Courting hyperlipidemia

Hydroxymethylglutaryl-coenzyme A (HMG-CoA) reductase activity peaks at night[1] or while the patient is fasting, with corresponding increases in hepatic cholesterol synthesis. Short-acting HMG-CoA reductase inhibitors (statins) must therefore be taken within a few hours of going to sleep. In contrast, atorvastatin[2] has a longer duration of action and can therefore be taken at any time of the day. In the following case a trivial change in timing of the patient's medication nullified the therapeutic effect.

In May 1997, a 70-year-old woman was given a prescription for simvastatin 20 mg daily, to be taken at bedtime. Her lipids were within the target range for the period March 1998 to April 2000 (Fig. 1), and she tolerated the medication well, with no side effects. Five months later, in September 2000, her lipids had risen to levels similar to those before she started the medication, and it appeared that she might have stopped her drug therapy. On questioning, she claimed that she had been taking simvastatin daily for the past 2 years. I then asked if there had been any changes in her routine over the previous 6 months that might have led to the changes in her lipid levels. She noted that about 5 months previously (late spring 2000) she had started dating someone, and they had been going out regularly for dinner and dancing. She claimed that she was watching her diet even though she was eating out more frequently. However, because she was coming home late at night, she sometimes forgot to take her medication before going to bed. To avoid missing doses, she had started taking the drug in the morning with breakfast.

This information solved the mystery. I discussed the timing of action of simvastatin with the patient and stressed the importance of taking the medication at night. She resumed evening dosing in October 2000, and by March 2001 her lipid levels had returned to within the target range.

This case illustrates the importance of proper timing of the daily dose for some medications and demonstrates that a seemingly trivial change in timing can affect the therapeutic outcome.[3]

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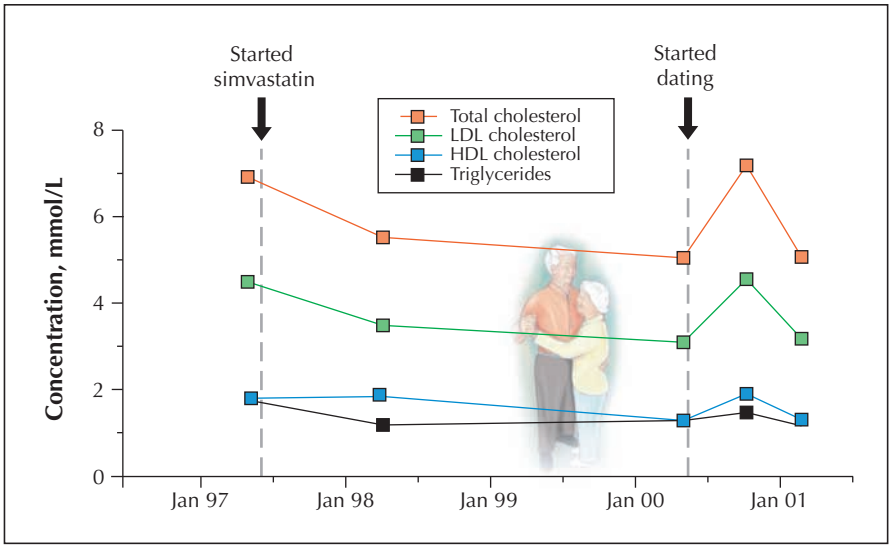

Fig. 1: Lipid values for a 70-year-old woman who started taking simvastatin 20 mg daily in May 1997. She started dating about a month after lipid levels were measured in April 2000 and subsequently started taking her simvastatin in the morning rather than before bed. In October 2000, she resumed taking the drug in the evening. HDL = high-density lipoprotein, LDL = low-density lipoprotein.

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1. Jones PJH, Schoeller DA. Evidence of diurnal periodicity in human cholesterol synthesis. *J Lipid Res* 1990;31:667-73.
2. Cilla DD, Gibson DM, Whitfield LR, Sedman AJ. Pharmacodynamic effects of atorvastatin after administration to normocholesterolaemic patients in the morning and evening. *J Clin Pharmacol* 1996;36:604-9.
3. Wallace A, Chinn D, Rubin G. Taking simvastatin in the morning compared with in the evening: randomised controlled trial. *BMJ* 2003; 327:788.

Competing interests: None declared.

Whence the Readers' Advisory Panel?

I think your Readers' Advisory Panel[1] is a wonderful idea and congratulate you on the same. However, given the addresses of the panel members, it

might be more appropriate to change the name of the journal to *JOMA: Journal of the Ontario Medical Association*.

