Treatment and Prevention of Periodic Paralysis”

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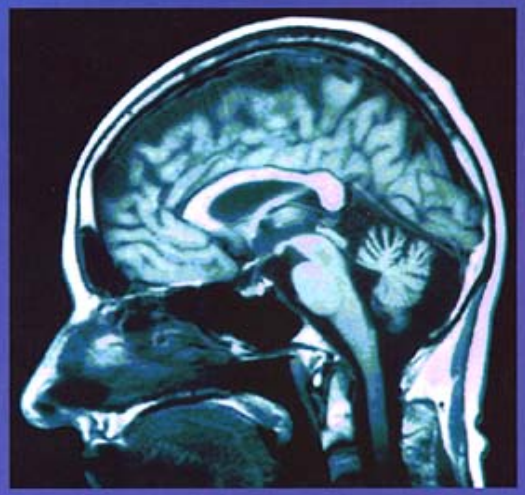
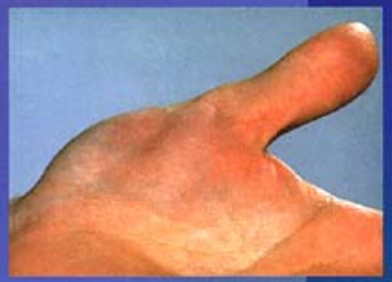
Channelopathies: Evolution of the Concept

- 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





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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, MD[2]

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, doubled-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.

Ann Neurol 2009;65:000–000

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