CASE REPORT

Hypnotic hiccups

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SUMMARY

Our patient presented with repetitive, self-limited bouts of forceful hiccups in sleep. Eszopiclone, a commonly prescribed hypnotic, appeared to cause these intermittent hiccups. This case is a reminder that eszopiclone may cause this adverse effect, and that it may be the bed partner and not the patient who furnishes critical sleep medicine history.

BACKGROUND

Diverse aetiologies may cause hiccups (singultus) including cardiac, pulmonary, neurological and abdominal disorders.^{1–7} In addition, gastro-oesophageal reflux disease (GERD) and numerous medications have been associated with hiccups.^{2–7–9} Although a cause for hiccups often is not identified, reports have linked sedation medications of different classes to hiccups. For example, patients undergoing gastrointestinal endoscopy and colonoscopy are more likely to experience hiccups when sedated with midazolam than when not receiving such sedation.¹⁰ Although often only an annoyance, hiccups can at times be vigorous. One case of hiccups related to propofol sedation (following premedication with glycopyrrolate, midazolam and butorphanol for a breast biopsy) was so violent, that succinylcholine and tracheal intubation were needed in order for the breast biopsy procedure to proceed.¹¹ We present a patient with well-controlled GERD with robust, bed-shaking eszopiclone sleep-related hiccups.

CASE PRESENTATION

A 56-year-old woman presented to the division of sleep medicine with “Hiccups when using Lunesta...”

For approximately one decade, she used the benzodiazepine receptor agonist agent eszopiclone for sleep maintenance insomnia that had begun with breast cancer diagnosis and treatment. Eszopiclone, taken nightly for 1 year, improved her insomnia. After a year, she began prn eszopiclone use owing to concerns regarding potential drug dependency. She used eszopiclone 1–2 times/month when stressors presaged poor sleep. For the 6–12 months before her office visit, her husband, 36 years, noted her sleep-related hiccups were consistently associated with eszopiclone administration. The patient herself denied ever being awakened by her forceful hiccups. Her bed-shaking hiccups began 5–10 min after sleep onset and lasted for 10–15 min. When she stopped eszopiclone for as long as 1 month, the hiccups ceased. Hiccups returned with the first dose when resuming eszopiclone. She rarely snored and denied pauses in respiration during sleep. She had no symptoms of restless legs syndrome.

Medical problems included GERD, which was well controlled on esomeprazole. She imbibed ≤ 4 caffeinated beverages daily, and denied alcohol, smoking or recreational drug use. She described a recent, resolved, upper respiratory infection as well as springtime postnasal drip and cough. She denied cardiac and neurological symptoms. She denied use of antidepressants, narcotics, dopaminergics or corticosteroids. Review of Systems was positive for intentional weight loss of 35 pounds over the past 8 months.

Her medical history revealed stage 1 right breast cancer treated by mastectomy in 2002 and chemotherapy (no recurrence), benign colon polyps, GERD, hyperlipidaemia, Hashimoto’s thyroiditis, osteopenia and low vitamin D. Surgical history was positive for total abdominal hysterectomy in 2003, and negative for cranial, intrathoracic or upper abdominal surgery. She denied undergoing upper endoscopy. Other medications included rosuvastatin, desloratadine, vitamin C, vitamin D, stool softener, aspirin and multivitamin.

Vital signs, pulmonary, cardiac and neurological examinations were normal. Body mass index was 30.7 kg/m². She manifested no hiccups. Abdominal examination 3 weeks prior by her primary care physician was normal. Glucose, renal and hepatic functions were normal. Contact with the patient’s physicians revealed no recent radiological scans given breast cancer long in remission.

Subsequent to her appointment, the patient received a portable sleep apnoea monitor (Apnea Link) for 1 month. She was given instructions to use the monitor on a night *she* deemed eszopiclone use necessary. If, by month’s end, she required no eszopiclone, she was asked to apply the monitor for one night.

The patient utilised the apnoea monitor once but could not easily initiate sleep and thus elected to take her eszopiclone. After taking eszopiclone, she fell asleep only to awaken. When she awakened, she then noted she was hiccupping (on follow-up telephone interview, she attributed this awakening specifically to the effort monitor and not to hiccups). On the night of eszopiclone use and apnoea monitoring, she reported 5 h of sleep with worse-than-usual sleep. The recording indicated minimal upper airway instability: apnoea hypopnoea index (AHI)=5, nadir oxygen saturation =82%, perhaps a consequence of movement artefact (baseline oxygen saturation = 95%). Hiccup activity was absent on the effort channel.

TREATMENT

The patient was followed conservatively for snoring and eszopiclone-induced hiccups.

