Original article

Use of off-label nephrology-related drugs in hospitalized pediatric patients: a retrospective study

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Background: **The information about the use of off-label drugs in pediatric nephrology is still lacking, which leads to increased adverse reactions and medical disputes. We retrospectively analyzed the use of off-label drugs in the in-patient ward of the nephrology department of Nanjing Children's Hospital, China in order to provide more complete information about the use of drugs for children.**

Methods: **Proportional stratified random sampling was applied to select patients with renal diseases aged 1 month to 18 years, who were admitted to the hospital from October 1, 2012 to September 30, 2013. All nephrology-related drugs prescribed in the hospitalization period and take-home drugs prescribed on discharge were recorded and evaluated as off-label drugs or not from three different perspectives: person-time, prescription, and drug category.**

Results: **From 385 person-times of patients with 1424 prescriptions, according to the ratio between off-label drugs and person-times, drug prescriptions, and drug products, the rates of off-label drugs were 40.78%, 16.64%, and 31.43%, respectively. Low-molecular-weight heparin, alfacalcidol and diltiazem were the most commonly used off-label drugs. Infants and younger children were the high-risk population of off-label drug use. The high rate off-label nephrology-related drug use in children was mainly related to lacking clinical research into drugs in children and the pace of drug label's revision, which cannot follow the development of medical science.**

Conclusions: **Approximaely half of pediatric patients with renal diseases are usually prescribed with off-label nephrology-related drugs. Analyzing the off-label conditions from different perspectives may lead to various results. More clinical research into drugs for infants and younger children is needed so as to update drug descriptions.**

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Key words: **in-patient;**
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Introduction

The use of off-label drugs in children's hospitals is a common worldwide phenomenon and has become one of the most prominent concerns in medical field.[1] Drug label is the official description of a drug product provided by the pharmaceutical's enterprises and approved by the Food and Drug Administration (FDA). The information of the label should include pharmacology, toxicology, pharmacodynamics, and drug safety and efficacy, which are derived from statistical studies and analysis. It is used as a guidance for the rational clinical use of the drug. The term "off-label" refers to the use of pharmaceutical drugs outside the terms indicated in the product license (an unapproved indication or in an unapproved age group, unapproved dosage, or unapproved form of administration by the FDA). Unlicensed drugs are defined as drugs without pediatric license (unlicensed medicines including chemicals used as drugs, modification of licensed medicines, imported medicines licensed in other countries and special manufactures or assemblies).[2-5] Since there is no detailed information about the criteria of off-label drugs, this research adopted the criteria from the study of Zhang et al.[6] The use of off-label drug is of significant importance in saving patient's life when it involves advanced medical knowledge, but the administration of high dosage off-label drugs especially in children can lead to adverse reactions and medical disputes.[6]

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Thus, detailed statistical analysis of off-label drug use in pediatric patients should be performed to support the rational use of the drugs.

Until recently, clinical trials in children are often regarded unethical. As a result, most of the drugs prescribed for children have not been studied in the pediatric population and the lack of pediatric information[7] leads to the increased use of off-label drugs in children's hospitals. A recent review demonstrates that up to 80% of prescriptions for children in hospitals and in general practice are either unlicensed (without a license for children) or used off-label (outside the product license).[4,8] In Europe, almost half of all drug prescriptions in pediatric wards (46%) were either unlicensed or off-labeled commonly because the drug was prescribed with different doses or frequencies, or in different formula.[1] In America, however, most pediatric patients (78%) hospitalized at tertiary care institutions received at least one medication which was off-labeled.[9] The study of unlicensed and off-label drug use in an Irish neonatal intensive care unit showed that 44% of infants received both unlicensed and off-label drugs, 3% received an unlicensed drug, and 32% received an off-label drug.[10] In addition, the study of off-label and unlicensed drugs in three pediatric wards in Finland revealed that of all prescriptions (n=629), 51% were related to licensed drugs, 36% to off-label use, and 13% to unlicensed drugs which were due to the difference in dosage and age.[3] A retrospective analysis of off-label drug use in 3 pediatric wards of Second Hospital of West China University in 2010 showed that the rate of off-label drug use was 98.00%, 78.96% and 88.05%, respectively. The high rate of off-label drug use is due to the drug label with limited clinical research information, and there is no regulation about update or supplement.[6]

