Original Article

Gastrointestinal Adverse Events of Methotrexate : A Descriptive Study

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Background : Methotrexate is widely used in the treatment of neoplasms, psoriasis and rheumatoid arthritis but it can cause several adverse events. The gastrointestinal system is where methotrexate side effects occur most frequently. The aim of the study was to describe the reported gastrointestinal adverse events of methotrexate.

Material and Methods : This was a retrospective, descriptive analysis that was conducted to analyze gastrointestinal adverse events of methotrexate that were reported to the Food and Drug Administration or to the World Health Organization (WHO).

Results : Methotrexate use has been linked to gastrointestinal side effects such as Nausea, Vomiting, Diarrhea, Stomach Pain, Stomatitis and Mouth Ulcers.

Conclusion : Methotrexate can be effective and safe when used and monitored properly, therefore it's critical to periodically check on patients and inform them of the side effects of methotrexate use and how to prevent or manage them.

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Key words **: Adverse events, FAERS, Methotrexate, Reporting, VigiBase.**

Methotrexate is widely used in the treatment of neoplasms, psoriasis and rheumatoid arthritis[1]. Whether taken alone or in conjunction with other medications, methotrexate has been used successfully to treat a variety of malignancies and autoimmune illnesses. Unfortunately, intestinal toxicity is the primary dose-limiting factor for the administration of methotrexate and patients are significantly burdened by methotrexate-induced intestinal mucositis[2]. Despite its effectiveness, methotrexate occasionally only receives restricted use because of its side effects, which include kidney or liver damage, bone marrow toxicity and gastrointestinal mucosal injury[1].

Although fatal mucosal necrosis caused by methotrexate is relatively rare, it is known that the drug can cause intestinal mucositis, hemorrhage, and peptic ulcers[1]. The gastrointestinal system is where methotrexate side effects occur most frequently[3]. Any amount of methotrexate can cause toxicity, although these effects become more frequent and severe with higher doses or more frequent dosing[4].

The public can now search for information about human adverse events reported to the Food and Drug Administration by the pharmaceutical industry, healthcare providers, and consumers using the highly interactive Food and Drug Administration Adverse Event Reporting System (FAERS) tool[5]. They also can use VigiBase which is a distinctive global database of reported possible drug side effects that is maintained by the World Health Organization[6]. With over 30 million suspected adverse drug reaction reports reported since 1968, it is the world's largest database of its sort. It is constantly updated as new reports arrive[6].

Editor's Comment :

- Methotrexate is widely used in the treatment of neoplasms, psoriasis, and rheumatoid arthritis but it can cause several adverse events.
- The most reported gastrointestinal adverse events of methotrexate were Nausea, Vomiting, Diarrhea, Abdominal Discomfort and Stomatitis.
- It is critical to periodically check on patients and inform them of the side effects of methotrexate use and how to prevent or manage them.

Aims and Objectives

The present study aimed to describe the gastrointestinal adverse events of methotrexate using the Food and Drug Administration Adverse Event Reporting System (FAERS) and the World Health Organization database (VigiBase).

Material and Methods

This was a retrospective, descriptive analysis that was conducted to analyse gastrointestinal adverse events of methotrexate that were reported to the Food and Drug Administration (FDA) or to the World Health Organization. The study included all of the reports

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that were submitted to the US FDA Adverse Event Reporting System (FAERS) before the 1st of July, 2022 and the reports that were submitted to the World Health Organization database (VigiBase) before 22 August, 2022.

The collected data included the total number of reports that were submitted to VigiBase, the geographical distribution of the reports, the gender and age of the patients who had adverse events, the number of gastrointestinal adverse events and the most reported gastrointestinal adverse events. The collected data also included the total number of reports that were submitted to FAERS, the gender of the patients who had adverse events, the age of the patients who had adverse events, the specialty of the reporters, and the most common gastrointestinal adverse events. The data were analysed descriptively and represented as numbers and percentages.

No IRB approval or informed consent was required because the research include only data about the adverse events reported and the data already available for the public and the researchers.

