Use of asthma drugs and risk of hepatotoxicity in children: a population-based, case-control study

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Background: Hepatotoxicity in relation to asthma drugs is rare. Some cases of hepatotoxicity have been described with use of Leukotriene Receptor Antagonists (LTRA). Our previous research on signal detection in children showed a new potential association between flunisolide, an inhaled corticosteroid, and liver injury.
Objective: To investigate the association between oral and inhaled use of asthma drugs and hepatotoxicity in children and adolescents.
Methods: A population-based case-control study was performed over 2000-2008 combining three European electronic primary care databases: The Integrated Primary Care Information database in the Netherlands, plus the PEDIANET and the Health Search/CSD Longitudinal Patient Database in Italy. Cases of hepatotoxicity in the pediatric population (<18 years old) were identified and validated in each database, retaining only idiopathic cases. Up to 100 controls were matched to each case based on age, gender and the date of case diagnosis (index date). Use of antiasthmatics was classified as current if a prescription for the drug of interest lasted until index date or ended within 60 days prior to the index date.
Results: We identified 938 pediatric cases of hepatotoxicity and these were matched to 93,665 controls. Significant unadjusted associations were found for current inhaled use of β_2-adrenergic agonists [OR 2.3 (95% CI, 1.6 to 3.4), corticosteroids (2.3, 1.7 to 3.2), cromoglicic acid/nedocromil (3.3, 1.1 to 10.6) and oral use of LTRA (2.6, 1.1 to 5.8), compared to non-use. When adjusting for concurrent use of antibiotics, the association remained significant only for the use of β2-agonists and corticosteroids. Use of LTRA was associated with an increased risk estimate of hepatotoxicity (adj. OR 1.8, 0.8 to 4.0), but no longer significant.
Conclusions: This study provides some evidence on the hepatic safety of anti-asthmatics in children. Use of β_2-agonists and corticosteroids was associated with an increased risk of hepatotoxicity; additional studies will be needed to perform in larger population setting to verify that this is not due to residual confounding.