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RESPIRATORY ALKALOSIS AS AN ADVERSE EFFECT OF SAFINAMIDE?

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ABSTRACT

Respiratory alkalosis is associated with central nervous system (CNS) diseases, drugs, lung diseases and others. Safinamide is a recent anti-parkinsonian drug with anti-dyskinetic properties and a good adjunct to L-dopa therapy during the activation period, with no significant adverse effects described. The authors present a case of a 71-year-old woman, with Parkinson's disease treated with levodopa/benserazide, safinamide, amitriptyline, sertraline and diazepam. She made multiple visits to the emergency department due to progressive dyspnoea and asthenia, with primary respiratory alkalosis, which was thought to be caused by anxiety-induced hyperventilation and treated accordingly. After a comprehensive study, it was determined that the most probable cause of the respiratory alkalosis was pharmacological. There was a clinical and temporal agreement with the introduction of safinamide.

KEYWORDS

Respiratory alkalosis, safinamide, Parkinson's disease

LEARNING POINTS

- Respiratory alkalosis is a multifactorial acid-base disorder, mostly associated with psychological factors and anxiety induced hyperventilation.
- Safinamide is a new drug for the treatment of Parkinson's disease with promising results in terms of efficacy and safety. However, there is only a limited number of studies on safinamide.
- Respiratory alkalosis could be an adverse effect of safinamide through several different mechanisms.

INTRODUCTION

Respiratory alkalosis is one of the most common acid-base disturbances encountered in clinical practice[1]. It is characterised by an elevated pH level in the blood, primarily due to a decrease in the partial pressure of carbon dioxide, below 35 mmHg. Multiple causes could be responsible for the decrease of $PaCO_2$ such as decreased of CO_2 production, hypoxemia, cardiopulmonary disorders like pneumonia, pulmonary fibrosis, pulmonary oedema and pneumothorax, central nervous system disorders like psychogenic or anxiety-induced hyperventilation syndrome, central nervous system infection or tumours, drugs such as salicylates,

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methylxanthines and quetiapine and a miscellaneous factors such as fever and sepsis, pain, alcohol withdrawal and hepatic failure[1,2]. Safinamide is an adjunctive therapy for Parkinson's disease. This drug has a unique mechanism of action, involving the modulation of dopaminergic and glutamatergic pathways. In this way, it could address not only motor symptoms, but also non-motor manifestations associated with Parkinson's disease and other related conditions[2]. Given the intricate relationship between carbon dioxide levels, cerebral blood flow, and neuronal function, alterations induced by safinamide may potentially influence the manifestation of respiratory alkalosis.

CASE DESCRIPTION

The authors present the case of a 71-year-old woman who presented in the emergency department (ED). Her medical history included hypertension, Parkinson's disease, depression and sinus bradycardia, with daily intake of candesartan, acetylsalicylic acid, amitriptyline, safinamide, levodopa/benserazide, sertraline and magnesium.

One month previously, the patient attended a routine Neurology consultation, during which the Parkinson's disease treatment was adjusted. These changes included the introduction of safinamide and an increased dosage of levodopa/benserazide. After 4 weeks, the patient presented multiple times to the ED due to worsening dyspnoea, asthenia, and decreased strength in the lower limbs. While a physical examination was performed and treatment provided, no additional diagnostic tests were performed. The patient was repeatedly diagnosed with an exacerbated anxiety attack and treated with benzodiazepines, which were anticipated to temporarily alleviate some symptoms. However, during the most recent visit, a thorough evaluation was made, and a detailed history of the current illness was obtained. The patient denied experiencing any other symptoms, including worsening of Parkinson's disease-related symptoms, and denied having taken any other medications or substances besides those previously mentioned. No evidence of accidental poisoning by salicylates or other toxicants was found. Physical examination revealed tachypnoea without desaturation, without other notable changes. Neurological examination was normal, with only slight joint stiffness and slowness in the beginning of movements. Blood gas analysis showed primary respiratory alkalosis with secondary metabolic acidosis *(Table 1)*. Laboratory analysis was negative for significant changes: there was no elevation of inflammatory parameters, no anaemia, no changes in iron kinetics, no elevation of N-terminal pro-B-type natriuretic peptide (NT-ProBNP) or markers of myocardial necrosis. There was a slight increase in D-dimers. Cranioencephalic computed tomography (CT) scan with venography study without evidence of CNS acute ischemia, haemorrhage or masses. CT angiography of the chest and abdomen was ruled out infection, masses in the chest, abdomen and pelvis, and pulmonary thromboembolism.

