Case report

Zopiclone-associated respiratory depression

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INTRODUCTION

Zopiclone is a non-benzodiazepine cyclopyrrolone hypnotic agent with pharmacological properties similar to those of benzodiazepines.[1,2] Because it is reportedly not associated with the respiratory depression seen with benzodiazepines,[3-6] it is often considered the preferred agent for patients with a history of respiratory dysfunction who encounter difficulty sleeping. However, patients with underlying lung disease whose respiratory status is compromised may be at risk of developing respiratory depression with zopiclone. We report a case of respiratory depression with low-dose zopiclone in an elderly patient with chronic obstructive pulmonary disease (COPD).

CASE

An 82-year-old male with a well documented history of COPD and prior CO_2 retention was admitted to hospital with an acute exacerbation of COPD manifested by increased shortness of breath for two days. He had recently been discharged from hospital following an admission for acute exacerbation of COPD.

His medical history included chronic atrial fibrillation, ischemic heart disease and peptic ulcer disease. He also suffered from incontinence and insomnia. He was an ex-smoker with a history of ethanol abuse. His medications on admission included salbutamol inhaler 400 mcg q4h prn, ipratropium inhaler 40 mcg q4h prn, beclomethasone inhaler 500 mcg bid, digoxin 0.125 mg po daily, furosemide 40 mg po qam and 20 mg po qpm, omeprazole 20 mg po daily and nitroglycerin spray 0.3 mg prn.

Review of symptoms was remarkable for increasing dyspnea and incontinence. He denied chest pain, fever, chills or change in sputum. Physical examination showed him to be in moderate respiratory distress using accessory muscles of respiration and exhibiting pursed-lip breathing. He was diaphoretic and restless at the time. His vital signs were a blood pressure of 120/80 mmHg, a heart rate of 90 beats per minute with an irregular rhythm, a respiratory rate of 30 per minute and a temperature of 36.5°C. Chest examination revealed good breath sounds, minimal wheezing and no crackles. The remainder of the physical examination was unremarkable. Routine serum biochemistries revealed no abnormalities except for an elevated HCO_3 of >40 mmol/L. Other laboratory tests revealed normal renal and hepatic function and normal hematological parameters. Digoxin level was 0.9 nmol/L (N 0.6–2.6). Urine culture was negative.

Initial capillary blood gases revealed PaO_2 61 mmHg (>60mmHg, decreases with age), pH 7.43 (N 7.4±.05), $PaCO_2$ 55 mmHg (N 40±5) and HCO_3 36 mmol/L (N 22±3) with an O_2 saturation of 92% while receiving oxygen at an FiO_2 of 28% (see Table I).

He was given nebulized treatments with salbutamol and ipratropium and a short course of prednisone. His oxygenation slowly improved. Subjectively he was less dyspneic and ready for discharge.

The patient remained in hospital while placement arrangements were being made. During this time the patient complained of insomnia. Since this was a quality of life issue and his respiratory status had stabilized, an attempt was made to assist the patient in sleeping. Due

Table I. Blood gases

Day of stay	Time (H)	PaO_2 (mmHg)	pH	$PaCO_2$ (mmHg)	HCO_3 (mmol/L)	SaO_2
2	0100	61	7.43	55	36	92%
2	0721	85	7.45	57	39	97%
19	2125	patient given 3.75mg of zopiclone po				
21	1445	53	7.38	78	46	86%
22	2200	patient given 3.75 mg of zopiclone po				
23	0900	43	7.33	91	47	76%
23	1020	64	7.37	85	48	92%
23	1210	69	7.37	83	47	93%
23	1640	60	7.39	74	44	91%
24	0900	55	7.35	84	45	88%
25	1410	60	7.40	76	47	90%

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to his underlying respiratory status, the use of benzodiazepines was avoided. It was elected, instead, to use low-dose zopiclone as a sedative. The patient received zopiclone 3.75 mg on day 19. The next morning the patient reported feeling drowsy and the zopiclone was discontinued. However, his complaints of insomnia persisted and it was decided that one more attempt to alleviate his nocturnal sleep difficulty with low-dose zopiclone would be made. Blood gases were followed to ensure no adverse effect on ventilation was occurring. On day 22 at 2200 hours, he was given 3.75 mg of zopiclone orally for insomnia. Blood gases taken at 0900 hours on day 23 revealed PaO_2 43mmHg, pH 7.33, $PaCO_2$ 91 mmHg, HCO_3 47 mmol/L with an O_2 saturation of 76% on 3L of oxygen by nasal prongs. The patient was drowsy but oriented. He denied any shortness of breath or chest pain. Cough and sputum production were unchanged. His respiratory rate was 34, with a heart rate of 90 beats per minute which was intermittently irregular. No cyanosis was noted. Oxygen flow was increased for a short period of time with subsequent improvement in PaO_2. He then was switched back to his maintenance regimen of oxygen therapy. Repeat blood gases were measured over several days with some improvement (see Table I). No other changes in drug therapy took place during this time.

