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Adverse Drug Reactions to Off-label Drugs on a Paediatric Ward: an Italian Prospective Pilot Study

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Abstract

Recently published studies examining the extent of off-label drug prescribing in various European paediatric wards have reported that off-label use is widespread and particularly high in Italy. So far, however, no studies have investigated the extent to which adverse drug reactions (ADRs) due to off-label drug use occur in Italy. To evaluate the risk associated with off-label drug use in paediatric inpatients, a prospective surveillance study was carried out in the paediatric ward of a teaching hospital over a 9 month period. Forty-one children (mean age: 7.2 years, 58% male), out of a study population of 1619 patients, experienced ADRs. In 29 children the ADRs were due to in hospital drug therapies, while in 12 they were due to medicines administered in the community. Urticaria (11 cases), vomiting and rash (5 cases each) and tremor (4 cases) were the most common ADRs. Eight ADRs (20%) were classified as severe. The drugs most frequently associated with ADRs were salbutamol (5 cases) and co-amoxiclav (4 cases). Off-label drug prescriptions were responsible for 38% of inpatient ADRs and for 42% of the ADRs occurring in the community that led to hospitalisation. The use of drugs not licensed for paediatric use (8 cases) or for indications for which the drug was not licensed (6 cases) were the off-label categories most frequently associated with ADRs. Drugs used for diagnostic tests in endocrinology were responsible for one third of ADRs due to off-label uses. The results of this study suggest a high risk of ADRs associated with off-label prescribing in children, both in the hospital and in the community. This pilot study also demonstrates the feasibility of an ADR monitoring system that could take into account important issues relating to rational drug prescribing in paediatric patients. In order to achieve a comprehensive risk assessment of off-label drug interventions in children, the study should be continued and expanded to involve the community setting as well.

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Introduction

A rational use of drugs implies a thorough evaluation of their benefit/risk profile[1]. Unfortunately, this does not occur in daily clinical practice. In fact, although drug benefits are well known, the frequency and severity of adverse drug effects are often lacking[2]. This gap in knowledge are even more marked in paediatric practice due to the scarce number of clinical trials carried out in children and the consequent difficulty in evaluating the risks and benefits of drug therapies[3,4].

Although one of the aims of current drug licensing legislation is to prevent tragedies such as those that have occurred in the past, most drugs used in children are still placed on the market without adequate safety evaluation in children[5]. The results of a recent review of published studies showed a high rate of unlicensed and off-label drug use in hospitalised children: 7-66% of prescriptions and 36–92% of children[6]. Many drugs are therefore prescribed without full knowledge of optimal dosage, metabolism and potential adverse drug reactions (ADRs), thus limiting the possibility of obtaining maximum efficacy and reducing ADR risk[7].

Little exists in the literature concerning epidemiological studies that prospectively evaluate and quantify the risks of drug therapies in children. The few existing studies involved limited contexts and settings and did not provide adequate information concerning factors that predispose children to ADRs. Even less information can be found concerning the risks associated with the off-label use of drugs[8]. Moreover, no study has yet been carried out analysing this problem in the Italian paediatric hospital setting, which is characterised by a high level of off-label drug use[9].

Many factors are involved in obtaining effective prevention of unnecessary risks associated with drug therapy. One essential factor is ADR reporting. A recent study in the UK evaluated the effectiveness of intensive education and promotion of ADR reporting in 20 hospitals and found that they significantly increased reporting and, therefore, also the knowledge about the safety of paediatric drug therapies[10]. This study also quantitatively evaluated the off-label status of the suspected drugs. ADR monitoring strategies that take into consideration the risks associated with off-label prescribing are, in fact, another important factor. Ignoring the complexities involved with drug use in children (and the consequent off-label use of drugs) cannot lead to effective risk prevention. The main objectives of this pilot study were, therefore, to identify ADRs related to off-label drug use and to evaluate their severity and likelihood of association with the suspected drug. The findings should allow for the development of more specific and effective strategies for evaluating the risks associated with paediatric drug therapy.

Materials and methods

A prospective monitoring of ADRs was carried out in the University of Chieti's Paediatric Unit for a nine month period (March-November 2000). Data collection forms previously used for other therapeutic surveys were modified in order to include information concerning off-label drug use.

The data collection form gathered general patient information (age, sex, weight, reason for admission, length of stay) as well as detailed information concerning all the drugs received (dosage, route, reason for prescription and duration of and changes in therapy). ADRs were defined as a noxious and unintended reaction following use of a drug for prophylaxis, diagnosis, or therapy[11]. Data were also collected on the intervention required to resolve the ADR. The ADRs were labelled as mild, moderate or serious and the association as definite, probable or possible. Other information collected concerned underlying clinical conditions and details of the patient's case history that may have been implicated in the ADR episode. Lastly, the drug monographs were examined in order to verify completeness of information. Two physicians (M.A. and C.F.) independently reviewed suspected and potential ADRs and classified them.

