Guidelines melatonin use in Smith Magenis syndrome need correction

Evaluation of treatment of insomnia and behavioral problems in 68 patients with Smith Magenis syndrome

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In our Smith Magenis syndrome (SMs) expert centre we have seen many patients with severe sleep maintenance problems and behavioural problems as a result of inadequate melatonin treatment. As these problems diminished or disappeared after a substantial dose reduction of melatonin, we adapted a different therapeutic approach than published guidelines.

Results

Between 2006 and 2016 we saw 68 SMs patients. Of these, 20 were prescribed melatonin elsewhere (Group 1.). The other 48 SMS patients were not using melatonin when they first attended our SMs centre (Group 2.).

Group 1 (melatonin use before admittance) N=20

At first visit 20 patients (12M, 8F) were already using melatonin. Their mean age was 9,6Y (3-52). The mean melatonin dose was 4,35mg (0,3 – 10 mg). Melatonin daytime levels were extremely high (>50 pg/ml) in all 20 patients. After a considerable dose reduction to a mean of 0,84 (0,1 - 3,0) mg, sleep improved in all of these patients.

Group 2 (no melatonin use at admittance) N=48

The other 48 SMS patients (29M, 19F) were not using melatonin (Group 2.). Mean age was 15,4Y (1-58). Mean salivary melatonin daytime levels were 11,6 pg/ml. Melatonin levels in Group 1. were higher in females (14,12 pg/ml N=18) than in males (9,96 N=28).

In both groups in most cases behavioral problems decreased after melatonin dose reduction and/or restoring a normal sleep-wake rhythm. However, if medication was necessary clonidine and methylphenidate were a good alternative to neuroleptics.

Conclusion

International accepted therapeutic guidelines should be reconsidered, as we found that a large proportion of our SMs patients were slow melatonin metaboliser. Following these guidelines resulted in over half of them in worsening of behavioural and sleep problems, which best were treated with a considerable melatonin dose reduction.

Slow metabolisation of melatonin

In slow metabolisers of melatonin exogenous melatonin may result in increasing daily melatonin levels. Consequently after some time this will lead to highly cumulated melatonin levels and the circadian melatonin rhythm is lost. This will result in poor sleep maintenance and early waking, while the positive effect on sleep latency however will remain. Melatonin is metabolized principally by the CYP1A2 enzyme. The half life of exogenous melatonin ranges between 28 to 120 minutes. Differences in melatonin half-life reflect the wide inter-individual differences (10 to 200-fold) in CYP1A2 activity. Several reports indicate that SNPs in the CYP1A2 gene are associated with decreased activity or even loss of activity of the CYP1A2 enzyme. The proportion of individuals with the slow phenotype narrowly ranges from 12% to 14% in Caucasians. It varies however among ethnic populations; Australians (5%), Japanese (14%) and Chinese (5%), while Asian and African populations have lower CYP1A2 activity compared with Caucasians.

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Smith Magenis syndrome

In Smith Magenis syndrome is a genetic syndrome caused by a 17p11.2 deletion or RAI1 gene mutation. It is characterized by an inversed day-night rhythm caused by an inversed circadian melatonin rhythm. This results in daytime somnolence and sleep problems with poor sleep maintenance and early waking. According to literature these problems are treated with an evening dose of time release melatonin (titrate 1-3 mg every 1-2 weeks to a maximum of 1 0mg) and a morning dose of a b1-adrenergic antagonist such as acebutolol 10 mg/kg. Disruptive behaviors and temper tantrums can be treated with risperidone.

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