Ulceration of the oral mucosa following direct contact with ferrous sulfate in elderly patients: a case report and a review of the French National Pharmacovigilance Database

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Objective: To report a series of cases of ulceration of the oral mucosa linked to direct contact with ferrous sulfate in elderly patients.

Case summary: The first case report concerns the occurrence of widespread oral ulceration in an 87-year-old woman with Alzheimer's disease. The ulceration extended from the side of the tongue to the floor of the mouth. No clear explanation was found and various local treatments were ineffective. Once it was realized that the ferrous sulfate tablets (given as an iron supplement) were crushed prior to administration (due to the patient's deglutition disorder), withdrawal of this treatment led to rapid resolution of the ulceration. Nine other cases of oral ulcerations associated with ferrous sulfate were identified in the French National Pharmacovigilance Database. All but one of the patients were over 80 years of age and the youngest patient (a 54-year-old) had dysphagia associated with facial paralysis.

Discussion: Only two other reports of oral ulceration due to ferrous sulfate have been published to date. Mucosal toxicity of ferrous sulfate (which is probably related to oxidative stress) has previously been reported for the hypopharynx, the esophageal lumen, and (after inhalation of a tablet) the tracheobronchial tree.

Conclusion: The mucosal toxicity of ferrous sulfate must be taken into account when deglutition disorders are present (as in elderly patients) and appropriate pharmaceutical formulations (such as syrups) should be administered to at-risk patients. The use of iron salts other than ferrous sulfate could be considered.

Keywords: ferrous sulfate, drug ulceration, oral ulceration, elderly

Introduction

In older patients, iron-deficiency anemia is associated with an elevated risk of mortality and various morbidities (such as cardiovascular disease and cognitive dysfunction).¹ Treatment of this type of anemia is based on oral iron supplementation (with ferrous sulfate tablets in most cases). Although iron supplementation is generally well-tolerated, mucosal injury to the upper gastrointestinal tract following iron overdose has often been described, particularly in children.^{2,3} Iron overdose is thought to exert a direct, corrosive effect that causes mucosal necrosis and ulceration.²⁻⁵ However, mucosal injury has very rarely been reported in patients receiving therapeutic dosages of ferrous sulfate, and the few case reports in the literature mainly concern gastric injury.⁶

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Here, we report the case of an elderly patient in whom oral ulceration was induced by direct, prolonged contact with ferrous sulfate. The presence of a causal relationship between mouth ulceration and ferrous sulfate was assessed in accordance with the current French guidelines.⁷ We also identified nine other cases of oral ulceration associated with ferrous sulfate in the French National Pharmacovigilance Database. To the best of our knowledge, this is the largest case series described to date.

Case report

An 87-year-old woman with progressing Alzheimer's disease and deglutition disorders developed a large, irregular area of oral ulceration. The lesion extended from the side of the tongue to the floor of the mouth. The patient was being treated with ferrous sulfate (80 mg per day), esomeprazole (20 mg per day), macrogol (10 mg four times a day), and lysine acetylsalicylate (75 mg per day).

Histologic examination of a tissue sample from the ulcerated area revealed acute inflammatory granular and hemorrhagic features. Perls' staining revealed the presence of siderophages.

At the time of onset, no clear explanation for the symptoms had been found and various local treatments were ineffective. Once it was realized that the ferrous sulfate tablets given as an iron supplement were being crushed prior to administration (due to the patient's deglutition disorders), withdrawal of this treatment led to rapid resolution of the ulceration.