Medication errors defined as errors in drug ordering, transcribing, dispensing or monitoring were not considered[12]. All prescriptions associated with ADRs were evaluated for off-label use based on a comparison with the drug monographs for each of the main drug use categories. The prescriptions were considered off-label when they were administered to a child even though the drug was authorised for use only in adults, at a dosage or frequency that differed from those in the product license, for unapproved indications, to children outside the specified age range or via a different route of administration.

The potential effect of ADR severity was controlled for using stratification and the Mantel-Haenszel procedure (χ^2_{MH}). Relative risks (RR) and 95% confidence intervals (CI) were estimated and P values < 0.05 were considered statistically significant.

Results

During the nine months studied, 1619 children were admitted to the University of Chieti's paediatric hospital ward. In 116 cases, the children were transferred to the paediatric ward from the emergency room. A total of 41 children (24 males, 17 females) experienced ADRs in the period studied. Their ages ranged from 3 months to 14 years (median 8 years). In 29 children (29/1619, 1.8%) the ADRs followed in hospital drug administrations. In 12 children, the ADRs were caused by drugs given in the community setting and led to emergency room visits; in 11 of these cases a paediatrician had prescribed the drugs and in 1 the parents had done so. ADRs were therefore the reason for emergency room visits in 10.3% of cases following consultation with the paediatrician (12/116).

Urticaria (11 cases), vomiting and rash (5 cases each) and tremor (4 cases) were the most common ADRs. The main drugs involved were salbutamol (5 cases) and co-amoxiclav (4 cases). The association between drug and ADR was considered definite in 29 cases, probable in 10 and possible in 2. In the latter 2, the ADRs were not listed in the drug monograph. The first concerned increased transaminase levels after administration of mesalazine for Crohn's Disease; the second involved confusion after paracetamol administration for fever.

The ADRs were considered serious in 8 cases (Table 1) and moderate in the remaining 33. The most common interventions undertaken to resolve the ADRs were drug discontinuation and drug therapy (11 cases each). In 10 cases, no intervention was necessary due to the mildness of the ADRs and their rapid and spontaneous resolution. In 4 cases, the drug dosage was decreased and in 5 the drug was substituted.

In 16 children (39%) the ADRs were caused by drugs used off-label. More specifically, off-label use was involved in 38% (11/29) of the ADRs that occurred during in hospital therapy (Table 2) and in 42% (5/12) of the out hospital ADRs that led to hospitalisation (Table 3).

The use of drugs without a paediatric license was the most common type of off-label use (8/16): three cases involved clonidine, two protirelin and one (each) naproxen, mesalazine and paracetamol (adult suppositories). In 6 cases, the ADRs were due to drugs given for unapproved indications: clonidine for diagnosis of growth hormone (GH) deficiency (3 cases), protirelin for diagnosis of hypothyroidism (2 cases) and co-amoxiclav given prophylactically for cystography.

Four ADRs, three of which involved drugs prescribed outside the hospital setting, resulted from administrations at a dosage or frequency different from those recommended in the drug monographs. In one case, co-amoxiclav oral suspension was given to a 7 year old at a daily dose of 1800 mg, while the drug monograph suggested 1250 mg for 7-12 year olds. In another, an 11 year old was given 1200 mg of acetylsalicylic acid daily, while the licensed dosage for 6–14 year olds was 600 mg. The other two cases involved ketoprofen and beclomethasone, given at a different frequency of administration than the one registered.

The last off-label use category involved the administration of a drug to children whose age was outside the licensed age range. This type of off-label use was linked to three ADR cases: salbutamol tablets (2 mg), licensed for use in children over 3 years of age, given to a 3 month old; scopolamine skin patches, licensed for use after 12 years of age, given to a 3 year old; and ceftibuten oral suspension, licensed for use after 6 months of age, given to a 5 month old.

Table 1. Severe adverse drug reactions observed in the paediatric population

Age / sex	ADR	Drug (Brand name)	Indication
1y / M	Gastric bleeding	Betamethasone (Bentelan)	Respiratory distress
10y / M	Coma	Phenytoin (Dintoina)	Epilepsy
10y / M	Coma	Carbamazepine (Tegretol)	Epilepsy
11y / M	Hepatic impairment	Acetylsalicylic acid (Ascriptin)	Rheumatoid arthritis
14y / F	Neutropenia	Methimazole (Tapazole)	Hyperthyroidism
Off-label use			
4y / F	Urticaria	Naproxen (Synflex)	Arthralgia
10y / F	Protracted hypotension	Clonidine (Catapresan)	GH deficiency diagnosis
11y / M	Urticaria	Ketoprofen (Oki)	Pain

