous tissue, as well as the process of connective tissue deposition in healing. While the formation of fibrous tissue is normal, and fibrous tissue is a normal constituent of organs or tissues in the body, scarring caused by a fibrotic condition may obliterate the architecture of the underlying organ or tissue.

[0013] To date, there are no commercially available therapies that are effective in treating or preventing fibrotic disease. Conventional treatment frequently involves corticosteroids, such as prednisone, and/or other medications that help improve muscle strength and delay the progression of certain types of muscular dystrophy. Also, heart medications, such as angiotensin-converting enzyme (ACE) inhibitors or beta blockers may be administered to muscular dystrophy patients, if the muscular dystrophy damages the heart.

SUMMARY OF THE INVENTION

[0014] It is an object of the present invention to provide new methods of treating muscular dystrophy in mammals, e.g., humans.

[0015] In accordance with the above objects, the present invention provides for methods of treating muscular dystrophy by administering a therapeutically effective amount of a thromboxane A2 receptor antagonist to a patient in need thereof.

[0016] In accordance with the above objects and others, the present invention is directed in part to a method of treating or ameliorating muscular dystrophy in a subject in need of treatment thereof, comprising administering a therapeutically effective amount of a thromboxane A2 receptor antagonist to the patient. The muscular dystrophy is fibrosis is selected from the group consisting of Duchenne MD (DMD), Becker MD, and Limb-Girdle MD. The thromboxane A2 receptor antagonist may be administered orally, intranasally, rectally, vaginally, sublingually, buccally, parenterally, or transdermally. In certain preferred embodiments, the method further comprises administering the thromboxane A2 receptor antagonist to the patient on a chronic basis. In certain embodiments, the thromboxane A2 receptor antagonist comprises a therapeutically effective amount of 5-[1-(1-cyclohexylcarbonyl)-2-[3-[4-[(Pentylamino)carbonyl]-2-oxazolyl]-7-oxabicyclo[2.2.1]hept-2-yl][methyl]-benzenepropanoic acid (Iloprost), and pharmaceutically acceptable salts thereof. In certain embodiments, the thromboxane A2 receptor antagonist comprises a therapeutically effective amount of 5-[1-(1-cyclohexylcarbonyl)-2-[3-[4-[(Pentylamino)carbonyl]-2-oxazolyl]-7-oxabicyclo[2.2.1]hept-2-yl][methyl]-benzenepropanoic acid, monosodium salt (Iloprost Sodium). In certain preferred embodiments, the cardiac function of the patient is maintained or improved. Certain embodiments of the invention are directed to the method, wherein the thromboxane A2 receptor antagonist is administered prophylactically to prevent cardiomyopathy in the patient, and/or to prophylactically to prevent gastrointestinal dysfunction in the patient. In certain preferred embodiments, the therapeutically effective amount is from about 50 mg to about 500 mg. In certain preferred embodiments, the thromboxane A2 receptor antagonist is Iloprost and the therapeutically effective amount is from about 150 mg to about 350 mg per day. In certain embodiments, the Iloprost is administered orally. In certain embodiments, the present invention is directed to a method of treating and/or ameliorating muscular dystrophy in a patient in need thereof, comprising administering to a patient in need thereof a therapeutically effective amount of a thromboxane A2 receptor antagonist to provide a desired plasma concentration of the thromboxane A2 receptor antagonist of about 0.1 ng/ml to about 10,000 ng/ml.

[0017] The invention is also directed to a method of providing cardioprotective effects to a human patient(s) suffering from muscular dystrophy via the administration of a thromboxane A2 receptor antagonist as described herein.

[0018] The invention is further directed to a method of improving right heart adaptation to load stress in a human patient(s) suffering from muscular dystrophy via the administration of a thromboxane A2 receptor antagonist as described herein.

[0019] The invention is further directed to a method of treating cardiac and/or gastrointestinal dysfunction in a human patient suffering from muscular dystrophy, comprising chronically administering a therapeutically effective amount of a thromboxane A2 receptor antagonist to the human patient. In certain preferred embodiments, the thromboxane A2 receptor antagonist is 1S-1-(1-cyclohexylcarbonyl)-2-[3-[4-[(Pentylamino)carbonyl]-2-oxazolyl]-7-oxabicyclo[2.2.1]hept-2-yl][methyl]-benzenepropanoic acid (Iloprost), and pharmaceutically acceptable salts thereof, and in certain most preferred embodiments the thromboxane A2 receptor antagonist is 1S-1-(1-cyclohexylcarbonyl)-2-[3-[4-[(Pentylamino)carbonyl]-2-oxazolyl]-7-oxabicyclo[2.2.1]hept-2-yl][methyl]-benzenepropanoic acid, monosodium salt (Iloprost Sodium). The therapeutically effective amount may be, e.g., from about 100 mg to about 500 mg. The thromboxane A2 receptor antagonist may be administered, e.g., in an amount from about 50 or 100 mg to about 500 mg per day. In certain embodiments, the thromboxane A2 receptor antagonist is Iloprost or a pharmaceutically acceptable salt thereof and the daily dose is from about 150 mg to about 350 mg per day. In certain embodiments, the Iloprost is administered orally. In certain embodiments, the gastrointestinal dysfunction is smooth muscle dysfunction. In certain embodiments, the therapeutically effective amount of Iloprost provides improved ventricular function to the heart of the patient.

[0020] The present invention also relates to methods and compositions for treating muscular dystrophy in a mammal (s) or human(s) in need of treatment thereof, the method comprising administering a therapeutically effective amount of a thromboxane A2 receptor antagonist to a subject (s) or patient (s) in need thereof. Preferably, the method of treatment comprises administering a composition comprising a therapeutically effective amount of a thromboxane A2 receptor antagonist to a muscular dystrophy patient in need thereof in an amount effective to improve heart function. Further provided is a method of preventing fibrosis or sclerosis in a subject (s) or patient (s) in need of such treatment, comprising administering a composition comprising a thromboxane A2 receptor antagonist in an amount effective to reduce the formation of fibrotic or sclerotic tissue that would occur in the absence of such treatment.

[0021] In a certain embodiment, the fibrosis is associated with a fibroproliferative disease selected from the group
consisting of heart fibrosis, kidney fibrosis, liver fibrosis, lung fibrosis, and systemic sclerosis.

