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CLINICAL TRIAL REPORT

Melatonin for Migraine Prevention

Mario Fernando Prieto Peres

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Alstadhaug KB, Odeh F, Salvesen R, Bekkelund SI. Prophylaxis of migraine with melatonin: A randomized controlled trial. Neurology. 2010;75:1527–32.

Rating: •• Of significant importance

Introduction: Melatonin has been linked to migraine in several ways, from mechanisms to treatment. This study is important to test the efficacy of melatonin in migraine prevention.

Aims: The objective of this trial was to evaluate the effect of melatonin, 2 mg, in migraine prevention.

Methods: This was a randomized, double-blind, placebo-controlled crossover study carried out in two centers in Norway. Men and women (ages 18 to 65 years) with migraine (experiencing two to seven attacks per month) but otherwise healthy were recruited from the general population. After a 4-week run-in phase, only 48 patients were randomly assigned to receive either placebo or extended-release melatonin (Circadin [Neurim Pharmaceuticals, Tel-Aviv, Israel]), 2 mg, for only 8 weeks (after a 6-week washout treatment was switched). The primary outcome was migraine attack frequency (AF). A secondary end point was sleep quality, assessed by the Pittsburgh Sleep Quality Index (PSQI).

Results: Only 46 patients completed the study after melatonin treatment headaches decreased in frequency from 4.2±1.2 to 2.8±1.6 attacks per month, but an unexpected high placebo response was found, and no difference from placebo was detected.

Comments

This is a negative study, but some critical methodological issues must be carefully considered when interpreting their negative results.

1. High placebo response rate. On the placebo arm, 19 (40%) patients had a greater than 50% reduction, a very high and unexpected rate; other migraine trials are, on average, in the 23% rate [1]. This could be due to the excellent tolerability of melatonin; patients may think they were getting melatonin treatment instead of placebo. The authors did not clarify how patients were enrolled. Patients prone to more natural treatments may be predisposed to a headache response, explaining the placebo rate observed. Previous migraine therapies used by patients could account for the clinical response and were not informed.
2. Melatonin dose. Melatonin was given in a 2-mg dose, which is lower than doses studied in other trials (melatonin was studied with 3 mg in migraine and 9 mg in cluster headache).
3. Short study length. Patients had only 8 weeks of treatment in this trial. All migraine prevention studies have been performed with a period of treatment no shorter than 12 weeks, and many studied patients over 16 weeks or more.

M. F. P. Peres (✉)
Instituto Israelita de Ensino e Pesquisa -Hospital Albert Einstein,
Sao Paulo, Brazil
e-mail: marioperes@yahoo.com

M. F. P. Peres
Escola Paulista de Medicina, Department of Neurology,
Universidade Federal de São Paulo,
Sao Paulo, Brazil

M. F. P. Peres
FMABC, Department of Neurology,
Sao Paulo, Brazil

4. Crossover design. The latest migraine prophylaxis trials have not been using the crossover design; the parallel design is more powerful. In this particular trial, the short length (only 8 weeks) limits the data interpretation crossing over arms.
5. Patient population. The trial enrolled patients from two centers in Norway. Given Norway's high latitude and significant influence of circannual and circadian rhythmicity, the 2-mg melatonin dose could be insufficient. In addition, the general rule of taking melatonin 30 min before bedtime could worsen phase shifts in patients sleeping after midnight.
6. Melatonin response rate. In this study, 21 patients (44%) responded to melatonin, similar to several other positive migraine prophylaxis trials. The mean decrease in headache frequency also was similar to the most recent and well-designed preventive trials.

Other studies with better trial methodology and design (higher melatonin doses, more than 8 weeks, not crossing over) should be done to clarify the role of melatonin in migraine management.

Disclosure

No potential conflicts of interest relevant to this article were reported.

Reference

1. Diener HC. Placebo effects in treating migraine and other headaches. Curr Opin Investig Drugs. 2010;11(7):735–9.