Results

Methotrexate adverse events that were submitted to VigiBase :

Table 1 shows the gender and age of the patients that had an adverse event. The reports that didn't specify the gender were excluded. More than 68% of the patients were females. The reports that didn't specify the age were excluded. The age of 39.43% of the patients was between 45 and 64 years and the age of 19.71% of the patients was between 65 and 74 years.

Among these reports, 32,882 reports were reports of Gastrointestinal disorders (19.03%). The most reported gastrointestinal adverse events were Nausea (34.20% of the gastrointestinal events), Vomiting (17.66%), Diarrhea (13.37%), Abdominal Discomfort (7.81%), Stomatitis (7.15%), Mouth Ulceration (6.85%), Abdominal Pain (6.56%), Gastrointestinal Disorder (4.78%), Upper Abdominal Pain (3.52%) and Dyspepsia (2.72%) (Table 2).

Table 1 — *The gender and age of the patients that had an adverse event*

Category	Number	Percentage
Gender :		
Male	50126	31.20
Female	110530	68.80
Age :		
0-27 days	68	0.05
28 days to 23 months	647	0.50
2-11 years	7980	6.22
12-17	5853	4.56
18-44	24375	18.98
45 -64	50625	39.43
65-74	25308	19.71
More than 74	13536	10.54

Methotrexate adverse events that were submitted to FAERS :

Till 30 June 2022, 1,52,823 reports were submitted to FAERS. The age of 57.51% of the patients was between 18 and 64 years and the age of 25.87% of them was between 65 and 85 years. More than 66% of the patients who had adverse events were females. About 81.90%of the reporters who submitted the adverse events were healthcare professionals (Table 3).

Table 4 shows the most reported gastrointestinal adverse events that were submitted to FAERS. The most reported gastrointestinal adverse events were Nausea (7.00%), Diarrhea (4.78%), Abdominal Discomfort (4.55%), Vomiting (4.27%), Abdominal Pain (3.59%), Stomatitis (2.45%), Glossodynia (2.39%), Gastrointestinal Disorder (2.15) and Mouth Ulceration (1.05%).

Table 2 — *The most reported gastrointestinal adverse events were submitted to VigiBase*

Gastrointestinal adverse events	Number	Percentage
Nausea	11244	34.20
Vomiting	5808	17.66
Diarrhea	4397	13.37
Abdominal discomfort	2568	7.81
Stomatitis	2350	7.15
Mouth ulceration	2253	6.85
Abdominal pain	2123	6.56
Gastrointestinal disorder	1573	4.78
Upper abdominal pain	1157	3.52
Dyspepsia	895	2.72
Constipation	557	1.69
Dysphagia	494	1.50
Pancreatitis	469	1.43
Colitis	462	1.41
Aphthous ulcer	443	1.35
Gastrointestinal haemorrhage	419	1.27
Abdominal distension	411	1.25

Table 3 — *The age and gender of the patients who had adverse events and the specialty of the reporters*

Category	Number of Cases*	Percentage
Age :		
0-1 Month	114	0.11
2 Months-2 Years	1706	1.65
3-11 Years	8125	7.86
12-17 Years	6320	6.11
18-64 Years	59444	57.51
65-85 Years	26734	25.87
More than 85 Years	912	0.88
Gender :		
Female	89139	66.97
Male	43955	33.03
The specialty of the reporters :		
Healthcare Professional	117828	81.90
Consumer	26041	18.10

Table 4 — *The most reported gastrointestinal adverse events were submitted to FAERS*

Gastrointestinal adverse events	Number	Percentage*
Nausea	10,704	7.00%
Diarrhea	7,300	4.78%
Abdominal Discomfort	6,948	4.55%
Vomiting	6,528	4.27%
Abdominal Pain	5485	3.59%
Stomatitis	3,750	2.45%
Glossodynia	3,646	2.39%
Gastrointestinal Disorder	3,289	2.15%
Mouth Ulceration	1,603	1.05%
Irritable Bowel Syndrome	1,495	0.98%
Helicobacter Infection	1,468	0.96%
Duodenal Ulcer Perforation	1,371	0.90%
Cohn's Disease	1,232	0.81%

