Naproxcinod, a dual acting compound donating nitric oxide and naproxen, is effective in two mouse models of muscular dystrophy

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Muscular dystrophies are a group of genetic degenerative diseases due to defects in muscle proteins, causing severe local inflammation, progressive weakness and wasting of the skeletal muscles. Nitric oxide (NO) plays a critical role in skeletal muscle function, including control of blood flow and muscle repair. In muscular dystrophies, synthesis of NO in the skeletal muscle is known to be defective therefore contributing to damage progression.

In the present study, we evaluated the effects of naproxcinod, an NO-donating anti-inflammatory compound, in two models of muscular dystrophy, the α-sarcoglycan (α-SG) null mice, a model for limb-girdle muscle dystrophy, and the *mdx* mouse model for Duchenne muscle dystrophy (DMD).

Naproxcinod (10 and 30 mg/kg/day) was administered orally for 7 months to *mdx* mice and for 4 months to α-SG null mice starting at 4 weeks of age. Muscle function was assessed by treadmill test at 4 months (both *mdx* and α-SG null mice) and 7 months of treatment (*mdx* mice). Serum creatine kinase (CK) was measured as index of skeletal muscle damage. Inflammatory infiltrates, as well as muscle regeneration were studied in diaphragm and tibialis anterior muscle.

In *mdx* mice naproxcinod at 30 mg/kg/day significantly improved muscle function in terms of resistance to exercise (*mdx* control mice: 89±24 meters *vs* naproxcinod treated *mdx* mice: 132±35 meters; $p<0.05$); significantly reduced skeletal muscle inflammation and serum CK activity; and increased muscle regeneration. Likewise in α-SG null mice, 4 months of naproxcinod treatment led to a significant improvement of resistance to fatigue (*mdx* control mice: 316±45 meters *vs* naproxcinod treated *mdx* mice: 900±95 meters; $p<0.001$) and to reduction of muscle inflammation and damage. Furthermore, both diaphragm and tibialis anterior muscles appeared fully regenerated, therefore supporting the marked beneficial effects observed for muscle function.

The results demonstrate that naproxcinod, through NO donation together with anti-inflammatory activity, produces significant and persistent therapeutic effects improving muscle function, reducing muscle inflammation and maintaining regeneration capacity of the muscle in two models of muscular dystrophies.