SAFINAMIDE REPOSITIONING IN NON DYSTROPHIC MYOTONIAS: A NEW THERAPEUTIC OPPORTUNITY FOR THIS RARE DISEASE

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Introduction: The antiarrhythmic sodium channel blocker mexiletine is used clinically to treat patients with myotonia. However, around 30% of patients do not benefit from mexiletine due to poor tolerability or suboptimal response possibly related to reduced sensitivity of myotonic sodium channel mutations. Safinamide (Xadago®) is an add-on therapy to levodopa for Parkinson's disease. Besides MAO-B inhibition, safinamide modulates glutamate release through blockade of neuronal sodium channels. Here, we investigated the effects of safinamide compared to mexiletine on wild-type and myotonic skeletal muscle $hNa_v1.4$sodium channels and in rat models of myotonia, in-vitro and in-vivo.

Materials and methods: Patch-clamp studies were used to evaluate the effects of safinamide on sodium current of myotonic mutant. Two-microelectrodes current-clamp method was applied to study safinamide effects on muscle fiber excitability in a myotonia-like condition induced by incubation with 50 2M 9-anthracene carboxylic acid (9AC), a chloride channel blocker. Finally the effects of safinamide were evaluated after an *in vivo* treatment in a rat model of myotonia induced by 9-AC.

Results: Safinamide reversibly inhibited wild-type hNav1.4sodium currents (INa) with an IC_{50} of 160 and 33μM at stimulation frequencies of 0.1and 10 Hz respectively, compared to 256and 46μM for mexiletine (holding potential (hp) -120 mV). In a condition mimicking myotonia, i.e. hp of -90 mV and 50-Hz stimulation, both drugs exerted similar INa inhibition with IC_{50} of 5-6μM. We previously showed that myotonic hNav1.4mutations altering channel gating may indirectly impair mexiletine inhibition (Farinato et al. Pharmacol Res 141, 224, 2019). Thus, safinamide was tested on sodium currents generated by 8myotonic hNav1.4mutants. Interestingly, safinamide was more potent than mexiletine in inhibiting all the myotonic mutants. When applied in vitro to isolated rat skeletal muscle fibers in a myotonia-like condition induced by 9-AC, safinamide inhibited action potential firing with an IC_{50} of 13μM, compared to 55μM for mexiletine. In vivo, oral safinamide was more potent than mexiletine in counteracting myotonia induced by 9-AC injection in the rat. Safinamide ED_{50} was 1.2mg/kg, compared to 7.0 mg/kg for mexiletine. At 10 mg/kg, antimyotonic effects developed within 20 min after safinamide administration and lasted for 1.5hours.

Discussion and conclusion: Safinamide inhibited skeletal muscle sodium channels in vitro and had more potent antimyotonic properties than mexiletine *in vivo* in rat model of myotonia. Further work is warranted to evaluate if safinamide may be clinically effective in non dystrophic myotonias.