Adverse drug reactions and off-label drug use in paediatric outpatients

Benjamin Horen, Jean-Louis Montastruc & Maryse Lapeyre-Mestre

Laboratoire de Pharmacologie Médicale et Clinique, Centre Midi-Pyrénées de Pharmacovigilance, de Pharmacopépidémiologie et d'Informations sur le médicament, Faculté de Médecine

Aims To investigate the potential relationship between off-label drug use and increased risk of adverse drug reactions in paediatric outpatients.

Methods A prospective pharmacovigilance survey of drug prescribing in office based paediatricians was carried out in Haute-Garonne County (south west of France).

Results The study involved a sample of 1419 children under 16 years old. Forty-two percent of patients were exposed to at least one off-label prescription. The incidence of adverse drug reactions was 1.41% (95% CI 0.79, 2.11). Off-label drug use was significantly associated with adverse drug reactions (relative risk 3.44; 95% CI 1.26, 9.38), particularly when it was due to an indication different than that defined in the Summary Product Characteristics (relative risk 4.42; 95% CI 1.60, 12.25).

Conclusions Our data suggest an increasing risk of adverse drug reactions related to off-label drug use. This risk would be acceptable if further studies prove the potential benefit of such a drug use.

Keywords: adverse drug reactions, off-label drug use, paediatric outpatients

Introduction

Despite large pharmacokinetic and pharmacodynamic differences between children and adults, pharmacological evaluations in children remain scarce [1–3]. This has led to only a few drugs being currently labelled for paediatric use and to a widespread off-label drug use, i.e. use of drugs outside the term of the Summary of Product Characteristics (SPC) [4]. In a hospital setting, 36–67% of children receive an unlicensed or an off-label prescription [5–7]. This proportion increases in children with complex diseases (renal or neoplastic diseases) and in the intensive care unit (up to 90% of children) [6, 8, 9]. In paediatric outpatients, 10–33% of prescriptions are either off label or unlicensed [10, 11] and 22–56% of children receive such prescriptions [11, 12].

As far as we know, few studies have investigated the consequences of this off-label drug use [13]. Gill *et al.* [14] and Turner *et al.* [15] have shown that one third to one half of adverse drug reactions (ADRs) occurring in paediatric hospital involved off-label drug use. In a pilot Paediatric Regional Monitoring Centre in the Trent region (UK), 25% of the prescriptions involved in ADRs between October 1998 and October 1999 were off label [16].

The aim of this study was to investigate the potential relationship between off-label drug use and increased risk of ADRs in paediatric outpatients.

Methods

A prospective pharmacovigilance study was carried out among children (below the age of 16 years) seen in office-based practice in Haute-Garonne county (south west of France) between October 2000 and January 2001. This study was a part of the collaborative project CHILDURG (Drug Utilization Research Group in Children), a working group of the EURO-DURG. This project, initiated in 1997, is a prospective observational study of drug prescribing in paediatric out-patients in different countries in Europe and elsewhere [1]. The main objectives of CHILDURG are to study drug utilization in children in different locations, to analyse existing differences in diagnosis patterns, therapeutic trends and traditions, and to detect problems in prescription and propose improvement. In each location, physicians are asked to participate on a voluntary basis. In the Haute-Garonne area, all paediatricians ($n = 79$) were contacted by mail and by phone, and we met the 51 physicians who agreed to participate in order to fully explain the study.

Each participating physician had to fill a total of 40 datasheets in a prospective way, without selection among the disease or the prescribed drugs, by including the first

Correspondence: Dr Maryse, Lapeyre-Mestre, Bp 7207, 37 allées Jules Guesde, 31073 Toulouse Cedex 7, France. E-mail: lapeyre@cict.fr

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patient seen during a medical visit or consultation. According to the results of the pilot study of Turner *et al.* [15], we assumed that one third of prescriptions would be off label and the relative risk of ADRs related to off-label drug prescribing would be 1.5. Thus, with a risk alpha (α) of 5% and a risk beta (β) of 20%, we calculated that we had to include at least 1218 children in our sample in order to observe such a result, with an expected number of drugs per child of 2.7 [17]. Data collected were: consultation and birth date, gender, weight, diagnosis, prescribed drugs (Anatomic Therapeutic and Chemical (ATC) code, indication, daily dosage and route of administration). Classes of age were defined according to the European Medicine Evaluation Agency: new-borns (0–27 days), infants (28 days to 23 months), children (2–11 years), adolescents (12–15 years) [18]. Physicians kept each datasheet 7 days after they had completed the part concerning their prescriptions, in order to describe a potential ADR.