DISCUSSION

As with many case reports it is not possible to be absolutely certain that the suspected agent was the causative agent. In our case, because the patient was stable and awaiting placement there were no gases obtained between day 2 and day 21. Had blood gases been obtained, they may have provided additional information to the case. The day after he first received zopiclone he was drowsy but no blood gases were done.

The use of hypnotic agents, particularly benzodiazepines, is generally avoided in patients with underlying respiratory dysfunction due to the potential of these agents to cause respiratory insufficiency.[3,5] Patients who have significant CO_2 retention are at even greater risk of respiratory depression with administration of these agents. In our centre, clinicians have adopted the use of zopiclone in patients with lung disease who have difficulty sleeping because it possesses many of the sedative properties of benzodiazepines but is not reported to result in depressant effects on respiration.

The literature suggests that zopiclone has limited effects on breathing. In a single-blind placebo-controlled study involving six males with severe COPD, Muir and colleagues[6] evaluated the effects of zopiclone on the respiratory system. Zopiclone 7.5 mg or placebo was administered at bedtime for one week. The $PaCO_2$ at baseline ranged from 38–58 mmHg in these patients. Three patients were hypercapnic. Treatment with zopiclone did not result in changes in daytime PaO_2 or $PaCO_2$. Further, no influence on inspiratory time, expiratory time or other expiratory spirogram parameters were reported.

Ventilatory effects of zopiclone were also investigated in healthy volunteers.[5] Single-dose administration of 7.5 mg iv of zopiclone did not result in depression of the respiratory drive nor in significant changes in pH. However, Muir et al showed that zopiclone increased the number of apneic spells and the duration of these in patients with chronic obstructive respiratory insufficiency, albeit not in a statistically significant fashion. Based on their study, the authors suggested that zopiclone acts as a moderate respiratory depressant but without any deleterious action on night time oxygen delivery.[6]

To our knowledge this is the first report of respiratory depression with zopiclone. The temporal association of zopiclone administered with the occurrence of respiratory depression and the absence of any other identified etiology support zopidone as cause.

This report indicates that patients with COPD with CO_2 retention may be at risk of developing respiratory depression with even very low doses of zopiclone. Caution should be exercised when administering zopiclone to this patient population.

Addendum

Since submission of this paper we have observed a second occurrence of potential respiratory depression associated with zopiclone.

A 76-year-old male with a history of bronchiectasis for several years and end-stage lung disease was admitted with an acute exacerbation of his chronic condition. He was administered ceftazidime and tobramycin for previously cultured Pseudomonas aeruginosa. On admission, he was tachypneic with a respiratory rate of 48 per minute and blood gases were P_aO_2 59mmHg, pH 7.35, P_aCO_2 34mmHg and HCO_3 of 18mmol/L. Oxygen saturation was 89% on room air. Subsequent improvement in oxygen saturation occurred after the patient began oxygen therapy at 3 litres per minute. Over the next week, he improved and was titrated off oxygen with oxygen saturation ranging from 92–97%. After 2 weeks–the intravenous antibiotics were stopped and due to the complaints of insomnia zopiclone 15mg (usual dose 3.75–7.5mg) was ordered on day 20. Six hours before administration of zopiclone, the patient had a recorded oxygen saturation of 94% on room air. Approximately 4 hours after zopiclone administration, the patient was found at the end of the bed, incontinent and asleep. The nurse noted upon awakening the patient that he was very drowsy and disoriented. Oxygen saturation at that time was noted to be 89%. He was given 2 litres per minute of oxygen and zopiclone therapy was

stopped. Approximately 18 hours after receiving zopiclone oxygen, therapy was discontinued and oxygen saturations remained above 92% until discharge 3 days later. The only other new therapy which he received was vancomycin with the first dose being given on the same day as zopiclone. While zopiclone was stopped vancomycin was continued without further incident.

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