Review of the French National Pharmacovigilance Database

We searched the French National Pharmacovigilance Database between July 1986 and July 2013 and found nine reports of mouth ulceration associated with the use of ferrous sulfate tablets (Table 1). The French National Pharmacovigilance system was established in 1973. A network of 31 regional centers receives spontaneous reports of "serious and/or unexpected" adverse drug reactions from health care professionals. Eight of the nine patients were women. The patients' mean age was 81.5 years (range: 54–97 years). Dysphagia or prolonged presence of tablets in the mouth were reported in three cases and the use of crushed tablets was reported in two other cases. Ferrous sulfate was always the only medication suspected and all the cases of oral ulceration resolved or improved rapidly after withdrawal of this treatment. No cases of oral ulceration

Table 1 Summary of cases of mouth ulceration with a suspected causal relationship with the administration of ferrous sulfate tablets (either alone or in combination with other drugs)

Case	Sex	Age (years)	Medical history	Daily dose (mg)	Duration of drug exposure	Reported adverse event	Concomitant drugs	Other drugs implicated
1	F	80	Anemia	80 (crushed tablets)	1 month	Mouth ulceration, stomatitis	Lysine acetylsalicylate, pantoprazole	None
2	F	81	Anemia, arteritis, gastric ulcer, head leaning to the side, salivary stasis	80	1 month	Mouth ulceration	Amitriptylin E, clonazepam, omeprazole, fraxiparine	None
3	F	80	Alzheimer's disease, cardiac insufficiency, hypertension, anemia, dysphagia	80 (crushed tablets)	Several years	Mouth ulceration	Amantadine, enalapril, lysine acetylsalicylate	None
4	F	82	Anemia	80	1 day	Mouth ulceration	Esomeprazole, clonazepam	None
5	M	90	Anemia, bedridden patient	80	Unknown	Mouth ulceration	–	None
6	F	83	Anemia, hypertension, diabetes, bladder cancer	80	14 days	Mouth ulceration	Gliclazide, nocardipine, clomipramine, lysine acetylsalicylate	None
7	F	85	Anemia, bedridden patient	80	Unknown	Mouth ulceration	–	None
8	F	54	Facial paralysis, dysphagia	80	5 days	Mouth ulceration	Clorazepate, omeprazole	None
9	F	97	Anemia	80	2 months	Mouth ulceration	Ranitidine, lysine acetylsalicylate	None

Note: Data from the French National Pharmacovigilance Database (1986–2013). – no concomitant drugs in addition to trospium was reported taken by the patient.
Abbreviations: M, male; F, female.

were associated with other iron salts (eg, iron fumarate and ascorbate, which are also widely prescribed) were found in the French National Pharmacovigilance Database. In accordance with the literature data mentioned, the database also featured cases of esophageal and gastric ulceration related to the administration of ferrous sulfate.

Discussion

This case series shows that the risk of oral ulceration must be taken into account when ferrous sulfate tablets are administered to patients (and especially elderly patients) in whom cognitive impairments and/or deglutition disorders may cause the tablets to remain in the mouth for more than a few seconds. Furthermore, patients with dementia may have difficulty expressing discomfort and pain.

Only two other publications have reported that prolonged stasis of ferrous sulfate tablets in the mouth can cause chemical burns to the oral mucosa.^{8,9} In both reports, the patients presented senile dementia.^{8,9} In one case, tablet stasis in the mouth was thought to be due to torticollis associated with ankylosis of the right shoulder.⁹

The mucosal damage caused by high local iron concentrations may be related to the formation of reactive oxygen species.¹⁰ Indeed, these species and free radicals have been implicated in mucosal alterations in gastric or intestinal injuries. The fact that some animal models of gastric ulceration are based on the administration of ferrous iron emphasizes the harmful effects of these salts on mucosal membranes.¹¹

The mucosal toxicity of ferrous sulfate has also been reported for the hypopharynx,¹² the esophageal lumen,¹³ and (after inhalation of a tablet) the tracheobronchial tree.^{14,15}

Direct, prolonged contact with a tablet reportedly induces alterations in both the digestive and respiratory mucosae. The latter resulted from accidental inhalation and bronchial stenosis; after removal of the tablet, the resulting, massive hemoptysis lasted for several days.^{15–18}

Conclusion

The above-described cases show that care must be taken when administering iron salts to elderly patients. Iron supplementation is frequent in this population. The risk of mucosal toxicity may be increased by age- or disease-related dysphagia and/or cognitive impairment. It would be useful to specifically evaluate the incidence and severity

of this adverse event and define the at-risk populations. Appropriate pharmaceutical formulations (such as syrups) should be administered to patients with deglutition disorders. The use of iron salts other than ferrous sulfate may be a better option for correcting anemia in at-risk patients.

