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The Impact of Unlicensed and Off-Label Drug Use on Adverse Drug Reactions in Paediatric Patients

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Abstract

Background and objective: Many drugs that are used to treat children are either not licensed for use in paediatric patients (unlicensed) or prescribed outside the terms of the product licence (off label). The incidence of adverse drug reactions (ADRs) associated with the use of such drugs is yet to be established. This study investigates, for the first time in a German patient population, the impact of unlicensed and off-label drug use on ADRs in paediatric patients.

Patients and methods: An 8-month prospective pharmacoepidemiological cohort-based survey was conducted on a ten-bed paediatric isolation ward at the University Hospital Erlangen-Nüremberg, Germany. All patients were intensively monitored for ADRs by a pharmacoepidemiological team. ADRs were characterised according to international classification methods. All drug prescriptions were evaluated retrospectively as to unlicensed or off-label use on the basis of the product information.

Results: A total of 178 patients were included in the study and 740 drug prescriptions were given to 156 patients (median three prescriptions per patient). In 198 cases (27.7% of all prescriptions) drugs were used in either an unlicensed (n = 3) or off-label (n = 195) manner. A total of 46 ADRs were observed in 31 patients (17.4%). Patients receiving at least one unlicensed or off-label drug prescription during hospitalisation (n = 92) experienced an ADR significantly more frequently (n = 26 patients) than patients receiving only licensed drugs (n = 64 vs 5 patients). ADRs were associated with 29 (5.6%) of the 517 licensed drug prescriptions and with 12 (6.1%) of the 198 unlicensed or off-label drug prescriptions. The majority of ADRs caused by unlicensed and off-label drug use were recognised by the attending physician. However, statistical analysis revealed no significant difference in the number of licensed and unlicensed/off-label drug prescriptions causing ADRs.

Conclusion: This study demonstrated that at a paediatric isolation ward the incidence of ADRs caused by unlicensed or off-label drug use was not significantly more than that caused by the licensed drug use. However, patients treated with

unlicensed or off-label drugs were shown to possess a significantly increased risk for developing ADRs.

Background

The incidence of adverse drug reactions (ADRs) and the extent of unlicensed and off-label drug use in paediatric patients have been discussed intensively, but only limited pharmacoepidemiological data exist concerning this issue.[1] Accordingly, it has been shown that many drugs used to treat children in hospitals are either not licensed for use in paediatric patients (unlicensed) or prescribed outside the terms of the product licence (off label). Several studies that assessed the extent of unlicensed and off-label drug use in paediatric patients[2-7] indicated a high proportion of unlicensed and off-label drug use in this group, with an overall incidence of at least one-third of drug prescriptions, depending on settings, group and age of patients. Drugs have been prescribed more often in an off-label than in an unlicensed manner. The proportion of unlicensed or off-label drug use in hospital was higher than in ambulatory settings.[1]

A recent meta-analysis[8] has shown that the overall incidence of ADRs in hospitalised paediatric patients was 9.5%, whereas in paediatric outpatients it was significantly lower (1.7%). In a study from our group that was performed using intensified methods for ADR surveillance, the ADR rate in paediatric inpatients was 21.5%.[9] However, the incidence of ADRs associated with unlicensed and off-label drug use in paediatric patients is still a matter of debate. The purpose of licensing is to ensure the safety, efficacy and high quality of drugs. Therefore, the use of unlicensed or off-label drugs would be expected to be associated with a greater risk of complications (e.g. ADRs).[10-12] So far, only one research group[13] has investigated the relationship between unlicensed and off-label drug use and ADRs in paediatric inpatients by using intensified ADR surveillance methods. In this study, a significant relationship between unlicensed and off-label drug use and the risk of an ADR was not found when using multivariate analysis. However, non-parametric analysis (i.e. Mann-Whitney test) revealed a statistically significant association between the percentage of unlicensed and off-label drug use and the risk of an ADR.[13] Another analysis performed on paediatric outpatients has demonstrated an association between off-label drug use and ADRs, notably when the indication is not registered.[14]

The aim of this exploratory study was to investigate the extent of unlicensed and off-label drug use and the relationship between ADRs and unlicensed and off-label drugs in paediatric inpatients. Furthermore, ADR characteristics such as awareness of physicians and preventability of ADRs in relation to unlicensed and off-label drug use were evaluated.