**BRIEF DESCRIPTION OF THE DRAWINGS**

[0022] The following drawings are illustrative of embodiments of the invention and are not meant to limit the scope of the invention as encompassed by the claims.

[0023] FIG. 1A is a photograph of a vehicle-treated DKO (double knockout) Mouse at 10 weeks;

[0024] FIG. 1B is a photograph of an ifetroban-treated DKO mouse at 10 weeks;

[0025] FIG. 2 is a graph showing plasma CTNL in dSG KO males at 3 months (vehicle-treated versus ifetroban-treated);

[0026] FIG. 3 is a graph showing 3 month Echo data in mice (WT(wild-type), dSG-vehicle and dSG-ifetroban treated);

[0027] FIG. 4 is a graph providing cardiac output data for male mice at 3 months (WT, dSG-KO-vehicle and dSG-KO-ifetroban treated);

[0028] FIG. 5 is a graph providing spontaneous exercise data for 6 month old males (WT, dSG-vehicle and dSG-ifetroban treated);

[0029] FIG. 6 is a graph showing average wire hang time in male mice at 6 months (WT, dSG-vehicle and dSG-ifetroban treated);

[0030] FIG. 7 is a graph showing the results of a wire hanging experiment (average hang time) at 6 months (WT, dSG-vehicle versus ifetroban-treated; P=0.0056 for genotype by 2-way ANOVA);

[0031] FIG. 8 is a graph showing 6 month wire hang time (longest time) for male mice tested (WT, dSG-vehicle, dSG-ifetroban treated);

[0032] FIGS. 9A (dSGKO-vehicle) and 9B (dSGKO-ifetroban) show cardiac histology in dSG KO males. Less fibrosis seen in ifetroban treated RV. Shown is Masson’s trichrome at 4x for gross histology. All tears/folds/red lumps from the preparation and not pathology. Some RV may also be affected by slicing (arrows).

[0033] FIGS. 10A(dSG-Veh), 10B(dSG-Veh), 10C(dSG-ifetroban) and 10D(dSG-ifetroban) show cardiac histology in dSG KO males (using Masson’s trichrome, 2x). It can be seen that there is less fibrosis in the ifetroban treated RV. RV→right ventricle.

[0034] FIGS. 11A, 11A2, 11A3 and 11A4 shows cardiac histology in dSG KO males (using Masson’s trichrome, 10x) in the left ventricle (11A1→mouse #1, dSG KO-vehicle; 11A2→mouse #2, dSG KO-vehicle; 11A3→mouse #1, dSG KO-ifetroban; and 11A4→mouse #2, dSG KO-ifetroban);

[0035] FIGS. 11B1, 11B2, 11B3 and 11B4 shows cardiac histology in the right ventricle (11B1→mouse #1, dSG KO-vehicle; 11B2→mouse #2, dSG KO-vehicle; 11B3→mouse #1, dSG KO-ifetroban; and 11B4→mouse #2, dSG KO-ifetroban). LV→left ventricle; RV→right ventricle. Less fibrosis was seen in ifetroban-treated KO mice.

[0036] FIGS. 12A(WT), 12B(dSG-KO-vehicle), 12C (WT) and 12D(dSG-KO-ifetroban) shows skeletal muscle histology in WT and dSG KO males (tibialis cross-section, using Masson’s trichrome). Some fibrosis may be due to specific section of muscle.

[0037] FIG. 13 shows that ifetroban-treated dSG KO mice have less fibrosis than vehicle-treated dSG KO mice.

[0038] FIGS. 14A and 14B are graphs showing the percent survival of dSG KO males (14A) and dSG females (14B) treated with ifetroban or vehicle.

[0039] FIG. 15 are graphs showing wire hang in WT and DKO males at 10 weeks (ifetroban-treated (“ifr”) versus vehicle);

[0040] FIG. 16 is a graph showing spontaneous running in WT and DKO mice measured from 9-10 weeks (DKO-vehicle and DKO-ifetroban treated); and

[0041] FIG. 17 is a graph showing survival for all DKO mice (vehicle and ifetroban treated).

**DETAILED DESCRIPTION OF THE INVENTION**

[0042] In accordance with the above stated objects, it is believed that administration of a therapeutically effective amount of a thromboxane A2 receptor antagonist to a subject (s) or patient(s) in need thereof can treat cardiomyopathy associated with muscular dystrophy.

[0043] The phrase “therapeutically effective amount” refers to that amount of a substance that produces some desired local or systemic effect at a reasonable benefit/risk ratio applicable to any treatment. The effective amount of such substance will vary depending upon the subject and disease condition being treated, the weight and age of the subject, the severity of the disease condition, the manner of administration and the like, which can readily be determined by one of ordinary skill in the art.

[0044] The TPr is a G protein-coupled receptor which is located in platelets, immune cells, smooth muscle, and cardiomyocytes, and its activation has deleterious consequences in the heart. We have previously shown (in our U.S. Patent Application Publication No. 2015/0328190) that blockade of the TPr with the antagonist ifetroban dramatically decreases right ventricular fibrosis and improves cardiac function in a pressure-overload model of pulmonary arterial hypertension. Although the TPr has multiple endogenous ligands including F2-isoP, thromboxane A2, prostaglandin H2, and 20-HETE, blockade of thromboxane synthetase with oxazagrel or prostaglandin/thromboxane synthesis with aspirin has no effect on fibrosis or cardiac function in our pressure-overload model. Thus, F2-isoP is an excellent candidate as an activating ligand of the TPr in the stressed heart. Beyond the right ventricle, TPr activation also contributes to LV hypertrophy and heart failure in mouse models of systemic hypertension and Gβγ-overexpression. In addition, TPr activation causes increased intracellular calcium, arrhythmia, and cell death in ventricular cardiomyocytes, and decreased peristalsis in the gut. Although the role of the TPr in MD is unknown, these actions position the receptor to have an impact on some of the most pressing concerns in DMD.

[0045] Applicants explored the possibility that TPr activity may contribute to pathology in muscular dystrophy. In preliminary studies, the effects of blocking TPr activity in a δ-sarcoglycan knock out (dSG KO) mouse model of limb-girdle muscular dystrophy (LGMD). We found that treatment with the antagonist ifetroban, given in drinking water, limits the formation of cardiac fibrosis and prevents a
decline in cardiac function while normalizing elevated plasma cardiac troponin I levels, a clinically-used biomarker for cardiac injury. The inhibition of LV epicardial fibrosis may have particular applicability to DMD patients, where cardiac fibrosis typically begins in the sub-epicardium of the left ventricular (LV) free wall and progresses to include the remaining LV free wall and septum. Ivermectin treatment also significantly improved survival in dsg KO mice, and in utrophin/dystrophin double knockout (DKO) mice, a model of severe DMD. TPR antagonism with ifetroban improved 10-week survival from 56% to 100%. Therefore, it is believed that TPR activity contributes to pathology in muscular dystrophy.