The hypothesis of a pharmacological interaction or adverse effect was made, with safinamide being the most likely cause, due to the time of introduction and the beginning of the symptoms. The patient had been using amitriptyline for 10 years prior to the introduction of safinamide; therefore, it

VALUES (units)	TIME				
	On safinamide		After suspension of safinamide and amitriptyline		
	Admission	**After 12h** (after treatment with diazepam)	**After 6h**	**After 24h**	**After 3 months** (with increase dosage of levodopa/ benserazide)
FiO_2 (%)	21	21	21	21	21
pH	7.68	7.56	7.38	7.45	7.42
pCO_2 (kPa)	1.34	2.4	4.51	4.05	4.93
pO_2 (kPa)	16.26	17.12	11.58	11.82	11.96
HCO_{3-} (mmol/l)	11.8	15.9	19.5	20.7	23.5
Na^+ (mmol/l)	138.7	138	137.9	-	139
K^+ (mmol/l)	3.51	3.85	3.69	-	4.13
Cl^- (mmol/l)	109	-	-	-	-
Ca^{2+} (mmol/l)	1.18	1.14	-	-	1.19
Lactate (mmol/l)	1.83	1.32	0.91	1.45	1.1

Table 1. Blood gas analysis evolution throughout time.

seemed unlikely that amitriptyline was the cause of this acute event. The neurology department was contacted and given the absence of an organic pathology and common toxicities and the clinical and temporal relation with the change in therapy, hyperdynamia in response to pharmacological therapy was suspected. Safinamide and amitriptyline were suspended, because of the interaction of these drugs and the dosage of levodopa/benserazide was reduced.

There was clinical improvement with resolution of the respiratory alkalosis within 24 hours *(Table 1)*.

The patient was discharged from the hospital and was evaluated in an internal medicine consultation after 3 months. The dosage of levodopa/benserazide had already been incremented and no symptoms were reported. Safinamide and amitriptyline were not reintroduced. An arterial blood analysis was performed, and no alterations were registered *(Table 1)*. In the following months the patient came to follow-up consultation and no symptoms of anxiety or psychiatric disorders or changes in blood gas analysis were detected.

The Naranjo Score[3] was calculated and a score of 6 was obtained, suggesting probable relationship between the drug and the clinical presentation. The case was reported to the National Authority of Medicines and Health Products in Portugal which concluded possible causality, according to the World Health Organization classification: "Pharmacologically, the reaction was explainable by the potential for development of psychiatric events through a dopaminergic mechanism, including hyperventilation. However, this adverse effect was not described and may have been enhanced or even caused by other anti-parkinsonian drugs used simultaneously".

DISCUSSION

Safinamide is a recent therapy for Parkinson's disease that is showing good results as a L-dopa adjunct, allowing the improvement of ON-time without troublesome dyskinesia[3]. The most recent systematic reviews on safinamide showed the efficacy and safety of this drug; however, the evidence is limited, and more studies about the therapeutic and adverse effects of safinamide are needed[4].

This case showed a possible correlation between the increase of safinamide doses and the development of a hyperventilation syndrome[5] and subsequent respiratory alkalosis. There are two possible pathophysiological explanations: i) The development of a psychogenic or anxiety-induced hyperventilation syndrome through an activation of dopaminergic pathways[1,4]; ii) The increased of diaphragmatic dyskinesias resulting in alterations in the ventilatory mechanism resulting in hyperventilation[4-6].

The hyperventilation syndrome is a pattern of over breathing in which the depth and rate exceed the metabolic needs of the body at that time promoting the elimination of carbon dioxide at a faster rate[7] and, consequently leading to respiratory alkalosis. At presentation, in this particular case, the hyperventilation syndrome could not be associated with alterations in the majority of the exams performed in the ED. Frequently, it is assumed that the syndrome is secondary to a psychiatric disease that leads to treatment with sedatives. In this case, the patient did not exhibit any signs of improvement with benzodiazepines, and the situation deteriorated, with increased limitations in daily activities at each ED visit. Consequently, alternative causes were investigated. Intracranial pathology, other medications or toxins, pulmonary disease, hyperthyroidism, and severe anaemia were ruled out. The patient had been on amitriptyline for an extended period, and given its mechanism of action, it was deemed unlikely to be the cause of this acute event. Finally, the discontinuation of safinamide led to a complete regression of symptoms, even with an increase in the remaining drugs, there was no recurrence of symptoms. This development supports the idea that a possible correlation between safinamide and respiratory alkalosis through a dopaminergic pathway is not only likely but was the aetiology of the patient's condition. The Naranjo Score suggested a probable link between the safinamide and the respiratory alkalosis. Thus, it became possible to establish a potential cause-and-effect relationship between the anti-parkinsonian medications and the respiratory alterations.

CONCLUSION

Respiratory alkalosis due to hyperventilation syndrome is commonly linked to anxiety, despite multiple potential causes. In such cases, it is essential to assess symptom severity and systematically rule out major contributing factors. This case suggests an alternative aetiology. Initially, the patient's hyperventilation and respiratory alkalosis were attributed to anxiety, but treatment with sedatives and anxiolytics was ineffective. Notably, the discontinuation of safinamide led to immediate symptom resolution, demonstrating a cause-effect relationship between the anti-parkinsonian drug and the respiratory disturbance.

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