Patients and Methods

Study Design

Over an 8-month period, a prospective pharmacoepidemiological cohort-based survey was conducted on a ten-bed paediatric isolation ward at the University Hospital Erlangen-Nüremberg, Germany. This investigation was planned as an explorative study that addressed unlicensed and off-label drug use with respect to ADRs in a German patient population for the first time. Accordingly, no sample size or power calculation was performed. Demographic data (age, sex, weight), the reason for admission, known diagnoses and administered drugs with dosage information were obtained from all admissions to the study ward and documented in a Microsoft Access® 2000 database. Standard intravenous replacement solutions, parenteral nutrition, heparin used to maintain the potency of intravenous lines and 0.9% sodium chloride for inhalation were excluded from documentation. Only patients <18 years of age were included. All study patients were categorised into different age classes (i.e. infants, children, adolescents) according to International Conference on Harmonization (ICH) guidelines[15] (table I). Patient charts were reviewed weekly for

Table I. Patient characteristics with respect to number, adverse drug reaction (ADR) incidence and incidence of unlicensed/off-label (u/o) drugs in different age groups

Age group	Total no. of pts	Incidence of ADRs (%)	Pts receiving u/o drugs [n (%)]
Neonates (0–27 days)	1	0	0
Infants (28 days–23 months)	68	16.2	37 (54.4)
Children (2–11 years)	76	14.5	32 (42.1)
Adolescents (12–17 years)	33	27.3	23 (69.7)*
Total	**178**	**17.4**	**92 (51.7)**

pts = patients; * $p < 0.05$ compared with infants and children.

ADRs by a pharmacoepidemiological team consisting of a clinical pharmacologist, a pharmacist and a paediatrician. All drug prescriptions were characterised retrospectively regarding their licence status using the previously generated database and the product information (Fachinfo compact disc 2001).[16] If a drug was not included on the Fachinfo compact disc, the German equivalent of the *Physician's Desk Reference*, *Rote Liste 2001®*, was used.[17]

Characteristics of Adverse Drug Reactions (ADRs)

Definitions of ADR vary in the literature. In this study, ADRs are defined according to the WHO definition as "an effect which is noxious and unintended, and which occurs at doses used in man for prophylaxis, diagnosis and therapy".

In accordance with the WHO questionnaire[18] only clinically relevant ADRs were included in this study. At least one of the following questions had to be answered with 'yes'.

- Did the adverse drug reaction impair the patient's quality of life?
- Was the adverse drug reaction potentially dangerous?
- Did the adverse drug reaction prolong or lead to hospitalisation?
- Did the adverse drug reaction cause temporary malfunction of an organ (system)?

All suspected ADRs were characterised with respect to their probability (using the Naranjo algorithm)[19] and evaluated for being preventable, not preventable or tolerated using an adapted method by Schumock and Thornton.[20] All preventable ADRs with a benefit greater than a respective risk were classified as tolerated. Furthermore, the physician's awareness regarding ADRs was determined. An ADR was categorised as 'recognised' if physician's chart notes recorded changes in drug regimen, additional laboratory tests or other actions subsequent and related to a specific ADR. In addition, ADRs were classified according to the WHO-ART (Adverse Reaction Terminology) System-Organ classes by the type of affected target organ.[21]

Unlicensed and Off-Label Drug Use

The system described by Turner et al.[7] was used to classify unlicensed or off-label drug use. Categories of unlicensed drug use were as follows: modifications to licensed drugs, drugs that are licensed but manufactured in a particular formulation under a special licence, new drugs available under a special manufacturing licence, use of chemicals as drugs, drugs used before a licence has been granted and imported drugs (where a drug is licensed in another country). The category 'off-label use' included use of a drug in situations not covered by the product licence, administration of a higher dose or more frequent administration, administration for indications not described in the licence, administration to paediatric patients outside the age range for which the product is licensed, use of alternative routes of administration and use when the product is contraindicated.

