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Methazolamide for essential voice tremor

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Article abstract—We studied the safety and efficacy of methazolamide (average dose 168 mg/day) in a placebo-controlled blinded investigation in nine patients with essential voice tremor. There were no significant differences for physician or patient clinical rating scores. Digital audio tape recordings showed no difference for amplitude modulation, but frequency modulation was significantly altered by methazolamide. Side effects were common with the drug. We conclude that methazolamide has limited usefulness in the treatment of essential voice tremor.

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Essential tremor (ET) is the most common movement disorder seen in clinical practice.[1] The hands are most frequently affected followed by involvement of the cranial musculature,[2,3] Although head and voice tremor may occur in isolation, commonly they occur in association with hand tremor,[3,4] and although usually present early in the course of ET, more commonly they are seen in advanced disease.[4] Voice tremor can impair speech intelligibility[5,6] and is considered more difficult to treat than hand tremor.[4,7] Muenter et al.[8] reported, in an open-label study, that the carbonic anhydrase inhibitor, methazolamide, was highly effective for hand, head, and voice tremor. However, a controlled study[9] did not find methazolamide effective for essential hand tremor. We performed a blinded study of methazolamide in essential voice tremor using objective measures.

Methods. Nine patients (1 man and 8 women, average age of 72.8 years) with the diagnosis of ET for an average of 32.3 years who had voice tremor were enrolled in a double-blind, placebo-controlled, crossover design study. Other body parts affected by tremor included upper extremities (9 patients), head (4 patients), lower extremities (2 patients), chin (1 patient). Two patients were taking primidone, one patient was taking beta-adrenergic blockers, three patients were taking both adrenergic blockers and primidone, one patient was taking alprazolam, and two patients were taking no medications. Medication dosages were not changed during the course of the study.

Methazolamide or placebo was administered in random order with look-a-like placebo. The dose of drug was started at 25 mg/day and increased by 25 mg every other day until a maximum dose of 300 mg/day was achieved if tolerated. Patients were phoned weekly to assess side effects and dosage increase. Patients remained on the maximally tolerated dose for 2 weeks and then had their drug discontinued over 1 week. After a 2-week washout period, the second drug was started.

Patient's voice tremor was assessed at baseline and after 2 weeks on the maximally tolerated dose. Evaluations consisted of clinical rating by the physician and patient according to the following scale: 0, normal; 1, slight, may be intermittent; 2, moderate amplitude, may be intermittent; 3, marked amplitude; 4, severe amplitude. Statistical analysis was performed using a Friedman two-way ANOVA ($p < 0.05$).

The patients were evaluated at the end of each treatment for the degree of change according to the following scale: +3, marked improvement (50 to 100%); +2, moderate improvement (25 to 49%); +1, mild improvement (10 to 24%); 0, unchanged; −1, mild worsening (10 to 24%); −2, moderate worsening (25 to 49%); −3, marked worsening (50 to 100%).

At each visit, digital audio tape (DAT) recordings were obtained in a sound-treated booth. A head-mounted microphone was positioned 6 inches from the lips, and subjects were instructed to "take a deep breath and say 'ah' as long as you can." This task was repeated until at least eight sustained phonations of 6 to 8 seconds were recorded. Subjects were then asked to read a standard reading passage. DAT recordings were blindly analyzed to determine amplitude modulation (AM), the fluctuation in intensity during a sustained vowel, and frequency modulation (FM), the fluctuation in fundamental frequency (which corresponds closely to pitch) throughout the vowel. The microphone signal was played back from the DAT recording into the vocal demodulator, an acoustic analysis tool designed and validated by Winholtz and Ramig.[10] This device, which extracts the amplitude and frequency components of vocal tremor, produces continuous analog outputs of DC voltages that correspond to the amplitude and frequency modulation of the voice during sustained phonation. In the present study, these AM and FM output signals were digitized at 500 Hz, and from these digitized waveforms, a fast

Table *AM and FM in essential voice tremor for baseline, placebo, and methazolamide*

	Baseline	Placebo	Methazolamide	Significance
AM (intensity units)	49.8 ± 4.9	47.5 ± 3.5	47.1 ± 5.0	$p = 0.42$
FM (intensity units)	45.6 ± 4.4	45.1 ± 3.9	42.8 ± 3.8	$p = 0.03$

Fourier transform (FFT) was computed to identify the frequency and magnitude of the largest tremor component. Starting 1 second into the vowel, successive 1-second windows were selected for the FFT analysis. The tremor peaks were quantified in dB from the FFT spectrum. The mean dB value of up to five adjacent 1-second windows was used as a measure of tremor severity. Some subjects were unable to sustain uninterrupted phonation this long, so the mean of three or four windows was used in some cases. Segments containing voice breaks were eliminated from analysis because the vocal demodulator requires a minimum 1 second of continuous phonation to provide modulation data. The present methodology differs slightly from that reported by Winholtz and Ramig in that the earlier study reported percent modulation in the amplitude and frequency domains for a weighted average of the tremor components. Statistical analyses were performed by Friedman two-way ANOVA with significance of $p \leq 0.05$. A Wilcoxon signed ranks test was done to determine which groups were different.

Results. One patient dropped out because of shortness of breath on drug. One patient dropped out during first treatment (placebo) because of complaints of increased tremor. Analysis was performed on the seven patients that completed both arms of the study. Average tolerated dose was 168 mg/day. There was no significant difference for physician scores ($p = 0.37$) or patient scores ($p = 0.65$) of voice tremor severity. Mild (2 patients) and moderate (1 patient) improvement on drug and mild improvement (1 patient) on placebo was recorded by the rater. Patient self-ratings included mild improvement (4 patients) on drug and mild improvement (1 patient) on placebo. DAT recording analysis was performed on 6 patients, as one patient's voice tremor was too severe to analyze numerically. There were no significant differences between any of the groups for AM measurements; however, FM measurements for the methazolamide condition were significantly different from both baseline and placebo (table).

Side effects on drug were common and included paresthesias (2 patients), drowsiness (3 patients), decreased appetite (2 patients), dizziness (2 patients), confusion (2 patients), headache (1 patient), depression (1 patient), and diarrhea (1 patient). Side effects reported on placebo included drowsiness (2 patients), decreased appetite (1 patient), dizziness (1 patient), confusion (1 patient), headache (1 patient), and anxiety (1 patient). No patients elected to continue on the drug at the end of the study.

Discussion. Muenter et al.[8] noted the frequent improvement of voice tremor and stated that the likelihood of a good response to methazolamide was increased if voice tremor was the initial symptom at onset of disease. Our experience indicates that assessing voice tremor in an open-label fashion from one clinic visit to the next is unreliable. In our blinded placebo-controlled study using objective techniques to analyze voice tremor, we found that methazolamide may have some effect on essential voice tremor, but the mild benefit that some patients experienced was not enough to warrant continuation of the drug. Methazolamide was commonly associated with adverse reactions. Therefore, we conclude that methazolamide has limited use for the treatment of essential voice tremor. Furthermore, this study confirms that open-label trials cannot accurately define efficacy of drugs for essential tremor.

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