At present, the study of off-label drug use in the nephrology departments of children's hospitals around the world is still rare. Only one research from China analyzed the off-label drug use from the perspective of categories of nephrology-related drugs.[11] In this study, we retrospectively analyzed the use of off-label drugs in the in-patient wards of the Nephrology Department of Nanjing Children's Hospital, China in order to provide more complete information about the use of drugs for children.

Methods

Definition of off-label drugs

Off-label drugs are described as pharmaceutical drugs prescribed outside the terms indicated in the product license (an unapproved indication or in an unapproved age group, unapproved dosage, or unapproved form of administration by FDA). There are six indexes to analyze the off-label conditions of all included prescriptions: 1) population (lack of information about children, age, etc); 2) indications; 3) dosage (standard dosage ±20%);[5] and 4) usage (frequencies and route of administration).

Participants

The Nephrology Department of Nanjing Children's Hospital is one of the biggest centers of pediatric nephrology in China, which is equipped with 75 beds for children with renal diseases. The participating children included patients aged between 28 days to 18 years who were admitted to the inpatient ward of the nephrology department in a year (October 1, 2012 to September 30, 2013). We investigated the person-time of each patient. Since patients with Henoch-Schonlein purpura were also admitted to this department and some of them were given nephrology-related drugs, this disease was also studied. All drugs prescribed within the period of hospitalization and take-home drugs prescribed at the time of discharge were recorded. Inclusion criteria included: 1) patients aged between 28 days to 18 years; 2) patients with kidney disease who were admitted to the inpatient ward of the nephrology department in a year, from October 1, 2012 to September 30, 2013. Exclusion criteria included: 1) incomplete medical record or medical prescriptions; 2) patients aged less than 28 days; 3) patients without kidney-associated diseases who were wrongly admitted to the nephrology department; 4) patients without administration of nephrology-related drugs or with administration of drugs not prescribed by pediatric nephrologists. According to the above criteria, 3014 person-times met the requirements for this study, involving 36 types of diseases. Because of few cases had some types of the diseases, we finally integrated the diseases into 10 categories according to their underlying mechanisms. The incidences of off-label drug use were calculated based on three different perspectives: person-time, prescription, and drug category. Person-time refers to the ratio between the number of off-label drugs to one person-time, prescription indicates the ratio of the number of off-label drugs to the number of prescriptions, and drug category refers to the ratio of the number of off-label drug use to the drugs.

Sampling method

When total person-times met the criteria above, we used the formula $n=(Z_{\alpha/2}/\delta)^2\times P\times(1\text{-}P)$, P=90%, δ=3%, α=0.05 (P is the estimated rate based on data reviewed before, and δ is the permissible error) to determine the sample size, and 385 person-times were included in the study. Based on the categories of kidney diseases, a proportional stratified random sampling method was

used, and random unrepeated integer was generated using the Excel 2012 program.

Criteria of nephrology-related drugs

Based on the pharmacological characteristics and the condition in our in-patient ward, nephrology-related drugs were classified into 6 groups: glucocorticosteroids, immunosuppressants, diuretics, anti-coagulation drugs, anti-hypertension drugs, and other complementary drugs. Other complementary drugs comprised drugs for maintaining bone development, treating anemia, and increasing plasma osmotic pressure. Because of the lack of lipid-lowering drug's dosage form for children, lipid-lowering drugs were not introduced in our hospital. Therefore, no data on lipid-lowering drugs were found in this study.

