Question: I've noticed that patients sometimes develop restless legs after IV diphenhydramine. Why does this happen? Can it be prevented?

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What is Restless Legs Syndrome?

Restless legs syndrome (RLS), also known as Willis-Ekbom disease, is a common neurological syndrome characterized by sensory symptoms in the legs with or without pain, an urge to move the limbs, and sleep disturbances. Symptoms typically occur at bedtime or when resting and may be relieved by activity. RLS is more common in women and older patients. Most cases of RLS are primary, or idiopathic. The pathophysiology of idiopathic RLS is not well understood, but has been associated with dopaminergic pathway dysfunction in the central nervous system. RLS can also occur secondary to several factors, including iron-deficiency anemia, pregnancy, end-stage renal disease, and several medications.[1-3]

Drug-induced restless legs syndrome (DI-RLS) has been reported as a result of several different medications. DI-RLS is most frequently associated with medications that modulate dopaminergic pathways, including antipsychotics, antidepressants, and antiepileptics. Cases of DI-RLS have also been reported with L-thyroxine, interferon-α, clindamycin, and perioperative anesthesia.[2]

The Association between Diphenhydramine and Restless Legs Syndrome

There is very limited evidence in the literature regarding DI-RLS secondary to diphenhydramine (Benadryl) and other antihistamines. This association has been published in case reports as a result of diphenhydramine and fexofenadine/pseudoephedrine therapy.[4,5] Additionally, a 2014 study of over 16,000 patients on dialysis showed a statistically significant association between antihistamine use and increased odds of an RLS diagnosis. However, the study had several limitations, including the trial design. Because it was not a randomized controlled trial, this evidence may not be strong enough to definitively determine a causal relationship between antihistamine use and RLS.[6]

An unpublished abstract detailed a 2005 study which sought to determine the effects of antihistamines and benzodiazepines on RLS symptoms.[7] The study included twelve patients with a diagnosis of RLS controlled on dopamine agonist therapy, and the patients were subject to three days of drug challenges with diphenhydramine, lorazepam, and placebo. Patients had more periodic limb movements per hour with the diphenhydramine doses vs. the lorazepam doses, and limb movements per hour were significantly greater with diphenhydramine vs. placebo. Patients also subjectively rated their RLS symptoms as more severe with diphenhydramine. Limitations of this study include its small sample size, limited duration of therapy, and lack of peer-reviewed publication.

Why does this Happen?

The mechanism by which antihistamines attribute to RLS symptoms is not well understood. It has been hypothesized that this reaction is secondary to anemia, which can occur secondary to antihistamine use and has also been associated with RLS symptoms. However, a 2020 observational study of over 13,000 blood donors displayed an association between antihistamine use and RLS symptoms independent of anemia.[8] This association also could be secondary to modulation of the dopamine pathway. Intravenous diphenhydramine and chlorpheniramine have been shown to increase dopamine levels in the brain in vivo in rat models.[9,10] However, it is unclear whether this dopamine action is robust enough to cause these symptoms.

Prevention and Treatment

Because the body of evidence for DI-RLS secondary to diphenhydramine use is so limited, there are currently no well-established prevention strategies. The most effective strategy for treating DI-RLS is discontinuation of the offending agent, when clinically appropriate.[1,2] This strategy has been effective for antihistamine-associated DI-RLS in case reports.[4,5] It is unclear whether switching to another medication of the same class would be effective, or if a similar reaction would precipitate. Nonpharmacologic recommendations include exercise, pneumatic compression, massage, good sleep hygiene, and avoidance of caffeine, alcohol, and nicotine.[2]

If pharmacologic treatment is needed, dopaminergic agents such as ropinirole, levodopa, pramipexole, gabapentin, and pregabalin may be used. However, these agents are associated with significant adverse effects, including nausea, vomiting, dizziness, and somnolence. Several non-dopaminergic agents have also demonstrated efficacy for RLS symptoms, including benzodiazepines, opioids, and anticonvulsants, but the benefit of these agents is limited by serious adverse effects and the development of tolerance and/or dependence.[2]

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