[0046] In accordance with the present invention, it is believed that increased isoprostane signaling through the TPR contributes to cardiomyopathy and smooth muscle dysfunction in DMD, and thus treatment with ifetroban, an orally active TPR antagonist, will improve cardiac and gut function and decrease spontaneous mortality in mammals (as demonstrated in preclinical mouse models of DMD). It is also believed that treatment with a thromboxane A2 receptor antagonist (ifetroban) may contribute to cardioprotection by increasing the regenerative capability of the heart, and therefore may provide functional improvement of the heart (e.g., improved ventricular function). Thus, the invention is directed in part to the use of TPR antagonists as a treatment for cardiac and/or gastrointestinal dysfunction in DMD. The invention is also directed in part to the use of TPR antagonists for providing cardioprotection by increasing the regenerative capability of the heart and/or providing functional improvement of the heart of a muscular dystrophy (human) patient.

[0047] The term “thromboxane A2 receptor antagonist” as used herein refers to a compound that inhibits the expression or activity of a thromboxane receptor by at least or at least about 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, 96%, 97%, 98%, 99%, or 100% in a standard bioassay or in vivo or when used in a therapeutically effective dose. In certain embodiments, a thromboxane A2 receptor antagonist inhibits binding of thromboxane A2 to the receptor. Thromboxane A2 receptor antagonists include competitive antagonists (i.e., antagonists that compete with an agonist for the receptor) and non-competitive antagonists. Thromboxane A2 receptor antagonists include antibodies to the receptor. The antibodies may be monoclonal. They may be human or humanized antibodies. Thromboxane A2 receptor antagonists also include thromboxane synthase inhibitors, as well as compounds that have both thromboxane A2 receptor antagonist activity and thromboxane synthase inhibitor activity.

Thromboxane A2 Receptor Antagonist

[0048] The discovery and development of thromboxane A2 receptor antagonists has been an objective of many pharmaceutical companies for approximately 30 years (see, Dogne J-M, et al., Exp. Opin. Ther. Patents 11: 1663-1675 (2001)). Certain individual compounds identified by these companies, either with or without concomitant thromboxane A2 synthase inhibitory activity, include ifetroban (BMS), ridogrel (Jansen), terbogrel (BI), UK-147535 (Pfizer), GR 32191 (Glaxo), and S-18868 (Servier). Preclinical pharmacology has established that this class of compounds has effective antithrombotic activity obtained by inhibition of the thromboxane pathway. These compounds also prevent vasoconstriction induced by thromboxane A2 and other prostanoids that act on the thromboxane A2 receptor within the vascular bed, and thus may be beneficial for use in preventing and/or treating hepatorenal syndrome and/or hepatic encephalopathy.

[0049] Suitable thromboxane A2 receptor antagonists for use in the present invention may include, for example, but are not limited to small molecules such as ifetroban (BMS; [1 S-[(1α,2α,3α,4α)-2-[(3-[4-[(pentylamino)carbonyl]-1-2-oxazolyl]-7-oxabicyclo[2.2.1]hept-2-yl]methyl]benzenepropanoic acid], as well as others described in U.S. Patent Application No. 2009/0012115, the disclosure of which is hereby incorporated by reference in its entirety.

[0050] Additional thromboxane A2 receptor antagonists suitable for use herein are also described in U.S. Pat. No. 4,839,384 (Ogletree); U.S. Pat. No. 5,066,480 (Ogletree, et al.); U.S. Pat. No. 5,100,889 (Misra, et al.); U.S. Pat. No. 5,312,818 (Rubin, et al.); U.S. Pat. No. 5,399,725 (Pess, et al.); and U.S. Pat. No. 6,509,348 (Ogletree), the disclosures of which are hereby incorporated by reference in their entireties. These may include, but are not limited to, interphenylene 7-oxabicyclo-heptyl substituted heterocyclic amide prostaglandin analogs as disclosed in U.S. Pat. No. 5,100,889, including:

[0051] [1S-[(1α,2α,3α,4α)-2-[[3-[[4-[[4-cyclo-hexy-buty] amino]carbonyl]-2-oxazolyl]-7-oxabicyclo[2.2.1]hept-2-yl]methyl]benzenepropanoic acid (SQ 33,961), or esters or salts thereof;

[0052] [1S-[(1α,2α,3α,4α)-2-[[3-[[4-[[4-chloro-phenyl]-butyl]amino]carbonyl]-2-oxazolyl]-7-oxabicyclo[2.2.1]hept-2-yl]methyl]benzenepropanoic acid or esters, or salts thereof;

[0053] [1S-[(1α,2α,3α,4α)-3-[[3-[[4-[[4-cyclo-h-exy-buty]-amino]carbonyl]-2-oxazolyl]-7-oxabicyclo[2.2.1]hept-2-yl]benzene acetic acid, or esters or salts thereof;

[0054] [1S-[[1α,2α,3α,4α)-2-[[3-[[4-[[4-cyclo-hexyl-buty] amino]carbonyl]-2-oxazolyl]-7-oxabicyclo[2.2.1]hept-2-yl]methyl]phenoxylacetic acid, or esters or salts thereof;

[0055] [1S-[[1α,2α,3α,4α)-2-[[3-[[4-[[7-dime-thyl-thoxy]-amino]carbonyl]-2-oxazolyl]-7-oxabicyclo[2.2.1]hept-2-yl]methyl]benzenepropanoic acid, or esters or salts thereof;

[0056] 7-oxabicycloheptyl substituted heterocyclic amide prostaglandin analogs as disclosed in U.S. Pat. No. 5,100,889, issued Mar. 31, 1992, including [1S-[[1α,2α(Z),3α,4α)-6-[[3-[[4-cyclo-hexyl-buty]amino]carbonyl]-2-oxazolyl]-7-oxabicyclo[2.2.1]hept-2-yl]-4-hexenoic acid, or esters or salts thereof;