Data collection and analysis

The data included the number of medical records, name, sex, age, clinical diagnosis and drugs prescriptions including drug name, dosage, and route of administration. Data analysis was performed by SPSS version 16 (IBM, USA). The data were expressed as mean±standard error. Comparisons were made between groups by one-way analysis of variance, and Student's *t* test was used for comparisons between two groups. *P* vales less than 0.05 were considered statistically significant.

Assessment of off-label drug use

A recent systematic review revealed various judgments of off-label drug use, some considered dose, frequency and route of administration, whereas others stressed only contra–indications or age range.[12] In this study, we used the latest package insert of product labels of drugs licensed by the FDA to judge nephrology-related drug prescriptions, whether the drug is categorized as off-label or not. To identify the off-label nephrology-related drug prescriptions, we collected data on drug information, indications, dosage, and route of administration. We investigated whether in the drug label there is any description about drug use for pediatric patients. If there is no information about drug use in children or obviously the drug is contraindicated for children, this drug should be included into the off-label drug category. The drugs which were beyond drug label indications and the dosage of drugs which was higher than 20% or above the recommended doses were considered as off-label drugs. Body weight was used to calculate drug dosage. The actual dosage out of ±20% standard dosage was regarded as off-label use. The following equation was used to calculate body surface area for drug dosage: body surface area (m^2)=weight (kg)×0.035+0.1.[6] We divided patients into the following four age groups according to the Guideline of the International Conference on Harmonization of the Technical Requirements for Registration of Pharmaceuticals for Humans: neonates (0 to 27 days), infants (28 days to 23 months), children (2 to 11 years), and adolescence (12 to 18 years).[6,13] In our hospital, neonates are treated in neonatology department, and will not be admitted to the nephrology department, so the data of off-label nephrology-related drug use in neonates were not calculated in this study. This study judged that the tablet form of drug is not an appropriate dosage form for infants, but this inappropriate form cannot be categorized as off-label drug prescription.

Results

Conditions of samples

Using the method of proportional stratified random sampling, from 3014 patient-times who met the criteria, 385 were enrolled to this study (253 male, 132 female). In the enrollment period, 36 patients didn't meet the criteria and were ruled out from the study, of whom 9 patients had incomplete medical records, 4 received no complete prescriptions, 3 were neonates, 10 had no any kidney diseases, and 10 were not prescribed with any kidney-related drugs. Age groups were divided into infant (35 person-times), children (295 person-times), and adolescence (55 person-times). We analyzed 10 categories of diseases (Table 1) involving 35 types of nephrology-related drugs, including 4 types of glucocorticosteroids, 5 of immunosuppressant, 4 of diuretics, 4 of anti-coagulation drugs, 7 of anti-hypertension drugs, and 11 of complementary drugs. Out of 1424 prescriptions analyzed, the average number of prescriptions per person-time was 3.70, three most frequently prescribed nephrology-related drugs were dipyridamole (258 prescriptions), calcium and vitamin D tablet (249 prescriptions), and prednisone acetate tablets (206 prescriptions). The top three diseases

Table 1. Conditions of off-label drug use

Categories of renal diseases	Total person-time of pts. (in one year)	Sample size	Prescriptions per person-time	Total precriptions
IgA nephropathy	121	15	4.47	67
HSP	682	87	2.19	191
HSP nephritis	484	62	3.98	247
Acute glomerulonephritis	106	13	1.54	20
Lupus nephritis	170	22	5.59	123
Chronic kidney failure	158	20	6.00	120
Urinary tract infection	201	26	0.93	24
Nephrotic syndrome	853	109	5.22	569
Renal tubular diseases	73	9	1.11	10
Others	166	22	2.41	53
Total	3014	385	3.70	1424

IgA: immunoglobulin A; HSP: Henoch Schonlein purpura; pts.: patients.

with the most drug prescriptions per person-time were chronic kidney failure (6.00 prescriptions), lupus nephritis (5.59 prescriptions), and nephrotic syndrome (5.22 prescriptions).