**The percentages represent the percentage of each adverse event among the total adverse events and not among the gastrointestinal events.*

Discussion

The present study showed that methotrexate frequently causes gastrointestinal adverse events such as Nausea, Vomiting, Diarrhea, Abdominal Discomfort, Stomatitis, Mouth Ulceration and Abdominal Pain. According to Maestá, *et al* the most common side effects of methotrexate were gastrointestinal disorders and abnormal laboratory findings. The most common gastrointestinal side effects were Oral mucositis, Nausea, Abdominal pain, Diarrhea and Vomiting[7]. According to Bulatovi-Alasan, *et al* Nausea (32.0%), Stomach Pain (11.3%) and Vomiting (6.5%) were the most common gastrointestinal symptoms following methotrexate administration and 42.3% of arthritis patients who received methotrexate experienced at least one gastrointestinal side event[8]. Asai, *et al* reported that using methotrexate can Result in Reflux, Stomach Discomfort, Indigestion, Diarrhea, or constipation. In their study, the high-dose methotrexate group showed a higher prevalence of Reflux (32% *versus* 24%) and Abdominal Pain (28% *versus* 18%) compared to the low-dose methotrexate group. They discovered that the prevalence of dyspepsia, diarrhea, and constipation did not differ significantly across groups[9]. Sherbini, *et al* reported that Gastrointestinal (42.0%), Neurological (28.6%), Mucocutaneous (26.0%), Pulmonary (20.9%), increased Alanine Transaminase (18.0%) and HAematological events (5.6%) were the most frequently reported adverse events in individuals with early rheumatoid arthritis[10]. Moreover, previous studies demonstrated that methotrexate's gastrointestinal side effects, such as Nausea, Stomach discomfort and Vomiting, frequently occur[11-17].

Despite its effectiveness, methotrexate sometimes only receives restricted use because side effects include kidney or liver damage, bone marrow toxicity, and gastrointestinal mucosal irritation, according to Tsukada, *et al* Additionally, they noted that intestinal mucositis, hemorrhage, and peptic ulcers are well-known methotrexate side effects of the gastrointestinal system, despite the fact that fatal mucosal necrosis instances are relatively uncommon[1]. Furthermore, according to Higuchi, *et al* methotrexate is stopped due to gastrointestinal side effects that are frequently seen during the treatment of rheumatoid arthritis[18]. Anticipatory and associative gastrointestinal symptoms may impair methotrexate use and negatively affect patients' quality of life. However, these symptoms are not very obvious clinically[13,19]. According to Zhou, *et al* methotrexate-induced intestinal mucositis places a heavy load on patients and is the main dose-limiting factor for methotrexate therapy[2].

Conclusion

Methotrexate use has been linked to gastrointestinal side effects such as Nausea, Vomiting, Diarrhea, Stomach pain, Stomatitis and mouth Ulcers. Methotrexate can be effective and safe when used and monitored properly, therefore it's critical to periodically check on patients and inform them of the side effects of methotrexate use and how to prevent or manage them.

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References

1 Tsukada T, Nakano T, Miyata T, Sasaki S — Life-Threatening Gastrointestinal Mucosal Necrosis during Methotrexate Treatment for Rheumatoid Arthritis. *Case Rep Gastroenterol* 2013; **7(3)**: 470-5.

2 Zhou B, Xia X, Wang P, Chen S, Yu C, Huang R, *et al* — Induction and Amelioration of Methotrexate-Induced Gastrointestinal Toxicity are Related to Immune Response and Gut Microbiota. *E Bio Medicine* 2018; **33**: 122-33.

3 BPAC — Methotrexate prescribing errors can be fatal. 2011. (https://bpac.org.nz/bpj/2011/february/methotrexate.aspx).

4 Pfizer — Methoblastin.2022.(www.medsafe.govt.nz).

5 FDA — FDA Adverse Event Reporting System (FAERS) Public Dashboard. 2022. (https://www.fda.gov/drugs/questions-and-answers-fdas-adverse-event-reporting-system-faers/fda-adverse-event-reporting-system-faers-public-dashboard).

