Scopolamine Patch Withdrawal Syndrome

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To the Editor:

Scopolamine patch, *Tranderm Scop*, is marketed by Baxter Healthcare for Novartis for surgical antiemetic control or for the control of motion sickness. Each patch contains 1.5 mg of scopolamine programmed to deliver 1 mg over 3 days transdermally through a layer of rate controlling membrane.[1] It was designed to be removed 24 hours after surgery. For control of motion sickness, it was to be changed every 72 hours and removed from the skin after the condition for motion sickness had passed. Scopolamine patch withdrawal syndrome is under-recognized and under-appreciated. A literature search and discussion with medical and pharmacy colleagues yielded very little information about adverse effects associated with discontinuation of scopolamine. Scopolamine is generally believed to be the most effective drug to control motion sickness, with a 75% reduction in motion-induced nausea and vomiting; others dispute that it is not any more effective than antihistamines like meclizine.[2] Scopolamine patch is generally not recommended for children or the elderly because of toxicity.

We had received several patient complaints about scopolamine patch withdrawal after using them for motion sickness control on vacations. The associated symptoms were described as being very debilitating, similar to exacerbated motion sickness with severe headache.[3] This syndrome affected mostly patients who used the patch for 3 days or more, although there was at least one case in which a patient who only used the patch for 24 hours was affected. Typically, symptoms manifested 18 to 72 hours after the patch was removed and could last from several days to weeks. Common symptoms included nausea, headache, and blurred vision. These symptoms were consistent with rebound cholinergic activity and included dizziness, nausea, vomiting, paresthesias of the hands and feet, dysphoria, and hypotension.

Mechanism

Scopolamine acts in the central nervous system (CNS) by competitively blocking cholinergic transmission and receptor sites from the vestibular nuclei to higher centers in the CNS and from the reticular formation to the vomiting center, which is the proposed mechanism for transdermal scopolamine in the prevention of motion sickness. With scopolamine, the receptor sites are sensitized over time and cholinergic neurotransmitters are accumulated, which results in rebound effects when scopolamine is stopped, causing an overstimulation of the vestibular nuclei and the reticular formation of the vomiting center and hence the sensation of motion sickness. Animal model suggest that the longer the patch is used, the more severe the rebound effects are.[4] The pharmacological half-life of scopolamine in the body is about 9 hours, but the sensitized effects in the vestibular nuclei center can last for days to weeks.

Case Studies

A man used a scopolamine patch on a cruise trip as directed behind his left ear. He started 4 hours before beginning the trip. After 2 days, the patch came loose off and on in showers. He left it on anyway for about 5 to 6 days, as the patch could still stick onto skin. It was totally off on day 6. He did fine until day 10 when he put on another new patch in anticipation that the ship would travel through rougher water on the way home. He took the patch off after 24 hours the night before the ship docked. Forty-eight hours after the last patch was off, he experienced motion sickness sensation with nausea and inability to stand upright for long but with no headache. He was unable to work for 2 days. He slowly recovered without any intervention after the third day and fully recovered in about a week.

A 30-year-old woman used a scopolamine patch for 10 days for a vacation. She experienced severe withdrawal symptoms that began 24 hours after the patch was removed and lasted several days. She developed severe and intractable nausea not related to motion. She felt better lying down, but experienced nausea when standing or walking. After 3 days, she began taking meclizine 25 mg every 12 hours with a resolution of symptoms after a day.[5]

A woman was given a scopolamine patch with surgery for 4 days. She began to suffer from significant and incapacitating nausea and vertigo 48 hours after the patch was taken off. The symptoms resolved when she continued with new patches and reappeared after she took the patches off. It took 4 weeks to resolve her symptoms.

A woman used a scopolamine patch for a 7-day cruise as directed, replacing the patch every 72 hours. She left the patch on for 7 days after the cruise ended as directed by her primary care physician. Twenty-four hours after removing the patch, she experienced terrible headache, nausea, and dizziness. The symptoms resolved within hours after she put on new patch.

