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Mesalazine-Induced Cardiotoxicity

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Abstract

Background: Inflammatory bowel disease (IBD) which includes ulcerative colitis and Crohn's disease can also affect other organs in the body including heart as extra-intestinal manifestation. Mesalazine is commonly used to treat this chronic inflammatory disorder and is usually well tolerated by most patients. However, there are certain situations where toxic effects of mesalazine involve heart, making it difficult to differentiate between extra-intestinal manifestation and a treatment related complication.

Aims/Objective: Main objective of this review was to determine features that can help early recognition of mesalazine-induced cardiac involvement. Moreover, relationship between mesalazine dose and occurrence of cardiotoxicity was also observed. Finally, management of this condition including role of re-challenge in these patients was evaluated.

Methods: A literature search for relevant studies of the MEDLINE database was conducted, including reported cases of mesalazine-induced cardiac involvement since 1989.

Findings: Mesalazine-induced myopericarditis usually occurs within 2–4 weeks of initial drug exposure but may be delayed due to concomitant steroid use. There does not appear to be a dose-dependent relationship. A clear improvement following discontinuation of the drug helps to make the diagnosis.

Mesalazine discontinuation and steroids are successfully used for treatment. Re-challenge usually results in recurrence of cardiac involvement. Cardiac dysfunction resolves completely with a return to previous baseline function. Thiopurines and anti-TNF therapies are used to manage inflammatory bowel disease.

Conclusions: It is very important to evaluate any patient presenting with fever, shortness of breath or chest pain within 4 weeks of initiating mesalazine for possible drug-induced inflammation. Mesalazine should be stopped immediately and patient should be treated with steroids. Inflammatory bowel disease should be managed with second line drugs including thiopurines and anti-TNF therapies.

Keywords: Inflammatory bowel disease (IBD); 5-ASA (5-Aminosalicylic acid); Mesalazine; Thiopurines; anti-TNFs; Myocarditis; Pericarditis

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Introduction

Inflammatory bowel disease (IBD) which includes ulcerative colitis (UC) and Crohn's disease (CD) is a chronic inflammatory disorder, characterized by repetitive cycles of active and quiescent disease. Ulcerative colitis is limited to the colon whereas Crohn's disease can affect any part of the gastrointestinal tract. Ulcerative colitis usually presents with bloody diarrhoea and rectal bleeding along with urgency and tenesmus whereas features of Crohn's disease are more heterogeneous but commonly include chronic diarrhoea, abdominal pain and weight loss. Both ulcerative colitis and Crohn's colitis can involve other organs as extra-intestinal manifestation including heart [1,2]. Mesalazine or 5-aminosalicylic acid (5-ASA) is one of the aminosalicylates and is widely used in the management of ulcerative colitis, both

for active disease as well as maintenance of remission [3,4]. Maintenance therapy with aminosalicylates reduces the risk of colorectal cancer by up to 75% [5]. However, cardiac involvement may be a manifestation of mesalazine related toxicity rather than extra-intestinal manifestation and sometimes it is difficult to differentiate between the two. Anti-inflammatory action of mesalazine in inflammatory bowel disease is through to be the result of its action on damaged epithelial cells in the gastrointestinal tract [6]. This action involves a variety of mechanisms including inhibition of pro-inflammatory cytokines (interleukin-1, 2 and 8 and tumour necrosis factor-α), increased expression of peroxisome proliferator-activated receptors as well as inhibition of cyclooxygenase (COX) [7-9]. Both oral and topical preparations of mesalazine are used in inflammatory bowel disease and usual dose of oral form is 2.4-4.8 gram daily [10,11]. A combination of oral and topical preparations appears to be more effective due to increased concentrations of the drug in the colon [12]. Mesalazine is usually well tolerated by most patients due to its favourable safety profile; however, up to 15% of patients can have some form of intolerance. This can manifest as diarrhoea (3%) which may resemble colitis flare-up, headache (2%), nausea (2%) and rash (1%). Rarely, nephrotoxicity (interstitial nephritis), cardiac involvement including pericarditis & myocarditis (0.3%), fibrosing alveolitis, pancreatitis, blood disorders and lupus erythematosus-like syndrome can present as drug related complications [13-15].

