EARLY RENAL FAILURE AFTER MESALAZINE (CASE REPORT)

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An early onset of asymptomatic renal failure in a young man with ulcerative colitis treated with high-dose mesalazine is the subject of this case report. After mesalazine withdrawal, renal function was quickly restored. In contrast with published case reports, the onset of renal impairment occurred very early. Serum urea reached pathological values 27 days and serum creatinine 15 days after mesalazine treatment was started. The diagnosis of renal impairment was supported by urine analysis (both semi-quantitative and quantitative) and dynamic renal isotope scanning.

5-Aminosalicylic acid (5-ASA) is the first line therapy for inflammatory bowel disease. It can be administered as sulfasalazine (5-ASA + sulfapyridine), mesalazine (5-ASA + resins) or olsalazine (5-ASA + 5-ASA). The recent trend prefers mesalazine and olsalazine to sulfasalazine due to their lesser frequent adverse effects but its potential myelotoxicity, hepatotoxicity and nephrotoxicity still must be considered^{2,3}.

Nephrotoxicity is manifested as indolent interstitial nephritis that – if not diagnosed and treated – can progress to terminal renal failure even after preparation withdrawal. Nephrotoxicity must be suspected in any case of renal function impairment in a patient treated with 5-ASA².

All published cases of renal failure due to mesalazine were caused by tubulointerstitial nephritis, usually confirmed with renal biopsy. There was no difference between number of patients with ulcerative colitis and Crohn disease. All the patients were young people under 34 years of age (20 to 34 years), more frequently men (86%) than women (14%). Patients used 1.2 to 3 g of mesalazine daily at least for 12 months (interval 12 months to 7 years). Previously reported cases describe chronic interstitial nephritis occurring after months to years of mesalazine use^{1,2,3,5,6,7,8,9}. We report the case of a young man with asymptomatic renal failure development after three weeks administration of mesalazine.

CASE DESCRIPTION

23-year-old university student suffered for three years from diarrhea, sometimes with blood in stools, and from painful rectal discomfort. He visited a physician first time on November 9th 1999, few days after fever, abdominal pain, anorexia and weight loss had occurred. So

far he was not ill and did not take any drugs. Sigmoidoscopy showed proctocolitis of grade II.–III. 30 cm from anus, other parts of colon were not examined due to pain. The diagnosis of ulcerative colitis was confirmed by biopsy of mucosa. The out-patient treatment started with Asacol orally (mesalazine 2.4 g daily), Salofalk enemas (4g of mesalazine daily) and iron substitution (Aktiferrin comp. 2 × 1 tbl.)

Two weeks of home treatment with mesalazine was not successful and on November 23rd the patient was admitted to our hospital. The treatment continued with the oral administration of prednisolone 60 mg daily, Salofalk (mesalazine 1.5 g daily), famotidine, iron, paracetamol and metronidazol. Since the 6th day of hospitalization gentamicine had been administered for four days (240 mg in intramuscular injection, since November 29th to December 2nd 1999). Hydrocortisone 300 mg daily in saline intravenous infusion was added on December 3rd for persisting bloody diarrhea, fever and abdominal pain and the mesalazine dose (Asacol) was raised to 3.2 g daily. Both parenteral (Nutriflex peri 2 200 ml daily) and enteral (Nutrison standard 1000 kcal per day) nutritions were administered.

During hospitalization asymptomatic renal failure developed. Serum urea and creatinine rapidly increased, the highest level reached on December 7th 1999, after 29 days of mesalazine administration (urea 15.8 mmol/l, creatinine 202 µmol/l – see Table 1). Simultaneously isostenuria (urine specific weight 1010), proteinuria and leukocyturia occurred that persisted after mesalazine withdrawal (see Table 2).

The quantitative urine analysis corresponded: high leukocyturia (16 667 elem./min – normally 0–4000) and mild proteinuria. Erythrocytes 1667 elem./min. (normal), cylinders 0, specific weight 1010.

