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Adverse events associated with weight-based, high-dose montelukast exposures in children

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TO THE EDITOR

Corticosteroids are the only U.S. Food and Drug Administration (FDA) approved anti-inflammatory treatment for acute asthma exacerbations but do not target leukotriene (LT) mediated inflammation.[1] Montelukast is an LT receptor antagonist (LTRA) approved by the FDA for chronic treatment of allergic rhinitis and asthma and for prevention of exercise-induced bronchospasm. However, LTRAs are not approved for treatment of acute asthma exacerbations. This letter reports adverse events associated with weight-based doses of single-agent, high-dose (defined as 50 mg) montelukast ingestions by children. This data will inform dose-ranging studies of high-dose oral montelukast to treat acute asthma exacerbations.

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LT synthesis by airway cells is induced by viral respiratory infections and aeroallergens. Untreated LT-mediated inflammation may explain why 17% of children with acute asthma exacerbations do not respond to systemic corticosteroids.[2] Non-response to corticosteroids has motivated investigators to assess montelukast as a treatment for acute asthma exacerbations. Randomized trials of intravenous (IV) montelukast for moderate and severe acute asthma exacerbations in adults demonstrated rapid and sustained improvement of lung function.[3] This benefit was observed as early as 10 minutes after administration and was maintained over 2 hours.

However, the IV formulation was never submitted for FDA approval, and clinical trials of oral montelukast for acute asthma exacerbations have been proposed. The total drug exposure after a 10 mg oral chewable tablet, expressed by the area under the plasma concentration time curve, was comparable to that of 9 mg of the IV preparation in adults, though peak concentrations were lower after the chewable tablet.[4] With this in mind, a sufficient dose of oral montelukast might rapidly achieve plasma concentrations that will improve lung function in children with acute asthma exacerbations.

We used data from the National Poison Data System (NPDS) of the American Association of Poison Control Centers to examine adverse events associated with single, weight-based, high-dose montelukast ingestions in children for calendar years 2000 – 2016.[5] As noted in our prior report, we used the NPDS variables “Substance Certainty,” “Quantity” and “Unit” as filters to identify the lowest possible montelukast dose ingested; a study limitation is potential error in lowest dose ingested.[5]

Body weight was available for 312 of 618 individuals with high-dose ingestions, with median [interquartile range, IQR] age 6 [5, 8] years, 173 (55%) male gender, weight-based ingested dose 3.3 [2.4, 4.7] mg/kg and dose range 0.5 – 17.8 mg/kg. For comparison, the FDA-approved montelukast dose of 5 mg daily for children 6 – 14 years of age is approximately 0.25 mg/kg for age 6 years and 0.10 mg/kg for age 14 years, based on 50th percentile body weights at these ages.

Among the 312 individuals with body weight available, 18 had 1 and 2 had 2 adverse events (Table 1). In a multivariable logistic regression model there was a trend toward increased adverse events with increasing mg/kg doses 50 mg (adjusted odds ratio 1.16, 95% CI 0.97 – 1.38, P = 0.10) after adjustment for age and gender.

These data, on a large number of children, demonstrate that weight-based doses of montelukast that greatly exceed approved daily doses are rarely associated with adverse events, and provide some assurance that clinical trials of high-dose oral montelukast in children with acute asthma exacerbations could be safely performed.

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Table 1.

Adverse events reported in 20 patients aged 5 – 17 years after 50 mg montelukast primary exposures reported to NPDS for calendar years 2000 – 2016.

Adverse event	Age (years)	Ingested dose (mg/kg)
Drowsiness or lethargy	5	9.4
	8	5.1
	5	3.2
	9	2.1
	6	1.9
	14	0.8
Nausea or vomiting	5	7.3
	5	3.9
	5	2.7
	17	2.2
	13	0.9
Abdominal pain	7	12.0
	8	11.7
	*8	2.3
	6	1.6
Dizziness or vertigo	*5	3.7
	11	0.9
Headache	*5	3.7
	8	3.1
Agitation or irritability	5	6.6
Diarrhea	*8	2.3
Tachycardia	7	2.1

Events are not mutually exclusive (*Had 2 adverse events).

Abbreviation: NPDS, National Poison Data System