Conditions of nephrology-related drugs use

According to the ratio calculation between off-label nephrology-related drugs use to 385 person-times, 1424 drug prescriptions, and 35 kinds of drug products, the incidences of off-label nephrology-related drug use were 40.78%, 16.64%, and 31.43%, respectively, with 0.615 prescriptions per patient. Based on the proportion of off-label nephrology-related drug use to person-time of specific disease, the highest incidence of off-label drug use were 85% in the chronic kidney failure, 81.81% in lupus nephritis, and 72.48% in nephrotic syndrome; however, according to the calculation of proportion of the off-label nephrology-related drug use to the drug prescriptions of each specific disease, the highest incidences of off-label drug use were 50% in renal tubular diseases, 32.5% in chronic kidney failure and 22.22% in acute glomerulonephritis (Table 2).

Out of 1424 prescriptions, complementary drugs (5.33%), anti-hypertension drugs (4.28%), and anti-coagulation drugs (4.14%) were the most common drugs prescribed off-label. The highest incidences of off-label drugs based on person-time were 17.66% for complementary drugs, 15.32% for anti coagulation drugs, and 10.65% for immunosuppressant. For the name of drug products, three top prescribed off-label nephrology-related drugs were low molecular weight heparin (4.14%), alfacalcidol (3.86%), and diltiazem (2.60%) (Table 3).

Statistically, there was no significant difference in the incidence of off-label nephrology-related drugs between male and female (P=0.107). Calculated on the number of drug prescriptions, the incidence of off-label nephrology-related drug use were higher in children (38.64%) and adolescence (60%). There was no significant difference between incidence of off-label nephrology-related drug use in infants and children (P=0.176), while the difference in incidence of off-label nephrology-related drug use between adolescence and patients less than 12 years (infants or children) was significant (P=0.003 and 0.005, respectively) (Fig.).

Table 2. The off-label drug use based on category of diseases (%)

Categories of renal diseases	Constituent ratio	Proportion of drug use to prescriptions	Proportion of drug use to person-time
IgA nephropathy	4.71	14.93	46.67
HSP	13.41	0.52	1.15
HSP nephritis	21.70	15.86	33.87
Acute glomerulonephritis	1.26	22.22	23.08
Lupus nephritis	8.64	21.14	81.81
Chronic kidney failure	8.43	32.50	85.00
Urinary tract infection	1.69	16.67	11.54
Nephrotic syndrome	39.96	19.68	72.48
Renal tubular diseases	0.70	50.00	33.33
Others	3.72	15.09	22.73
Total	100.00	16.64	40.78

IgA: immunoglobulin A; HSP: Henoch Schonlein purpura.

Table 3. The off-label drug use based on category of drugs (%)

Categories of renal drugs	Constituent ratio	Proportion of off-label drug use to prescriptions	Proportion of off-label drug use to person-times
Glucocorticosteroids	22.61	0	0
Immunosuppressants	10.18	2.88	10.65
Diuretic drugs	3.02	0	0
Anti-coagulation drugs	22.75	4.14	15.32
Anti-hypertension drugs	12.57	4.28	4.94
Complementary drugs	28.86	5.33	17.66
Total	100.00	16.64	40.78

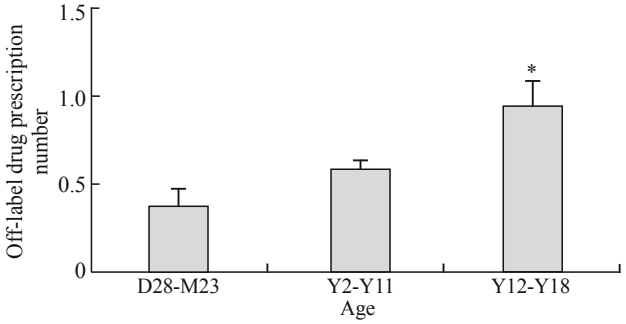

Fig. The comparison of off-label drug use among different age groups. D: day; M: month; Y: year. *: P=0.003 and 0.005 compared with group D28-M23 and Y2-Y11, respectively.

