

Mesalazine treatment and urinary stones composed of mesalazine

Introduction

Mesalazine (5-aminosalicylic acid / 5-ASA) is indicated for *mild to moderate ulcerative colitis* and for *Crohn's disease*.

The mechanism underlying the anti-inflammatory effect of mesalazine is unknown; inhibition of lipoxygenase might play a role, effects on prostaglandin concentrations in bowel mucosa were shown, and mesalazine can act as binder of reactive oxygen compounds. The therapeutic effect of mesalazine occurs mainly locally on the bowel mucosa and the submucosal tissue on the luminal side of the bowel. Mesalazine and its metabolite N-Ac-5-ASA are excreted through the faeces (largest part), the kidneys (ranging between 20 and 50%, depending on the administration form, the galenic preparation and the mode of delivery) and the bile (smallest part). The renal excretion mainly occurs as N-Ac-5-ASA. Mesalazine was granted marketing authorization in the Netherlands in 1987 [1].

Urinary stones can have various compositions. It has been estimated that 0.44% of the urinary stones are formed by the precipitation of a drug or one of its metabolites [2,3].

Ulcerative colitis and Crohn's disease are chronic inflammatory diseases of the gastrointestinal tract. Frequently, patients with inflammatory bowel disease suffer from extraintestinal complications, including nephrolithiasis [4,5]. Inflammatory bowel diseases (IBD) and calcium oxalate stones are commonly associated, where it is assumed this results from intestinal inflammation, causing malabsorption of bile salts and fatty acids, leading to increased oxalate absorption and subsequent hyperoxaluria [6,7].

Recently results of a cohort study were published, showing that out of 2323 patients with IBD, kidney stones were described in 61 (4.6%) patients with Crohn's disease and 30 (3.0%) patients with ulcerative colitis. In this study male gender, disease activity, intestinal surgery, NSAID usage and reduced physical activity were significant risk factors [4].

Reports

From 16 April 2007 until 2 November 2018 The Netherlands Pharmacovigilance Centre Lareb received two reports of nephrolithiasis in association with the use of mesalazine [8]. In both cases the compositions of the urinary stones were not reported.

Report number NL-LRB-64812

This serious spontaneous report from a consumer concerns a male aged 51-60 years, with kidney stones following administration of mesalazine for Crohn's disease with a latency of several years after start. After the start of using mesalazine, the patient regularly experienced kidney stones, and the stone formation further increased after removal of the largest part of the colon because of Crohn's disease. Despite drinking a lot of fluids, kidney stones with sizes of 8 mm occurred, which blocked the urinary track. Several times the patient was admitted to the hospital. Two times temporary drains were inserted. The reaction was treated with sodium citrate and citric acid. The dose of mesalazine was not changed. The patient had not recovered at the moment of reporting. The composition of the stones was not reported. Concomitant medication was ferrogluconate.

Report number NL-LRB-00285679

This non-serious spontaneous report from a consumer concerns a female aged 31-40 years, who experienced kidney stones three times following administration of mesalazine for colitis with unknown latency. The dose of mesalazine was not changed. Treatment of the reaction included medication against pain. The outcome of the reaction was unknown. The composition of the stones was not reported.

Other sources of information

SmPC

The Dutch SmPC of mesalazine does not mention urinary stones composed of mesalazine, crystaluria, urinary stones or nephrolithiasis as adverse reactions. The SmPC of mesalazine does mention reduced renal function, including acute and chronic interstitial nephritis and renal impairment as a very rare (<0.01%) adverse drug reaction [1].

Beside mesalazine, two other aminosalicylate are available in the Netherlands, that is olsalazine and sulfasalazine [9].