A drug course was defined 'off label' according to the French drug formulary (Dictionnaire Vidal®) [19]. This dictionary is a convenient reference source for most physicians and pharmacists and the unique commonly available indirect source about SPC in France. We classified each off-label prescription into seven categories: drug used when contra-indicated, used for indication different from which is licensed, used in a different dose, used in child of inappropriate age, used by a different route of administration, and used in inadvisable coprescription. We ascribed only one off-label status per drug, giving priority to contraindication or different indication, followed by age, route of administration, different dose and inadvisable coprescription. Homeopathy, hygiene and dietetic products were not included in off-label drug use.

Causality assessment of ADRs for each drug was made using the French method of imputability. This validated method is used by the French pharmacovigi-

lance system, as well as by regulatory agency than by pharmaceutical companies [20]. A serious ADR was defined as one resulting in death, or which is life-threatening or leads to hospitalization, disability or congenital abnormalities according to international definitions [21]. Physicians were aware of the aim of the study. All data were collected anonymously with regard to patient and physician.

Quantitative data, presented as mean with standard deviation (s.d.), were compared with ANOVA or Kruskal-Wallis non parametric test and qualitative variables with χ^2 or Fischer exact test. Incidence rate of ADRs during 7 days was calculated with its 95% confidence interval (CI) according to the Poisson model for rare events. The risk of ADRs related to off-label drug use or to classes of drugs was estimated by odds ratio as an estimate of the relative risk (RR). Calculation was performed by logistic backward stepwise regression. The dependent variable was the presence of an ADR. Independent variables included in the multiple regression model were off-label drug use, classes of age (as category indicator variables, using new-borns as reference), gender, number of drugs, and classes of drugs (level I of ATC classification). We performed a model for global off-label drug use, and for each class of off-label drug use. Analyses were carried out using the EPI-INFO software package (version 6.04) and the SPSS statistical analysis program.

Results

Patients and drugs

Thirty-nine physicians (76.4%) participated in the study and included 1419 patients, who were mainly infants or children (Table 1). There were significantly more boys than girls. The mean number of prescriptions was 3.04 ± 1.49 per patient. Boys were more likely to receive

Table 1 Off-label drug use, number of prescriptions and ADRs, in the total sample and according to sex and age.

	Treated patients n	Off label n (%)	ADR n	Mean number of prescriptions n (s.d.)
Total	1419	601 (42.35)	20	3.04 (1.49)
Male	735 (53.03%) (CI: 50.40, 55.65)	328 (44.62)	9	3.15 (1.49)
Female	651 (46.95%) (CI: 44.35, 49.60)	265 (40.71)	11	2.92 (1.48)
<i>P</i>	—	0.14	0.47	0.01
New-borns	60	9 (15.00)	0	2.47 (1.66)
Infants	773	315 (40.75)	10	3.19 (1.53)
Children	562	270 (48.04)	10	2.95 (1.39)
Adolescents	18	6 (33.33)	0	2.17 (1.10)
<i>P</i>	—	0.01	0.63	0.01

ADR: adverse drug reaction, s.d.: standard deviation, CI: 95% confidence interval.

drugs than girls and the mean number of prescriptions was higher in infants than in other age groups.

According to the ATC classification, drugs belonged mainly to 'Respiratory system' (29.7% of prescriptions), 'Alimentary tract and metabolism' (23.6%), 'General anti-infectious drugs for systemic use' (15.6%), 'Nervous system' (13.8%) and 'Dermatological drugs' (5.4%). The characteristics of drug exposure and medical diagnosis according to the different classes of age are presented in Table 2.

Off-label drug use

Forty-two percent of patients were exposed to at least one off-label prescription. Children were the most exposed (Table 1). There was no difference between boys and girls. The mean number of drugs was higher in

children exposed to off-label drugs (3.6 ± 1.5) *vs* others (2.6 ± 1.2 , $P = 0.0001$).

According to the whole number of prescriptions, 18.9% were off label, i.e. 11.5% for a different indication, 4.7% for a different dosage, 1.1% for age, 0.6% for inadvisable coprescription, 0.6% for contra-indication and 0.4% for route of administration. Table 3 shows the different categories of off-label drug use. Off-label prescribing was mainly related to a different indication. Twenty-four patients (1.69%) received a contraindicated prescription.

ADRs

Twenty ADRs were reported, 10 in children and 10 in infants. They involved 15 different drugs: antibiotics

Table 2 Medical diagnosis according to the International Classification of Diseases, 9th revision, and classes of prescribed drugs according to the first level of the Anatomical, Therapeutic and Chemical Classification. Results are presented as percentage of patients and as percentage of the total of drugs, in the total sample and in the different classes of age.

