SHORT COMMUNICATION

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Factors influencing extent of nausea in the patients on oral iron therapy

Faktori koji utiču na stepen mučnine kod pacijenata na terapiji oralnim preparatima gvožđa

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Abstract

Background/Aim. Nausea after oral administration of iron is frequent phenomenon (11% of patients) and it is believed to be consequence of accumulation of free radicals in mucosa of gastrointestinal tract. The aim of our study was to measure the extent of nausea in outpatients taking oral supplementation with iron, and to investigate possible factors that may have an influence on it. **Methods.** The study was of the cross-sectional type, and conducted on a sample of outpatients on oral iron supplementation. The sample was consecutive, including all patients coming to a community pharmacy for oral iron supply during the study period. Frequency and severity of nausea were measured by the 5-item Drug-Induced Nausea Scale (DINS). **Results.** The mean score of the DINS from the sample of 128 patients was 8.56 ± 5.07 (range from 5 to 25). Each additional cup of coffee per week increased the DINS score for 0.143 points, the history of gastrointestinal disease had protective effect and decreased the DINS score for 5.923 points. **Conclusion.** Frequency and severity of oral iron-induced nausea are not dependent on oral iron burden, but rather on coffee intake and previous experience of patients with symptoms of gastrointestinal diseases. Modification of diet and education about types and severity of symptoms of gastrointestinal diseases could be useful preventive measures to avoid or at least mitigate oral iron-induced nausea and/or vomiting.

Key words:
iron; administration, oral; nausea; risk factors.

Apstrakt

Uvod/Cilj. Mučnina posle oralne primene preparata gvožđa je česta pojava (11% bolesnika). Veruje se da je posledica akumulacije slobodnih radikala u sluzokoži gastrointestinalnog trakta. Cilj istraživanja bio je da se ustanovi stepen mučnine kod ambulantnih bolesnika koji su bili na terapiji oralnim preparatima gvožđa i da se istraže mogući faktori koji mogu uticati na njega. **Metode.** Studija preseka sprovedena je na uzorku ambulantnih bolesnika koji su bili na terapiji oralnim preparatima gvožđa. Uzorak je bio slučajan, uključujući sve bolesnike koji su dolazili u apotekarsku ustanovu radi nabavke oralnih preparata gvožđa tokom perioda istraživanja. Učestalost i stepen izraženosti mučnine su mereni pomoću skale (5 parametara) za mučninu izazvanu lekovima (DINS). **Rezultati.** Ustanovljena je srednja vrednost i standardna devijacija (8,56 ± 5,07) u rasponu od 5 do 25 prema DINS. Svaka dodatna šoljica kafe nedeljeno je povećavala DINS rezultat za 0,143 poena, dok je istorija gastrointestinalne (GIT) bolesti imala zaštitni efekat i ispoljila se kroz smanjenje DINS za 5,923 poena. **Zaključak.** Učestalost i stepen izraženosti mučnine izazvane oralnom primenom preparata gvožđa ne zavise od primenjene doze, već od unošenja kafe i prethodnog iskustva bolesnika sa simptomima GIT. Modifikacija ishrane i edukacije o vrstama i ozbiljnosti simptoma gastrointestinalnih oboljenja mogla bi biti korisna preventivna mjera za izbjegavanje ili barem ublažavanje mučnine i/ili povraćanja izazvanih oralnom primenom preparata gvožđa.

Ključne reči:
gvožđe; oralna primena; mučnina; faktori rizika.

Introduction

Nausea after oral administration of iron salts happens in 11% of patients [1], and it is believed to be a consequence of accumulation of free radicals in mucosa of gastrointestinal tract [2]. Almost 50% of patients who take iron salt orally become eventually non-adherent to the treatment, primarily due to gastrointestinal side effects, which makes nausea caused by oral iron salts to be significant public health problem, too [1]. Especially ferrous sulfate causes nausea, about 2.32 times more often than other drugs or placebo [3]. Type of oral iron salt may affect rate and severity of nausea

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as was reported that ferrous salts (Fe^{2+}) were better tolerated, especially ferrous gluconate in liquid form [3]. However, a recent systematic review of efficacy and safety of oral iron preparations did not confirm existence of differences in rate of nausea and vomiting among different iron salts [4]. Other factors that may influence the rate and severity of nausea after oral iron therapy has not been investigated up to date.

The aim of our study was to measure the extent of nausea in outpatients taking oral supplementation with iron and to investigate possible factors that may have an influence on it.

