

## High dose melatonin therapy for patients with extremely intractable epilepsy

Kazuhiro HAGINOYA, Mamiko ISHITOBI, Noriko TOGASHI,  
Mitsutoshi MUNAKATA, Hiroyuki YOKOYAMA, Kazuie IINUMA

*Department of Paediatrics, Tohoku University School of Medicine, Sendai, Japan*

The anticonvulsive effect of melatonin has been reported clinically and experimentally.<sup>1,2</sup> However, most of clinical reports are based on relatively low dose administration (3-10mg/day) and small number of patients. We applied high dose melatonin therapy for treatment of extremely intractable epilepsy in childhood in order to evaluate its clinical efficacy.

Twelve patients of 2 to 19 years old were enrolled in this study. Among 10 patients who were classified as secondary generalized epilepsy, 8 had West syndrome in infancy and their seizures had not been controlled since then. Two patients were classified as cryptogenic localization-related epilepsy. All patients had daily seizures in spite of intensive treatment with various antiepileptic drugs, and had severe mental retardation. Five patients had abnormal sleep-wake cycle. After receiving written informed consent from the parents and an approval of local ethical committee, melatonin was added to the baseline anti-epileptic drugs with gradual increase to about 1 mg/kg/day (10 mg to 40mg/day), taken once every night. Seizure frequency and side effects were monitored. Period of high dose melatonin therapy ranged from 17 days to 90 days. Seizure frequency during high dose melatonin was compared with the same period before melatonin administration. More than 50% decrease in seizure frequency was taken as significant response.

Two patients showed complete seizure disappearance with melatonin administration. One patient with infantile spasms showed complete disappearance of spasms and hypsarrhythmia at 1 mg/kg/day. She started walking alone, and her irregular sleep-wake cycle improved significantly. However, spasms re-appeared one month later and EEG showed worsening. In another patient with localization-related epilepsy, seizures completely disappeared after increasing the dose to 1 mg/kg/day, with seizure free period lasted more than 12 months. However, there was no significant improvement of EEG which showed multi-focal spike. Three other patients showed partial decrease in seizure frequency of >50%. Among them one patient had transient decrease that lasted for 2 months. Decrease in seizure frequency seen in these patients was associated with an improvement of abnormal sleep-wake cycle. There were no serious side effects and no abnormal laboratory tests including liver and kidney functions. Three patients showed somnolence in the morning or daytime.

High dose melatonin may be considered as an alternative choice of treatment for extremely intractable epilepsy, since 5 out of 12 patients (42%) responded partially after administration of melatonin and there were no serious side effects. Patients with abnormal sleep-wake cycle may be particularly good candidate for the melatonin add-on therapy. However, habituation of anti-convulsive effect may be a significant drawback. Double blind controlled study is needed for better evaluation of the treatment.

### References

1. Rudeen PK, Philo RC, Symmes SK. Period of high dose melatonin therapy ranged from 17 days to 90 days. *Epilepsia* 1980; 21:149-54.
2. Fauteck J, Schmidt H, Lerchl A, Kurlmann G, Wittkowski W. Melatonin in epilepsy: first results of replacement therapy and first clinical results. *Biol Signals Recept* 1999; 8:105-10.