For each drug prescription, the official licence information was evaluated regarding licensing of the drug in general, age of the patient, dosage and route of administration. Drugs were not examined regarding licensed indications. The product information was studied concerning the possible use in children and the minimum age for administration. If

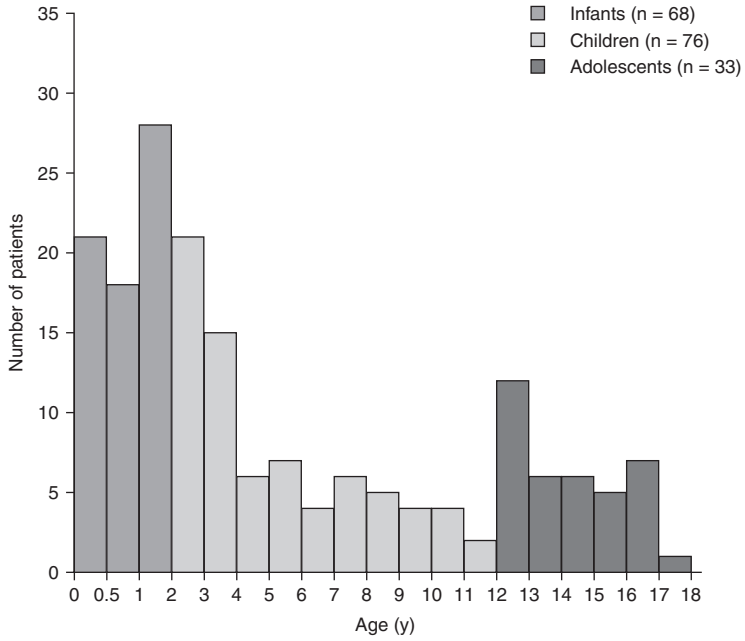

Fig. 1. Age distribution of the study population.

use in children was not mentioned, the age was set to a minimum of 18 years and the respective drug use was classified to be off-label use. In situations where use in children was mentioned but without age specifications, the latter was set to a minimum of 0 years.[6] If the appropriate age for drug administration was mentioned, the prescription was evaluated regarding route of administration and the dosage used. If a drug prescription was judged to be off label, no further evaluations were performed. If a drug had different dosage recommendations depending on indication, the highest mentioned dose was included. In cases where insufficient information was available to determine the licence status, the prescription was categorised as incomplete and excluded from further analysis.

Statistics Analysis

Arithmetic mean, standard deviation, median and upper and lower quartiles were calculated for continuous variables and frequency tables were calculated for discrete variables. Statistical dependence of discrete variables and differences of continuous variables were explored using the Fisher's exact test and the Chi-Quadrat test where appropriate.

Results

Patient Characteristics

Of the total 214 patients admitted to the study ward during the 8-month study period, 178 were <18 years of age (median age 6 years) and were included in the study; the youngest patient was 5 days old. The age distribution of the other patients is shown in figure 1. Among this population 90 patients (50.6%) were female. Of the 178 patients in the study population, 156 received at least one drug and 22 did not receive any drugs. Altogether, 740 drug prescriptions were given to the study population (median three prescriptions per patient) representing 142 different drugs.

Unlicensed and Off-Label Drug Prescriptions

Ninety-two (51.7%) patients in this study received at least one unlicensed or off-label drug prescription. Adolescents (n = 23, 69.7%) received

at least one drug outside the term of its product licence significantly more often ($p < 0.05$) than infants (n = 37, 54.4%) and children (n = 32, 42.1%) [table I]. The difference between unlicensed or off-label drug use and licensed drug use increased significantly with the number of drugs prescribed to a patient ($p < 0.001$). Patients receiving seven or more drug prescriptions had at least one drug prescription outside the term of their product licence.

