

Treatment and Prevention of Periodic Paralysis”

Robert C. Griggs, M.D.

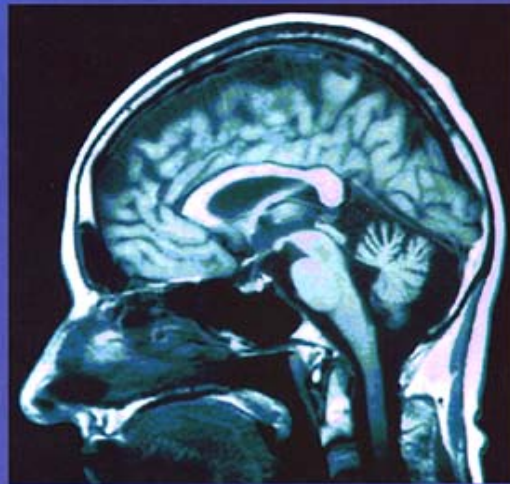
Chair, Executive Committee Muscle Study Group

Principal Investigator, Clinical Investigation of
Neurological Channelopathies (CINCH)

Channelopathies: Evolution of the Concept

- 1952 – Hodgkin and Huxley propose channels
- 1976 – Neher and Sachman – patch clamp demonstration
- 1991 – Ptacek et al – First mutation in human channel causing periodic paralysis
- 2009 – Over 100 neurological channelopathies

Channelopathies of the Nervous System



Michael R. Rose
Robert C. Griggs

Neuromuscular Channelopathies – Hereditary - Examples

- Periodic paralysis (Na^+ , K^+ , Cl^- , Ca^{++})
- Myotonias (DM-1/DM-2; Na^+ , Cl^+)
- Episodic ataxias (K^+ , Ca^{++})
- Myasthenias – 14 types, voltage/ligand gated
- Rippling muscle disease
- Malignant hyperthermia

Neuromuscular Channelopathies - Acquired

- Myasthenias (4 types)
- Rippling muscle disease
- CIDP (? Na⁺)
- Neuromyotonia/myokymia (K⁺)
- Autonomic neuropathies
- Stiff person syndrome
- Ataxias
- Other

Specific hypotheses:

- (1) Channelopathies must have both a specific molecular lesion (mutation) and intercurrent, triggering factor(s) to manifest symptoms

Specific hypotheses:

(2) Repeated attacks result in progressive neural or muscle injury

Specific hypotheses:

- (3) Prevention of attacks by modifying triggering factors will improve symptoms and quality of life and prevent/reverse target-tissue injury.

Treatment Trials in Neuromuscular Channelopathies (Currently Recruiting)

Dichlorphenamide in the periodic paralyses (HYP-HOP)

14-centers (5 countries): Muscle Study Group

Mexilitine in Non-Dystrophic Myotonia - CINCH Study
(PI Richard Barohn)

7 Centers (2 countries)

Acetazolamide/K⁺ in Andersen-Tawil Syndrome

3 Centers (2 countries) CINCH study (PI Paul
Twydell)

Modified Protocol: Dichlorphenamide vs Placebo in Hypokalemic and Hyperkalemic Periodic Paralysis

- 9 week placebo – controlled trial: Attack frequency and severity
- Year-long extension study strength, muscle mass
- Quality of life, side effects

Sites Recruiting Periodic Paralysis Patients for HYP HOP Trial

- USA:
 - Brigham & Women's Hospital (Boston)
 - Columbia-Presbyterian Medical Center (New York)
 - Mayo Clinic (Rochester, MN)
 - Ohio State University (Columbus)
 - University of California - San Francisco (San Francisco)
 - University of Kansas Medical Center (Kansas City)
 - University of Rochester School of Medicine (Rochester, NY)
 - University of Texas Southwestern (Dallas)
 - Johns Hopkins (Baltimore)
 - University of Florida (Gainesville)
 - Washington University (St. Louis)