Discussion

Our study suggested that the incidences of off-label drug use were 40.78% and 16.64% according to the proportion of off-label nephrology-related drug use to person-time of specific disease and to drug prescriptions of specific disease, respectively. Despite the proportion of off-label nephrology-related drugs was calculated based on the number of prescriptions or person-times, the incidences of off-label use of anti-coagulation and complementary drugs were rather high, whereas immunosuppressant was among the top three off-label drugs as the ratio was calculated by 385 person-times. Compared to adolescents, children below 12 years old was the high-risk population of off-label drug use. The high incidence off-label nephrology-related drug use in children was mainly related to the lack of drug clinical research in children and the delayed pace of drug label's revision which could not follow the development of medical science.

In this study, there was no phenomenon of off-label nephrology-related drug use related to dosage or form of administration. In this study, we provided comprehensive data about the condition of pediatric off-label nephrology-related drug use from three different ways, person-time, prescription and drug categories in China. To our knowledge, it still lacks this kind of data in the field of pediatric nephrology in the world.

In the study of off-label drugs in pediatric nephrology conducted by Ye et al,[11] the incidence of off-label drugs was analyzed based on the drug categories, while in our study it was based on the number of prescriptions and person-times, and immunosuppressant off-label use varied. This significant difference is one of the reasons why it is important to analyze the data from different aspects. Calculating the incidence from only one aspect can miss some significant points which may lead to insufficiency of data. For instance, from the aspect of person-time the proportion of immunosuppressant off-label use was high if one patient was given any one of the off-label drugs. When calculated according to the whole drugsprescriptions, one off-label prescription would be "diluted" by many other in-label prescriptions. That is why it is essential to comprehend the analysis from several aspects to get a better idea about the off-label drug use.

In this study, the high incidence of off-label drug use for children was mainly due to the lack of pediatric drug information and the use of drugs beyond the drug label indications. The lack of pediatric drug information derives from the fact that drug clinical research is not as widely done in children as in adults. Drug clinical research for establishing drug efficacy and safety in children has not been carried out because of ethical problems, logistical difficulties, financial and legal concern.[4] Pediatric studies still leg behind the need of pediatric drugs despite the overall increase of medicines available for children.[7,12] Alfacalcidol or 1(alpha)-hydroxylated which was the second most prescribed off-label drugs in our study is an analogue of vitamin D used for supplementation. It has been widely and successfully used to manage renal bone disease in patients undergoing dialysis since the early 1970s. Evidence has suggested that early administration of alfacalcidol could safely and beneficially alter the natural course of renal bone disease in adult patients with mild to moderate impairment in renal function.[14] There is few clinical research into alfacalcidol in children, and the information on drug use in children is still unavailable leading to the high incidence of off-label drug use. According to the FDA, low molecular weight heparin (LMWH) is an anticoagulant that prevents the formation of blood clots in the veins, arteries, or lung. In our center, anticoagulation therapy is given to the patients with high-risk of thrombosis. LMWH is also believed to have proteinuria-lowering effect in several studies. In an animal study, Hedberg et al[15] discovered an inverse correlation of heparin treatment with the development of proteinuria. A meta-analysis of seven studies concluded that antiplatelet therapy resulted in reduced the level of proteinuria and protected kidney function in patients with moderate to severe immunoglobulin A nephropathy.[16] A study of patients with diabetic nephropathy showed that treatment with LMWH enoxaparin effectively lowers the level of proteinuria in patients with diabetic nephropathy.[17] However, Kidney Disease: Improving Global Outcomes (KDIGO) guidelines do not support this since there is low-quality of evidence and lack of multicenter randomized clinical trials to verify the efficacy and safety. Tacrolimus (FK-506) is an immunosuppressive drug for the prophylaxis of organ rejection in patients receiving allogeneic organ transplants. Recent *in vitro* studies have suggested that FK506 has immunosuppressive properties similar to those of cyclosporine (Cys) A.[18] Nowadays, it has been proved that FK-506 his efficatious in treating refractory nephrotic syndrome.[19-23] However, due to the slow and complex procedure of drug label revision, although recommended by the KDIGO guidelines, the indication of FK-506 on the drug label is still only for anti-rejection and arthritis treatment. Additionally, diltiazem, another one among top three off-label drugs in our center, has the ability to elevate tacrolimus drug concentrationss by inhibiting Cytochrome P450, family 3, subfamily A (CYP3A) and P-glycoprotein, since tacrolimus is known to be a substrate for P-glycoprotein and metabolized by CYP3A.[24] Jones et al[25] suggested that diltiazem affects tacrolimus serum concentrations longer than that would be predicted from the half-life of diltiazem in plasma. It is also effective in increasing CsA concentration in the blood to optimize its efficacy and but to limit its toxicity.[26,27] Therefore, in our center, diltiazem is frequently co-administered with calcineurin inhibitor to increase the blood concentration of calcineurin, reduce the dosage, protect the kidney function, and lighten patients' economic burden.[28] However, this kind of use of diltiazem is off-labeled. Thus, close monitoring of serum drug concentration is necessary to prevent drug risks.