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Disclosure

The authors report no conflicts of interest in this work.

References

1. Zakai NA, Katz R, Hirsch C, et al. A prospective study of anemia status, hemoglobin concentration, and mortality in an elderly cohort: the Cardiovascular Health Study. *Arch Intern Med.* 2005;165(19):2214–2220.
2. Banner W Jr, Tong TG. Iron poisoning. *Pediatr Clin North Am.* 1986;33(2):393–409.
3. Tenenbein M, Littman C, Stimpson RE. Gastrointestinal pathology in adult iron overdose. *J Toxicol Clin Toxicol.* 1990;28(3):311–320.
4. McGuigan MA. Acute iron poisoning. *Pediatr Ann.* 1996;25(1):33–38.
5. Nayfield SG, Kent TH, Rodman NF. Gastrointestinal effects of acute ferrous sulfate poisoning in rats. *Arch Pathol Lab Med.* 1976;100(6):325–328.
6. Zhang X, Ouyang J, Wiecek R, DeSoto F. Iron medication-induced gastric mucosal injury. *Pathol Res Pract.* 2009;205(8):579–581.
7. Begaud B, Evreux JC, Jouglard J, Lagier G. [Imputation of the unexpected or toxic effects of drugs. Actualization of the method used in France]. *Therapie.* 1985;40(2):111–118. French.
8. Fernandez-Viadero C, Pena Sarabia N, Verduga R, Crespo D. A large mouth ulcer, caused by a ferrous sulphate tablet in direct contact with oral mucosa in a patient with senile dementia. *J Am Geriatr Soc.* 1998;46(11):1483–1484.
9. Jones TA, Parmar SC. Oral mucosal ulceration due to ferrous sulphate tablets: report of a case. *Dent Update.* 2006;33(10):632–633.
10. Abraham SC, Yardley JH, Wu TT. Erosive injury to the upper gastrointestinal tract in patients receiving iron medication: an underrecognized entity. *Am J Surg Pathol.* 1999;23(10):1241–1247.
11. Naito Y, Yoshikawa T, Yoneta T, et al. A new gastric ulcer model in rats produced by ferrous iron and ascorbic acid injection. *Digestion.* 1995;56(6):472–478.
12. Cimino-Mathews A, Broman JH, Westra WH, Illei PB. Iron pill-induced tumefactive mucosal injury of the hypopharynx. *Am J Surg Pathol.* 2010;34(11):1720–1722.
13. Areia M, Gradiz R, Souto P, et al. Iron-induced esophageal ulceration. *Endoscopy.* 2007;39(1):E326.
14. Kim ST, Kaiser OM, Clarke BE, et al. 'Iron lung': distinctive bronchoscopic features of acute iron tablet aspiration. *Respirology.* 2003;8(4):541–543.
15. Lamaze R, Trechot P, Martinet Y. Bronchial necrosis and granuloma induced by the aspiration of a tablet of ferrous sulphate. *Eur Respir J.* 1994;7(9):1710–1711.

16. Godden DJ, Kerr KM, Watt SJ, Legge JS. Iron lung: bronchoscopic and pathological consequences of aspiration of ferrous sulphate. *Thorax*. 1991;46(2):142–143.
17. Mizuki M, Onizuka O, Aoki T, Tsuda T. [A case of remarkable bronchial stenosis due to aspiration of delayed-release iron tablet]. *Nihon Kyobu Shikkan Gakkai Zasshi*. 1989;27(2):234–239. Japanese.
18. Evrard C, Coffin O, Kaladji C, et al. [Massive hemoptysis 10 days after the removal from the bronchus of an iron protosulfate tablet accidentally inhaled]. *Presse Med*. 1990;19(1):34. French.

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