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PRIMARY HYPERSOMNIA : RESPONSE TO FLUOXETINE AND METHYLPHENIDATE

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ABSTRACT

Primary hypersomnia, a rare clinical syndrome, was diagnosed in a 14-year-old boy. The syndrome showed partial response to high dose fluoxetine therapy (120 mg/day) which recruited insomnia, an adverse effect of the drug, for therapeutic purposes. Response was enhanced with intermittent methylphenidate in association with a lower dose of fluoxetine. A possible pharmacokinetic interaction developed, comprising fluoxetine-induced augmentation of methylphenidate activity; such an interaction has not been previously reported.

Key words : Primary hypersomnia, hypersomnia, Narcolepsy, fluoxetine, methylphenidate, drug interaction, pharmacokinetic interaction

Primary hypersomnia (DSM-IV; American Psychiatric Association,1994) is a rare clinical syndrome, and little information is available about its incidence, prevalence and management. This report illustrates a case of primary hypersomnia and discusses its response to an experimental (fluoxetine) as well as a conventional (methylphenidate) treatment. A possible pharmacokinetic interaction between the two treatments is also considered.

CASE REPORT

VM, a 48-kg, 14 year old schoolboy, was brought by his parents with a history of excessive daytime drowsiness followed by periods of sleep. The complaints had been present all through his life since early childhood, and interfered significantly with daily activities; for example, he would fall asleep during class for periods of 15 mins to an hour at a time, several times a day. Or, he would fall asleep while being transported to and from school. Or, he would doze during social visits. As a result, his studies suffered, and he was much teased by his friends.

The episodes of sleep were always preceded by progressively increasing drowsiness and were never sudden in onset. The occurrence of drowsiness was directly related to the degree of environmental stimulation; for example, he remained alert during maths or science classes, or while working at a computer, but would doze during history lectures or when his mind was not actively engaged in a task. These episodes of sleep varied in number and duration depending on the challenges during the day. The sleep episodes were rarely refreshing. It was not possible to increase alertness during one part of day (e.g. during the evening) by restructuring his sleep habits or by enforcing naps (e.g. during the afternoon). The duration and quality of nighttime sleep was normal : he would sleep around 10 P.M. and awake around 6 A.M.

There were no symptoms suggestive of hypnagogic or hypnopompic hallucinations; sleep paralysis, cataplexy, breathing disturbances associated with sleep or any other symptom associated with sleep. There was no symptom to suggest the existence of significant current or previous psychiatric or medical morbidity. There was no history of drug use, nor a family history of a similar disorder. Physical

examination was unremarkable. Repeated EEGs revealed consistently reduced sleep latency but no sleep onset REM periods; no other abnormality was present. The clinical picture completely met DSM-IV criteria for Primary Hypersomnia (APA, 1994).

After discussion with his parents, fluoxetine was begun as an experimental treatment because fluoxetine is known to produce dose-dependent decrease in sleep. For VM's disorder, therefore, an adverse effect of fluoxetine would be recruited as a therapeutic effect. Treatment commenced at 20 mg/day and was gradually stepped up at 3-4 week intervals. There was progressive decrease in daytime drowsiness with each increase in dose. At the maximum recommended dose of 80 mg/day, however, parents and VM rated the improvement at only 40-50%. This dose was maintained for 6 months and the clinical gains continued.

Subsequently, VM's mother independently increased the dose by 20 mg and then by another 20 mg/day. Thus, VM was receiving 120 mg/day, which is 50% above the maximum recommended dose. When VM reported for his quarterly follow-up, he reported 80-90% improvement. There was little or no drowsiness in the morning; drowsiness and sleep spells during the afternoon occured only during 'boring' classes; and, except for a nap during his bus ride home, he was alert during the evening. However, his drowsiness and desire for sleep became strong by 8-9 p.m., and he would retire after a bath and meal to rise at around 5 a.m. the next day.

VM continued fluoxetine in the dose of 120 mg/day for 6 months with no untoward effects. There were no symptoms such as gastrointestinal distress, headaches, restlessness or anxiety, nor was there disturbance in sexual functioning. As time passed, however, clinical gains with fluoxetine showed a mild decrease. In view of continued problems associated with examinations (during which he would fall asleep), psychostimulant therapy with methylphenidate was recommended. The dose of fluoxetine was stepped down to 60 mg/day because of uncertainty of its possible interaction at high doses with the psychostimulant.

