THE OFFICIAL NEWSMAGAZINE OF THE AMERICAN ACADEMY OF PEDIATRICS
AAP News

New labeling on TMP-SMX products warns of acute respiratory failure

by from the Food and Drug Administration's Office of Pediatric Therapeutics and Center for Drug Evaluation and Research, Division of Pediatric and Maternal Health, Division of Anti-Infectives, and Office of Surveillance and Epidemiology

New warnings have been added to the labeling for trimethoprim-sulfamethoxazole (TMP-SMX) products regarding the risk of acute respiratory failure.

The Food and Drug Administration (FDA) approved revised labeling for Septra and Septra DS (double strength) tablets, Bactrim and Bactrim DS tablets and Bactrim injection and pediatric suspension. The updated labeling includes new safety information on acute eosinophilic pneumonia, acute and delayed lung injury, interstitial lung disease and acute respiratory failure resulting in prolonged mechanical ventilation, extracorporeal membrane oxygenation (ECMO), lung transplantation or death.

Labeling for other TMP-SMX products is being updated with the new safety information.

The warnings come after a case series published in June 2019 described severe acute respiratory failure related to TMP-SMX treatment in five previously healthy adolescents within days to weeks of TMP-SMX initiation (Miller JO, et al. *Pediatrics*. 2019;143:e20183242). Four patients required prolonged ECMO support, one underwent a heart and lung transplant, and two died. Four of the adolescents had been prescribed TMP-SMX for treatment of acne vulgaris, an unapproved indication.

The FDA assessed the potential risk of acute respiratory failure by reviewing the five case reports, searching the FDA Adverse Event Reporting System and the National Electronic Injury Surveillance System - Cooperative Adverse Drug Event Surveillance, conducting a literature search and evaluating claims data using the FDA Sentinel System. The FDA also required the drug manufacturer to review its postmarket safety database.

Through these inquiries, the FDA and drug manufacturer identified additional cases of respiratory failure with likely causal relationship to TMP-SMX.

The incidence rate of acute respiratory failure related to TMP-SMX could not be reliably established due to the small number of cases and data limitations.

The mechanism of pulmonary toxicity related to TMP-SMX, particularly in previously healthy individuals, has not been elucidated. Clinicians should obtain a history of TMP-SMX exposure in otherwise healthy pediatric and adult patients presenting with severe acute respiratory failure of unclear etiology.

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