From evidence-based to personalized medicine in skeletal muscle channelopathies;

Bas Stunnenberg, MD
Departments of Neurology and Health Evidence

Dublin, August 2018
Experienced Based Medicine - 1887
'the conscientious, explicit, and judicious use of the best current evidence in making decisions about the care of individual patients'
Evidence Based Medicine \( \rightarrow \) Healthcare

- a new approach in teaching medicine
- Guidelines, protocols, reviews, economic decisions

“The gospel of EBM”
Evidence Based Medicine – quality of evidence

Level 1 evidence

Systematic Reviews and Meta-analyses
Randomized Controlled Double Blind Studies
Cohort Studies
Case Control Studies
Case Series
Case Reports
Ideas, Editorials, Opinions
Animal Research
In vitro (‘test tube’) research

Problem – *The value of the RCT in the treatment of rare diseases?*

**Methodological obstacles:**
- small patient numbers
- clinical and genetic heterogeneity

**Difficulties with interpretation:**
- results are only presented for the population level
- frequentist statistics

**Therapeutic misconception**

Gupta et al. *Journal of Clinical Epidemiology* (2011)
Middel tegen duchenne blijkt niet goed te werken

Een veelbelovend Nederlands medicijn tegen de dodelijke spierziekte van Duchenne is in de laatste fase van het onderzoek als nog gesneuveld.

VAN ONS VERSLAGGEESTER ELLEN DE VISSE 24 september 2013, 00:00

Amsterdam - Het Leidse biotechbedrijf Prosensa leek de sleutel in handen te hebben voor behandeling van de ziekte van Duchenne en haalde daarmee een miljoenencontract en een beursnotering binnen maar het middel blijkt bij patiënten toch niet effectief genoeg.

Door onze redacteuren Rinke van den Brink en Hugo van der Parre

De dure medicijnen tegen de zeldzame ziekten van Pompe en Fabry worden ook na dit jaar gewoon vergoed uit de basisverzekering. Dat heeft minister Schippers aan de Tweede Kamer laten weten.

Vorige zomer onthulde de NOS een plan van het College voor Zorgverzekeringen om de vergoeding te schrappen. Het CVZ had twijfels over de effectiviteit van de middelen in relatie tot de prijs die ervoor betaald moest worden.

Prijsverlaging

Op jaarbasis kosten de medicijnen voor een patiënt met Pompe tussen de 400.000 en 700.000 euro. De medicijnen voor iemand met Fabry kosten 200.000 euro per jaar.

Onderhandelingen met de producenten van de middelen hebben volgens de minister een substantiële prijsverlaging opgeleverd. Hoewel de prijs omlaag gaat, wordt niet bekendemaakt. Dat is een voorwaarde die de producenten van de geneesmiddelen gesteld hebben.
Randomized, placebo-controlled trials of dichlorphenamidine in periodic paralysis

Table 2  Treatment effects on efficacy outcomes in the double-blind phase

<table>
<thead>
<tr>
<th>Hypokalemic periodic paralysis</th>
<th>Placebo (n = 20)</th>
<th>DCP (n = 24)</th>
<th>Treatment effect</th>
<th>95% CI</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Attack rate per week</td>
<td>2.4</td>
<td>0.3</td>
<td>−2.2</td>
<td>−6.8 to −0.4</td>
<td>0.02</td>
</tr>
<tr>
<td>Severity-weighted attack rate</td>
<td>5.7</td>
<td>0.6</td>
<td>−5.2</td>
<td>−25.2 to −1.2</td>
<td>0.02</td>
</tr>
<tr>
<td>Total attack duration per week</td>
<td>20.0</td>
<td>2.7</td>
<td>−19.8</td>
<td>−151.3 to −4.9</td>
<td>0.02</td>
</tr>
</tbody>
</table>
Time for one-person trials

N-of-1 trials - definition

“multi-cycle within-patient, randomized, double-blind, cross-over comparisons of a drug and placebo (or another drug) using standardized measures of effect.”