At present, VM is still mildly to moderately impaired by his symptoms. He uses menthylphenidate intermittently, in a dose of 5 mg before important occasions such as examinations. At this dose, he is able to complete his examination satisfactorily; at the higher dose of 10 mg, he experiences profuse sweating and tremors. With this treatment, VM has for the first time in his life passed (with credit !) in his exminations.

DISCUSSION

Primary hypersomnia is a DSM-IV term; a more usual term in sleep research is Idiopathic Central Nervous System Hypersomnia (Guilleminault,1994a). This syndrome was earlier known as essential narcolepsy, independent narcolepsy, NREM sleep narcolepsy, functional hypersomnia and harmonious hypersomnia. Primary hypersomnia differes from narcolepsy in several regards, as is evident from the divergent DSM-IV descriptions of the two disorders (APA,1994).

The symptoms of primary hypersomnia more commonly develop during adolescence or adult life and may be intermittent; this case is unusal in that the symptoms appeared during early childhood and were continuous in course. The syndrome is extremely rare and there are therefore no published data on its incidence or prevalence in the population; a clinician may not come across a case during a lifetime of practice. Behavioural approaches to treatment and sleep hygiene measures have little positive impact on the syndrome. Medications such as tricyclic antidepressant drugs, monoamine oxidase inhibitors, clonidine, L-dopa, bromocriptine, amantadine, methysergide and 5-hydroxy-tryptophan are experimental treatments which usually do not work well. The only medications that offer at least partial and intermittent relief

are psychostimulants such as pemoline, methylphenidate, mazindol, phenmetrazine hydrochloride and dextroamphetamine (Guilleminault,1994a). Modafinil, a drug recently approved of for the treatment of narcolepsy, may also be effective.

Psychostimulant therapy is associated with several disadvantages. In addition to the actual adverse effects of the drugs, these disadvantages include the development of tolerance to the beneficial effects and the occurrence of withdrawal symptoms when the dose is lowered or the drug is discontinued. Therefore, therapy for VM was initiated with fluoxetine rather than a psychostimulant with the hope that insomnia as an adverse effect of the drug would benefit the patient. Fluoxetine has been used with modest success in the narcolepsy syndrome (Guilleminault,1994b); however, a MEDLINE search revealed no reports of its use in primary hypersomnia. Happily for VM, positive results were obtained with initiation of therapy. These benefits, as might have been expected were dose dependent.

VM showed the best response to a dose of 120 mg/day. The maximum recommended dose of fluoxetine is 80 mg/day not because higher doses lead to morbid risk, but because at higher doses the likelihood of additional clinical gain is small and the risk for additional adverse effects is high; in fact, there are reports of patients tolerating overdoses of fluoxetine amounting to 1-3 gm (Barbey & Roose,1998). For this reason, in exceptional cases fluoxetine and related drugs have been used in doses that are higher than recommended (Byerly et al., 1996; Agarwal, 1998; Andrade,1999).

Treatment gains with fluoxetine showed slight decrease with the passage of months and drowsiness continued to be present during examinations and other periods of low stimulation. As a result, psychostimulant therapy became inevitable. The dose of fluoxetine was lowered to accomodate the initiation of methylphenidate therapy because of the uncertainty of the nature of the pharmacodynamic interaction between very high dose fluoxetine and methylphenidate.

The response to methylphenidate was good; while doses of 10-40 mg/day have been used for patients with narcolepsy (Guilleminault, 1994b) and clozapine-associated hypersomnia (Miller,1996), VM appeared to do well with just 5 mg/day. The efficacy of this low dose may have been because intermittent administration precludes the development of tolerance. However, it is also conceivable that the effective dose that VM received was higher through a pharmacokinetic interaction: fluoxetine is known to produce dose-dependent inhibition of the metabolism of several psychotropic agents and (particularly in high doses) it may hence retard the metabolism of menthylphenidate as well. This hypothesis is supported by evidence which suggests that methylphenidate, like fluoxetine, inhibits the metabolism of tricyclic and other agents (Reynolds, 1993), suggesting that the drug is itself metabolized by the same cytochrome P-450 subgroup. This hypothesis is also supported by the occurrence of profuse sweating and tremors when VM used a higher dose (10 mg) of methylphenidate; such symptoms are due to methylphenidate-induced overstimulation of the central nervous system, but do not usually occur with doses as low as 10 mg/day. While methylphenidate augmentation of selective serotonin reuptake inhibitor therapy has been described in patients with depression (Stoll et al.,1996), a MEDLINE search identified no literature on the pharmacokinetic effects of fluoxetine on methylphenidate; this, therefore, may be the first report.

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