Serious immunologic abnormalities were not found: autoantibodies (ANF, ANCA, revmatoid factor) were negative, circulating immune complexes normal, complement C3 and C4 measurement slightly lower. Serum immunoelectrophoresis – non-significant increase in the all groups of immunoglobulines and higher increase in IgA: IgM 2.95 g/l (normally under 2 g/l), IgA 6.65 g/l (normal range 1.5–4.0), IgG 20 g/l (normal range under 15 g/l), IgE 173 g/l (normal under 150 g/l). Serum proteinase 3 and myeloperoxidase were negative.

The functional renal examination: decreased glomerular filtration rate (0.73 ml/s) and tubular resorption (0.974). Repeated urine cultures brought negative results. The ultrasound: normal ultrasonographic image of both kidneys. The patient's diuresis at the beginning was normal, later during restitution of the renal function polyuria appeared (see Table 2).

During the period of maximal renal function impairment the patient underwent dynamic renal isotope scanning. The excretion started in time but it was considerably slowed down. Kidneys were normally shaped, radioisotope transport slowed down, relatively more at the left side (left kidney excretion half-time 148 minutes, maximal transit time 810 seconds, right kidney excretion half-time 50 minutes, maximal transit time 290 seconds). Kidney biopsy was not carried out.

Since the patient had never been treated for any kidney disease or diabetes mellitus, had not any symptoms or clinical signs of previous renal impairment, had been well-hydrated and without fever and all other investigations had not explicitly shown bilateral renal parenchyma impairment, we considered a role of the mesalazine nephrotoxic effect. This effect was consecutively confirmed by rapid normalization of both renal function and urine findings after mesalazine withdrawal.

On December 8th 1999 Asacol was withdrawn and the ulcerative colitis treatment continued only with corticosteroids. During a short time period serum urea and creatinine decreased to normal levels, glomerular filtration rate increased partially (December 20th 1999: 1.26 ml/sec, normally 2.19 ml/s, i.e. minus 38%) and proteinuria disappeared. Polyuria, isostenuria and leukocyturia persisted (see Table 2). The patient was discharged after 18 days of hospitalization was in good condition, without fever or colitic symptoms, treated only with prednisolone (40 mg daily).

4 and 8 weeks after discharge is the patient without problems. Laboratory findings after 8 weeks showed neither signs of the ulcerative colitis activity nor renal impairment (negative chemical and microscopic urine analysis, urine specific weight 1023, urea 4.1 mmol/l, creatinine 82 µmol/l).

DISCUSSION

The recent trend in the therapy of IBD prefers 5-ASA preparations, especially mesalazine, to sulfasalazine for frequent adverse effects, linked usually to contained sulfapyridine. However, mesalazine treatment has its risks - and tubulointerstitial nephritis as obviously most serious of them. Laboratory tests in rats have proved the nephrotoxic effect of mesalazine after its short-time intravenous application¹².

5-ASA is released in the colon, after the resin coat dissolution of the mesalazine tablet. Then about one fifth of mesalazine is absorbed and later excreted by kidneys. Tubular and papillary necrosis after 5-ASA had been proved in the early 1970s¹², cases of nephrotic syndrome both after sulfasalazine¹¹ and mesalazine¹⁰ were described in the 1980 s. Nephrotoxicity was most frequently described with the preparation Asacol – the reason can be that the preparation has been sold for the longest time^{2, 3, 6}.

The 5-ASA structure is similar to that of salicylates and phenacetine and 5-ASA can cause nephropathy like the non-steroid antiinflammatory drugs (NSAIDs) – and the nephropathy reminds one of analgetic nephropathy characterized by interstitial nephritis and papillary necrosis^{6, 9}. The comparison of acetylsalicylic acid (ASA) and its derivatives (3-, 4- and 5-Aminosalicylic acids) cytotoxicity on in vitro cell cultures have not been found to have any characteristic nephrotoxic effect. The explanation of tubulointerstitial nephritis after 5-ASA has not been found yet⁴.

