

Case report

QJM

Olfactory disturbance related to pyrazinamide

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Learning Point for Clinicians

Pyrazinamide could induce smelling disturbance. The severity is dose-dependent, and it is usually resolved after the drug is withdrawn. Careful re-introduction of drugs step-by-step could reduce the symptom and promote the safety of patients, their quality of life and drug compliance during anti-tubercular treatment.

A 63-year-old man was admitted to our hospital to receive treatment for pulmonary tuberculosis. He had the habit of smoking two to three cigarette packs per day for 40 years, and had been treated for hypertension with amlodipine for a period of 5 years. The patient began receiving anti-tubercular treatment with Rifater 5 tabs/day (equivalent to isoniazid 400 mg/day, rifampicin 600 mg/day, pyrazinamide 1250 mg/day), ethambutol 800 mg/day and streptomycin 750 mg/day. On the fourth day of treatment, skin itching, poor appetite and nausea were noted. The patient complained of smell disturbance, with change of the original smell of food to a disgusting odor that negatively and severely impacted on his appetite (Figure 1). The patient had not previously experienced this type of smell disturbance. All anti-tubercular drugs were discontinued and the symptoms relieved gradually.

One week later, rifabutin 300 mg/day and isoniazid 300 mg/day were administered without recurrence of discomfort. Then, ethambutol 800 mg/day and pyrazinamide 1500 mg/day were added 3

and 4 days later consequently, but again the patient complained of skin itching and smell disturbance the day after retaking pyrazinamide. The smell disturbance was more intense than before, especially with regards to greasy food. Under suspicion of drug-induced side effect, pyrazinamide was withdrawn and the smelling disorder resolved gradually.

The patient restarted taking pyrazinamide at a lower dosage (500 mg/day) 10 days later. The problem with smell developed again on the next day, but the symptoms were less severe and more acceptable. In time, the patient learned how to tolerate the related symptoms and continued taking pyrazinamide at a dosage increased to 1000 mg/day, combined with isoniazid, ethambutol and mycobutin under close observation.

Dysosmia, or smelling disorders, can have a substantial impact on quality of life and may represent a significant underlying disease, but they are quite often overlooked.¹ It can be caused by many factors, such as upper respiratory infection, head trauma, nasal or paranasal sinus disease. Medication is also an important cause of dysosmia and it is usually resolved after the drug is withdrawn.²

In the case of this patient, the most plausible cause of smelling disturbance was pyrazinamide due to the high correlation between symptom attack/recurrence and drug intake (Figure 1). In addition, re-introduction of pyrazinamide at a lower dosage (500 mg/day) also induced recurrence of smelling disorders but with less severity, implying that this side effect was both dose dependent and reversible.

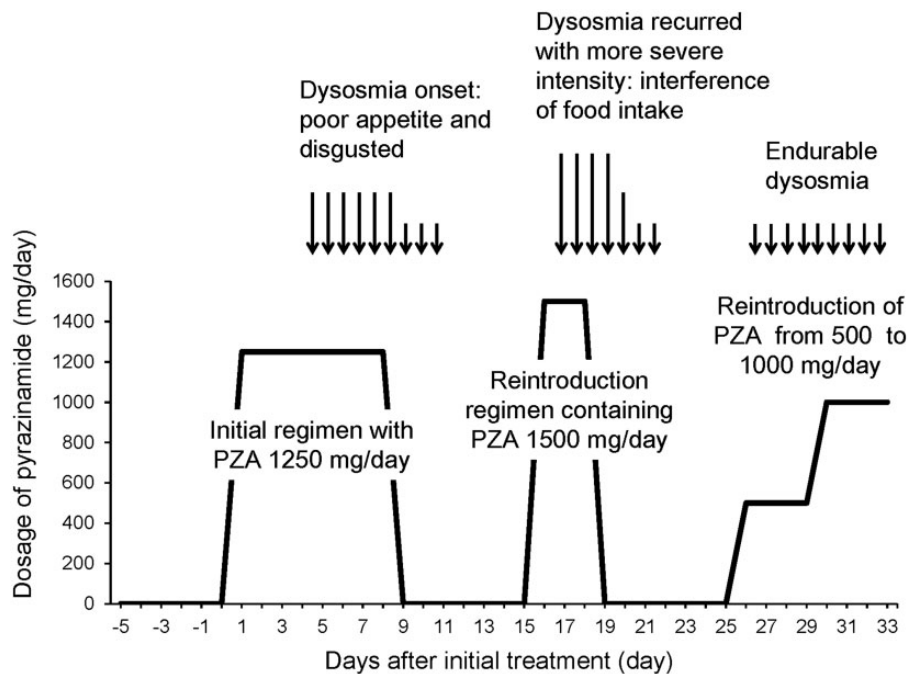


Figure 1. Time-course of dysosmia (upper panel) and dosage of pyrazinamide (PZA) (lower panel) during anti-tuberculosis treatment.

The possible mechanism of dysosmia caused by pyrazinamide is still unknown. However, some have proposed that pyrazinoic acid, the active moiety of pyrazinamide, could accumulate within the bacilli, acidifying the interior, and probably be lethal by disrupting membrane energetics and membrane transport function³; perhaps the characteristic of membrane damage contributed to smelling disturbance, similar to the hypothesis of digoxin-induced smelling disturbance by intermediation of Na-K-ATPase of the chemosensory receptor cell.⁴

Smelling disorders had also been reported with pyrazinamide plus levofloxacin,⁵ pyrazinamide plus isoniazid as well as rifampicin and gatifloxacin.⁶ In addition to pyrazinamide, the other possible anti-tubercular drugs related to olfactory impairment include amikacin, kanamycin, streptomycin, ofloxacin, prothionamide and clarithromycin.^{1,2} Tracing back to our case, even if the role of pyrazinamide in inducing smelling disorders was most considered, the involvement of streptomycin, long-term daily use of amlodipine and chronic cigarette smoking, may together have had a role to play—thus, increasing the risk of olfactory problems.

In conclusion, pyrazinamide-induced olfactory problem is a rare but easily ignored side effect. Careful evaluation of any clinical symptoms is

imperative to promote the safety of patients, their quality of life and drug compliance during anti-tuberculosis treatment.

Conflict of interest: None declared.

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