6 WHO — About VigiBase. 2022. (https://who-umc.org/vigibase).

7 Maestá I, Nitecki R, Horowitz NS, Goldstein DP, Moreira MDFS, Elias KM, *et al* — Effectiveness and toxicity of first-line methotrexate chemotherapy in low-risk postmolar gestational trophoblastic neoplasia: The New England Trophoblastic Disease Center experience. *GynecolOncol* 2018; **148(1)**: 161-7.

8 Bulatoviæ Æalasan M, van den Bosch OF, Creemers MC, Custers M, Heurkens AH, van Woerkom JM, *et al* — Prevalence of methotrexate intolerance in rheumatoid arthritis and psoriatic arthritis. *Arthritis Res Ther* 2013; **15**: 1-5.

9 Asai S, Nagai K, Takahashi N, Watanabe T, Matsumoto T, Asai N, *et al* — Influence of methotrexate on gastrointestinal symptoms in patients with rheumatoid arthritis. *Int J Rheum Dis*. 2019; **22(2):** 207-13.

10 Sherbini AA, Gwinnutt JM, Hyrich KL, Adebajo A, Ahmed K, Al-Ansari A, *et al* — Rates and predictors of methotrexate-related adverse events in patients with early rheumatoid arthritis: results from a nationwide UK study. *Rheumatology* 2022; **2022**: keab917.

11 Murray KJ, Lovell DJ — Advanced therapy for juvenile arthritis. *Best Pract Res Clin Rheumatol* 2002; **16(3)**: 361-78.

12 van der Meer A, Wulffraat NM, Prakken BJ, Gijsbers B, Rademaker CM, Sinnema G — Psychological side effects of MTX treatment in juvenile idiopathic arthritis: a pilot study. *Clin Exp Rheumatol* 2007; **25(3)**: 480-5.

13 BrunnerHI, Johnson AL, Barron AC, Passo MH, Griffin TA, Graham TB, *et al* — Gastrointestinal symptoms and their association with health-related quality of life of children with juvenile rheumatoid arthritis: validation of a gastrointestinal symptom questionnaire. *J Clin Rheumatol* 2005; **11**: 194-204.

14 Hashkes PJ, Laxer RM — Medical treatment of juvenile idiopathic arthritis. *JAMA* 2005; **294(13):** 1671-84.

15 Ruperto N, Murray KJ, Gerloni V, Wulffraat N, de Oliveira SK, Falcini F, *et al* — A randomized trial of parenteral methotrexate comparing an intermediate dose with a higher dose in children with juvenile idiopathic arthritis who failed to respond to standard doses of methotrexate. *Arthritis Rheum* 2004; **50(7)**: 2191-201.

16 Ramanan AV, Whitworth P, Baildam, EM — Use of methotrexate in juvenile idiopathic arthritis. *Arch DisChild* 2003; **88(3)**: 197-200.

17 Alsufyani K, Ortiz-Alvarez O, Cabral DA, Tucker LB, Petty RE, Malleson PN — The role of subcutaneous administration of methotrexate in children with juvenile idiopathic arthritis who have failed oral methotrexate. *J Rheumatol* 2004; **31(1)**: 179-82.

18 Higuchi T, Yoshimura M, Oka S, Kawasaki A, Warabi E, Mizuno S, *et al* — Dietary Factors Modulate Gastrointestinal Adverse Effects of Methotrexate. *JPS* 2018; **2018**: PO3-13.

19 Bulatovic M, Heijstek MW, Verkaaik M, van Dijkhuizen EH, Armbrust W, Hoppenreijs EP, *et al* — High prevalence of methotrexate intolerance in juvenile idiopathic arthritis: development and validation of a methotrexate intolerance severity score. *Arthritis Rheum* 2011; **63(7)**: 2007-13.