104 cases of renal impairment or pathological urinary tests connected with the mesalazine treatment have been reported during the past 13 years (1985–1998) in Great Britain (Committee on Safety of Medicines). 35 cases (33.7%) involved interstitial nephritis².

Exact incidence of the complication is not known but it is estimated to be about one percent of patients treated with mesalazine and cases of clinically important interstitial nephritis are less than one in 500 patients treated with mesalazine².

Bioptic samples mentioned in literature showed both glomerular and tubular damage, usually with plasmocytic and eosinophilic infiltrates^{1, 2, 9}.

Severe chronic and progressive interstitial nephritis is the most frequent clinical form, that appears after few months of treatment – all described cases involve the mesalazine administration for at least 12 months, the diagnosis was made even after 7 years of the continual treatment in a case⁷. The early signs were sterile pyuria and the low urine specific weight, as in salicylates⁶.

Usually, the renal impairment was asymptomatic, unveiled by regular follow up during hospitalization, for the relapse of IBD^{1, 2, 3, 6}. Only in one of the cases⁵ there were six months of weight loss, fatigue and dyspnea and another case showed “foamed” urine, which was noticed by the patient².

If the mesalazine nephrotoxicity is diagnosed earlier than 10 months after the treatment started, the renal

function restoration after withdrawal is observed in 85% of patients. Only the partial improvement of renal function can be expected in one third of patients after 18 months of the treatment². The prognosis is uncertain⁶.

The precise mechanism of impairment is not clear, but most probably it is a type IV hypersensitivity reaction².

Renal failure in our patient, contrary to cases published so far, has developed very early. The serum urea level reached to a pathological value after 27 days. Also the creatinine level rose 15 days after the mesalazine administration started and progresses rapidly.

Gentamicine influence at renal function can be passed – the therapy started later and lasted only for 4 days. Also the influence of prerenal mechanism (dehydration) can be excluded – the patient has been well-hydrated all the time.

The rapid progress of renal failure as described here is quite unusual but other features are characteristic – a young man with high doses of mesalazine and asymptomatic renal failure, was retreated after mesalazine withdrawal.

Mechanisms of renal impairment can be only supposed – some features (allergy in patient's history, higher serum IgE and a quick onset and regression of renal damage) could lead to thoughts about the first type hypersensitivity reaction but other characteristic signs and symptoms were missing (rash, urtica or eosinophilia).

CONCLUSION

The case of asymptomatic renal failure with an early onset in a young man with ulcerative colitis treated with high-dosed mesalazine is the subject of this case report. Quick and complete restoration of renal function succeeded after mesalazine withdrawal. The 5-ASA nephrotoxicity must be considered in any patient treated with this drug. Serum urea and creatinine should be checked monthly for the first three months, 3-monthly for the remainder of the first year and annually thereafter and in every relapse of IBD or clinical signs of renal impairment.

The 5-ASA therapy in a patient with known history of its nephrotoxicity should be stopped, instead the patient should be treated with a long-time treatment using prednisolone or prednisolone + azathioprine^{1, 2, 3, 11}.

Table 1. Asymptomatic renal failure

Serum levels of urea and creatinine

Date (days of mesalazine administration)	24.11.99 (15 days)	7.12.99 (29 days)	17.12.99
Urea (mmol/l)	4.6	15.8	6.0
Creatinine (μmol/l)	126.2	202.0	99.0

Table 2. Urine analysis

	24.11.99	7.12.99	9.12.99	13.12.99
Protein	1	3	1	0
Leucocytes	40-50	10-15	4	10
Erythrocytes	0-4	1	0	0
Spec. Weight (kg/m ³)	1010	1010	1010	1010
Diuresis (ml/day)	1500	2500	3000	3000

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