- Canada: London Ontario
- UK: London
- France: Paris
- Italy: Milan

Rare Disease Research: The U.S. Regulatory Approval Process

- Gold standard: 2 randomized, double-blind, placebo-controlled trials
- Orphan drugs:
 - Extended exclusivity (patent protection)
 - Tax benefits
 - Longer period for children

Pivotal Studies of Orphan Drugs Approved for Neurological Diseases

Jun Mitsumoto, MPH,¹ E. Ray Dorsey, MD, MBA,² Christopher A. Beck, PhD,³ Karl Kieburtz, MD,²
and Robert C. Griggs, MD²

Objective: To identify design elements of clinical trials leading to US Food and Drug Administration approval of drugs for neurological diseases with and without orphan indications.

Methods: We used publicly available information to identify approvals for drugs for neurological diseases with an orphan indication ($n = 19$) and compared them with recent approvals for drugs for neurological diseases without an orphan indication ($n = 20$). We identified “pivotal trials” from drug labels and drug approval packages, and assessed them on four elements of clinical trial design: control, blinding, randomization, and size.

Results: All drugs for neurological diseases (100%) approved without an orphan indication included at least two randomized, double-blind, placebo-controlled trials. In comparison, 32% of drugs with an orphan indication had at least two such trials ($p < 0.001$) and 74% had at least one ($p = 0.02$). Thirty-three pivotal trials were conducted for the 19 drugs approved with an orphan indication. Of the 33 trials, 11 (33%) did not use a placebo control, 9 (27%) were not double blind, and 4 (12%) were not randomized. Drugs approved without an orphan indication had more pivotal trials per drug (3.8 vs 1.7 trials; $p < 0.001$) and a larger mean trial size (506 vs 164 trial participants; $p < 0.001$).

Interpretation: The US Food and Drug Administration has approved orphan drugs for neurological diseases without randomized, double-blind, placebo-controlled pivotal trials. As orphan drug development grows, demand will likely increase for alternative designs for conducting adequate and well-controlled studies to demonstrate drug efficacy.

Publication Conclusion:

“Orphan drugs for neurological diseases have been approved by the FDA without randomized, doubled-blind, placebo-controlled clinical trials. As therapeutic development for orphan diseases is increasing, the design of alternative clinical studies will likely become more important.”

Treatment of Acute Weakness Hypokalemic Periodic Paralysis

- Treatment needed only for severe weakness
- Oral treatment if possible
 - Swallowing impairment is rare
 - Nausea or vomiting can occur
 - Potassium solutions –KCl is the least palatable
- IV treatment: most diluents lower serum K even with large concentrations of K
 - Bolus KCl (5mEq total)
 - Mannitol 5% as diluent

Treatment of Acute Weakness Hyperkalemic Periodic Paralysis

- Treatment rarely needed
- Oral treatment if possible
 - Glucose; other simple sugars
 - Avoid K-containing foods
- Parenteral (rarely necessary)
 - IV glucose (and insulin?)
 - IV calcium gluconate
 - Ion-exchange resin (Kayexelate) – never needed for periodic paralysis

New Studies Under Development for Periodic Paralysis Treatment

- Carbonic anhydrase—worsened or unresponsive patients
- Sulfonamide-allergic patients (?)
- CAI-inadequate response

Representative Publication (1)

“Pivotal Studies of Orphan Drugs Approved for Neurological Diseases.”

Authors: J Mitsumoto (CINCH medical student), ER Dorsey, CA Beck, J Thompson, T Nguyen, K Kieburtz, RC Griggs

Comparing orphan drugs with non-orphan drugs

Other Considerations in Attack Prevention

- Exercise
- Diet
- Stress
- Hormonal changes
- Coincidental medications
 - Insulin
 - Diuretics
 - Beta blockers

Acknowledgements

Investigators: The Muscle Study Group (MSG) and Clinical Investigation of Neurological Channelopathies (CINCH).

Especially: Richard Barohn, Rabi Tawil, Emma Ciafaloni, Barbara Herr, Michael Hanna, Louis Ptacek, Steve Cannon, Anthony Amato, Valeria Sansone, Bertrand Fontaine