SOCIETÀ ITALIANA DI FARMACOLOGIA

RELAZIONE DI FINE PERIODO

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TIPOLOGIA DI BORSA RICEVUTA: SIF-ASSOGENERICI

TIPOLOGIA DI RELAZIONE (es.: metà periodo o finale): FINALE

TITOLO DELLA RELAZIONE: Medicines Use and Safety in CHILDREN

BACKGROUND OF THE PROJECT

Randomized controlled trials (RCTs), the main component of the premarketing clinical phases of drug development are the gold standard for evaluating drug efficacy but are much less effective at detecting adverse drug reactions (ADRs), especially in vulnerable population such as children. Moreover, evidence from studies on adult population are not generalizable to children because of considerable medical, scientific, practical and ethical issues such as high variability of pharmacological characteristics, type of diseases, drug exposure among age groups.

As a consequence, prescriptions of off-label and unlicensed medicine in children often represent the only evidence-based and experience-supported therapeutic options; nevertheless, their extensive use is associated with an increased risk of drug/vaccine-related adverse reactions (ADR/AEFI), especially serious events.

Following this increase of health concerns over the recent years, the new EU paediatric regulation (PDCO) specifies the need for a Paediatric Investigation Plan (PIP) as a mandatory part of each new license application and the potential for a Paediatric Use Marketing Authorisation (PUMA) for older off-patent drugs if studies on the efficacy and safety of these older drugs in children are going to be conducted. Equally, in the US Food and Drug Administration, paediatric research is stimulated via the Paediatric Research Equity Act. Despite, as a consequence, the number of pre-marketing clinical trials in children has being increased, drug safety in children remained unsatisfactorily investigated because they did not reflect the risks of a medicinal product in the 'real-life' setting. It is also clear that RCTs on their own are not sufficient to detect and assess the frequency of ADRs. Thus, identification, quantification, and prevention of ADRs are still main concerns of paediatric Pharmacovigilance and Pharmacoepidemiology.

Post-marketing safety of a medicine bases on monitoring of reports of ADR/AEFI collected in spontaneous reporting system databases after registration. Along with this system, the increasing

availability of electronic healthcare/claims databases allows to monitor the safety of a under "real life" circumstances and to explore a larger sample size and long-time follow-up. Also, drug utilization studied (DUS) have been used to describe the effect of regulatory actions and media attention on the use of medicines, as well as to develop estimates of the economic burden of the cost of medicines. DUS can also be used to examine the relationship between recommended and actual clinical practice. These studies can help to determine whether a medicine has the potential for abuse by examining whether patients are taking escalating doses or whether there is evidence of inappropriate repeat prescribing. Monitoring both systems is important to know to which extent the medicines are used in children and which adverse drug reactions (ADRs) are frequently reported in children and require to be carefully monitored.

OBJECTIVES

The main goal of this project is to create a network of different data source available in post-marketing surveillance system to promote research in paediatrics and to promote a safer use of medicines in children. During these years, I focused my research on the specific objectives, as follows:

1. Evaluation of medicines use in Italian children.

To improve the knowledge for a correct and safe use of medicines prescription, the pattern of medicines prescription data, in both hospitalized and outpatient children, has been analyzed in terms of:

a. Prevalence of use during the observation period by age groups, gender, and calendar time;
b. Drug consumption (expressed as DDD/1000 inhabitants day) by age, gender and calendar time;
c. Mean days of patients exposure per active agent (duration of use);
d. Specific paediatric parameters including: indications, dose, formulations and switching patterns.

2. Assessment of safety-outcomes reported as ADR/AEFI in National Spontaneous Reporting system (from Italian Medicine Agency).

As first step for evaluating new signals, understanding the structure and the scope of the spontaneous reporting system database and its respective strength and limitations is essential for its correct use and interpretation. Suspected drug-related adverse reactions due to long-term treatments in children have been investigated by exploring the National Spontaneous Reporting system.

3. Synthesis of existing evidence

A comprehensive review of observational studies on safety and effectiveness of medicines in children has been carried out to identify what is already known and what is still missing about drug use in children and to determine the quality of such published studies.

In order to give an overview of the entire project, details of each task are provided below.

1. Gender Specific Drug Use in Pediatrics by exploring Real World Data

Background

Several nationwide studies have been performed on medicine prescribing in children as well as several comparisons among different countries, using different measures and in different health care settings. Children are widely exposed to drugs with a large variability between countries and also between Northern and Southern Italy. However, gender differences in medicine use in children and adolescents are not in-depth explored. Nevertheless, there are several gender differences on disease prevalence in paediatric population (e.g. respiratory diseases, infections). Moreover, boys and girls with same diseases show different symptoms, development and treatment response because of sex.

Objectives

The aim of this drug utilization study is to provide an overview of gender-specific pattern of drug use in outpatient pediatric population and to explore the traceability of their use through a real word data analysis.