Methods

Our study was of the cross-sectional type and was conducted during 2016 on a sample of outpatients on oral iron supplementation in the town Osečina, Serbia. The sample was consecutive, including all patients coming to a community pharmacy for oral iron supply from January,1st to December, 31st, 2016. The inclusion criteria were: age over 18 and below 75 years, diagnosis of iron deficiency anemia, oral supplementation of iron lasting at least two weeks prior visit to the community pharmacy and literacy. The exclusion criteria were previous gastrectomy, cognitive disorders (score at the Mini-Mental State Examination below 24), mood disorders and mental retardation. An investigator was a pharmacist employed in the same community pharmacy where the study took place. The study was approved by the Ethics Committee of Clinical Center Kragujevac, Serbia. The patients were enrolled only after they had signed the informed consent form.

Existence and extent of oral iron-induced nausea were measured by the 5-item Drug-Induced Nausea Scale (DINS), which we had constructed, with the following questions rated on the 1–5 Likert's scale [5]: 1) Did you feel nausea during the drug therapy?; 2) Did you feel nausea during the drug therapy aways at the same time during a day?; 3) How often did you feel unable to perform your daily activities due to nausea during the drug therapy?; 4) Did your appetite decrease due to nausea during the drug therapy?; and 5) Did you feel an urge to vomit during the drug therapy? Presence of both independent (type of iron salt in an oral preparation, daily dose of iron, timing of oral iron in relation to a meals, timing of oral iron during a day, smoking, intake of alcohol and intake of coffee) and confounding [sex, age, education, employment status, place of living, pregnancy, knowledge about gastrointestinal adverse effects of oral iron, previous experience with nausea after taking drugs orally, comorbidities (diabetes, asthma, chronic obstructive pulmonary disease, chronic heart failure and hypertension), oral intake of other drugs, concomitant gastrointestinal disease (gastroesophageal reflux disease, peptic ulcer, chronic pancreatitis or inflammatory bowel diseases), chronic renal failure and liver cirrhosis] variables was established by an open-ended questionnaire offered to the patients.

Statistics

The data were primarily processed by the descriptive statistics, calculating frequencies and percentages of different values of categorical variables as well as means and standard deviations of continuous variables. The total score of DINS was calculated as a simple summation of scores on individual questions. Effects of independent and confounding variables on the total DINS score were estimated by the multiple linear regression, through sign and size of coefficients of variables with a significant statistical influence. Optimal regression model was established by backward deletion method. All calculations were performed by the Statistical Program for Social Sciences (SPSS), version 18.

Results

Total of 128 patients with iron deficiency anemia and taking oral supplementation with iron took part in the study. Characteristics of the study sample are shown in the Table1.

The mean score of the DINS was 8.56 ± 5.07 (range from 5 to 25). The optimal multiple regression model (R^2 = 0.114, F = 2.204, p = 0.039) after backward deletion included the following variables: oral intake of other drugs, knowledge of adverse effects of oral iron, experience with nausea after oral intake of drugs, sex, average number of coffee cups weekly, history of gastrointestinal disease and type of iron salt. However, only two variables showed a significant influence on the DINS score: average number of coffee cups weekly (B = 0.143, range 0.022–0.264; p = 0.021) and history of gastrointestinal disease (B = -5.923, range -11.814–0.033; p = 0.049).

Discussion

Many drugs have significant potential to induce nausea and/or vomiting. Main center for vomiting in medulla oblongata is stimulated by certain blood-borne substances, by input from nerve endings in gastrointestinal tract and by projections from the chemioreceptor zone. There are several neurotransmitters which are involved in the functioning of center for vomiting: acetylcholine, histamine, 5-hydroxytriptamine, dopamine, endogenous cannabinoids and substance P [6]. The patients receiving cytostatic drugs experience nausea in 10% (low emetogenic drugs) to 90% (highly emetogenic drugs) of chemotherapy sessions [7], while the patients on opioids feel nausea in 48% of cases when these drugs were used for treatment of cancer pain and in 27% when used for postoperative pain [8]. As already mentioned, nausea due to oral iron supplementation is also frequent phenomenon, occurring in 11% of patients [1].

Our study revealed only two factors with a significant influence on frequency and extent of nausea after oral iron supplementation: coffee intake and history of gastrointestinal disease. While each additional cup of coffee per week increased the DINS score for 0.143 points, the history of gastrointestinal disease had protective effect and decreased the DINS score for 5.923 points.

