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LETTER TO THE EDITOR

Next-morning vomiting as a withdrawal symptom of immediate-release methylphenidate

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Dear Editor,

Methylphenidate (MPH) has been a first-line and effective treatment option for attention-deficit/hyperactivity disorder (ADHD) for many years (1). Various formulations are available, including immediate-release (IR) and long-acting (OROS) preparations, which differ in duration of action, efficacy, and side-effect profiles (2). Although MPH is generally well tolerated, the most commonly reported adverse effects include nausea, abdominal pain, headache, and decreased appetite, particularly during the initial phase of treatment (3–5). Here, we report an unusual adverse event: morning vomiting as a possible withdrawal symptom occurring during treatment with IR-MPH in a young adult male.

A 19-year-old male presented with his parents, reporting attention difficulties, forgetfulness, poor academic performance, and inability to complete examinations on time. Following a detailed psychiatric evaluation, he was diagnosed with attention-deficit/hyperactivity disorder, inattentive presentation, and specific learning disorder, according to the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5). His developmental history was unremarkable. He had graduated from high school with moderate academic success and had no prior history of pharmacological treatment for attention-related problems. Treatment was initiated with immediate-release methylphenidate (IR-MPH) at a dose of 10 mg administered at 9:00 a.m. while he was attending a university entrance examination preparation course. He reported no significant side effects during the day following administration of IR-MPH 10 mg. However, approximately 30 minutes after awakening the next morning, around 8:30 a.m., he experienced multiple episodes of vomiting. These episodes occurred regardless of food intake, were not self-induced, and were typically not accompanied by nausea or abdominal pain. The vomiting lasted approximately 10–15 minutes and consisted of 5–6 episodes with gradually decreasing intensity. When he omitted his morning dose on a day when vomiting had occurred, he did not experience vomiting the following morning. Conversely, upon resuming IR-MPH, next-morning vomiting reappeared. Despite recognizing a probable association between his symptoms and IR-MPH, he continued treatment because of the marked improvement in his inattention and learning difficulties. Over a period of approximately four weeks, he took IR-MPH 10 mg at around 9:00–9:30 a.m. on 12 separate occasions, each followed by next-morning vomiting. Vomiting occurred consistently after all 12 doses and was absent on days without medication. The intensity and duration of symptoms remained similar across episodes, indicating no evidence of tolerance development over this short exposure period. During this time, the patient was evaluated by an internal medicine specialist to exclude

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alternative causes of vomiting. Physical examination revealed no gastrointestinal or systemic abnormalities. Laboratory investigations, including complete blood count and infection screening, were within normal limits. His past medical history was unremarkable, and he was not taking any concurrent medications. Although the patient was experiencing stress related to preparation for the university entrance examination, there were no anticipatory symptoms or situational triggers suggestive of psychogenic vomiting.

Subsequently, his treatment was switched to OROS MPH 36 mg, administered in the morning. During one month of treatment with OROS MPH, he reported no significant side effects or episodes of next-morning vomiting. For further evaluation, he was asked to substitute IR-MPH 10 mg for Concerta for one day. When IR-MPH was administered at 11:30 a.m., he experienced vomiting the following day at approximately 5:00 p.m., with slightly reduced intensity. He did not take any medication on the day the vomiting occurred. He was then advised to continue treatment with OROS MPH 36 mg. These findings were interpreted as indicating that the vomiting episodes were most likely a withdrawal symptom associated with IR MPH. Assessment using the Naranjo Causality Assessment Scale yielded a score of 7, indicating probable causality (6). However, it should be noted that the Naranjo algorithm is not specifically designed to assess withdrawal-related or delayed adverse effects, which represents a methodological limitation.

Methylphenidate remains the primary pharmacological treatment for ADHD, with an estimated therapeutic response rate of 70–80% (1). Its mechanism of action primarily involves inhibition of dopamine and norepinephrine transporters in presynaptic neurons, resulting in increased extracellular concentrations of these neurotransmitters, particularly within the prefrontal cortex (7). While these dopaminergic and noradrenergic effects underlie MPH's therapeutic efficacy, they are also associated with a range of adverse effects (8–11). The onset and severity of such effects depend on the concentration of MPH in the bloodstream, which varies significantly between immediate-release and extended-release formulations because of their different pharmacokinetic profiles (2, 12–15).

