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Navigating side effects: a case report on nintedanib induced diarrhea

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ABSTRACT: This case report explores Nintedanib, a medication used to treat lung fibrosis, and its potential side effect of severe diarrhea.The report details two cases. The first patient, a 66-year-old man with lung disease, experienced fatigue, decreased food intake, and frequent bowel movements for a month while taking Nintedanib. Stool tests revealed Clostridium difficile infection, but the gastroenterologist attributed the diarrhea to Nintedanib. Treatment with Loperamide and Nitazoxanide improved his condition. The second patient, a 75-year-old man with lung fibrosis, presented with abdominal pain and watery stools. Stool tests were negative for bacterial infections. After initial improvement with antispasmodic medication, his loose stools persisted. Nintedanib was replaced with Pirfenidone, another antifibrotic drug, and his diarrhea resolved.The report emphasizes Nintedanib-induced diarrhea as a potential concern, particularly for vulnerable populations. It highlights the importance of healthcare providers being aware of this side effect when prescribing Nintedanib. Additionally, the report mentions Pirfenidone as a potential alternative for patients experiencingNintedanib-induced diarrhea. Pirfenidone works by disrupting a different pathway involved in fibrosis. This case report contributes to the existing knowledge by providing real-world examples of Nintedanib's side effects and suggesting Pirfenidone as a treatment option for patients who cannot tolerate Nintedanib.

KEYWORDS: Nintedanib, Lung fibrosis, Diarrhea, Antifibrotic, Pirfenidone.

I. INTRODUCTION

Adverse reactions of medicines are a challenge in modern health care. Nintedanib is a medication designed to combat lung fibrosis in various lung diseases. Originally developed for cancer treatment, nintedanib's impact on growth factors relevant to both cancer and fibrosis led researchers to explore its use in lung conditions. Nintedanib essentially blocks specific cellular receptors, preventing them from receiving signals that trigger scarring. This reduces the activity and movement of these cells, ultimately slowing down fibrosis and the growth of new blood vessels in the lungs. As a result, nintedanib helps prevent the progression of lung diseases like idiopathic pulmonary fibrosis (IPF) and interstitial lung disease (ILD).Nintedanib use can come with a variety of side effects (1).

Nintedanib can cause diarrhea by either drawing excess water into the intestines or disrupting the natural balance of gut bacteria. This disruption allows harmful bacteria to thrive, which in turn inflame the intestines and trigger fluid secretion, leading to diarrhea. In some instances, simply stopping the medication can be enough to get rid of the diarrhea. There are various types of medications used to manage diarrhea, but they typically don't cure the underlying cause, instead offering relief from symptoms. These fall into categories like motility inhibitors, binders, secretion blockers, antibiotics, digestive enzymes, and gut flora supplements. Opioids and similar drugs slow down the movement of material through the intestines, allowing for better absorption of fluids. However, these drugs can be addictive with long-term use and may even worsen certain types of infectious diarrhea. Loperamide is a common choice for treating both short-term and ongoing diarrhea, but if symptoms last more than two days after starting it, consult a doctor. Another option for symptom relief are adsorbents like kaolin pectin. These work by grabbing onto various things in your gut, including nutrients, toxins, medications, and digestive fluids. Bismuth subsalicylate is another option for treating or preventing diarrhea, especially traveler's diarrhea. It works in several ways, including reducing fluid secretion, calming inflammation, and fighting bacteria. However, be cautious about taking too much, as some components can be toxic. Finally, Lactobacillus supplements aim to replenish good gut bacteria, which can help restore normal

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function and fight off bad bacteria. Interestingly, research suggests that simply eating a yogurt-based diet with 200-400 grams of lactose or dextrin might be just as effective(2).

Nintedanib targets specific molecules (growth factors) within cells to slow down lung scarring (fibrosis). This inhibitor (TKI) works by attaching to receptors and preventing the overactivity of cells that contribute to scarring. Originally approved in 2014 for idiopathic pulmonary fibrosis (IPF), nintedanib's effectiveness has been shown in animal studies and clinical trials for other lung scarring conditions. These include rheumatoid arthritis (RA) and systemic sclerosis (SSc) related interstitial lung diseases (ILD). Nintedanib has been shown to improve lung function (FVC) in patients with IPF, particularly those with a specific type of scarring. It can also be beneficial when other treatments are not suitable. Due to its success in improving patient outcomes, nintedanib received FDA approval in 2020 for treating progressive fibrotic ILD and SSc-ILD.

Studies suggest similar lung function benefits in patients with other types of lung scarring, including bleomycin-induced fibrosis and even lung fibrosis associated with COVID-19. Nintedanib comes in capsules of two strengths: 100mg and 150mg. It's important to swallow the capsules whole with food and drink to avoid a bitter taste. The typical dose is 150mg taken twice a day. This dose might be lowered to 100mg twice a day for certain patients, such as those with mild liver problems, low body weight, or persistent digestive issues. If you miss a dose, don't take extra medication - just resume your regular schedule. Store the medication in its original container, tightly closed, and out of reach of children(2).