Guyatt et al. NEJM (1986)
# N-of-1 trials – *indications and limitations*

<table>
<thead>
<tr>
<th>Disease and treatment</th>
<th>Indications</th>
<th>Limitations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stable, non-progressive disease</td>
<td>Doubt about efficacy - new treatment - evaluation of chronic treatment</td>
<td>Time</td>
</tr>
<tr>
<td>With measurable symptoms</td>
<td>Causality of side-effects</td>
<td>Money</td>
</tr>
<tr>
<td>Symptomatic, fast acting treatment</td>
<td></td>
<td>Logistics</td>
</tr>
<tr>
<td></td>
<td></td>
<td>IRB</td>
</tr>
</tbody>
</table>

*Guyatt et al. NEJM (1986)*

*McLeod et al. Lancet (1986)*
N-of-1 trials – *timeline*

1968 - First N-of-1 trial in the medical field (Kellner et al.)

1986 - “*Start of a movement*” (Guyatt, Sackett et al.)

>> multiple N-of-1 trials and "*N-of-1 trial services*"

1996 - Validation of individual N-of-1 trials vs. regular care (*Mahon et al.*)

1997 - Aggregating N-of-1 trials using Bayesian statistics (Zucker et al.)

2015 - Publication of CONSORT extension for reporting of N-of-1 trials guidelines (CENT)
Non-dystrophic myotonia (NDM) and mexiletine

- Mutations in Na\(^+\) or Cl\(^-\) muscle ion channels
- Delayed muscle relaxation after voluntary muscle contraction (myotonia)

- Classe IB anti-arrhythmics
- Sodium channel blocker
- Coverage discontinuation in 2007 by lack of level-1 evidence

Study aims

To validate the aggregated N-of-1 trials design as alternative level-1 trial design for investigation of the treatment in chronic, rare diseases

Unique opportunity to compare our results with the gold standard of evidence: the RCT

Mexiletine for Symptoms and Signs of Myotonia in Non-Dystrophic Myotonia: A Randomized Controlled Trial

Statland et al. JAMA (2012)
Methods – design

blokrandomisatie

N=30
Methods – outcome measures
Methods – primary outcome measure (IVR)

Interactive Voice Response

- Stiffness
- Tiredness
- Weakness
- Pain

No complaints | Most severe complaints
## Methods – secondary outcome measures

<table>
<thead>
<tr>
<th>ECG + lab</th>
<th>Questionnaires</th>
<th>Clinical myotonia tests</th>
<th>Electrophysiological myotonia tests</th>
</tr>
</thead>
<tbody>
<tr>
<td>IVR</td>
<td>INQoL</td>
<td>SF-36</td>
<td>Eyelid closure myotonia</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Handgrip myotonia</td>
<td>Handgrip myometry</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Timed Up and Go test</td>
<td>Needle-EMG</td>
</tr>
</tbody>
</table>
Methods – Bayesian statistics

<table>
<thead>
<tr>
<th>I</th>
<th>II</th>
<th>III</th>
<th>IV</th>
</tr>
</thead>
<tbody>
<tr>
<td>M</td>
<td>P</td>
<td>M</td>
<td>P</td>
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<td>P</td>
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<tr>
<td>M</td>
<td>P</td>
<td>M</td>
<td>P</td>
</tr>
</tbody>
</table>

Patient 1

Patient 2

Patient 3

Patient 4

Patient 5

III

SCN4A

CLCN1

NDM

Probability of meaningful difference

μ, mean

σ, variance
Question. What kind of object is flying in this slide?
(a) Plane
(b) Probably a bird
(c) Fly
(d) Drone
Conclusions

1. We validate the aggregated N-of-1 trial design as a more efficient and personalized method for producing level 1 evidence of treatment in patients with chronic, rare diseases than the RCT.

2. Furthermore, we strengthen the evidence of the clinical and cost-effectiveness of mexiletine in patients with NDM.
Discussion

1. Can we perform individual and aggregated N-of-1 trials in periodic paralysis?

2. For future trials, what outcome measures, meaningful difference and intervention(s) should we use?
1. Can we perform individual and aggregated N-of-1 trials in periodic paralysis?