Of all 740 drug prescriptions, three prescriptions (three different drugs; 0.4%) were found to be unlicensed and 195 drug prescriptions (60 different drugs; 26.3%) were judged to be off label according to the study criteria. Of the unlicensed or off-label drug prescriptions, 61.1% were administered to female patients ($p < 0.05$). Most of the unlicensed or off-label drug prescriptions were given to adolescents (n = 72, 36.4%), followed by children (n = 67, 33.8%) and infants (n = 59, 29.8%). Regarding the total number of drug prescriptions in the different age groups, 35% of all prescriptions for adolescents were unlicensed or off label compared with 25.6% of prescriptions for children and 23.9% for infants ($p < 0.05$).

As shown in table II, the most frequently prescribed drugs were antibacterials (232 prescriptions), vitamins (80 prescriptions), antitussive/expectorant agents (73 prescriptions) and bronchodilators/anti-asthmatics (71 prescriptions). All prescriptions of antidiabetics and antihypertensives, 84.2% of gastrointestinal agents and 80% of antispasmodics were judged to be unlicensed or off label.

The highest rates of unlicensed or off-label prescriptions (n = 198) were found in the following groups: antibacterials (n = 52, 26.3%), gastrointestinal agents (n = 32, 16.2%) and vitamins (n = 28, 14.1%).

Classification of Drugs

The most common reasons for a drug use being classified as off label were inappropriate age

Table II. Drug groups and percentage of licensed and unlicensed/off-label (u/o) drug prescriptions in the respective drug group

Drug group	Licensed (%)	U/o (%)	Total prescriptions[a]
Antibacterials/anti-infectives	77.6	22.4	232 (10)
Vitamins	65.0	35.0	80 (2)
Antitussives/expectorants	80.8	19.2	73 (2)
Bronchodilators/anti-asthmatics	95.8	4.2	71 (1)
Gastrointestinal agents	15.8	84.2	38
NSAIDs	97.1	2.9	35 (2)
Antihypertensives	0	100.0	27
Corticosteroids	74.1	25.9	27
Antiepileptic drugs	57.9	42.1	19 (1)
Diuretics	86.7	13.3	15
Immunosuppressives	66.7	33.3	12
Antiallergics	100.0	0	11
EENT (vasoconstrictors)	100.0	0	11
Cholagogues/biliary tract agents	88.9	11.1	9
Antianaemics	75.0	25.0	8 (1)
Laxatives	100.0	0	7
Antidiabetics	0	100.0	6
Cardiac agents	83.3	16.7	6
Antispasmodics	20.0	80.0	5
Others	73.9	26.1	23 (6)
Total	**72.3**	**27.7**	**715 (25)**

a The numbers in parenthesis represent the number of prescriptions that were excluded from further analysis because of missing data.

EENT = eye, ear, nose and throat agents.

Table III. Number of prescriptions in the different drug use categories

Licence status	Type of u/o drug use	Prescriptions (%)
Licensed		517 (69.9)
Unlicensed		3 (0.4)
	Modification to licensed drugs	3
Off label		195 (26.3)
	Inappropriate age	116
	Different dose	70
	Different route of administration	9
Incomplete data		25 (3.4)
Total		**740 (100)**

u/o = unlicensed/off label.

(59.5%) and different dose (35.9%). Twenty-five (3.4%) drug prescriptions could not be classified because of missing data and were therefore excluded from further analysis (table III).

ADRs and Patients

Forty-six ADRs were detected in 31 patients, representing an ADR incidence of 17.4% (15.9% in male and 18.9% in female patients). The occurrence of ADRs in the corresponding age groups is shown in table I.

As with the incidence of unlicensed and off-label drug use, the incidence of ADRs also increased significantly with the number of drugs prescribed ($p < 0.05$).

Patients receiving at least one unlicensed or off-label drug prescription during hospitalisation (n = 92) experienced at least one ADR significantly more frequently (n = 26; 28.3%) than patients receiving drugs only in the licensed manner (n = 64 vs 5; 7.8%).

Table IV shows the detected ADRs and their related drugs grouped by System-Organ Classes of WHO-ART.