Mechanism of Mesalazine Related Cardiotoxicity

The exact mechanism by which mesalazine might prompt myocardial inflammation is not clearly identified but hypersensitivity seems to be the likely underlying phenomenon. Hypersensitivity reaction is probably a result of accelerated metabolism of arachidonic acid to leukotrienes due to cyclooxygenase-1 enzyme inhibition. Leukotrienes in turn result in overproduction of eosinophil stimulating cytokines which cause a hypersensitivity reaction resulting in myocarditis [16,17]. Hypersensitivity due to humoral-mediated response has also been suggested resulting in the formation of antibodies against mesalazine, with cross-reactivity to myocardium or pericardium [18]. Hypersensitivity is further evidenced by eosinophilic infiltration of the myocardium on myocardial biopsy along with a clear improvement following discontinuation of the drug [19,20]. Hypersensitivity appears to be an idiosyncratic reaction rather than dose dependant phenomenon due to its occurrence in patients on very low doses of mesalazine such as 0.5 gram a day [21,22].

Recognition of Mesalazine Related Cardiotoxicity

Mesalazine-induced cardiotoxicity is a rare but potentially serious complication. First reported in 1989, with the first death was reported in 1990 [23,24]. Cardiac events associated with mesalazine-induced toxicity include cardiomyopathy, myocardial infarction, conduction defects and ventricular dysfunction with a reported frequency of 0% - 0.3% [25,26]. Cardiogenic shock due to mesalazine related cardiomyopathy has also been reported [27]. So far, over 100 cases of myocarditis and pericarditis have been reported in the literature [28]. Myocarditis has been reported more in ulcerative colitis than Crohn's disease [29]. Most of the cases have been reported following systemic administration of mesalazine; however, topical preparations have also been responsible for cardiotoxicity in some cases [30]. Onset is usually within days to a few weeks after the initial exposure to the drug but may be delayed in patients on steroids [31,32]. This is in contrast to inflammatory bowel disease where cardiotoxicity usually occurs years after initial diagnosis, although it can occur at initial presentation as well [33,34]. Patients usually present with chest pain, fever and shortness of breath. On examination, pericardial rub is the usual finding in these patients [35,36]. Eosinophilia is sometimes seen on differential analysis of white cell count but not a constant finding [37,38]. Drug lymphocyte stimulation tests (DLSTs) for mesalazine has been reported to be positive in some cases [39]. Blood tests often show raised cardiac enzymes whereas electrocardiogram (ECG) usually reveals T wave changes [40,41]. Myocardial biopsy is the gold standard which usually shows eosinophilic infiltration of the inflamed myocardium but rarely performed due to safety reasons and availability of non-invasive imaging techniques such as echocardiography and Cardiac MRI, which offer an alternative with a good diagnostic yield [42,43]. There are no signs, symptoms or investigations that are pathognomonic of mesalazine-induced cardiotoxicity. Clinically, diagnosis is supported by two facts: it usually occurs within 2–4 weeks after initial exposure to the drug; and there is clear improvement following discontinuation of the drug.

Treatment

Treatment of mesalazine-induced cardiotoxicity consists of mesalazine discontinuation, use of analgesics and steroids. Discontinuation of the mesalazine is the mainstay of treatment and usually results in resolution of symptoms within days [33,35]. Steroids are commonly used to expedite the resolution of cardiotoxicity [44,45]. Non-steroidal anti-inflammatory drugs (NSAIDs) and colchicine are used for symptomatic control. However, these drugs should be used in low doses due to concerns regarding increased mortality related to their use [46]. NSAIDs may also exacerbate underlying inflammatory bowel disease in some patients so caution is advised regarding their use [47]. Treatment options for underlying inflammatory bowel disease then include thiopurines (azathioprine or 6-Mercaptopurine) and cytokine modulators (anti-TNF therapies) [48-51]. Advantages and disadvantages of thiopurines and anti-TNFs are shown in **Table 1** [52].

Rechallenge

Re-challenge with mesalazine or a different aminosalicylate (balsalazide or sulfasalazine) has been considered in some case reports but tolerated by a few patients only and in most cases there was a recurrence of cardiotoxicity. **Table 2** summarizes previously published cases of mesalazine-related cardiac toxicity

Table 1: Thiopurines and anti-TNFs.