Of 35 types of nephrology-related drugs in this research, 21 have inappropriate drug formulations, especially for children under 2 years old. And from 60 prescriptions of drugs prescribed for children under 2 years old, 50% (30 prescriptions) don't have specific formulations for children. Dosage forms suitable for pediatric use were liquid preparations (e.g., suspensions, elixirs, drops), dispersible tablets, injection solutions/powders, creams/ointments/lotions, nasal solutions and drops, inhalation solutions, eardrops and

ointments, eyedrops and ointments, scalp applications, rectal preparations (e.g., suppositories), and powders (e.g., powders for reconstitution, nutritional powders).[29] In fact, most drugs are in form of pills and tablets, and only few have formulations specifically for children. When child-specific dosage form of medicines are not available, healthcare workers and parents often use fractions of adult dosage forms or prepare doses of medicines for children by crushing tablets or dissolving portions of capsules in water. This practice is difficult for the parent or care-giver and hard for the child to take. It also results in inaccurate administration of the medicine with either under- or over-dosing, leading to unsuccessful treatment or possible adverse reactions. Improving the quantity and quality of clinical trials is also essential to formulating proper dosage forms for children.

In this study, the incidence of off-label nephrology-related drug use in less than 11 years old infants was higher than in 11 years old and above children. It suggested that infants and younger children were the high-risk population of off-label drug use. Kimland and Odlind[30] found that infants had the highest exposure to drugs that were insufficiently documented with regard to efficacy, safety, and dosage. This situation underscores the need for clinical trials in these age groups. Lack of evidence on safety and efficacy of drugs in children younger than 2 years is related to the high-incidence of off-label drugs use.[31-34]

This study was limited by neither follow-up nor analysis of the short-term and long-term effect of the off-label drugs.

In conclusion, about half of pediatric patients with renal diseases were prescribed with off-label nephrology-related drugs more or less. Off-label nephrology-related drug use in children was due to two aspects, drug information and drug indication. Incomplete drug label information for children, drug prescriptions beyond the standard drug indications, and contraindications for pediatric patients were the main factors for the use of nephrology-related drugs. The high incidence of off-label nephrology-related drug use in children was mainly related to the lack of drug clinical research in children and the delayed pace of drug label's revision which could not follow the development of medical science. This study might encourage the clinical trials of drugs to promote the renewal information of pediatric drugs.

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