A woman surgeon used a scopolamine patch for 5 weeks during a vacation and experienced severe nausea and vomiting 17 hours after she removed the patch at the end of the vacation. After 2 very debilitating days of lying in bed, she

started high-dose meclizine, 50 mg every 6 hours for 3 days. She started tapering the dose to 25 mg every 8 hours for another 3 days and was totally off after 5 more days without any further symptoms.
A man was on a scopolamine patch for 10 days for a cruise vacation and within 24 hours after the patch removal, he experienced light headedness, loss of appetite, fatigue, and disorientation. The first 4 days were particularly debilitating. He recovered to his normal state after 9 days.

Incidences

No data were available for the incidence rate of scopolamine withdrawal syndrome. Baxter Healthcare Corporation, the marketing company of Novartis for *Transderm Scop*, indicated that the company keeps track of this side effect but cannot share the cases with us. The company could not calculate the incidence rate, because the number of scopolamine patch users could not be determined.
We conducted a retrospective telephone survey at Seton Northwest Hospital in Austin, Texas, of all the patients who used a scopolamine patch for the most recent 45 days to evaluate both the effectiveness and adverse reactions. There were 25 patients who used scopolamine patches during that surveying period. We were unable to reach 7 patients by telephone on multiple occasions; one patient was excluded because of severe gastroparesis, which made it difficult to access the effects of the patch. Of the 17 remaining patients, all used the patch for postoperative nausea control because of prior difficult experiences. The patches were applied for 4 to 72 hours, with the average duration being 42 hours. All these patients found the scopolamine patches to be very effective and experienced no nausea or vomiting as compared to their previous surgical experiences. None of these patients experienced any signs of withdraw symptoms after the patches were stopped.

Treatments

Meclizine, a piperazine-derivative H_1-receptor antagonist, possesses anticholinergic activity and is also effective in the treatment of motion sickness. The mechanism of action of meclizine, although not completely understood, is believed to be related to its centrally acting anticholinergic property. It is thought to affect the medullary chemoreceptor trigger zone and decrease labyrinth excitability and vestibular stimulation.[6]
Meclizine has been used successfully to treat scopolamine withdrawal syndrome.[5] A suggested meclizine regimen for scopolamine withdrawal is 50 mg orally every 6 to 8 hours before or at the onset of the withdrawal symptoms for 2 to 3 days, tapering gradually to 25 mg every 8 hours and finally tapering off over a week. High-dose meclizine can have significant sedative effects that vary with each patient. Caution should be used with the 50 mg dose.
Alternatively, some patients were successfully treated by leaving the last scopolamine patch on for a week uninterrupted, supplemented with meclizine 25 mg orally every 8 to 12 hours on day 5 and beyond as needed. At the end of 72 hours, each scopolamine patch still contains 0.5 mg in the patch reservoir. Neither Baxter Healthcare nor Novartis were able to provide pharmacokinetic data for use beyond 72 hours.

Discussion

Case reports of scopolamine withdrawal syndrome appear in the literature as early as 1990.[7] Numerous anecdotal case reports appear online, while others have been seen in practice by the authors. The syndrome, while debilitating, was self-limiting in most cases. To our knowledge, despite some emergency room visits, no deaths have been attributed to withdrawal. There is little incentive to elucidate the mechanism, but it could be related to an upregulation of cholinergic receptors in the vestibular system or a supraphysiological release of acetylcholine following discontinuation of the patch. The longer the patches were used, the higher the incidence of withdrawal symptoms. In our study, we found no withdrawal symptoms when the scopolamine patch was used for less than 72 hours; the incidence rate of extended use is still unknown. Further studies with a larger population can help refine the results. Patients using the patch need to be made aware of the possibility of withdrawal syndrome, especially when an extended use of the patch is anticipated. No reports of withdrawal from meclizine that is used for motion sickness prophylaxis could be found in a literature search. Meclizine could be an appropriate first-line choice for motion sickness in patients who have experienced scopolamine withdrawal previously or for patients who need extended motion sickness prevention. However, if meclizine is not adequate, management options for scopolamine patch withdrawal as mentioned should be helpful. Further research is warranted in the areas of incidence, mechanisms, and treatment.