Classes of age	Total sample*	New-borns	Infants	Children	Adolescents
<i>ICD 9th (% of patients)</i>					
Infectious diseases	9.3	13.3	8.5	10.1	5.5
Tumours	0.07	—	0.1	—	—
Endocrine system	0.07	—	—	0.1	—
Blood	0.3	—	0.6	—	—
Mental diseases	1.5	—	0.4	3.0	5.5
Nervous and sensorial system	15.3	8.3	16.4	14.7	16.6
Circulatory system	0.07	—	0.1	—	—
Respiratory system	56.5	20.0	51.8	67.9	22.2
Digestive system	8.3	8.3	10.6	5.7	—
Genito-urinary system	1.3	—	0.4	2.3	11.1
Skin	7.4	13.3	9.5	4.3	—
Musculo-skeletal system	0.9	—	0.5	1.2	11.1
Congenital abnormalities	0.4	1.6	0.2	0.5	—
Perinatal diseases	0.3	6.6	0.1	—	—
Symptoms	11.5	13.3	9.3	14.2	16.6
Injuries	1.1	—	1.3	1.0	—
Health status	28.7	53.3	36.5	15.5	27.7
<i>ATC (% of drugs)</i>					
Digestive tract and metabolism	23.6	41.9	25.9	18.4	28.2
Blood	0.7	3.4	0.6	0.6	—
Cardiovascular system	0.1	—	0.1	0.2	—
Dermatological drugs	5.4	10.8	6.5	3.4	2.6
Genito-urinary system	0.1	—	—	0.3	—
Systemic hormones	1.7	0.7	1.2	2.5	5.1
Systemic anti infectious drugs	15.6	6.1	16.7	14.6	12.8
Muscle and skeletal system	1.7	0.7	1.7	1.8	2.6
Nervous system	13.8	7.4	13.7	14.6	10.3
Anti protozoal drugs	0.4	—	0.1	1.0	—
Respiratory system	29.7	10.8	26.1	36.9	30.7
Sensorial system	3.2	8.8	3.2	2.5	5.1
Miscellaneous**	1.9	4.7	1.8	1.6	2.6
'Homeopathy'	2.1	4.7	2.4	1.6	—

*The total sum is superior to 0, since children could present more than one diagnosis. **Miscellaneous drugs correspond to allergens and nutriment.

Table 3 Risk of ADRs related to off-label drug use.

Off-label status	Patients n = 1419	Percentage (95% CI)	RR* (95% CI)
Total of off label	601	42.35 (39.78, 44.92)	3.44 (1.26, 9.38)
Contraindication	24	1.69 (1.01, 2.45)	5.38 (0.62, 46.57)
Different indication	391	27.55 (25.23, 29.87)	4.42 (1.60, 12.25)
Higher dose	89	6.27 (4.97, 7.65)	1.65 (0.36, 7.57)
Lower dose	105	7.40 (5.98, 8.89)	1.12 (0.19, 6.55)
Age	45	3.17 (2.24, 4.18)	1.71 (0.21, 13.80)
Route of administration	18	1.27 (0.68, 1.94)	3.71 (0.42, 32.48)
Inadvisable coprescription	29	2.04 (1.30, 2.87)	No ADR

ADRs, adverse drug reactions; RR, relative risk; CI, confidence interval. *Adjusted according to classes of age, gender, ATC classes and number of prescription.

(4 ADRs with amoxicillin with clavulanate, 1 with amoxicillin, 1 with oxacillin, 2 with third generation cephalosporins (cefexime and cefpodoxime), 1 with clarithromycin, vaccines (3 ADRs with pentavalent vaccine, 1 with influenza virus vaccine and 1 with an oral bacterial vaccine), phenobarbitone, racecadotril, betamethasone, clomipramine, domperidone and fenspiride. The ADRs were gastrointestinal (8 ADRs), cutaneous (6), neurological (3), fever (2) and rhinitis. None of these ADRs was serious. The causality assessment was: 'likely' in 5 cases, 'plausible' in 10 cases and 'possible' in 5 cases.

The incidence of ADRs was 1.41% (95% CI 0.79, 2.11) in the whole population study and 2.00% (95% CI 1.03, 3.49) in patients exposed to at least one off-label prescription. Incidence of ADRs did not vary according to gender, age or number of prescriptions.

In the multivariate analysis, the risk of ADRs was significantly related to off-label drug use (Table 3), and to exposure to 'General anti-infectious drugs' (3.06; 95% CI 2.32, 8.11) and 'Systemic hormonal Preparations' (4.20; 95% CI 1.08, 16.40) and the risk of ADRs was decreased with exposure to drugs of 'Respiratory System' (0.20; 95% CI 0.07, 0.60). Off-label drug use due to a different indication was also associated with an increased risk of ADR (Table 3), particularly in the group of infants (3.94; 95% CI 1.12, 13.84).