II.CASE REPORT

A 66-year-old male patient with a known case of type 1 respiratory failure, type 2 diabetes mellitus, and interstitial lung disease on home oxygen was admitted to KIMS ALSHIFA Super Speciality Hospital following complaints of tiredness, fatigue, decreased food intake, and increased frequency of stools for one month. On evaluation, he was found to have type 2 respiratory failure. On admission, the patient was conscious and oriented with a respiratory rate of 26/minute, blood pressure of 160/60 mm Hg, pulse rate of 92/minute, and SpO2 of 77% on room air. Cardiology consultation was taken to check cardiac function. ECHO showed normal RV and LV function with no evidence of PAH. A psychology consultation was done in view of a mood disorder, and counseling sessions were conducted. A gastroenterology consultation was done in view of diarrhea. His stool investigation revealed that the consistency was semi-formed, with no fat globules and a pH of 6.0. Routine examination showed no blood in stools, mucus present, and pus cells 2-3/hpf. Microscopic examination of stool showed no ova, cysts, flagellates, or RBCs. The stool tested positive for Clostridium difficile toxin A and B, with a rapid test positive for GDH antigen and toxin A and B. The patient's medication history revealed that he was on Nintedanib 150 mg twice daily for pulmonary fibrosis. Following admission, he was managed appropriately with oxygen, IV fluids, and supportive care. The patient had been on Nintedanib 150 mg for three years and experienced severe diarrhea for the first time. The patient confirmed that he was still taking Nintedanib 150 mg. The gastroenterologist confirmed that the diarrhea was an adverse effect of Nintedanib. The physician advised administering Loperamide at bedtime and Nitazoxanide 500 mg twice daily for three days. The patient's condition improved. Nitazoxanide belongs to the class thiazolides. A similar finding was reported by Hirasawa et al in which combining multiple antidiarrheal medications might be a practical strategy to allow continued use of nintedanib treatment, compared to using just one medication or stopping nintedanib altogether(3).

A 75-year-old male patient, weighing 55 kg and with a height of 150 cm, with a known case of idiopathic pulmonary fibrosis, parkinsonism, CKD stage III, and hypothyroidism, was taking Nintedanib 150 mg. He was admitted to the Department of General Medicine with complaints of abdominal pain for four days and watery stools (8-10 episodes per day) for the same duration. The abdominal pain was diffuse in nature, with no aggravating or relieving factors, and no postural or diurnal variation associated with the pain. There was no history of vomiting. The patient was conscious and oriented. His blood pressure was 100/70 mm Hg, pulse rate 74/min, respiratory rate 22/min, and SpO2 90% on room air. Urine culture showed E. coli bacterial growth, while stool culture showed no growth. Stool CD toxin was negative. A pulmonology consultation was done, and the patient was started on protein powder. A gastroenterology consultation was also done, and the patient was started on Mebeverine, an antispasmodic that works by relaxing muscles in the gut to ease painful stomach cramps. By

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continuing the medication, the patient was symptomatically better.

The patient returned after 10 days with complaints of loose stools for five days. The loose stools were watery in nature (8-10 episodes per day). There was no history of hematuria or vomiting. The patient was conscious and oriented with a blood pressure of 120/80 mm Hg, pulse rate of 74/min, and SpO2 98%. On routine stool examination, the stool pH was 6, mucus was present, and pus cells were 2-4/hpf. On microscopic examination, ova, cysts, flagellates, RBCs, and blood were absent. A CTPA showed pulmonary hypertension and interstitial pulmonary fibrosis. Stool CD toxin was negative for GDH antigen and negative for toxin A and B. Pulmonology consultation was done, and Nintedanib was changed to Pirfenidone 200 mg twice daily.The patient reported an improvement in symptoms after Nintedanib was replaced with Pirfenidone. Notably, their diarrhea resolved upon discontinuing Nintedanib, suggesting Pirfenidone may be a suitable alternative.

Pirfenidone (PFD) is an oral drug with antifibrotic properties. A promising therapeutic target for lung fibrosis is the transforming growth factor-beta (TGF-β) signaling pathway. PFD's effective in disrupting this pathway. PFD hinders the production of fibronectin and alpha-smooth muscle actin (α-SMA) by lung fibroblasts exposed to TGF-β. α-SMA plays a critical role in transforming fibroblasts into myofibroblasts, a key driver of fibrosis. Furthermore, PFD suppresses TGF-β induced fibrotic changes and reduces the activity of SMAD3 and p38 MAPK, both essential downstream elements of TGF-β signaling. This evidence suggests that PFD's anti-fibrotic effects may stem from its ability to disrupt this pathway (4).

III.CONCLUSION

This report highlights a rare but serious side effect of Nintedanib - severe diarrhea. This can be particularly concerning for vulnerable populations like young children, older adults, or those with compromised immune systems. Since severe diarrhea can quickly lead to dehydration, electrolyte imbalances, and even shock if not addressed, it's vital for healthcare providers to be mindful of this potential reaction when prescribing Nintedanib.

REFERENCES

[1]. Gole S, Bankole A. Nintedanib. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2024 [cited 2024 May 16]. Available from: http://www.ncbi.nlm.nih.gov/books/NBK585049/

[2]. DiPiro, Joseph T., et al. Pharmacotherapy Handbook, Ninth Edition. McGraw-Hill Education, 2014.

[3]. Hirasawa Y, Abe M, Terada J, Sakayori M, Suzuki K, Yoshioka K, et al. Tolerability of nintedanib-related diarrhea in patients with idiopathic pulmonary fibrosis. Pulmonary Pharmacology & Therapeutics. 2020 Jun 1;62:101917.

[4]. Aimo A, Spitaleri G, Nieri D, Tavanti LM, Meschi C, Panichella G, et al. Pirfenidone for Idiopathic Pulmonary Fibrosis and Beyond. Card Fail Rev. 2022 Jan;8:e12.