2. For future trials, what outcome measures, meaningful difference and intervention should we use?
Design – individual N-of-1 trial
Results – weakness attack characteristics

The graph shows the average attack duration and severity over time for different periods.

- **Period 1**: Salbutamol (12 weeks), average attack duration: 120 minutes, average attack severity: 1.2
- **Period 2**: Placebo (11 weeks), average attack duration: 110 minutes, average attack severity: 0.9
- **Period 3**: Placebo (11 weeks), average attack duration: 110 minutes, average attack severity: 0.8
- **Period 4**: Salbutamol (11 weeks), average attack duration: 110 minutes, average attack severity: 0.8

The x-axis represents time in weeks, ranging from 0 to 8 weeks.
### Results – Bayesian plots

#### Bayesian statistical analysis

<table>
<thead>
<tr>
<th>Outcome measure</th>
<th>Placebo Mean (SD)</th>
<th>Ventolin Mean (SD)</th>
<th>Treatment Effect (Ventolin – Placebo) Mean (95% CI*)</th>
<th>Probability &gt;20% improvement (meaningful difference)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of attacks/day</td>
<td>0.76 (0.46)</td>
<td>0.82 (0.50)</td>
<td>0.07 (-0.19 ; 0.31)</td>
<td>4.31%</td>
</tr>
</tbody>
</table>

- **A**
  - Distribution of the Mean of the attacks
  - **PDF**
  - **Placebo**
  - **Ventolin**

- **B**
  - Difference in attacks: Mean Placebo - Mean Ventolin
  - Distribution of the Mean difference
  - **PDF**
  - **favors salbutamol**
  - **favors placebo**
Discussion

1. Can we perform individual and aggregated N-of-1 trials in periodic paralysis?

2. For future (aggregated) N-of-1 trials, what outcome measures, meaningful difference and intervention should be used?
Acknowledgements

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UMCG, Groningen
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Thera Links

Rochester, USA
Robert Griggs

Kansas, USA
Jeffrey Statland

Texas, USA
Jaya Trivedi

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Most recent diagnostic supportive criteria for periodic paralysis

Dublin, August 2018
INVITED REVIEW

REVIEW OF THE DIAGNOSIS AND TREATMENT OF PERIODIC PARALYSIS

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Accepted 7 November 2017
Table 2. Supportive diagnostic criteria for HypoPP

1. Two or more attacks of muscle weakness with documented serum K < 3.5 mEq/L
2. One attack of muscle weakness in the proband, and 1 attack of weakness in 1 relative with documented serum K < 3.5 mEq/L in at least 1 attack
3. Three of 6 clinical or laboratory features:
   a. Onset in the first or second decade
   b. Attack duration (muscle weakness involving 1 or more limbs) > 2 hours
   c. Positive triggers (high carbohydrate rich meal, rest after exercise, stress)
   d. Improvement with potassium intake
   e. Positive family history or genetically confirmed skeletal calcium or sodium channel mutation
   f. Positive McManis long exercise test
4. Exclusion of other causes of hypokalemia (renal, adrenal, thyroid dysfunction; renal tubular acidosis; diuretic and laxative abuse)
5. Absence of myotonia (clinically or latent detected by needle EMG), except eye lids
Table 3. Supportive diagnostic criteria for HyperPP

1. Two or more attacks of muscle weakness with documented serum K >4.5 mEq/L
2. One attack of muscle weakness in the proband, and 1 attack of weakness in 1 relative with documented serum K >4.5 mEq/L in at least 1 attack
3. Three of 6 clinical or laboratory features:
   a. Onset before third decade
   b. Attack duration (muscle weakness involving 1 or more limbs) <2 hours
   c. Positive triggers (exercise, stress)
   d. Myotonia
   e. Positive family history or genetically confirmed skeletal sodium channel mutation
   f. Positive McManis long exercise test
4. Exclusion of other causes of hyperkalemia (renal, adrenal, thyroid dysfunction; potassium-sparing diuretics use)
**Table 4. Supportive diagnostic criteria for Andersen-Tawil syndrome.**