The SmPC of sulfasalazine reports nephrolithiasis as adverse drug reaction with unknown frequency and reports the precaution to drink enough fluids because sulfasalazine can cause crystaluria and kidney stones. The paragraph "Overdosing" reports, that at intake of large amounts of the drug renal damage might occur because of crystal formation of the badly soluble sulfapyridin and its acetylderivates. Sulfasalazine is an azo bond of 5-aminosalicylic acid and sulfapyridine and the azo bond is split under the influence of bacterial enzymes into sulfapyridine and 5-aminosalicylic acid. Sulfapyridine is absorbed and acetylated in the liver. The largest part of 5-aminosalicylic acid is excreted unchanged with the faeces; the rest is absorbed and in acetylated form excreted with the urine [10].

The SmPC of olsalazine does not mention urinary stones, crystaluria or nephrolithiasis as an adverse reaction. Olsalazine consists of two molecules 5-aminosalicylic acid covalently bound by an azo bond and is almost completely converted to 5-aminosalicylic acid in the colon [11].

Literature

In the scientific literature two cases were described concerning urinary stones composed of mesalazine in association with treatment with mesalazine.

A 31-40 years old woman developed recurrent episodes of renal colic six weeks after initiation of oral mesalazine for ulcerative colitis. The medical history did not indicate renal stones. No concrements or dilatation of the ureters were visible on computer tomography of the urinary tract. During the course of 3-4 months, the patient experienced several episodes of flank pain and hematuria and several times the patient passed concrements in the urine. The biggest of the concrements was 6–7 mm, their shape varied from round to pellet-shaped, and they were yellowish-brown in color and easily crumbling. Initial chemical analysis of the stones was inconclusive regarding the composition of the stones. Further testing of the stones, demonstrated composites of mesalazine. The mesalazine was withdrawn and the patient did not experience symptoms of obstructive renal disease any more [12].

A 21-30 years old woman with ulcerative colitis, was treated with oral mesalazine 4 g, rectal mesalazine 500 mg, prednisone, potassium chloride and calcium carbonate. The medical history did not indicate urolithiasis. After two years of mesalazine treatment, the patient experienced colic pain of the left flank.

Non-contrast enhanced computed tomography (NCCT) did not show dilatation of the renal tract or a stone. One year later, the left renal colic occurred again. Again NCCT did not show dilatation of the renal tract or a stone. Eventually, the patient passed a soft, crumbly, orange-beige coloured stone in her urine (See figure 1). Morphological analysis and infrared spectrophotometry was performed, where the infrared spectrum revealed a 100% mesalazine composition. The patient received the recommendation of hyperhydration and the mesalazine was continued. There had been no recurrence eleven months later [13].



Figure 1. Macroscopic appearance of mesalazine stone.

Figure originating from the article: Corbery B, Lebdaï S, Borojeni S, Bigot P, Azzouzi AR, Culty T. Mesalazine: A Novel Etiology For Drug-Induced Urinary Calculi. Urol J. 2018 May 3;15(3):132-133 [13].

Databases

For the Lareb [8], Eudravigilance [14] and WHO databases [15], the ROR's were not calculated, because the PT nephrolithiasis may comprise stones of various compositions, and the ROR's were therefore considered not to be of added value for this Signal.

Eudravigilance database

On 2 November 2018 the Eudravigilance database contained 48 cases (including four possible duplicates based on the information available to Pharmacovigilance center Lareb) of urolithiasis in association with mesalazine [14]. More details of all these reports are described in the addendum.

Stones composed of mesalazine

In four reports (excluding possible duplicates) in the Eudravigilance database, urinary stones composed of mesalazine were described. Two of these reports were also reported in the scientific literature [12,13] and details of these two cases were describe in the paragraph "Literature" of this Signal. Details on the other two reports in the Eudravigilance database where stones composed of mesalazine were described, are described here:

Safety Report #EU-EC-10137585-DE-BFARM-15406153

This serious, spontaneous report from a German physician, concerned a 31-40 years old female, who experienced renal colic caused by ureteric stone during treatment with oral mesalazine Pentasa®, sachet 1 g, 2000 mg daily, for ulcerative colitis. Concomitant medication included Colifoam Rektalschaum®. The patient experienced ureteric stone. Analysis of the stone showed it was 100% mesalazine. About 3 months later, the patient experience more ureteric stones which spontaneously passed. Analysis showed again that it was 100% mesalazine. The treatment with mesalazine was discontinued. The patient recovered both times from the ureteric stones.