Methods

A drug utilization study was performed in pediatric population through anonymized claims databases of Caserta Local Health Unit (LHU), covering a population of around 1 million subjects. Children with at least one dispended drug between January 1st, 2009 and December 31st, 2015 were identified as treated children. Yearly prevalence per 100 inhabitants (with 95% CI) was measured and stratified by Anatomic Therapeutic Classification (ATC) codes, age categories (according ICH classification) and gender. Sensitivity analyses were performed in the last year of observation, 2015, in order to check gender differences for specific therapeutic classes and active substances use.

To assess the traceability of medicine dispended in pediatrics we analyzed pharmacy sales data for pediatric-specific formulations distinguishing between National Health System-covered and private purchase of drugs.

Results

Among 274,628 residents aged <18 years in Caserta LHU, 224,070 (82%) had at least one drug dispensing during the observation period. Yearly prevalence of overall drug use in children decreased by 10% over calendar time, from 63.5 (CI 95% 63.3-63.7)/100 inhabitants in 2009 to 53.5 (53.3-53.8)/100 in 2015. This trend seems to be mostly due to antimicrobial, with yearly prevalence from 57.1 (56.9-57.4)/100 in 2009 to 42.9 (42.7-43.1)/100 in 2015. Prevalence use for girls was lower than for boys, even if the decreasing trend over time was consistently observed in both sexes.

Similarly, higher prevalence was found in boys than in girls when looked at the top three therapeutic classes used in paediatrics overall on 2015, as follows: 43.5 (43.2-43.8)/100 in boys vs. 42.3 (42.0-42.6)/100 in girls, for anti-infectives; 29.0 (28.7-29.2)/100 vs. 26.1 (25.8-26.4)/100, for respiratory drugs; and 13.2 (12.9-13.4)/100 vs. 11.3 (11.1-11.5)/100, for hormones. These gender differences remained while exploring each age category.

Amoxicillin clavulanate was the mostly prescribed antibiotic drug (36.2% of treated boys vs. 34.3% of treated girls), followed by beclomethasone, among respiratory drugs, (28.4% vs. 28.3% respectively) and betamethasone, among hormonal preparations, (21.3% vs. 18.9%, respectively).

Regarding traceability, we observed relevant differences among privately purchased and NHS-covered drugs across different drug formulations. For instance, around 40% of overall products containing amoxicillin clavulanate for specific use in children is privately purchased, especially in children less than 1 year old.

Conclusions

Trend of dispended medicines in children decreased from 2009 to 2015, probably due to a decrease of antibiotic class use, even if the mostly used drug in children remains amoxicillin/clavulanic acid. Gender seems to be an important factor to consider when examining patterns of drug use in children. Traceability of medicines by using only dispensing data is not comprehensive of overall drug used in children, particularly for less expensive formulations.

2. Long Term Drug Safety in Children: Analysis on Spontaneous Reporting System of Suspected Adverse Drug Reactions.

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.

3. Pharmacoepidemiological safety studies in children: a systematic review

(PDS 2016 Aug;25(8):861-70)

Background

The availability of large scale healthcare and claims databases provides an outstanding opportunity to perform safety studies. However, since the studies are observational, their design requires extra attention to avoid misclassification and address potential confounding. Although the field of pharmacoepidemiology has grown substantially in the last 20 years, very few researchers focus on pediatrics.

Objectives

We conducted a systematic review of the medical literature in order to assess the characteristics of pharmacoepidemiological studies evaluating the safety of drugs in children, and to identify challenges in pediatric pharmacoepidemiological safety studies.

Methods

Relevant articles from 1979 to 2013 were retrieved from Embase and Medline. We sequentially screened titles, abstracts and full texts with independent validation. We systematically collected data regarding general information, study methods, and results. We compared studied drugs with published data regarding drug utilization and spontaneous (adverse event) reporting in children.

Results

Out of 4825 unique articles, 268 full texts were retained; 54.9% pertained to drugs rather than vaccines. Most studies concerned children and adolescents (2 to 11 years) and only 14 studies

included preterm newborns. Most originated from North America (57.5%) or Europe (34.3%), only few studies (17.5%) were privately funded. Cohort studies represented the most frequent design. Most studies (73.1%) collected data retrospectively and 1/3 of studies used claims or primary care medical or dispensing data. Only 2.0% of 147 drug (exclusively) studies investigated rarely used drugs. Out of 268 studies, only 10.1% reported sample size or power calculation. Most (51.0%) drug studies corrected confounding by multivariate modelling while stratification was mostly applied in vaccine studies (55.9%). Most studies with statistically non-significant results did not discuss lack of power.

Conclusions

Although the field of pediatric pharmacoepidemiology is steadily developing evaluation seldom includes neonates, is mainly focused on few drug classes and safety outcomes and concerns mainly drug use in developed countries. Small study size is a specific challenge in paediatrics. Based on the reviewed literature, we conclude that there is a need to build global collaborative capacity and funding opportunities for pediatric pharmacoepidemiology since this is one of the most powerful ways to provide evidence of drug safety in children.