ADRs and Drug Prescriptions

Forty-one drug prescriptions were associated with 46 ADRs. In five cases, one drug prescription was associated with two ADRs. Thirteen of the 41 prescriptions were found to be off label, and one prescription was judged to be unlicensed. ADRs were associated with 29 (5.6%) of the 517 licensed drug prescriptions and with 12 (6.1%) of the 198 unlicensed or off-label drug prescriptions.

Results concerning probability, preventability and physician awareness of ADRs caused by licensed and by unlicensed or off-label drug use are shown in table V.

Regarding the probability, 21.4% of all ADRs caused by unlicensed or off-label drug prescriptions were judged to be definite, whereas only 12.9% of all ADRs caused by licensed drug prescriptions were categorised as definite. ADRs associated with 64.3% of the unlicensed or off-label drug prescriptions were detected by the treating physician, whereas only 43.8% of ADRs caused by licensed drug prescriptions were detected by the treating physician. Among the unlicensed and off-label drug prescriptions 35.7% of ADRs were classified as tolerated by the patients, but among the licensed drug prescriptions only 25% of ADRs were classified as tolerated. However, these differences were not statistically significant by Fisher's exact test and Chi-Quadrat test.

Discussion

ADRs

This study demonstrated a high incidence of ADRs (17.4%) in patients treated with drugs prescribed both for licensed and unlicensed or off-label use. In line with the study by Turner et al.[13] our investigation showed no significant difference in the number of unlicensed or off-label drug prescriptions

causing ADRs compared with licensed drug prescriptions.

Differences in the awareness of physicians while using drugs in an unlicensed or off-label manner were shown to result in an increased recognition of ADRs associated with such prescriptions. Furthermore, these ADRs were more often judged to be tolerated than ADRs caused by licensed drug use, although no statistical significance could be found in this regard. However, it may be assumed that the drugs prescribed in an unlicensed or off-label manner were used carefully and there was probably no alternative therapy available.

A significantly higher incidence of ADRs (28.3%) was observed in the group of patients receiving drugs as unlicensed or off label than in patients only treated with licensed drugs (7.8%). Similar results have been reported in paediatric outpatients.[14] Furthermore, the incidence of ADRs was found to increase with the number of drug prescriptions per patient and the number of patients treated with unlicensed or off-label drugs. On the basis of these data it can be assumed that more severe illnesses prevail in patients treated with drugs in an unlicensed or off-label manner, necessitating more complex therapeutic interventions and medication regimens. However, whether a complicated course of illness itself or the licence status of the drug therapy is a risk factor for the occurrence of ADRs has to be elucidated.

Unlicensed and Off-Label Drug Prescriptions

Confirming prior findings that many drugs are, in principle, not evaluated in children, 27.7% of the drug prescriptions in this study have been judged to be unlicensed or off label. Comparable data in the literature vary between 25% and 46%[3,4,7] for hospitalised general patients and up to 65% for children with complex diseases and in an intensive care unit,[22,23] depending on methods and patient groups. In paediatric outpatients, 10–33% of prescriptions are either off label or unlicensed.[2,5,14]

Antihypertensives (100%), antidiabetics (100%), gastrointestinal agents (84.2%) and antispasmodics (80%) showed in terms of relative numbers the highest percentage of unlicensed or off-label prescription within each drug group. In terms of the absolute numbers of drug prescriptions in our study, antibacterials showed the highest rate of unlicensed or off-label use as in other studies[3-5,7] because of

Table IV. Type and numbers of adverse drug reactions (ADRs) according to the WHO Adverse Reaction Terminology (WHO-ART) System-Organ Classes (SOC) and their causative drugs