[0057] [1S-[[1α,2α(Z),3α,4α)-6-[[3-[[4-cyclo-hexyl-buty]methylamino]carbonyl]-2-oxazolyl]-7-oxabicyclo[2.2.1]hept-2-yl]-4-hexenoic acid, or esters or salts thereof;

[0058] [1S-[[1α,2α(Z),3α,4α)-6-[[3-[[4-cyclo-hexyl-buty]methylamino]carbonyl]-2-oxazolyl]-7-oxabicyclo[2.2.1]hept-2-yl]-4-hexenoic acid, or esters or salts thereof;

[0059] [1S-[[1α,2α(Z),3α,4α)-6-[[3-[[1-pyrrolidinyl]-carbonyl]-2-oxazolyl]-7-oxabicyclo[2.2.1]hept-2-yl]-4-hexenoic acid, or esters or salts thereof;

[0060] [1S-[[1α,2α(Z),3α,4α)-6-[[3-[[4-cyclo-hexyl-lamino]carbonyl]-2-oxazolyl]-7-oxabicyclo[2.2.1]hept-2-yl]-4-hexenoic acid, or esters or salts thereof;

[0061] [1S-[[1α,2α(Z),3α,4α)-6-[[3-[[2-cyclo-hexyl-ethyl]amino]carbonyl]-2-oxazolyl]-7-oxabicyclo[2.2.1]hept-2-yl]-4-hexenoic acid, or esters or salts thereof;
[0062] [1S-[1α,2α(Z),3β,4α]]-6-[3-[4-[[2-(4-chlorophenyl)ethyl]amino][carbonyl]-2-oxazolyl]-7-oxacyclo[2.2.1]hept-2-yl]-4-hepxenoic acid, or esters or salts thereof; [0063] [1S-[1α,2α(Z),3β,4α]]-6-[3-[4-[[4-(4-chlorophenyl)amino][carbonyl]-2-oxazolyl]-7-oxacyclo[2.2.1]hept-2-yl]-4-hepxenoic acid, or esters or salts thereof; [0064] [1S-[1α,2α(Z),3β,4α]]-6-[3-[4-[[4-(4-chlorophenyl)amino][carbonyl]-2-oxazolyl]-7-oxacyclo[2.2.1]hept-2-yl]-4-hepxenoic acid, or esters or salts thereof; [0065] [1S-[1α,2α(Z),3β,4α]]-6-[3-[4-[[6-(cyclpent-1-ylhexyl)amino][carbonyl]-2-oxazolyl]-7-oxacyclo[2.2.1]hept-2-yl]-4-hepxenoic acid, or esters or salts thereof; [0066] [1S-[1α,2α(Z),3β,4α]]-6-[3-[4-[[6-(cyclpent-1-ylhexyl)amino][carbonyl]-2-oxazolyl]-7-oxacyclo[2.2.1]hept-2-yl]-4-hepxenoic acid, or esters or salts thereof; [0067] [1S-[1α,2α(Z),3β,4α]]-6-[3-[4-[[propylamino][carbonyl]-2-oxazolyl]-7-oxacyclo[2.2.1]hept-2-yl]-4-hepxenoic acid, or esters or salts thereof; [0068] [1S-[1α,2α(Z),3β,4α]]-6-[3-[4-[[4-butyloxymethyl]amino][carbonyl]-2-oxazolyl]-7-oxacyclo[2.2.1]hept-2-yl]-4-hepxenoic acid, or esters or salts thereof; [0069] [1S-[1α,2α(Z),3β,4α]]-6-[3-[4-[[2,3-dihydro-1H-indol-1-yl]carbonyl]-2-oxazolyl]-7-oxacyclo[2.2.1]hept-2-yl]-4-hepxenoic acid, or esters or salts thereof; [0070] [1S-[1α,2α(Z),3β,4α]]-6-[3-[4-[[4-(cyclpent-1-ylhexyl)butyloxy]methyl]carbonyl]-2-oxazolyl]-7-oxacyclo[2.2.1]hept-2-yl]-N-(phenylsulfonyl)-4-hepanemide; [0071] [1S-[1α,2α(Z),3β,4α]]-6-[3-[4-[[4-(cyclpent-1-ylhexyl)butyloxy]methyl]carbonyl]-2-oxazolyl]-7-oxacyclo[2.2.1]hept-2-yl]-N-(phenylsulfonyl)-4-hepanemide; [0072] [1S-[1α,2α(Z),3β,4α]]-7-[3-[4-[[4-(cyclpent-1-ylhexyl)butyloxy]methyl]carbonyl]-2-oxazolyl]-7-oxacyclo[2.2.1]hept-2-yl]-5-heptenoic acid, or esters or salts thereof; [0073] [1S-[1α,2α(Z),3β,4α]]-6-[3-[4-[[4-(4-chlorobenzylimido)ethyl]amino][carbonyl]-1H-imidazol-2-yl]-7-oxacyclo[2.2.1]hept-2-yl]-4-hepxenoic acid, or esters or salts thereof; [0074] [1S-[1α,2α(Z),3β,4α]]-6-[3-[4-[[7,7-dimethylhexyl][carbonyl]-2-oxazolyl]-7-oxacyclo[2.2.1]hept-2-yl]-4-hepanemide, or esters or salts thereof; [0075] [1S-[1α,2α(Z),3β,4α]]-6-[3-[4-[[4-(4-chlorobenzylimido)ethyl]amino][carbonyl]-2-oxazolyl]-7-oxacyclo[2.2.1]hept-2-yl]-4-hepanemide; [0076] [1S-[1α,2α(Z),3β,4α]]-3-[4-[[4-(4-chlorobenzylimido)ethyl]amino][carbonyl]-2-oxazolyl]-7-oxacyclo[2.2.1]heptan-2-hepanemide, or esters or salts thereof; [0077] [1S-[1α,2α(Z),3β,4α]]-6-[3-[4-[[4-(4-chlorobenzylimido)ethyl]amino][carbonyl]-2-oxazolyl]-7-oxacyclo[2.2.1]hept-2-yl]-4-hepanemide, or esters or salts thereof; [0078] 7-oxacycloheptane and 7-oxacycloheptane compounds disclosed in U.S. Pat. No. 4,357,981 to Snitman et al., the disclosure of which is hereby incorporated by reference in its entirety, such as [1S-[1α,2α(Z),3β,4α]]-7-[3-[4-[[3-(hydroxy-4-phenyl-1-pentenyl)oxy]-2-(4-morpholinyl)-3-oxo-cyclopentyl]-4-heptenoic acid (AH 23846-Glaxo, Circulation 72(6):1208, December 65, levallophan allyl bromide (CM 32,191 Sanofi, Life Sci. 31 (20-21):2261, November 15, 82), (2,2-endo-3-oxo)-7-(3-acetyl-2-bicyclo[2.2.1]hept-5-hept-3-en-2-ene, 4-phenylthiosemicarbazone (EP092-Univ. Edinburgh, Brit. J. Pharmacol. 84(3):595, March 85); GR 32,191 (Vapiprost)- [1R-1 alpha,(Z),2 beta,3 beta,5 alpha,7 alpha,7 beta] (+)-7-[5-[1,1'-biphenyl]-4-ylmethoxy]-3-hydroxy-2-(1-piperidinyl)cyclo-
pentylyl-4-heptenoic acid; IC1 192,605-4(Z)-6-((2,4,5-cis)-2-
(2-chlorophenyl)-4-(2-hydroxyphenyl)-1,3-dioxan-5-yl)
hexenoic acid; [α]D 3405 (ramatopranol)-3-[1-(4-fluorophenyl)-sulfonyl]amino]-1,2,3,4-tetrahydro-9H-
3-carbazole-9-propanoic acid; or ONO 3708-7-[2-\(\alpha\)-alpha-(dimethylamino)-6-benzotri-2-cyclopentyl-2-benz-
hydroxystyrarnid]-1,3,4-endo-(phenylsulfon)amino]-bicyclo
[2.2.1]hept-2-ew-y]heptanoc acid (S-1452, Shionogi
domirorban, Anboxan®); (-)-6,8-difluoro-9-p-methylsulfo-
nylbenzyl-1,2,3,4-tetrahydrocarbazol-1-yl-acetic acid
(1.670596, Merck) and (5-bromo-1-methyl-4-phenylsulfon)-2-
(2,5-dimethyl-2,5-dihydrofuran-2-yl)benzeneacetic acid (1.655240,
Merck).