A. Presence of 2 of the following 3 criteria:
   - Periodic paralysis
   - Symptomatic cardiac arrhythmias or ECG evidence of enlarged U-waves, ventricular ectopy or a prolonged QTc or QUc interval
   - Characteristic facies, dental anomalies, small hands and feet, and at least 2 of the following:
     - Low-set ears
     - Widely spaced eyes
     - Small mandible
     - Fifth-digit clinodactyly
     - Syndactyly of toes 2 and 3

B. One of the above 3 in addition to at least 1 other family member who meets 2 of the 3 criteria.\(^\text{18,24,30}\)
Puzzling case of periodic paralysis

Bas Stunnenberg, MD
Departments of Neurology and Health Evidence

Dublin, August 2018
Clinical information

31-year-old male

History:
1989 Craniopharyngeoma, resection and radiotherapy, panhypopituïitarism.
2014 (6) Epileptic seizure, meningeoma parietal lobe, resection
2014 (12) Thyreoïdectomy, dissection of papillary thyroid carcinoma

Medication:
Desmopressin, hydrocortison, levetiracetam, thyroid hormone.
Growth hormone suppletion was stopped in april 2015.
Presentation at the ER (aug 2015)

• Since a period of 5 months, weakly, episodic complaints of muscle weakness in legs>arms, usually early in the morning

• Duration of weakness between 1-3h

• First time that he could not stand without assistance

• Thinks the levetiracetam is causing his symptoms

No clear triggers, muscle pain of cramps, sensibel complaints or postive family history
Doctor, Doctor
What Do You Do?
### Lab test

<table>
<thead>
<tr>
<th>ELECTROLIETEN (BLOED)</th>
<th>9-8-2015 02:12</th>
<th>9-8-2015 02:19</th>
<th>9-8-2015 03:11</th>
</tr>
</thead>
<tbody>
<tr>
<td>Na</td>
<td>2.38</td>
<td></td>
<td></td>
</tr>
<tr>
<td>K</td>
<td>1.13</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ca</td>
<td>2.6</td>
<td>2.7</td>
<td></td>
</tr>
<tr>
<td>Mg</td>
<td>0.76</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Na (bloedgas)</td>
<td>139</td>
<td>138</td>
<td></td>
</tr>
<tr>
<td>K (bloedgas)</td>
<td>2.6</td>
<td>2.7</td>
<td></td>
</tr>
<tr>
<td>Cl (bloedgas)</td>
<td>100</td>
<td>100</td>
<td></td>
</tr>
<tr>
<td>Gecalcium</td>
<td>1.21</td>
<td>1.19</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>NIERFUNCTIE (BLOED)</th>
<th>9-8-2015 02:12</th>
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<th>9-8-2015 03:11</th>
</tr>
</thead>
<tbody>
<tr>
<td>Urea</td>
<td>2.2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kreatinine</td>
<td>77</td>
<td></td>
<td></td>
</tr>
<tr>
<td>MDRD-GFR</td>
<td>&gt;90 *</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### ENZYMEN & LEVERFUNCTIE

| ALAT | 57 | ▲ |
| ASAT | 36 | ▲ |
| CK   | 164|    |
| Gamma GT |    |    |
| Alkalische fosf. |    |    |
| Bilirubine totaal |    |    |
| Bilirubine direct |    |    |

### EIWIT (BLOED)

| Albumin | 44 |    |

### ONTSTEKING

| Bezinking | 2 |    |
| CRP       | <5 * |    |

### CARDIALE BIOMARKERS

| CK | 164 |    |

### METABOLIETEN

| Glucose |    |    |
| Glucose (POCT) |    |    |
| Glucose (bloedgas) | 6.1 | ▲ |
McManis long-exercise-test (LET)
Genetics

- *SCN4A, CACNA1S* and *KCNJ2*: negative (no mutation)
- Whole exome sequencing: negative (no mutation in known neuromuscular disease genes)
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Management (1)

- Prophylactic treatment: Diamox 250mg twice a day, oral potassium supplements
- Attack treatment: KCl drink (3 times 60 ml), i.v. KCl in hospital
- ask PubMed...
Hypokalemic periodic paralysis in a patient with acquired growth hormone deficiency.

