Olfactory disturbance related to pyrazinamide

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A 63-year-old man was admitted to our hospital to receive treatment for pulmonary tuberculosis. He had the habit of cigarette smoking 2 to 3 packages 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 400mg/day, rifampicin 600mg/day, pyrazinamide 1250mg/day), ethambutol 800mg/day and streptomycin 750mg/day. On the fourth day of treatment, skin itching, poor appetite and nausea were noted. Smelling disturbance was also complained of with change of the original smell of food to a disgusting odor that negatively and severely impact 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 300mg/day and isoniazid 300mg/day were administrated without recurrence of discomfort. Then, ethambutol 800mg/day and pyrazinamide 1500mg/day were added 3 and 4 days later consequently, but the again patient complained the skin itching and the same smell disturbance problem on the day after retaking pyrazinamide. The smell disturbance was more intense than before, especially for with regards to greasy food. Under suspicion of drug induced side effect, pyrazinamide was
withdrawn and the smelling disorder was gradually resolved.

The patient tried to restart taking pyrazinamide at a lower dosage (500mg/day) 10 days later. The smelling problem 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 1000mg/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 cause 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 Medication is also an important cause of dysosmia and it is usually resolved after the drug is withdrawn [2].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, reintroduction of pyrazinamide at a lower dosage (500mg/day) also induced recurrence of smelling disorders but with less severity, implying that this side effect was both dose dependent and reversible.
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 function [3]; 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.
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.

Figure Legend

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

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

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