Immediate-release methylphenidate reaches peak plasma concentrations within 1–2 hours of administration and is commonly associated with peak-related adverse effects, including insomnia, appetite suppression, and nausea (3). As drug levels decline, some patients experience rebound symptoms—transient worsening of ADHD symptoms—or withdrawal-like effects, which may include both physical and behavioral manifestations attributable to abrupt reductions in dopaminergic activity (16). These rebound and withdrawal phenomena are well documented and typically occur within predictable time frames that correspond to MPH pharmacokinetics. In the present case, however, the onset of vomiting nearly 24 hours after dosing suggests an atypical withdrawal mechanism extending beyond the expected pharmacodynamic window of IR-MPH. Notably, the literature also describes atypical presentations that fall outside these conventional temporal boundaries. For example, acute dystonia has been described in an adolescent following a missed dose of MPH and was interpreted as an atypical withdrawal phenomenon (17). Additionally, next-day neuromuscular pain—manifesting as painful morning leg cramps—has been reported after discontinuation of IR-MPH, further supporting the notion that withdrawal-like effects may extend temporally beyond the dosing day (18). Notably, those reports involved longer prior exposure, whereas in the present case the delayed adverse effect occurred consistently from the initial doses during ongoing treatment, highlighting a distinct temporal pattern.

Vomiting is a well-documented adverse effect of MPH, although its precise pathophysiology remains incompletely understood (3). Accumulating evidence suggests that abrupt fluctuations in dopaminergic transmission may precipitate gastrointestinal dysregulation, either through direct dopaminergic pathways or via secondary neurotransmitter alterations (19). While dopaminergic overstimulation, rather than a decrease, is more commonly associated with emesis, the occurrence of vomiting in this patient during a phase of declining dopamine levels raises the possibility of a compensatory withdrawal-related mechanism triggering the emetic response. The complete resolution of symptoms following a switching to an extended-release formulation further supports this hypothesis. Extended-release formulations, such as OROS MPH, provide more gradual drug delivery, resulting in steadier plasma concentrations throughout the day (2). This pharmacokinetic profile minimizes abrupt neurotransmitter fluctuations associated with IR-MPH. Previous studies have demonstrated improved tolerability and reduced rebound effects with extended-release MPH compared to IR formulations (20).

This case also highlights that adverse effects may vary substantially across individuals. Interindividual differences in drug metabolism, receptor sensitivity,

and downstream neurotransmitter responses can influence both the phenotype and timing of adverse events (3). From a pharmacokinetic perspective, genetic polymorphisms in enzymes such as carboxylesterase 1 (CES1) (and, to a lesser extent, cytochrome P450 2D6 [CYP2D6]) can alter methylphenidate metabolism. Variability in the formation and clearance of ritalinic acid—the major but pharmacologically inactive metabolite—may indirectly contribute to delayed adverse responses by reflecting individual differences in elimination pathways (2). Beyond peripheral metabolism, central pharmacodynamic factors are also relevant: although MPH is rapidly cleared from plasma, synaptic and receptor-level adaptations may persist longer than systemic drug levels (21). Taken together, these sources of variability provide a plausible explanation for why some patients experience adverse effects outside the expected pharmacokinetic window, even early in treatment.

Although a single case cannot definitively establish causality, the Naranjo score of 7 in this case indicates a probable association between IR-MPH use and next-morning vomiting (6). Clinicians should therefore remain vigilant not only for commonly expected adverse reactions (e.g., decreased appetite, insomnia) but also for atypical presentations, particularly when prescribing short-acting stimulant formulations. In cases of delayed-onset or persistent adverse events, switching to an extended-release formulation or adjusting the dosage regimen may alleviate symptoms without compromising therapeutic benefit (22). Recognition of such rare presentations in clinical practice is important, as it may inform individualized treatment strategies and ultimately improve the safety and effectiveness of ADHD pharmacotherapy.

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