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Montelukast sodium-induced hematuria: a case report and literature review of 19 cases in mainland China

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Key words

montelukast sodium –
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– psychiatric disorders
– hematuria – rash –
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Abstract. We report a rare case of montelukast sodium-induced hematuria in a 58-year-old female patient with allergic rhinitis. Renal function returned to normal after drug withdrawal. We reviewed 19 case reports of adverse reactions associated with montelukast sodium in mainland China and found that (1) 37% of patients were pediatric patients, (2) psychiatric disorders, rashes and uropoietic organs symptom were common, (3) uropoietic organ symptoms reported in mainland China were very rare abroad. The clinician in China should be vigilant about the adverse reaction of montelukast sodium and further studies are needed to explore the pathogenesis of montelukast-induced uropoietic organ symptoms.

Introduction

Montelukast sodium is a selective and orally active leukotriene receptor antagonist that inhibits the cysteinyl leukotriene CysLT₁ receptor. Montelukast sodium is indicated for the prophylaxis and chronic treatment of asthma in adults and pediatric patients [1]. It is also used for the relief of symptoms of allergic rhinitis [2]. Here we report a rare case of gross hematuria in a patient with allergic rhinitis after montelukast sodium administration. We also performed a literature overview on adverse drug reaction (ADR) caused by montelukast sodium in mainland China [3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17].

Case report

A 58-year-old woman received Singulair® (montelukast sodium) 10 mg every night for treatment of allergic rhinitis. She developed

total gross hematuria on Day 3 of drug administration. No other symptoms were found in clinical observation. After referral to our hospital, Type B ultrasonic examinations of both kidneys, ureter and bladder revealed no significant pathologic changes in these organs. The urine sediment examination showed: pH 7.5, protein (++) , WBC 1.2/HP, RBC 125/HP. Blood test showed: BUN 5.8 mmol/l, SCr 96 µmol/l, Ca²⁺ 2.52 mmol/l, K⁺ 3.5 mmol/l, Na⁺ 128.5 mmol/l, Cl⁻ 89 mmol/l, Mg²⁺ 0.9 mmol/l. The pathogenesis of hematuria needed to be checked. Gross hematuria was improved on Day 7 of montelukast sodium withdrawal. Two weeks later, renal function returned to normal.

The patient had no history of drug and food allergy. She did not take other medications, over-the-counter drug or herbal products after initiation of therapy with montelukast sodium.

Literature review

We searched the montelukast ADR reports using the keywords “montelukast” in CNKI, WANFANG and VIP databases in mainland China spanning 15 years (1999 to 2013). We finally obtained 15 articles related to ADRs with repeated reports excluded (Table 1). There were a total of 19 ADR cases including the present one.

In these cases, all patients took Singulair® (montelukast sodium) adequately and had no history of montelukast allergy. ADRs induced by montelukast sodium, which were reported more than once, included mental symptoms (5 cases), erythema (4 cases), uropoietic system symptoms (3 cases), gastro-

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Table 1. Description of the 15 ADR literatures concerning montelukast in mainland China.