	Thiopurines (Azathioprine, 6-MP)	**Anti-TNFs** (Infliximab, Adalimumab, Vedolizumab)
Indications	-Steroid dependant IBD -Fistulating Crohn's disease	-Treatment of IBD unresponsive to aminosalicylates, steroids and thiopurines -Fistulating Crohn's disease
Mode of action	Metabolised to 6-MP which in turn is metabolised to 6-thioguanine nucleotide (6-TGN) 6-TGN leads to inhibition of DNA synthesis	Tumor necrosis factor (TNF) blocking monoclonal antibodies
Dose	Azathioprine: 2-2.5 mg/Kg daily 6-MP: 1-1.5 mg/kg daily	Initially 5 mg/Kg by IV infusion at 0, 2 and 6 weeks Maintenance with 5mg/kg every 8 week
Advantages	-Oral preparation -Steroid sparing agent	Rescue treatment in flare-ups
Disadvantages	-Not used for induction of remission because takes 8-12 weeks to work -Side effects including leukopenia (4%), Pancreatitis (5%), hepatitis, Myalgia (15%), Lymphoma (<1%) -Require frequent monitoring of bloods	-Only parenteral preparation -Antibody formation (30%) resulting in loss of response -Risk of opportunistic infections -Requires monitoring of bloods
Comments	-Thiopurine methyl transferase (TPMT) levels should be checked before starting treatment (1 in 300 patients deficient and should be avoided in these patients) -Dose reduction (25%) in patients taking allopurinol	Acute infection, TB must be excluded before commencing treatment

Table 2: Re-challenge in patients with mesalazine-related cardiac toxicity.

Case	Age (Years)	Gender	Disease	Dose	Onset	Presentation	Cardiac disease	Treatment	Re-challenge /Recurrence
Sonu et al. [53]	20	F	UC	mesalazine (enemas) + 2g Sulfasalazine	3 week	Chest Pain	Myocarditis, Pericarditis	Ibuprofen and colchicine	Yes/Yes
Sabatini et al. [54]	22	M	UC	1.6 g	3 weeks	Chest Pain, fever	Myocarditis	Steroids	Yes/Yes
Park et al. [38]	26	M	UC	2.4 g	1 month	Chest Pain, Fever	Myocarditis, Pericarditis	Steroids	Yes/Yes
Bernal-Sprekelsen et al. [30]	54	M	UC	1.5 g	3 week	Chest Pain, Fever	Pericarditis, Pericardial Effusion	Symptomatic	Yes/Yes
Merceron et al. [17]	41	F	CD	ND	Years	Chest Pain	Myocarditis	Symptomatic	YES/YES
Freeman et al [44]	26	M	UC	1.6 g	3 week	Chest Pain, Fever	Myocarditis	Steroids	YES/NO
Ishikawa et al. [55]	17	M	UC	1.5 g	2 week	Chest Pain, Fever	Pericarditis, Pericardial Effusion	Steroids	Yes/Yes

in patients with inflammatory bowel disease, where a re-challenge was considered. Mesalazine was re-introduced in four cases, with the same dose in three cases and reduced dose in one case but there was recurrence of symptoms in almost all cases. In one case, balsalazide was tried but there was a recurrence of symptoms. Sulfasalazine was introduced in one case and there was no recurrence of symptoms.

Prognosis

If managed appropriately, cardiac dysfunction has been shown to resolve completely with a return to previous baseline function [33,39,53-58].

Conclusion

1. Cardiac involvement in patients with inflammatory bowel disease may represent an extra-intestinal manifestation or could be related to treatment with mesalazine.
2. Mesalazine-induced myopericarditis usually occurs within days to a few weeks of initial drug exposure but may be delayed due to concomitant steroid use.
3. A clear improvement following discontinuation of the drug helps to make the diagnosis.
4. Mesalazine-induced myopericarditis is successfully treated with drug discontinuation and steroids.
5. Re-challenge usually results in recurrence of cardiac involvement.
6. Cardiac dysfunction has been shown to resolve completely with a return to previous baseline function.
7. Inflammatory bowel disease can be managed with thiopurines and if not tolerated with anti-TNF therapies.

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