[0086] The preferred thromboxane A2 receptor antagonist of
the present invention is etiflotan or any pharmaceutically
acceptable salts thereof.

[0087] In certain preferred embodiments the preferred thromboxane A2 receptor antagonist is etiflotan sodium
(known chemically as [1S-(1α,2α,3α,4α,5)]-3-[1-(4-
Pentylamino)carbonyl]-2-oxaoyl]-3-oxaoyl]bicyclo[2.2.1]hept-2-
y]methyle]-benzenepropanic acid, monosodium salt.

Methods of Treatment

[0088] In certain embodiments of the present invention
there is provided a method of treating and/or ameliorating
cardiomyopathies in a patient or patient population by administration of a therapeutically effective amount of a
thromboxane A2 receptor antagonist to a patient(s) in need
thereof.

[0089] The administration of a therapeutically effective
amount of a thromboxane A2 receptor antagonist may be
accomplished via any therapeutically useful route of admin-
istration, including but not limited to orally, intranasally,
rectally, vaginally, sublingually, buccally, parenterally, or
transdermally. In certain preferred embodiments, the throm-
oxane A2 receptor antagonist is administered parenterally.
In certain further embodiments, the thromboxane A2 recep-
tor antagonist is administered by intravenous or injection.
In certain further embodiments, the thromboxane A2 recep-
tor antagonist is administered directly to the affected anatomic
site. In another embodiment, the thromboxane A2 receptor
antagonist is administered through the hepatic artery.

[0090] In certain preferred embodiments, the plasma con-
centrations of thromboxane A2 receptor antagonists range
from about 0.1 ng/mL to about 10,000 ng/mL. Preferably,
the plasma concentration of thromboxane A2 receptor antag-
ons range from about 1 ng/mL to about 1,000 ng/mL.

[0091] When the thromboxane A2 receptor antagonists is
etiflotan, the desired plasma concentration for treatment of
cardiomyopathies in muscular dystrophies in certain
embodiments should be greater than about 10 ng/mL
(etiflotan free acid). Some therapeutic effects of thrombox-
ane A2 receptor antagonist, e.g., etiflotan, may be seen at
concentrations of greater than about 1 ng/mL.

[0092] The dose administered should be adjusted accord-
ing to age, weight and condition of the patient, as well as
the route of administration, dosage form and regimen and
the desired result.

[0093] In order to obtain the desired plasma concentration
of thromboxane A2 receptor antagonists for the treatment of
cardiomyopathy in muscular dystrophy patients, daily doses
of the thromboxane A2 receptor antagonists preferably range
from about 0.1 mg to about 5000 mg. In certain preferred
embodiments, the thromboxane A2 receptor antagonist is administered on a chronic basis. Daily doses may range from
about 1 mg to about 1000 mg; about 10 mg to about 1000
mg; about 50 mg to about 500 mg; about 100 mg to about
500 mg; about 200 mg to about 500 mg; about 300 mg to
about 500 mg; or from about 400 mg to about 500 mg per
day. In certain preferred embodiments where the patient is
a human patient, the therapeutically effective amount is from
about 100 mg to about 2000 mg per day, or from about 10
mg or about 100 mg to about 1000 mg per day, and certain
embodiments more preferably from about 50 to about 500
mg per day, or from about 100 mg to about 500 mg per day.
The daily dose may be administered in divided doses or in
one bolus or unit dose or in multiple dosages administered
concurrently. In this regard, the etiflotan may be adminis-
tered orally, intranasally, rectally, vaginally, sublingually,
buccally, parenterally, or transdermally. In certain preferred
embodiments, the pharmaceutical composition described
above, the therapeutically effective amount is from about
10 mg to about 1000 mg etiflotan (or pharmaceutically ac-
terably salt thereof) per day. In certain preferred embodiments,
the therapeutically effective amount is from about 100 to
about 500 mg per day, and in certain embodiments from
about 150 mg to about 350 mg per day will produce therapeutically effective plasma levels of etiflotan free acid
for the treatment of muscular dystrophy. In certain preferred
embodiments, a daily dose of etiflotan sodium from about
10 mg to about 250 mg (etiflotan free acid amounts) will
produce therapeutically effective plasma levels of etiflotan
free acid for the treatment of muscular dystrophy.

[0094] Preferably, the therapeutically effective plasma
concentration of thromboxane A2 receptor antagonists
ranges from about 1 ng/mL to about 1,000 ng/mL for the
administration of muscular dystrophy.