Discussion

To our knowledge, this study is the first to observe an increased risk of ADRs in paediatric outpatients exposed to off-label drug use. However, several studies had previously suggested that they may be at greater risk in relation to such usage, but only one has tried to evaluate this risk objectively [15]. In this study involving more than 1000 paediatric in-patients, Turner *et al.* found that ADRs occurred in 6% of off-label drug courses *vs* 3.9%

of other prescriptions. However, the relative risk of an ADR related to off-label drugs was not significantly increased.

Characteristics of our sample of outpatients are very similar to those observed in other French studies in the community setting, as well as for demographic characteristics and medical diagnosis than for prescribed drugs. Drugs from 'General anti-infectious drugs for systemic use' (antibiotics and vaccines) and 'Respiratory system' classes were commonly used, like in other prescription studies in paediatric ambulatory care [22, 23]. Prophylactic drugs including vitamin D and fluorine are also systematically prescribed in infants in France. As in other surveys, the mean number of prescription was significantly higher in infants [17, 23, 24] and in young boys compared with girls [17]. This fact could explain the higher number of boys in this drug prescribing survey.

Our results need to be read with caution due to some potential bias. Selection bias could be one of the most important. First of all, the study was performed among a sample of voluntary paediatricians for convenience and feasibility reasons. Although one can suspect that children seen by paediatricians present different disease and could be treated by different drugs, characteristics of medical diagnosis and patterns of prescription observed in our study were very similar than those described in other community contexts in France or in other countries [11, 17, 22, 23]. The most frequent reasons for medical consultations were related to respiratory symptoms, fever and infectious diseases, and systematic or prophylactic consultations which represented one third of cases. In comparison with a French national survey about patterns of prescription in ambulatory care, as well as the mean number of prescriptions than the classes of prescribed drugs were not different between general practitioners and paediatricians, and were very close to those observed in our sample [17].

We found a prevalence of off-label prescription in accordance with other studies among ambulatory care [10–12]. Our population was very similar to that described by Chalumeau *et al.* [11], despite seasonal differences. In comparison with this latest study, the percentage of patients receiving at least one off-label prescription or the percentage of off-label drugs among the total of prescriptions were very important but slightly lower, respectively, about 40% and 20% of cases. This very slight difference could be due to the definition of the off label: actually, we chose only one category of off label, giving priority to different indication or contra-indication over age, which was the first cause of off label in the Chalumeau study. Moreover, we did not take into account other prescriptions such as food or homeopathy (5% of the prescriptions and 10% of patients), which could be defined as unlicensed. The report of potential ADRs could be underestimated, because either the ADR occurred after the survey, or physicians may not have been informed about the occurrence of ADRs. Despite this potential bias due to under-reporting, the incidence of 1.41% of ADRs observed in our study is very similar to that obtained in other studies in paediatric medical practice [26, 27] or in adult outpatients [29], and was slightly higher than that observed in a recent survey in another French area [28]. In these studies, the most common ADRs were related to anti-infectious gastrointestinal troubles and skin rashes and none of them was serious. Several authors found that ADRs are less common in paediatric patients than in adults, and most of them are mild [25–28]. The drugs most frequently suspected of causing ADR were anti-infectious drugs (antibiotics and vaccines), in agreement with results of other studies carried out in both paediatric in-patients and out-patients [27], and also with authors using data from voluntary ADR reporting systems [25, 26]. In these studies, authors suggest that this is due to the fact that antibiotics and vaccines are the most widely used drugs in children. In our study, exposure to drugs from 'General anti-infectious for systemic use' and also from 'Systemic hormonal preparation' (namely with betamethasone, commonly used for bronchiolitis in infants, despite a different indication in the SPC) are associated to the risk of ADRs, which confirms findings of previous studies. In contrast, the risk of ADRs was lower in patients exposed to 'Respiratory system' drugs. These drugs were often prescribed as a symptomatic treatment for rhinitis or bronchitis in our study. Actually the efficacy of N-acetylcysteine, a mucolytic drug generally well tolerated with few adverse effects has never been proved in upper respiratory tract infection where it is widely prescribed in France. In the multivariate analysis, the risk of ADR was significantly associated with exposure to at least one off-label prescription, and also

to exposure to drugs prescribed in a different indication. Concerning potentially deleterious causes of off label such as contra-indication or route of administration, the risk was high but not statistically significant due to a few number of cases. Most of ADRs were represented by fever, cutaneous or digestive reactions in children treated with antibiotics or corticoids for an unapproved indication (rhinitis, common cold), or by vaccines in children previously suffering vaccine related ADRs.

This observational study underlines the high level of off-label drug use in ambulatory paediatric patients. Moreover, our data suggest an association between exposure to off-label prescribing and ADRs, notably when the indication is not registered. This survey may guide further studies on classes of drugs where off-label drug use or ADRs are the most frequent in paediatric ambulatory care or in hospital setting. These studies may evaluate the expected efficacy of off-label drug use because the risk of ADRs could be acceptable if the therapeutic benefit is largely greater.

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