SOC	ADR	ADR-causative drugs	n (u/o)
100	Skin and appendages disorders (hypertrichosis, exanthema)	Ciclosporin, vancomycin, cefpodoxime, amoxicillin	6 (3)
410	Central and peripheral nervous system disorders (dysequilibrium, seizures)	Promethazine, streptomycin	2
432	Hearing and vestibular disorders (hearing impairment)	Streptomycin	1
600	Gastrointestinal system disorders (diarrhoea, nausea/vomiting, gastric haemorrhage)	Indometacin, amoxicillin/clavulanic acid, ciclosporin, methylprednisolone, dipyridamole	10 (3)
700	Liver and biliary system disorders (increased hepatic enzymes)	Phenobarbital, isoniazid, ethambutol	4
800	Metabolic and nutritional disorders (hypokalaemia, growth retardation, weight increase)	Corticosteroids, furosemide (frusemide)	5 (1)
900	Endocrine disorders (pubertas arda)	Prednisolone	1
1030	Heart rate and rhythm disorders (tachycardia)	Epinephrine	1 (1)
1220	White cell and reticuloendothelial system disorders (eosinophilia, leukocytosis)	Cefotiam, omeprazole, theophylline	8 (4)
1230	Platelet, bleeding and clotting disorders (increased clotting time, thrombocytosis)	Imipenem, metronidazole	4 (1)
1810	Body as a whole – general disorders (allergy)	Vancomycin, cefotaxime	2 (1)
1830	Resistance mechanism disorders (mycosis, herpes zoster)	Azathioprine, tobramycin	2

n = number of ADRs; **u/o** = unlicensed/off label.

Table V. Classification of adverse drug reactions (ADRs) in terms of probability, preventability and physician's awareness according to the licence status of the related drugs

Category	Licensed (%) [n = 32]	U/o (%) [n = 14]	Total (%) [n = 46]
Probability[a]			
Possible	6.5	14.3	8.9
Probable	80.6	64.3	75.6
Definite	12.9	21.4	15.6
Preventability			
Preventable	21.9	21.4	21.7
Not preventable	53.1	42.9	50.0
Tolerated	25.0	35.7	28.3
Physician's awareness			
ADR recognised	43.8	64.3	50.0
ADR not recognised	56.2	35.7	50.0

a Data missing for one ADR.

u/o = unlicensed/off label.

the high rate of their total prescriptions (22.4%) [table II]. Among antibacterials and the respiratory agents (i.e. bronchodilators/anti-asthmatics [4.2%]), the relative number of their unlicensed or off-label prescription rate was not so high. Therefore, antibacterials and respiratory agents seem to be well established for therapy in children.

Other studies that evaluated the extent of unlicensed and off-label drug use reported that more off-label than unlicensed drugs have been prescribed.[2,3,5,7] Our results are in line with these findings. This study found age and dosage to be the predominating reasons for classifying drug prescriptions as off label, which is in line with previously published studies.[2,4,7] In some studies, dosage and indication have been found to be the main reasons for this classification.[5,24] However, differences in definitions and in methods used to identify unlicensed and off-label drug use may account for these discrepant results. For example, if the official licence information states 'should not be used in children', this is classified as unlicensed by some[24] but as off label by others.[3,7]

Another limitation of evaluating the licence status of drugs retrospectively, as done in our study, may lie in the incompleteness of the available data, particularly regarding the extent of unlicensed drug prescriptions. For instance, categories of unlicensed drug use included modifications to licensed drugs (such as crushing a tablet to prepare a suspension) or drugs that are licensed but the formulation is manufactured under a special licence (such as liquid preparation of a drug that is licensed only in tablet form). The database we generated for analysis was based on the patient record, which usually does not contain this information. Furthermore, we did not evaluate whether the drugs were licensed or not for the indication that they had been used in for each individual case. Therefore, the real extent of unlicensed and off-label drug use may actually be greater than established in this study.

Conclusion and Implications

The present study revealed two major outcomes. First, the incidence of ADRs caused by unlicensed or off-label drug use was not found to be significantly more than that caused by licensed drug use. Second, patients treated with drugs in an unlicensed or off-label manner were shown to possess a significantly higher risk for developing ADRs. However, because of the relatively small number of ADRs, limited study population and limitations while evaluating the licence status, further investigation is required to validate these results.

Nevertheless, more data are needed to provide children with the same effectiveness in drug therapy as in adults. One possibility to improve drug safety in children is the widespread implementation of

systematic, computer-supported drug and therapy monitoring using knowledge-based databases and automatic signal generation. Within this method, data of high quantity and quality could be extracted, allowing risk analysis of different drug regimens in children.[25-31]

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