[0095] When the thromboxane A2 receptor antagonist is
etiflotan, the desired plasma concentration for providing an
inhibitory effect of A2p prostaglandin endoperoxide receptor
(TM) activation, and thus a reduction of cerebral microvas-
cular activation should be greater than about 10 ng/mL
(etiflotan free acid). Some inhibitory effects of thrombox-
ane A2 receptor antagonist, e.g., etiflotan, may be seen at
concentrations of greater than about 1 ng/mL.

[0096] The dose administered must be carefully adjusted
according to age, weight and condition of the patient, as well
as the route of administration, dosage form and regimen and
the desired result.

[0097] However, in order to obtain the desired plasma
concentration of thromboxane A2 receptor antagonists, daily
doses of the thromboxane A2 receptor antagonists ranging
from about 0.1 mg to about 5000 mg should be administered.
Preferably, the daily dose of thromboxane A2 receptor antag-
ons ranges from about 1 mg to about 1000 mg; about 10
mg to about 1000 mg; about 50 mg to about 500 mg; about
100 mg to about 500 mg; about 200 mg to about 500
mg; about 300 mg to about 500 mg; and about 400 mg to
about 500 mg per day.

[0098] In certain preferred embodiments, a daily dose of
etiflotan sodium from about 10 mg to about 250 mg
(etiflotan free acid amounts) will produce effective plasma
levels of etiflotan free acid.

Pharmaceutical Compositions

[0099] The thromboxane A2 receptor antagonists of the
present invention may be administered by any pharmaceuti-

tically effective route. For example, the thromboxane A₂ receptor antagonists may be formulated in a manner such that they can be administered orally, intranasally, rectally, vaginally, sublingually, buccally, parenterally, or transdermally, and, thus, be formulated accordingly.

[0100] In certain embodiments, the thromboxane A₂ receptor antagonists may be formulated in a pharmaceutically acceptable oral dosage form. Oral dosage forms may include, but are not limited to, oral solid dosage forms and oral liquid dosage forms.

[0101] Oral solid dosage forms may include, but are not limited to, tablets, capsules, caplets, powders, pellets, multiparticulates, beads, spheres and any combinations thereof. These oral solid dosage forms may be formulated as immediate release, controlled release, sustained (extended) release or modified release formulations.

[0102] The oral solid dosage forms of the present invention may also contain pharmaceutically acceptable excipients such as fillers, diluents, lubricants, surfactants, glidants, binders, dispersing agents, suspending agents, disintegrants, viscosity-increasing agents, film-forming agents, granulation aid, flavoring agents, sweetening coating agents, solubilizing agents, and combinations thereof.

[0103] Depending on the desired release profile, the oral solid dosage forms of the present invention may contain a suitable amount of controlled-release agents, extended-release agents, modified-release agents.

[0104] Oral liquid dosage forms include, but are not limited to, solutions, emulsions, suspensions, and syrups. These oral liquid dosage forms may be formulated with any pharmaceutically acceptable excipient known to those of skill in the art for the preparation of liquid dosage forms. For example, water, glycerin, simple syrup, alcohol and combinations thereof.

[0105] In certain embodiments of the present invention, the thromboxane A₂ receptor antagonists may be formulated into a dosage form suitable for parenteral use. For example, the dosage form may be a lyophilized powder, a solution, suspension (e.g., depot suspension).

[0106] In other embodiments, the thromboxane A₂ receptor antagonists may be formulated into a topical dosage form such as, but not limited to, a patch, a gel, a paste, a cream, an emulsion, liniment, balm, lotion, and ointment.

**DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENTS**

[0107] The following examples are not meant to be limiting and represent certain embodiments of the present invention.

**Example I**

[0108] In this example, ifetroban sodium tablets are prepared with the following ingredients listed in Table 1:

<table>
<thead>
<tr>
<th>Ingredients</th>
<th>Percent by weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>Na salt of Ifetroban</td>
<td>35</td>
</tr>
<tr>
<td>Mannitol</td>
<td>50</td>
</tr>
<tr>
<td>Microcrystalline Cellulose</td>
<td>8</td>
</tr>
<tr>
<td>Cospovidone</td>
<td>3.0</td>
</tr>
<tr>
<td>Magnesium Oxide</td>
<td>2.0</td>
</tr>
</tbody>
</table>

**Example II**

[0109] The sodium salt of ifetroban, magnesium oxide, mannitol, microcrystalline cellulose, and cospovidone is mixed together for about 2 to about 10 minutes employing a suitable mixer. The resulting mixture is passed through a #12 to #40 mesh size screen. Thereafter, magnesium stearate and colloidal silica are added and mixing is continued for about 1 to about 3 minutes.

[0110] The resulting homogeneous mixture is then compressed into tablets each containing 35 mg, ifetroban sodium salt.

**Example III**

[0111] In this example, 1000 tablets each containing 400 mg of ifetroban sodium are produced from the following ingredients listed in Table 2:

<table>
<thead>
<tr>
<th>Ingredients</th>
<th>Amount</th>
</tr>
</thead>
<tbody>
<tr>
<td>Na salt of Ifetroban</td>
<td>400 mg</td>
</tr>
<tr>
<td>Corn Starch</td>
<td>50 g</td>
</tr>
<tr>
<td>Gelatin</td>
<td>7.5 g</td>
</tr>
<tr>
<td>Microcrystalline Cellulose (Avicel)</td>
<td>25 g</td>
</tr>
<tr>
<td>Magnesium Stearate</td>
<td>2.5 g</td>
</tr>
</tbody>
</table>

**Example IV**

[0112] An injectable solution of ifetroban sodium is prepared for intravenous use with the following ingredients listed in Table 3:

<table>
<thead>
<tr>
<th>Ingredients</th>
<th>Amount</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ifetroban Sodium</td>
<td>2500 mg</td>
</tr>
<tr>
<td>Methyl Paraben</td>
<td>5 mg</td>
</tr>
<tr>
<td>Propyl Paraben</td>
<td>1 mg</td>
</tr>
<tr>
<td>Sodium Chloride</td>
<td>25,000 mg</td>
</tr>
<tr>
<td>Water for injection q.s.</td>
<td>5 liter</td>
</tr>
</tbody>
</table>

[0113] The sodium salt of ifetroban, preservatives and sodium chloride are dissolved in 3 liters of water for injection and then the volume is brought up to 5 liters. The solution is filtered through a sterile filter and aseptically filled into pre-sterilized vials which are then closed with pre-sterilized rubber closures. Each vial contains a concentration of 75 mg of active ingredient per 150 ml of solution.

