Dichlorphenamide reduced the severity and frequency of attacks in the primary periodic paralyses.

Clinical Problem: A 20-year old male with hypokalemic periodic paralysis heard from a cousin that acetazolamide decreases attacks of weakness. He is wondering if medication will reduce the severity of his attacks.

Clinical Question: Is Dichlorphenamide (carbonic anhydrase inhibitor) an effective and well tolerated medication in the treatment of ion channel disorders such as periodic paralyses?

Search Strategy: The SUMSEARCH and PubMed databases were searched for “acetazolamide” and “ion channel,” “channelopathy,” “episodic ataxia,” or “periodic paralysis/paralyses,” and limited to “therapy.” No relevant articles were found. Discussion with an expert confirmed that there are no double blind RCTs for acetazolamide in ion channel disorders, but that there was a single, recent double blind RCT for dichlorphenamide, another carbonic anhydrase inhibitor, in the periodic paralyses. This article was chosen for review.

Clinical Bottom Lines:

1. Dichlorphenamide reduced mean attack rates compared to placebo in both hypokalemic (0.9 (SD±1.4), p=0.02) and hyperkalemic periodic paralysis (2.3 (SD ±2.9), p=0.006).
2. Dichlorphenamide prevented trial withdrawal due to an intolerable increase in attack frequency and severity as compared to placebo in hypokalemic periodic paralysis.

The Evidence: A multi-center, randomized, double-blind, placebo-controlled crossover trial of dichlorphenamide versus placebo was done in patients with hypokalemic periodic paralysis (hypoPP) or potassium sensitive periodic paralysis [PSPP] (hyperkalemic periodic paralysis or paramyotonia congenita). 42 subjects with hypoPP and 31 with PSPP were evaluated at baseline over >8 weeks for attack rate, then randomized to two treatment sequences, for 9 weeks’ duration, separated by a washout period of at least 9 weeks. Pre-study treatment was discontinued during the treatment phases, but was taken during the washout period. Dichlorphenamide dosing varied in 3 ways: one fifth of the subjects’ acetazolamide dose, the subjects’ usual dose, or 50mg bid.

For hypoPP the primary outcome was the endpoint of withdrawal from treatment due to an intolerable increase in attack frequency or severity. Secondary endpoints were the average number of attacks per week, the severity-weighted attack rate, and the subjects’ preferred treatment. Subjects recorded the maximum severity (range 1-4) and duration of every attack in diaries that were mailed in each week.

For PSPP the primary outcome was the attack rate. Secondary outcomes were severity-weighted attack rate and the preferred treatment.

Data:

HypoPP Trial: (1) Primary outcome – 15 out of 34 who completed both treatment phases reached the endpoint of an intolerable increase in frequency and severity of symptoms. Of the 13 subjects who expressed a preference for one treatment, 11 reached the endpoint on placebo versus 2 on dichlorphenamide (p=0.02). (2) Secondary outcome – see table 1.

PSPP Trial: See Table 1 for primary (attack rate) and secondary outcomes.

<table>
<thead>
<tr>
<th>Outcome</th>
<th>HypoPP +/- SD</th>
<th>PSPP +/- SD</th>
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</thead>
<tbody>
<tr>
<td>Mean improvement in attack rate per week (on dichlorphenamide vs. placebo)</td>
<td>0.9+/−1.4 (p=0.02)</td>
<td>2.3+/−2.9 (p=0.006)</td>
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<tr>
<td>Mean improvement in severity-weighted attack rate (on dichlorphenamide vs. placebo)</td>
<td>1.1+/−1.5 (p=0.01)</td>
<td>4.6+/−5.7 (p=0.003)</td>
</tr>
<tr>
<td>Number of subjects who preferred dichlorphenamide treatment</td>
<td>15/24 (62.5%)</td>
<td>15/21 (71.4%)</td>
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</table>

Table 1: Outcomes in the periodic paralyses on dichlorphenamide vs. placebo.

Most adverse events were commonly associated with carbonic anhydrase inhibitors – anorexia, dysgusia, diarrhoea, dizziness, pruritus, skin rash, paresthesias, and flank pain. There was an unexpected high frequency of cognitive complaints such as slowed mentation, confusion, irritability and depression (24% in hypoPP and 21% in PSPP).

**Comments:**
1. There were no double blind RCTs of acetazolamide in ion channel disorders.
2. This was a well-designed crossover study in subjects with a strict clinical diagnosis, computer-generated randomization, and adequate concealment.
3. The characteristics of the subjects at baseline in each treatment group were not reported.
4. Masking was not very effective due to the efficacy and adverse effects of dichlorphenamide. For the hypoPP trial 22/24 subjects and 20/23 investigators correctly guessed the treatment sequence, while for the PSPP trial, 22/22 and 23/23 guessed correctly.
5. There was a high dropout rate, as only 34/42 (81%) of hypoPP subjects completed both treatment phases, while 24/31 (77.4%) of PSPP subjects completed both phases.
6. Dichlorphenamide is currently not available in Canada or in the United States.


**Key Words:** periodic paralyses, episodic ataxia, channelopathy, acetazolamide, dichlorphenamide

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