Table 2. Adverse drug reactions associated with in hospital off-label drug use

Age/ sex	ADR	Drug (brand name)	Indication	Off-label use
10y/F	Protracted hypotension	Clonidine (Catapresan tablet)	GH deficiency diagnosis	No paediatric licence No indication
12y/M	Hypotension	Clonidine (Catapresan tablet)	GH deficiency diagnosis	No paediatric licence No indication
10y/M	Lipothymia	Clonidine (Catapresan tablet)	GH deficiency diagnosis	No paediatric licence No indication
14y/F	Vomiting	Protirelin (Irtonin vial)	Hypothyroidism diagnosis	No paediatric licence No indication
14y/F	Vomiting	Protirelin (Irtonin vial)	Hypothyroidism diagnosis	No paediatric licence No indication
3m/M	Tremor	Salbutamol (Ventolin tablet 2mg)	Bronchiolitis	Outside age range
8y/M	Vomiting	Co-amoxiclav (Augmentin syrup)	Prophylaxis (cystography)	No indication
4y/F	Urticaria	Naproxen (Synflex tablet 550 mg)	Arthralgia	No paediatric licence
14y/M	Increased transaminase levels	Mesalazine (Pentasa tablet)	Crohn's Disease	No paediatric licence
12y/F	Rash	Beclomethasone (Clenil A aerosol)	Laryngospasm	Dosage
11y/M	Confusion	Paracetamol (Tachipirina suppository 1000 mg)	Fever	Adult formulation

Despite the study's limited population size, pharmacological treatment of ADRs was greater and statistically significant for severe ADRs following off-label drug use (χ^2_{MH} 4.23; P=0.04; RR=7.0; IC 95%:1,1-62).

Discussion

The issue of drug safety in children is becoming more of a priority both for the scientific community and the public[13]. This shift in priority is partly the result of recent studies conducted mainly in Europe that highlighted the lack of information on paediatric drug use for many of the more common drugs prescribed to children, even outside the hospital setting[14-15].

However, only two studies have been carried out evaluating the risks associated with off-label drug use[16,17]. Both studies found an association between off-label drug use and ADRs; the more recent study found that it was stronger with severe ADRs. Although characterised by a small population size, this pilot study supports these findings in that it also found a relationship between off-label drug use and serious ADRs (requiring drug therapy).

Off-label use was implicated in over 40% of the ADRs resulting from drugs prescribed in the community setting. This data is original in that no studies have been found in the literature evaluating the risks involved in off-label drug use in the community setting. Moreover, the only information available on this issue, although indirect, comes from an analysis of spontaneously reported ADRs. A recent study that analysed data collected by a regional pharmacovigilance centre in France found that about 3% of spontaneously reported paediatric ADRs were associated with drugs lacking a paediatric license or prescribed outside the licensed age ranges[18].

The present study found a smaller rate of ADRs occurring in hospital than that reported in the literature. A systematic review of prospective epidemiological studies showed that ADRs occur in 4–16% of inpatient children[8] the results of a more recent study fall into this range as well (11.4%)[19]. However, the review also showed that this variability can largely be explained by the different number of drugs prescribed to children in the various studies. A recent, multicentre study concerning off-label prescriptions administered in nine Italian paediatric hospital wards showed that

Table 3. Adverse drug reactions associated with off-label drug use that led to hospital admission

Age/Sex	ADR	Drug (brand name and formulation)	Indication	Off-label use
7y/F	Urticaria	Co-amoxiclav (Augmentin oral suspension)	Pharyngitis	Dosage
3y/M	Rash	Scopolamine (Transcop skin patch)	Nausea	Outside age range
11y/M	Urticaria	Ketoprofen (Oki granular)	Pain	Dosage
5y/F	Dizziness	Acetylsalicylic acid (Aspirinetta tablet)	Rheumatic disease	Dosage
5m/M	Rash	Ceftibuten (Isocef oral suspension)	Respiratory tract infection	Outside age range

the same ward that also participated in the present study was characterised by a low prescription rate[6]. This can explain the low prevalence of ADRs observed.

The prescription and ADR data collected in this study partly reflect the participating centre's specialisation in paediatric endocrinology. The ward, in addition to general paediatrics, is specialised in the diagnosis of short stature. This characteristic may limit the extrapolation of our results to other paediatric wards, but it does however offer the opportunity to examine an issue that has so far been overlooked: the off-label use of drugs for diagnostic purposes in paediatrics. In diagnosing GH deficiency, for example, various substances are used: levodopa, insulin, glucagon, arginine and clonidine. However, none of these drugs' monographs list diagnosis of GH deficiency among the indications. This is due to the lack of information on the use of these drugs in diagnosis and on the risks associated with their use in children. Health workers, therefore, generally rely more on personal experience and judgement in choosing which drugs to use than on findings of diagnostic efficacy and safety. In the diagnosis of GH deficiency, as in that of many other paediatric conditions requiring specialised centres, off-label use will continue into the future because a lack of consent on first choice testing, based on available findings, still exists[20].

The results of this pilot study are limited to a small population size, but reveal that a significant number of ADRs are associated with off-label drug use and that most of these ADRs are serious in that they require attention and pharmacological therapy.

The study should be continued and expanded to include other paediatric wards, as well as the community setting, in order to evaluate drug benefit and risk profiles more adequately and to therefore allow for the promotion of a more rational use of drugs in the Italian paediatric population.

Notes

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