Preclinical in vivo evaluation in a rat model of myotonia congenita of marketed and investigational sodium channel blockers

J.-F. Desaphy [1], R. Carbonara [1], T. Costanza [1], G Lentini [2], F. Corbo [2], C. Franchini [2], D. Conte Camerino [1]

[1]Section of Pharmacology and [2]Section of Medicinal Chemistry, Dept. of Pharmacy & Drug Sciences, University of Bari – Aldo Moro, Italy

A clinical trial recently confirmed the sodium channel blocker, mexiletine, as a first-choice drug in the treatment of non-dystrophic myotonias, a series of inherited disorders characterized by skeletal muscle stiffness due to mutations in chloride or sodium channel genes.[1] However the use of mexiletine is limited by contraindications or occurrence of side effects limiting the compliance. Moreover mexiletine has been withdrawn from a number of European countries, leaving patients with an unmet medical need. Thus there is a critical need to indentify possible alternatives to mexiletine. In this study, we tested the in-vivo antimyotonic activity of different marketed sodium channel blockers and a new tocainide analogue (namely To042), by using a rat model in which myotonia is pharmacologically induced by i.p. injection of 9-anthracene carboxylic acid.[2] The myotonic state is assessed by measuring the time of righting reflex (TRR) of rats, that is the time taken by the rat to turn back on his four limbs, after being posted in supine position. The TRR increases from <0.5 seconds in control conditions to a maximum of 3-4 seconds thirty minutes after 9-AC injection. An antimyotonic drug, administrated per os 10 minutes after 9-AC, is expected to shorten the TRR. The dose-response curves show an ED_{50} of 7.0 ± 1.4 mg/kg for mexiletine and a reduced ED50 for other sodium channels, including propafenone and carbamazepine (2-fold reduction), orphenadrine and flecainide (7-9 fold), lubeluzole and riluzole (70-fold), and To042 (100-fold reduction). The *in vivo* antimyotonic activity was in accord with the relative activity of sodium channel blockade in vitro, determined with patch-clamp technique on skeletal muscle hNav1.4 channels permanently expressed in HEK cells. Two exceptions regard carbamazepine, which was more efficient in vivo compared to in vitro, and propafenone, which was less efficient in vivo than in vitro. Such discrepancies are likely related to pharmacokinetic mechanisms. The comparison of antimyotonic doses in the rat with clinical doses used in human indications suggest that all the tested sodium channels might be used safely in myotonic patients, except for lubeluzole that may present some cardiac risk. Supported by Telethon-Italy (grant GGP10101) and Association Française contre les Myopathies (grant #15020).

1. Statland JM, Bundy BN, Wang Y, et al; Consortium for Clinical Investigation of Neurologic Channelopathies. Mexiletine for symptoms and signs of myotonia in nondystrophic myotonia: a randomized controlled trial. JAMA 2012;308(13):1357-1365.
2. DesaphyJF, Costanza T, carbonara R, Conte Camerino D. In vivo evaluation of antimyotonic efficacy of b-adrenergic drugs in a rat model of myotonia. Neuropharmacology 2013;65:21-27.