Table 1

Characteristics of study sample

Variable	Number	Values
Sex, n (%)		
male	16	(12.5)
female	112	(87.5)
Age (years), mean ± SD	47.9 ± 17.1	
Education, n (%)		
elementary or no school	34	(26.4)
high school	66	(51.6)
higher education	28	(22.0)
Employment status, n (%)		
employed	52	(40.6)
unemployed	49	(38.3)
retired	27	(21.1)
Place of living, n (%)		
urban	83	(64.8)
rural	45	(35.2)
Pregnancy, n (%)		
yes	16	(12.5)
no	112	(87.5)
Iron salt, n (%)		
ferrous-fumarate	90	(70.3)
ferric-hydroxyde	16	(12.5)
ferrous-gluconate	19	(14.8)
ferrous pyrophosphate	3	(2.4)
Daily dose of iron salt (mg), mean ± SD	480.9 ± 258.3	
Average duration of iron supplementation (months), mean ± SD	15.1 ± 32.6	
Timing of dose in relation to a meal, n (%)		
before a meal	38	(29.7)
during a meal	7	(5.5)
after a meal	68	(53.1)
I do not care	15	(11.7)
Timing of dose during the day, n (%)		
morning	24	(18.8)
late afternoon or evening	9	(7.0)
morning and evening	86	(67.2)
I do not care	9	(7.0)
Knows about the adverse effects of oral iron, n (%)		
yes	70	(54.7)
no	58	(45.3)
Experience with nausea after oral intake of drugs, n (%)		
yes	16	(12.5)
no	112	(87.5)
Comorbidity, n (%)		
yes	53	(41.4)
no		
Oral intake of other drugs, n (%)	75	(58.6)
no	62	(48.4)
cardiovascular drugs	22	(17.2)
psychotropic drugs	6	(4.7)
antidiabetics	5	(3.9)
several drug groups	33	(25.8)
Smoking, n (%)		
yes	27	(21.1)
no	101	(78.9)
Intake of alcohol, n (%)		
yes	5	(3.9)
no	123	(96.1)
Average number of coffee cups weekly, mean ± SD	12.3 ± 7.5	
History of a gastrointestinal disease, n (%)		
yes	3	(2.3)
no	125	(97.7)
History of gastroscopy, n (%)		
yes	11	(8.6)
no	117	(91.4)
Chronic renal failure, n (%)		
yes	0	(0)
no	128	(128)
Liver cirrhosis, n (%)		
yes	0	(0.0)
no	128	(100.0)

n (%) – number (percentage) of patients; SD – standard deviation.

It seems that coffee somehow augmented nausea as an adverse effect of drugs. It was shown in a group of patients receiving emetogenic chemotherapy that intense aversion to coffee developed after first cycle of therapy, and the patients avoided to take coffee in order to avoid nausea [9]. The patients who were treated by the prostaglandin inhibitors for premenstrual syndrome in a small observational study benefited from avoidance of coffee and they experienced nausea as side effect of the therapy less frequently [10]. The pregnant females who suffer from morning sickness also have strong aversion to coffee [11]. Mechanism of emetogenic action of coffee remains obscure, but probably caffeine increases cholinergic transmission within the vomiting center, as it was recently shown that it blocked acetylcholinesterase [12].

History of gastrointestinal disease means that a patient has experience with nausea and possibly vomiting. It was shown that some psychological treatments like autogenic training, help patients to control nausea due to motion sickness more effectively [13], which could be an explanation why the patients in our study had lower DINS scores if previously exposed to some gastrointestinal disease. Probably, the experience with nausea helped them to be less anxious when they felt it after taking oral iron, and therefore the score was lower on the DINS.

Our study did not find an association among the type of iron salt, daily dose or dosing regimen with severity of nausea, which are the same findings as those published in two systematic reviews of the studies on this topic [4, 14]. Although it seems logical that oxidative stress imposed to mucosa of the stomach by iron depends on its dose and relation to meals, probably this is not the only mechanism by which oral iron causes nausea. It was shown that iron produced a clearly different sensation from the traditional basic tastes, including both olfactory and oral sensations [15], so the taste of metal instead of gastric irritation may be the main factor in pathogenesis of oral iron-induced nausea. Whether intermittent (once weekly) iron supplementation could decrease problems with nausea in comparison to daily iron intake remains unclear and further studies are necessary to answer this question [14, 16].

Limitations of the study

Our results should be taken with caution, since almost two-thirds of patients did not intake iron before the meal, what is recommended dosing regimen. Non-adherence to the prescribed regimen could have influenced indirectly emetogenic action of oral iron and confounded the effects of other factors, including coffee and experience with gastrointestinal diseases.

Conclusion

Frequency and severity of oral iron-induced nausea are not dependent on oral iron burden, but rather on coffee intake and previous experience of patients with symptoms of gastrointestinal diseases. Modification of diet (avoidance of coffee during oral iron supplementation) and educating the patient about types and severity of symptoms of gastrointestinal diseases could be useful preventive measures to avoid or at least mitigate oral iron-induced nausea and/or vomiting.

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