LONG TERM DRUG SAFETY IN CHILDREN: ANALYSIS ON SPONTANEOUS REPORTING SYSTEM OF SUSPECTED ADVERSE DRUG REACTIONS WITHIN MUSIC PROJECT

1)Ferrajolo C.. 2)Trifiro' G.. 3)Cimmaruta D.. 4)Ientile V.. 5)Moretti U.. 6)Sottosanti L.. 7)Rossi F.. 8)Capuano A..

University of Naples

Background

Pre-marketing clinical trials are often limited by reduced sample size and length of follow-up to be able to detect adverse reactions occurring long after start of drug therapy. Premarketing assessment of drug safety is even more difficult in paediatrics because of rare enrollment of children in long-lasting trial.

In this scenario, traditional spontaneous Adverse Drug Reactions (ADRs) and Adverse Events Following Immunization (AEFI) reporting system databases represent a valid source of information to evaluate ADRs occurrence in relation to duration of treatment. We explored pattern of ADR reports in paediatrics in relation to the lag time between start of treatment and onset of ADR across different drug classes and age categories, as part of MUSiC project, funded by Italian Ministry of University and Research.

Methods

Suspected ADR reports in the paediatric population (< 18 years) were retrieved from Italian Pharmacovigilance Network (RNF) over a fifteen years period (2001-2016). For those reports for which the starting date of the drug (classified by ATC code) and the date of the event occurrence (coded as Medical Dictionary for Regulatory Activities, MedDRA, terms) were known, the time to event was calculated. Long-term adverse events were defined as events occurring after at least 6 months from start date therapy. Long-term ADRs were analyzed overall, by age-categories (according to ICH classification: neonates, <1 month; infants, from 1 to 24 months; children, from 2 to 11 years; and adolescents, from 12 to 18 years), implicated drug and suspected adverse event.

Results

During the study period, 56,206 reports of ADR/AEFI concerned pediatric population have been collected in RNF and had correct information on dates of drug treatment start and event onset. Most of these reports (N= 55,197, 98.2%) were of ADRs occurring within 6 months after therapy was initiated (N= 43,845, 78.0% within the first five days from the start treatment), while only 1.8% (N= 1,009) occurred after at least 6 months of start treatment. This proportion slightly increased (N= 867; 4.9%) after excluding AEFI reports. The proportion of ADRs after long-term use increased significantly with increasing age, ranging from 6.5% (N= 80) among neonates and infants less than 2 years to 48.7% (N= 651) among adolescents.

In terms of MedDRA-SOC, ‘Investigations’ (12% vs. 2.2%), ‘Metabolism and nutrition disorders’ (7.0% vs. 1.5%), and ‘Nervous system disorders’ (11.7% vs. 8.0%), were more often reported after long-term exposure to drugs. On the contrary, ’Skin and subcutaneous tissue disorders’ (37.2% vs. 9.7%) and ‘Gastrointestinal disorders’ (13.9% vs. 6.4%) were mostly reported after short term drug use. Drugs implicated in ADRs reported after long-term drug use were risperidone (N= 139, 14.6%), somatotropin (N= 94, 9.9%) and valproic acid (N= 34, 3.6%).

Conclusions

The pattern of ADR reporting in relation to lag time between treatment start and time of ADR onset differed significantly across age categories and types of ADRs. The much larger frequency of long-term ADR reporting among adolescents could be due to increased exposure to of chronic therapy as compared to neonates and toddlers. Skin and gastrointestinal adverse reactions are expected to rapidly occur, mainly within few hours/days after starting treatment, while increase of liver enzymes (as part of MedDRA-SOC ‘Investigations’) usually occurs after long-term treatment, thus emphasizing the inability to be detected in (short-term) clinical trials.