**Example IV**

[0114] dSG KO mice, chosen for their cardiac phenotype, are a model of LGMD, but DMD which occurs in approximately 1:3500 male births (1), is far more common a disease than LGMD. The mdx mouse model of DMD poorly replicates the shortened life expectancy, cardiac fibrosis, and cardiomyopathy seen in DMD patients. The utrophin/dystrophin DKO model had significant mortality by 10 weeks, although treatment with the TFR antagonist ifetroban led to 100% survival to this predetermined timepoint. Although
TPR antagonism may prevent spontaneous death in DMD, due to severe kyphosis and frailty we were not able to obtain much useful cardiac data with the DKO model of DMD.

[0115] Example 4 utilized WestCarrier Muscular Dystrophy Animal Models (Delta-sarcoglycan knock-out mice (sgd/--/-)). Mice devoid of DSG develop cardiomyopathy and MD with signs of progressive disease such as necrosis, muscular regeneration, inflammation and fibrosis within the first 3 months of life. Mice that are homozygous for the targeted mutation are viable, fertile and normal in size. No gene product (protein) is immunodetected in skeletal muscle microsmal preparations. At 8 weeks of age there is an onset of sudden mortality, with a 50% survival rate at 28 weeks. Elevated creatine kinase serum levels are indicative of striated muscle degeneration. Histopathology of skeletal muscle tissue reveals degeneration and regeneration of muscle fibers, inflammatory infiltrate, perivascular fibrosis and calcification. At 12 weeks of age, cardiac muscle tissue also begins to show degeneration, inflammatory infiltration and perivascular fibrosis. Myofiber membranes have permeability defects as assessed by Evans blue dye uptake into myofiber cytoplasm. Skeletal muscle of mutant mice have an enhanced sensitivity to mechanically induced sarcolemmal damage. Dys trophy deficient mice have minimal clinical symptoms with lifespan reduced by only 25% unlike humans with DMD reduced by 75%, possibly due to compensatory mechanisms upregulated in mice. A major function of dystrophin is to strengthen the sarcolemma by cross-linking the ECM with the cytoskeleton. Utrophin and α7b1 integrin fulfill the same function and are upregulated in mdx mice. They work to connect sarcolemma to cytoplasmic actin cytoskeleton. Dysfunction produces membrane instability, elevated [Ca2+]i and disrupted NO signaling. γ- and β-SG form a core necessary for delivery/retenion of other SG to the membrane.

[0116] While the DSG KO (sgd/--) mice lack functional delta-sarcoglycan, the MD phenotype is milder than the human disease. Since utrophin, a dystrophin-related protein, is able to compensate for the loss of dystrophin, loss of utrophin and dystrophin (DKO) results in a more severe phenotype. DKO are significantly smaller and show severe muscle disease (similar or worse than that of humans with MD). The mice are difficult to generate and care for, and often die prematurely. Iferoban treatment was started at 3 weeks upon weaning.

[0117] In Example IV, vehicle-treated mice were carefully cared for to get them to reach 10 weeks of life (e.g., the mice were checked on them constantly and a low dish of crushed food and water was placed right next to where the mice huddled in the cage, in an attempt to get them some nutrition without them needing to move much).

[0118] FIG. 1A is a photograph of a vehicle-treated DKO mouse. FIG. 1B is a photograph of an Iferoban-treated DKO mouse at 10 weeks. The ability to wrap the tail around the wire is dependent on muscle function. A reason the DKO mice are really hard to evaluate in the wire hang is that they have such severe scoliosis that their hind paws are very close to their front paws, so raising their hind paws to get a 4-limbed grip is not difficult despite their affliction.

[0119] FIG. 2 shows plasma cETNI in DSG KO males at 3 months. The term “cETNI” means plasma cardiac troponin I. The term “KO” means knockout. The term “DSG” means Delta sarcoglycan. The term “WT” means wildtype. Plasma cardiac troponin I (cETNI) is highly specific and sensitive for myocardial tissue and can be measured rapidly. It is a reliable biomarker for cardiac damage. In FIG. 2, it can be seen that the plams cETNI levels are much higher in dSG KO mice than in WT mice.

[0120] FIG. 3 provides 3 month Echo data. The results shown therein demonstrate that at 3 months dSG KO males show cardiac dysfunction and Iferoban prevents cardiac dysfunction.

[0121] FIG. 4 provides cardiac output data for male dSG KO mice at 3 months. FIG. 4 shows that the dSG KO mice treated with Iferoban have improved cardiac dysfunction compared to vehicle. The cardiac function improved similar to WT levels.

[0122] FIG. 5 provides spontaneous exercise date for 6 month old males. The exercise was voluntary wheel running-free access to the wheel for 10 days after 4.5M of treatment. Males demonstrate a skeletal function deficit at 6M that is seen to a less extent in Iferoban-treated DSG KO mice. No difference is seen in females who run more compared to males regardless of genotype.

[0123] FIG. 6 shows wire hang in dSG mice at 6 months. An improved wire hang time is apparent in the dSG mice treated with Iferoban. *p<0.05 from WT by one-way ANOVA followed by Dunnett’s multiple comparison post-test. Veh and Iferoban-treated groups were NS tested against each other. N in parentheses. * “i” = Iferoban.

[0124] FIG. 7 shows the results of a wire hanging experiment at 6 months, with the average hang time plotted for dSG and WT mice.

[0125] FIG. 8 depicts wire hang time for mice tested. Male mice do not hang for a long time compared to females. It was difficult to measure any difference caused by Iferoban if any.

[0126] FIGS. 9A (dSGKO-vehicle) and 9B (dSGKO-if eroban) show cardiac histology in dSG KO males. Less fibrosis seen in Iferoban treated RV. Shown is Masson’s trichrome at 4× for gross histology. All tears/folds/red hotspots from slice preparation and not pathology. Some RV may also be affected by slicing (arrows).

[0127] FIGS. 10A(dSG-Veh), 10B(dSG-Veh), 10C(dSG-Iferoban) and 10D(dSG-Iferoban) show cardiac histology in dSG KO males (using Masson’s trichrome, 2×). It can be seen that there is less fibrosis in the Iferoban treated RV. RV=right ventricle.