Safety Report #EU-EC-6186019-SE-FERRINGPH-SE-010313

This serious, spontaneous report from a Swedish physician, concerned a 31-40 years old male, who experienced nephrolithiasis during treatment with mesalazine Pentasa®, prolonged-release granules, 2 g, 4 g / 6 g daily for ulcerative colitis. The patient was diagnosed with IBD. Mesalazine Asacol® was initiated but due to hair loss, mesalazine Pentasa®, sachet 2 g 2+0+0 was initiated about 2 months after the diagnosis IBD. About 3 months after start of Mesalazine Pentasa® treatment was stopped, 1 day later followed by re-initiation of Mesalazine Pentasa® at an increased dose of 2 g 2+0+1. About 6 months after the initial start of Mesalazine Pentasa®, the patient started experiencing acute episodes of nephrolithiasis (9 episodes in 8 weeks). Lithiasis was not seen on the MRI, but the patient collected the stones and an analysis of the stones showed content of mesalazine. At the time of

reporting, the outcome was unknown. It was reported that mesalazine Pentasa® was stopped.

Other reports

In three reports in the Eudravigilance database, urinary stones with another composition were described, that is oxalocalcic stones in one report, 100% hydroxyl-apatite in one report, and 100% calcium phosphate in one report.

In the other reports no compositions of the stones were described in the information available to Pharmacovigilance Centre Lareb.

Prescription data

Table 2. Number of patients using mesalazine in the Netherlands [16].

Drug	2013	2014	2015	2016	2017
A07EC02 Mesalazine (Salofalk®)	49,521	49,185	49,476	50,605	50,630

Mechanism

In the four cases described in this Signal urinary stones that were composed of mesalazine were detected.

Discussion and conclusion

Pharmacovigilance center Lareb received two reports of urinary stones associated with the use of mesalazine. Of these reports the compositions of the stones were unknown. During additional analyses of the reports in the Eudravigilance database of urinary stones associated with mesalazine, four cases were detected concerning patients who were treated with mesalazine and experienced urinary stones that were composed of mesalazine. Two of these cases were also described in the literature. It may be possible that in some reports in the Pharmacovigilance databases of urinary stones in association with mesalazine where the compositions of the stones were not reported, these stones also concerned stones composed of mesalazine.

Corbery *et al.* described that mesalazine stones are radiotransparent on both radiography and CT [13]. Of the four cases described in this Signal (including the case described in the article by Corbery *et al.* [13]), in one case it was described that MRI had not shown lithiasis, and in two cases that the CT (in one case CT and in one case NCCT) had not shown concrements or dilatation of the ureters. In the other case no information was described concerning imaging.

Furthermore Corbery *et al.* described that the soft consistency of the mesalazine stones, may explain the absence of complete obstruction and therefore absence of dilatation of the renal cavities on the CT [13]. In two cases (including the case described in the article by Corbery *et al.* [13]), the consistency of the urinary stones was described. The consistencies were described as easily crumbling, and as soft, crumbly. In the other two cases no information on the consistency of the stones was available.

In one report it was described that initial analysis of the stones was inconclusive and that additional testing, demonstrated composites of mesalazine. In another report it was reported that morphological analysis and infrared spectrophotometry were performed, and the infrared spectrum revealed the mesalazine composition. In the other two reports no information was available concerning the way the stone analysis revealed its composition.

In three cases mesalazine was withdrawn after occurrence of the reaction, where two patients recovered from the reaction and in one report the outcome of the reaction was unknown at the moment of reporting. In one case the patient received the recommendation of hyperhydration and the mesalazine was continued, and there had been no recurrence eleven months later.