References	Age (years)	Sex	Dose (mg/day)	Symptoms of ADR	Time to ADR onset	Serious	Intervention	Concomitant drug
Li et al. (2005) [3]	4	F	4	Sleeping disorder,	3-4days	N	Drug withdrawal	Procaterol
	2	M	4	Diarrhea	1 week	N	Drug withdrawal	Beclometasone dipropionate aerosol, salbutamol sulfate aerosol
Chen et al. (2007) [4]	12	F	5	Enuresis	2 days	N	Drug withdrawal	Ketotifen tablets
Yang (2008)[5]	30	M	10	Hives urticaria	5 days	N	Drug withdrawal	Fluticasone aerosol
Hou (2008) [6]	51	F	10	Erythra	3 days	N	Loratadine was given	None
He (2008) [7]	72	M	10	Diarrhea	2 days	N	Drug withdrawal	None
	64	F	10	Headache	30 min	N	Paracetamol was given	None
Gao et al. (2008) [8]	5	F	5	Knee arthralgia	1 days	N	Drug withdrawal	None
Li et al. (2008) [9]	73	M	10	Dysuria	1 days	N	Drug withdrawal	None
Gao et al. (2009) [10]	76	M	10	Eosinophilia, fever, cough	28 days	N	Symptomatic treatment	Sulbactam+cefoperazone, aminophylline, ambroxol
Zhang et al. (2009) [11]	44	M	10	rash	5 days	N	Symptomatic treatment	Compound methoxyphenamine, salmeterol xinafoate, fluticasone propionate powder for inhalation
Zhu et al. (2009) [12]	38	F	10	rash	4 days	N	Drug withdrawal	None
Zhang (2011) [13]	74	M	10	Drug hepatitis	6 days	Y	Symptomatic treatment	Loratadine, nifedipine, finasteride, alfuzosin
Li et al. (2011) [14]	5	M	5	Excitation	2 days	N	Drug withdrawal	Azithromycin, procaterol hydrochloride tablets, budesonide nebulising suspension
Li et al. (2011) [15]	72	M	10	Tremor	16 days	N	Drug withdrawal	Aminophylline, bromhexine, cefoperazone+tazobactam
Fei (2012) [16]	86	M	10	Excitation	1 days	N	Drug withdrawal	Cefoxitin, ambroxol, salbutamol, budesonide suspension
Pu et al. (2012) [17]	6	F	5	Inattention	4 days	N	Drug withdrawal	Salbutamol sulfate, pulmicort respules
	3	M	4	Excitation	3 days	N	Drug withdrawal	Pulmicort respules, procaterol hydrochloride tablets
Present patient	58	F	10	Hematuria	3 days	Y	Drug withdrawal	None

F = female; M = male; N = no; Y = yes.

intestinal symptoms (2 cases), and locomotor system symptoms (2 cases). The shortest time from exposure to ADR was 1 day (knee arthralgia) and the longest time was 4 weeks (eosinophilia) [8, 10]. It is noteworthy that 37% (7/19) of patients reported in mainland China are pediatric patients, and in these patients the adverse reactions included psychiatric disorders (4 cases), diarrhea (1 case), knee arthralgia (1 case) and enuresis (1 case). The mean time to onset of ADRs in 7 pediatric patients was 3 ± 1.3 days. Table

2 summarizes adverse reactions caused by montelukast in 19 patients. Time from exposure to onset of erythema, mental symptoms, gastrointestinal symptoms, uropoietic system symptoms and locomotor system symptoms were 4–5, 2–4, 2 and 7, 1–3, 1 and 16 days, respectively. Two of the ADRs were classified as serious (drug hepatitis and hematuria) [13]. All reported patients recovered. In 13 of these 19 cases the drug was withdrawn successfully. 12 patients were treated with other drugs concomitantly, in-

Table 2. ADR symptom distribution.

ADR diagnosis	Patients	Percentage (%)
Psychiatric disorders	5	26
Rashes	4	21
Uropoietic system symptom	3	16
Diarrhea	2	10
Locomotor system symptom	2	10
Others*	3	17

*headache, eosinophilia, drug hepatitis.

cluding 7 patients who were treated concomitantly with inhaled corticosteroids.

Discussion

In the present case, gross hematuria was probably caused by montelukast sodium because of the temporal relationship between the use of montelukast sodium and the development of hematuria. The Naranjo probability scale showed a probable relationship between hematuria and montelukast treatment. We got only one record after searching PubMed using the keywords “hematuria AND montelukast” [18]. This report describes a 77-year-old Japanese woman who was treated for bronchial asthma with a combination of inhalant corticosteroid with β_2 -agonist and montelukast for 15 months. She developed Churg-Strauss syndrome (CSS) with microscopic hematuria. Urinary findings became normal rapidly after treatment with oral prednisolone at an initial dose of 40 mg. Bibby et al. [19] concluded that leukotriene receptor antagonist (LTRA) treatment was a suspect medication in most reported cases of CSS.