Lanzi R¹, Previtali SC, Sansone V, Scavini M, Fortunato M, Gatti E, Meola G, Bosi E, Losa M.

Abstract

CONTEXT: Hypokalemic periodic paralysis (HypoPP) is a rare disorder consisting of sudden episodes of muscle weakness with areflexia involving all four limbs, which spontaneously resolve within several hours or days. Primary HypoPP is genetically determined, while secondary acquired HypoPP has been described in association with thyreotoxicosis, hyperaldosteronism, kidney diseases, diuretics and liquorice abuse, gastrointestinal potassium loss, or cisplatinum therapy.

OBJECTIVE: To report a case of HypoPP associated with GH deficiency.

PATIENT: A 33 yr-old man with hypopituitarism and diabetes insipidus secondary to pituitary stalk-localized sarcoidosis, and documented HypoPP episodes.

CLINICAL PRESENTATION: Neurologic exam outside HypoPP episodes was normal. Needle electromyography was normal without myotonia or other spontaneous electric activity. Muscle biopsy documented a vacuolar myopathy with tubular aggregates. However, genetic analysis ruled out common mutations of the voltage-gated calcium channel observed in primary HypoPP. Common causes of secondary HypoPP were also ruled out. The patient was diagnosed with severe GH deficiency with modest fasting hyperinsulinaemia and insulin resistance and started on GH replacement therapy, an alpha-glucosidase inhibitor (acarbose) and a diet low in simple carbohydrates.

CONCLUSIONS: GH replacement therapy, acarbose and a diet low in simple carbohydrates resulted in the complete long-term (>2 yr) remission of HypoPP episodes. This is consistent with the hypothesis that the hyperinsulinaemia associated to GH deficiency may trigger HypoPP episodes by increasing Na+/K+ ATPase activity and K+ transport into the intracellular compartment with subsequent hypokalemia.

PMID: 17556873 DOI: 10.1007/BF03346302
Hypokalemia and hypomagnesemia related to levetiracetam use.

Aksoy D¹, Cevik B², Kurt S², Pekdas E², Solmaz V².

Abstract
Levetiracetam (LEV), used for both partial and generalized seizures, is a frequently preferred antiepileptic because of its few side effects. We present a 23-year-old man who developed hypokalemia after switching from valproate to LEV. The patient was sent to our clinic due to hypokalemia 1 month after initiation of LEV, and his neurological examination was normal. Further examinations revealed hypokalemia (3.1 mmol/L) and hypomagnesemia (0.56 mmol/L). His hemogram, blood urea nitrogen, creatinine, total cortisol, thyroid function tests, creatinine clearance, and renal Doppler ultrasound were normal. LEV was tapered off and treatment with 200mg/day lamotrigine begun. Potassium and magnesium levels returned to normal ranges in subsequent tests. While hypokalemia and hypomagnesemia have not been reported before to our knowledge, interstitial nephritis and renal failure after the use of LEV have been. Hypokalemia, found in the early period in this case, may be an indicator of a recently developed renal tubular disorder. This experience indicates that unpredictable side effects of increasingly used new antiepileptic drugs should be taken into consideration.

Keywords: Epilepsy; Hypokalemia; Levetiracetam

PMID: 24906211 DOI: 10.1016/j.jocn.2014.03.013
[Indexed for MEDLINE]
Management (2)

Based on the case reports:
• Restarted growth hormone; no effect
• Stopped Levetiracetam → no more attacks!
Management (2)

Based on the case reports:
- Restarted growth hormone; no effect
- Stopped Levetiracetam → no more attacks!

Lessons learned

• **Listen to your patient!**

• **HypoPP care:**
  - Importance of a multi-disciplinary team (including the patient)
  - Potassium shift vs renal potassium loss
  - Importance of case-reports

• **Levetiracetam and growth hormone treatment can give sec. HypoPP**
Video of a patient with a PP-attack at the ER

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Dublin, August 2018