Adverse Reactions to Antihistamines More Common than Thought

By Diana Phillips

Antihistamines are associated with a variety of adverse reactions in children, including headaches, sleepiness, rashes, behavioral changes, and convulsions, new research suggests. Although prior studies have suggested that newer antihistamines have few adverse reactions in children, there are some reactions worth noting, according to Tjalling W de Vries, MD, from the Department of Pediatrics, Medical Centre Leeuwarden, the Netherlands, and Florence van Hunsel, PharmD, PhD, from the Netherlands Pharmacovigilance Centre Lareb, Den Bosch, the Netherlands.

"[T]he [adverse drug reactions (ADRs)] we found were never described in these safety studies, which were all sponsored by the manufacturers." They continue, "When prescribing antihistamines, clinicians should be aware of ADRs such as somnolence, altered behaviour, skin eruptions and headache. Moreover, there is a possible relation between convulsions and (des)loratadine."

Dr. de Vries and colleagues report their findings in an article published online April 18 in the *Archives of Disease in Childhood.* They reviewed data from children aged 0 to 18 years with adverse reactions to systemic antihistamines reported to the Netherlands Pharmacovigilance Centre Lareb between 1991 and 2014. Reactions to promethazine and deptropine were excluded from the analysis, "because prescribing promethazine for children was discouraged after multiple reports of serious ADRs, and deptropine was marketed only in the Netherlands and withdrawn for the same reason," the authors explain.

A total of 228 reports extracted from the database met review criteria. Of those, 16% referred to desloratadine, 15% to loratadine, and 13% to ketotifen. Five serious ADRs were reported, including Malignant neuroleptic syndrome and death in a 4 year old girl after use of alimemazine as a sedative, which is administered at a much higher dose (2 mg/kg) than for allergy treatment (0.25 mg/kg). Atrioventricular reentry tachycardia in a 14 year old boy after taking azithromycin for respiratory tract infection and fexofenadine for allergy after an 8 day latency period. In this patient, "[c]oncomitant drugs were nasal fluticasone and inhaled fluticasone/salmeterol 100/50 µg twice daily," the authors write, noting that the causal relationship was deemed probable for the drug.

Convulsions in three children: an 11 year old girl who took loratadine, as well as cromoglicic acid and salbutamol (relationship deemed possible); a 2 year old girl who had convulsions after taking loratadine, with a latency of 3 days after starting treatment (relationship deemed possible); and a 16yearold boy who experienced tonic clonic seizures after administration of desloratadine for an allergy to grass pollen, with a latency of 8 days after treatment initiation

(relationship deemed probable). Reports of non-serious adverse drug events included headache (n = 16) after treatment with levocetirizine, terfenadine, loratadine, desloratadine, cetirizine, and fexofenadine; somnolence (n = 12) with cetirizine, levocetirizine, desloratadine, astemizole, cyproheptadine, dimetindene, fexofenadine, oxatomide, oxomemazine, and dexchlorpheniramine; aggression (n = 9) with ketotifen, desloratadine, cetirizine, levocetirizine, and cyproheptadine; and hyperactivity (n = 5) with desloratadine, ketotifen, terfenadine, loratadine, and dementindene.

Skin eruptions of various types, observed in 33 patients, "were reported after nearly all antihistamines," including cetirizine, desloratadine, loratadine, terfenadine, ketotifen, oxomemazine, levocetirizine, fexofenadine, astemizole, dimetindene, oxatomide, and dexchlorpheniramine.

"Details of all serious ADRs have not been published. However, the published safety studies we found were all sponsored by the manufacturers, which might have led to bias," the authors note. The strength of the current review is the breadth of the study material, which "consisted of all paediatric ADRs reports on systemic antihistamines located in the database of the Netherlands Pharmacovigilance Centre Lareb," the authors write.

However, reporting is voluntary, which may lead to underreporting, and there remains uncertainty around causality. "On the other hand, because reporting is voluntary, it will occur only when patients, parents or professionals suspect a correlation," the authors write. In this regard, "[a] voluntary reporting system provides early warnings of drug related harm."

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