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OUTCOME AND FOLLOW-UP

Approximately 7 months after her initial consultation, the patient was contacted by telephone. She reported that she had not used eszopiclone in 5 months and, according to her husband, no sleep-related hiccups had occurred. Her GERD continued to be symptomatically quiescent. Two months prior to this phone call, an oncology follow-up examination was normal. One month prior to the same phone contact, a physical examination and laboratory work performed by her primary physician were also normal. She had initiated exercise before sleep and determined that her sleep had improved.

DISCUSSION

Physicians wrote over 5.7 million eszopiclone prescriptions in 2010.¹² We believe this case merits attention given the association reported of sleep-related hiccups with a commonly prescribed sleeping pill. Given the 6–12 month duration of our patient's sleep-related hiccups, we considered a broad differential diagnosis. Enquiry for intrathoracic, intra-abdominal and intracranial abnormalities, though typically associated with prolonged, intractable hiccups, yielded only well-controlled GERD (the patient's asymptomatic state on esomeprazole confirmed with a call just prior to this case report). While medications⁹ including chlorthalidopoxide¹³ and midazolam^{10–14} can trigger hiccups, the patient denied any use of those agents, or others previously associated with hiccups.^{2–9}

A recent case associated severe obstructive sleep apnoea syndrome (OSAS) with chronic hiccups.¹⁵ Our patient gave little history for OSAS. Her home sleep testing revealed minimal upper airway instability.

Eszopiclone appears to have caused our patient's hiccups, which may have dissipated as her sleep deepened. A study by Arnulf *et al*¹⁶ found sleep-suppressed hiccups; hiccups were associated with increased sleep latency, but not awakenings. Vigorous hiccups did not awaken our patient, perhaps due to increased arousal threshold with hypnotic use. This lack of awakening from sleep with hiccups is also consistent with the aforementioned study. One possible mechanism for this patient's 'bed-shaking' hiccups could be an eszopiclone-induced GERD exacerbation with drug suppression of normal hiccup reflex inhibition. GERD can cause hiccups,^{2–17} and zolpidem has been linked to prolonged reflux events and reduced arousal response.¹⁸ Furthermore, midazolam accentuated hiccups during upper endoscopy have been associated with a significant increased likelihood of endoscopic findings of GERD.¹⁰

Although her husband (per the patient) gave a clear and convincing report, the lack of objective hiccups documentation is a limitation of this report. The greater sensitivity of a full nocturnal polysomnogram with video monitoring may have allowed us to link hiccups with eszopiclone use. However, the clinical presentation of low probability for moderate-to-severe OSAS did not warrant ordering a full polysomnogram.

In addition, the patient's spouse, not the patient, described the sleep-related hiccups as the patient did not awaken from these. Sleep-related symptoms such as snoring often require description by the spouse or bed partner. We find fascinating, but have no definitive answer for, the apparent absence of sleep-related hiccups during 1 year of regular eszopiclone use. The patient stated that her dose of eszopiclone was 3 mg during her 1 year of regular use and the same when she transitioned to prn usage. Thus, onset of sleep hiccups was not dose related, and she did not report any other changes in medications that were temporally related to hiccups. Finally, although worsening reflux could have

caused the onset of eszopiclone sleep hiccups, we did not measure this, for example, with 24 pH-probe study. The patient's hiccups began after her cancer surgery and, within 6 months, esomeprazole was initiated. The proton pump inhibitor has since controlled GERD symptoms, but it is interesting to posit that the proton pump inhibitor use could mask underlying GERD events and mechanisms potentially related to hiccupping.

This case specifically associates eszopiclone with sleep-related hiccups and detects little consequence of hiccups after up to 1 year of occurrence in this patient. The morbidity of eszopiclone-induced sleep hiccups apparently is low; nevertheless, patients' and *bed partners'* concerns are important to address. Given the frequency with which eszopiclone is prescribed, we believe that further examination of the physiological basis underlying this relationship is of interest. Medication package inserts have described hiccups as side effects of benzodiazepine receptor agonists. However, recent work suggests that medication package inserts have little impact on clinicians' prescribing actions.¹⁹ While other aetiologies for hiccups beyond reflux cannot be definitively ruled out, then these seem unlikely given the hiccups' self-limited nature and the clear temporal linkage between the hypnotic and hiccups in this patient. Clinicians should be aware that eszopiclone may trigger sleep-related hiccups.

Learning points

- ▶ Although apparently unusual, sleep hiccups can occur with the benzodiazepine receptor agonist eszopiclone.
- ▶ Sleeping pills may worsen gastroesophageal reflux.
- ▶ Clinicians should remember to obtain sleep history from the patient and from the bed partner or spouse.

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Contributors RDV was the clinician who cared for the patient and first conceived of the idea of this case report. He acquired, analysed and interpreted the data, drafted the work and revised it. He approved the final version to be published. He is the guarantor. MS-C and JCW contributed to analysis of the data, drafting the case, revising it critically and approved the final version.

Competing interests None.

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