ANTIEPILEPTIC DRUGS: DON'T SWEAT IT!

Oligohydrosis and Hyperthermia: Pilot Study of a Novel Topiramate Adverse Effect

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In a 6-year-old boy with partial complex seizures, recurrent episodes of hyperthermia developed 2 months after topiramate (TPM) was introduced into his antiepilepsy drug regimen. Further investigation revealed that the febrile episodes were related to environmental temperature and physical activity. A pilocarpine iontophresis sweat test showed that the amount of sweat produced by the child was 5% that of age-matched controls. TPM discontinuation resulted in the disappearance of febrile episodes and normalization of sweat quantity in repeated sweat testing. Based on this observation and the previous data on zonisamide (ZNS) and isolated case reports on TPM-related hyperthermia and the effect on sweat production, TPM was suspected of causing oligohydrosis. A pilot study was carried out involving 13 additional children and young adults (age range, 1–37 years) receiving TPM. All patients were directly questioned regarding symptoms of decreased sweating and heat intolerance, went through a pilocarpine iontophoresis sweat test, and were compared with 14 age-matched controls who went through the sweat test for unrelated reasons. Nine of the patients were found to have reduced sweat quantity on the pilocarpine iontophoresis sweat test (including index case) (mean, 0.089 g/30 min; SD, 0.082; age-matched control: mean, 0.21 g/30 min, SD, 0.06). Eight of them were children (younger than 16 years). However, only three patients revealed symptoms related to heat intolerance. TPM is most likely responsible for decreased sweat production as detected by a pilocarpine iontophoresis sweat test. The effect seems to be more significant in children than in adults. A discrepancy exists between test results and clinical symptoms. Interestingly, oligohydrosis was found to be a relatively common side effect of ZNS. Both ZNS and TPM share a carbonic anhydrase inhibitor activity. The significance of oligohydrosis in hot climates should not be underestimated. Its extent, the role of sweat test prediction, and clinical significance during TPM treatment should be further estimated.

COMMENTARY

This article highlights the ability of topiramate (TPM) to reduce sweating, particularly in children. Oligohydrosis has been identified as an adverse event both for TPM and zonisamide (ZNS). As the authors point out, in addition to oligohydrosis, TPM and ZNS share several potential adverse effects, including development of renal calculi and occurrence of metabolic acidosis. This similarity may be related to the fact that ZNS and TPM are both carbonic anhydrase inhibitors.

How concerned should practitioners be about the potential for developing serious adverse consequences from oligohydrosis? The answer to this question is not clearly known. In this current investigation, after a symptomatic case of oligohydrosis (recurrent fevers) was seen in the clinic, the next 16 consecutive patients receiving TPM were studied. None of the 16 patients, of whom 11 were children, had spontaneously reported decreased sweating. Yet, on direct questioning, three children admitted to symptoms related to oligohydrosis, including heat intolerance, dry flushed skin, or, in one case, recurrent hyperthermia. It is not known whether any of these children would be at risk for heatstroke in the setting of a high ambient temperature or excessive activity. If nothing else, it would certainly appear prudent to question children receiving TPM about symptoms related to oligohydrosis, and to caution the parents of these patients about avoiding circumstances that might lead to consequences that are more serious. Risks of oligohydrosis appear to be lower in adults, and no reports of heat stroke have been made in this population; therefore a warning may not be necessary.

Oligohydrosis is one of several adverse events of the new antiepileptic drugs (AEDs) that was not identified until after drug approval. Like several other side effects, including visual field defects with vigabatrin (VGB) (1) and acute closed-angle glaucoma with TPM (2), these adverse events were not discovered during postmarketing trials or by systematic surveillance methods. Rather, they were first reported by vigilant physicians after they had seen one or more incident cases in their practice. It

is critically important not only to recognize unusual events that occur after initiation of a drug but also to report these events both to the Federal Drug Administration's MedWatch system (3,4) and in the literature. However, it is usually not possible to prove a causal relation from a single patient, or even several patients, presenting with an unusual event. That is why careful follow-up investigations, such have been performed here, are critically important. By performing sweat tests on children treated with TPM, Ben-Zeev and colleagues have provided important information on the frequency of occurrence of oligohydrosis (nine of 13) as well as providing further confirmation that children are at greater risk than adults. Among their subjects, all symptomatic patients were children, and the incidence of oligohydrosis was much lower (one in six) in adults. The researchers also have provided a possible screening mechanism to identify children at risk. The next step, already in progress by the same group, will be a larger prospective study that will examine body temperature, electrolyte composition, and sympathetic skin response of patients both before and during periods of TPM administration.

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References

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