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Reference

1. Thomas J, Hoey J. Introducing *CMAJ*'s Readers' Advisory Panel [editorial]. *CMAJ* 2003;169 (7):676.

[A Deputy Editor responds:]

In our efforts to ensure that *CMAJ* readers working in community settings were represented on the Readers' Advisory Panel,[1] we overlooked the fact that so many of the physicians we selected were from Ontario. When we add new members to the panel in the future, we will try for a more balanced geographic representation.

Jennifer Thomas
CMAJ

Reference

1. Thomas J, Hoey J. Introducing *CMAJ*'s Readers' Advisory Panel [editorial]. *CMAJ* 2003;169 (7):676.

Missing information on DEET

In their review of the safety implications of DEET (*N*,*N*-diethyl-*m*-toluamide) for children and pregnant and lactating women, Gideon Koren and associates[1] did not mention the results of animal trials involving dermal application of this repellent.

Abdel-Rahman and colleagues[2] reported diffuse neuronal cell death in the brains of adult rats after 6 days of daily dermal application of DEET. They concluded that motor deficits and dysfunction of learning and memory could ensue from these changes. Similarly, Abou-Donia and collaborators[3] observed impaired sensorimotor performance in rats at 30, 45 and 60 days after 60 days of daily dermal application of DEET. The impossibility of such studies in humans necessitates consideration of these data in any risk analysis.

It appears that the review by Koren and associates[1] deals only with acute adverse reactions and that no long-term controlled trials measuring neurologic function in humans after dermal application of DEET have been done.

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1. Koren G, Matsui D, Bailey B. DEET-based insect repellents: safety implications for children and pregnant and lactating women. *CMAJ* 2003; 169(3):209-12.
2. Abdel-Rahman A, Shetty AK, Abou-Donia MB. Subchronic dermal application of *N*,*N*-diethyl-*m*-toluamide (DEET) and permethrin to adult rats, alone or in combination, causes diffuse neuronal cell death and cytoskeletal abnormalities in the cerebral cortex and the hippocampus, and Purkinje neuron loss in the cerebellum. *Exp Neurol* 2001;172(1):153-71.
3. Abou-Donia MB, Goldstein LB, Dechovskaia A, Bullman S, Jones KH, Herrick EA, et al. Effects of daily dermal application of DEET and epermethrin, alone and in combination, on sensorimotor performance, blood–brain barrier, and blood–testis barrier in rats. *J Toxicol Environ Health A* 2001;62(7):523-41.

[One of the authors responds:]

Robert Nevin cites 2 studies on the effects of DEET in rats[1,2] without mentioning the most important variable in such research, the dose applied. Many compounds, including water, will cause toxic effects if given in large enough doses. In both studies cited by Nevin, the doses given were astronomical (between 4 and 400 mg/kg body weight), but these doses are not relevant to the use of DEET in humans. In contrast, the findings from several studies in rodents, such as that by Schoenig and colleagues,[3] have not concurred with the results obtained by Abdel-Rahman and associates[1] or Abou-Donia and collaborators.[2]

The anxiety regarding the toxic effects of DEET in young children has stemmed from a small number of widely publicized case reports of acute seizures in toddlers, as cited in our article.[4] However, our analysis suggests that an association between the seizures and use of DEET is unlikely.[4] To the best of our knowledge, no similar claim has been made regarding chronic neurotoxicity of DEET in children, and no published clinical data have been presented to support such a possibility.

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References

1. Abdel-Rahman A, Shetty AK, Abou-Donia MB. Subchronic dermal application of *N*,*N*-diethyl *m*-toluamide (DEET) and permethrin to adult rats, alone or in combination, causes diffuse neuronal cell death and cytoskeletal abnormalities in the cerebral cortex and the hippocampus, and Purkinje neuron loss in the cerebellum. *Exp Neurol* 2001;172(1):153-71.
2. Abou-Donia MB, Goldstein LB, Dechovskaia A, Bullman S, Jones KH, Herrick EA, et al. Effects of daily dermal application of DEET and epermethrin, alone and in combination, on sensorimotor performance, blood–brain barrier, and blood–testis barrier in rats. *J Toxicol Environ Health A* 2001;62(7):523-41.
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4. Koren G, Matsui D, Bailey B. DEET-based insect repellents: safety implications for children and pregnant and lactating women. *CMAJ* 2003; 169(3):209-12.

Bodychecking in hockey

Anthony Marchie and Michael Cusimamo,[1] in reviewing some of the available research, have established that concussions are more likely to occur when hockey is played with body contact and that concussions may have serious effects on the well-being and functioning of children. In my clinical and research work, I have seen the often-devastating effects of traumatic brain injury, including concussions, from a variety of causes. As the coach of a competitive girls' hockey team, I have seen the high calibre of hockey that is possible without bodychecking. And as the parent of an 11-year-old boy, I have observed concussions occurring as the result of even "clean" bodychecks and have worried about the safety of our children.

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