[0128] FIGS. 11A1, 11A2, 11A3 and 11A4 shows cardiac histology in dSG KO males (using Masson’s trichrome, 10×) in the left ventricle (11A1=mouse #1, dSG KO-vehicle; 11A2=mouse #2, dSG KO-vehicle; 11A3=mouse #1, dSG KO-vehicle) and 11A4=mouse #2, dSG KO-Iferoban); FIGS. 11B1, 11B2, 11B3 and 11B4 shows cardiac histology in the right ventricle (11B1=mouse #1, dSG KO-vehicle; 11B2=mouse #2, dSG KO-Iferoban; 11B3=mouse #1, dSG KO-Iferoban; and 11B4=mouse #2, dSG KO-Iferoban). LV=left ventricle; RV=right ventricle. Less fibrosis was seen in Iferoban treated KO mice.

[0129] FIGS. 12A(WT1), 12B(dSGKO-vehicle), 12C (WT2) and 12D(dSGKO-Iferoban) shows skeletal muscle histology in WT and dSG KO males (tibialis cross-section, using Masson’s trichrome). Some fibrosis may be due to specific section of muscle.

[0130] FIGS. 13A(WT-vehicle), 13B(WT-Iferoban), 13C (dSG KO-vehicle) and 13D(dSGKO-Iferoban) are crosssections of intestinal tissue showing that Iferoban may
prevent the loss of intestinal smooth muscle in the large intestine. Muscularis. The DSG KO mice were missing smooth muscle (especially missing longitudinal smooth muscle) while ifetroban-treated mice have similar sections to WT smooth muscle. *H&E*—Hematoxylin & eosin.

**[0131]** FIG. 13 shows that ifetroban-treated dSG KO mice have less fibrosis than vehicle-treated dSG KO mice.

**[0132]** FIGS. 14A and 14B are graphs showing the percent survival of dSG KO males (14A) and dSG females (14B) treated with ifetroban or vehicle.

**[0133]** FIG. 15 are graphs showing wire hang in DKO males at 10 weeks (ifetroban-treated (“life”) versus vehicle). The results show that the ifetroban-treated mice had significantly longer average hang times than mice treated with vehicle.

**[0134]** FIG. 16 shows spontaneous running in DKO mice: measured from 9-10 weeks.

**[0135]** FIG. 17 shows survival for all DKO mice. The ifetroban-treated mice survived beyond 70 days, while the vehicle-treated mice (both male and female) did not.

**CONCLUSION**

**[0136]** In the preceding specification, the invention has been described with reference to specific exemplary embodiments and examples thereof. It will, however, be evident that various modifications and changes may be made thereto without departing from the broader scope of the invention as set forth in the claims that follow. The specification and drawings are accordingly to be regarded in an illustrative manner rather than a restrictive sense.

What is claimed is:

1. A method of treating or ameliorating muscular dystrophy in a subject in need of treatment thereof, comprising administering a therapeutically effective amount of a thromboxane A2 receptor antagonist to the patient.
2. The method of claim 1, wherein the muscular dystrophy is fibrosis selected from the group consisting of Duchenne MD (DMD), Becker MD, and Limb-Girdle MD.
3. The method of claim 1, further comprising administering the thromboxane A2 antagonist to the patient on a chronic basis.
4. The method of claim 3, wherein the cardiac function of the patient is maintained or improved.
5. The method of claim 3, wherein the thromboxane A2 receptor antagonist is [1S-(1α,2α,3α,4α)]-2-[[3-[4-[[Pentylamino]carbonyl]-2-oxazolyl]-7-oxabicyclo[2.2.1]hept-2-y]methyl]-benzenepropanoic acid (Ifetroban), and pharmaceutically acceptable salts thereof.
6. The method of claim 3, wherein the thromboxane A2 receptor antagonist is [1S-(1α,2α,3α,4α)]-2-[[3-[4-[[Pentylamino]carbonyl]-2-oxazolyl]-7-oxabicyclo[2.2.1]hept-2-y]methyl]-benzenepropanoic acid, monosodium salt (Ietroban Sodium).
7. The method of claim 1, wherein the thromboxane A2 receptor antagonist is administered orally, intranasally, rectally, vaginally, sublingually, buccally, parenterally, or transdermally.
8. The method of claim 1, wherein the thromboxane A2 receptor antagonist is administered parenterally.
9. The method of claim 1, wherein the thromboxane A2 receptor antagonist is administered orally.
10. The method of claim 3, wherein the thromboxane A2 receptor antagonist is administered prophylactically to prevent cardiomyopathy in the patient.
11. The method of claim 3, wherein the thromboxane A2 receptor antagonist is administered prophylactically to prevent gastrointestinal dysfunction in the patient.
12. The method of claim 3, wherein the therapeutically effective amount is from about 50 mg to about 500 mg.
13. The method of claim 5, wherein the therapeutically effective amount is from about 150 mg to about 350 mg per day and the ifetroban is administered orally.
14. A method of treating cardiac and/or gastrointestinal dysfunction in a human patient suffering from muscular dystrophy, comprising chronically administering a therapeutically effective amount of a thromboxane A2 receptor antagonist to the human patient.
15. The method of claim 14, wherein the therapeutically effective amount is from about 100 mg to about 500 mg.
16. The method of claim 3, wherein the thromboxane A2 receptor antagonist is [1S-(1α,2α,3α,4α)]-2-[[3-[4-[[Pentylamino]carbonyl]-2-oxazolyl]-7-oxabicyclo[2.2.1]hept-2-y]methyl]-benzenepropanoic acid, monosodium salt (Ifetroban Sodium).
17. The method of claim 16, wherein the thromboxane A2 receptor antagonist is [1S-(1α,2α,3α,4α)]-2-[[3-[4-[[Pentylamino]carbonyl]-2-oxazolyl]-7-oxabicyclo[2.2.1]hept-2-y]methyl]-benzenepropanoic acid, monosodium salt (Ietroban Sodium).
18. The method of claim 16, wherein the therapeutically effective amount is from about 150 mg to about 350 mg per day and the ifetroban is administered orally.
19. The method of claim 3, wherein the gastrointestinal dysfunction is smooth muscle dysfunction.
20. The method of claim 16, wherein the therapeutically effective amount of ifetroban provides improved ventricular function to the heart of the patient.

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