It is known that CSS is characterized by symptoms of asthma, allergic rhinitis and marked increase in peripheral eosinophils. Almost 13% of CSS patients had renal symptoms. Patients with renal CSS symptoms often presented with microscopic hematuria and only rarely with severe renal symptoms. The clinical symptoms and signs of CSS were different. In the present case, it is possible that the woman had a subclinical form of CSS, and hematuria occurred through CSS aggravated by montelukast sodium, or CSS was an anaphylactic reaction

to montelukast therapy [20]. However, it was not known whether the patient had already developed CSS, and the underlying cause of gross hematuria due to use of montelukast is still unclear. CSS caused by montelukast has not been reported in mainland China.

Montelukast has proven to be safe and well tolerated in adults and children [21, 22, 23]. The most common published ADRs related to montelukast sodium in mainland China were psychiatric disorders, rashes and uropoietic organ symptoms. Psychiatric disorders include excitation (3 cases), inattention (1 case) and sleeping disorder (1 case). The mean time to psychiatric disorder onset was 2.5 ± 1 day and in all cases the drug was withdrawn successfully. Among the patients experiencing psychiatric ADRs, 4 were children (3 – 6 years of age) who developed excitation, sleeping disorder and inattention. The psychiatric disorders induced by montelukast were reported abroad [24, 25]. Wallerstedt et al. [24] analyzed all reports of psychiatric disorders during montelukast treatment in children (< 18 years) in the Swedish ADR database SWEDIS (1998 – 2007) and concluded that psychiatric disorders caused by montelukast seem to be reported often in small children, and 80% of children from the time of exposure to ADR was less than 1 week. The US Food and Drug Administration (FDA) reports a suspected association between montelukast and depression, suicidal thinking and behavior, but the published case reports concerning the same symptoms are not reported in the authority database of mainland China. The 4 patients who developed rashes were adults and rashes included Hives urticaria (1 case), the type of skin eruption of the others was not reported. Time from exposure to erythema was 3 – 5 days and we assumed an immunoallergic pathogenesis. The same case report was published abroad [26]. PubMed was searched using the keywords “montelukast AND enuresis” and “montelukast AND dysuria”, respectively, but the search was negative. In all cases the withdrawal of the drug was successful and the pathogenesis is still unclear.

We reviewed the latest prescribing information for Singulair® (montelukast, 8/28/2009) of the FDA and the Singulair® package insert revised by the FDA (12/2010). The ADRs associated with montelukast

which were reported in mainland China were also mentioned by the FDA except for the uropoietic system symptoms (enuresis, dysuria and hematuria). The FDA classified headache, fever, cough and diarrhea as the most common adverse reactions of montelukast (incidence $\geq 5\%$ and greater than placebo). Psychiatric disorders and rashes (incidence 1.6%, FDA) induced by montelukast that were frequent in case reports in mainland China were not included in the FDA list. These ADRs are reported voluntarily from a population of uncertain size, so it is impossible to evaluate their incidence. The reasons for the differences between the FDA data and the cases in mainland China might involve race difference and the difference between ADR symptom proportion and incidence.

In summary, it is worth noting that in mainland China there is a high percentage of children (37%) who developed adverse reactions after treatment with the drug. Psychiatric disorders, rashes and uropoietic organ symptoms were frequent. Among the patients who developed psychiatric disorders 80% were ≤ 6 years old. The reports of uropoietic organ symptoms associated with montelukast that were reported in mainland China were very rare worldwide. Further studies should investigate the pathogenetic mechanism of montelukast-induced uropoietic organ symptoms.

Conflict of interest

None.

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