Based on the four reports described in this Signal, it is suggested that treatment with mesalazine can result in urinary stones composed of mesalazine.

References

1. Dutch SmPC mesalazine Salofalk® 250 mg / 500 mg maagsapresistente tabletten. (version date: 20-11-2017, access date: 28-11-2018) https://db.cbg-meb.nl/smpc/h11086_smpc.pdf;
2. Hess B. Drug-induced urolithiasis. *Curr Opin Urol.* 1998 Jul;8(4):331-4;
3. Daudon M, Donsimoni R, Hennequin C, Fellahi G, Le Moel G, Paris M, Troupel S, Lacour B. Sex- and age-related composition of 10 617 calculi analyzed by infrared spectroscopy;
4. Fagagnini S, Heinrich H, Rossel JB, Biedermann L, Frei P, Zeitz J, Spalinger M, Battegay E, Zimmerli L, Vavricka SR, Rogler G, Scharl M, Misselwitz B. Risk factors for gallstones and kidney stones in a cohort of patients with inflammatory bowel diseases. *PLoS One.* 2017 Oct 12;12(10):e0185193;
5. Bennett RC, Hughes ES. Urinary calculi and ulcerative colitis. *British medical journal.* 1972;2(5812):494-6;
6. Durando M, Tiu H, Kim JS. Sulfasalazine-Induced Crystalluria Causing Severe Acute Kidney Injury. *Am J Kidney Dis.* 2017 Dec;70(6):869-873;
7. Trinchieri A, Lizzano R, Castelnuovo C, Zanetti G, Pisani E. Urinary patterns of patients with renal stones associated with chronic inflammatory bowel disease. *Arch Ital Urol.* 74 (2) (2002), pp. 61-64;
8. Lareb database. (version date: 2018, access date: 2-11-2018) Search criteria: Generic Name mesalazine% and HLGT Urolithiasis. <http://www.lareb.nl/Bijwerkingen/Zoek-op-geneesmiddel>;
9. National Health Care Institute. Farmacotherapeutisch kompas. (version date: 2018, access date: 5-12-2018) <https://www.farmacotherapeutischkompas.nl/bladeren/preparaatteksten/m/mesalazine#groepsoverzicht>;
10. Dutch SmPC sulfasalazine Salazopyrine E.C.® 500 mg maagsapresistente tabletten. (version date: 9-8-2015, access date: 28-11-2018) https://db.cbg-meb.nl/smpc/h11086_smpc.pdf;
11. Dutch SmPC olsalazine natrium Dipentum® 250 mg harde capsules. (version date: 12-02-2015, access date: 5-12-2018) https://db.cbg-meb.nl/smpc/h11790_smpc.pdf;
12. Jacobsson H, Eriksen J, Karlén P. Mesalazine-induced renal calculi. *Am J Case Rep.* 2013 Dec 23;14:551-3;
13. Corbery B, Lebdai S, Borojeni S, Bigot P, Azzouzi AR, Culty T. Mesalazine: A Novel Etiology For Drug-Induced Urinary Calculi. *Urol J.* 2018 May 3;15(3):132-133;
14. Eudravigilance database. (version date: 2018, access date: 2-11-2018) Search criteria: Generic Name mesalazine% en HLGT Urolithiasis; the access of Pharmacovigilance center Lareb was limited to the narratives of the reports. <http://bi.eudra.org> (access restricted);
15. WHO Global Individual Case Safety Reports database (Vigibase). (version date: 2018, access date: 12-12-2018) <https://tools.who-umc.org/webroot/> (access restricted);
16. College for Health Insurances. GIP database. (version date: 19-7-2018, access date: 5-12-2018) https://www.gipdatabank.nl/databank#/g/B_01-basis/gebr/A07EC02.

This signal has been raised on February 7, 2019. It is possible that in the meantime other information became available. For the latest information, including the official SmPC's, please refer to website of the MEB www.cbg-meb.nl