INTERNATIONAL JOURNAL OF NURSING EDUCATION & RESEARCH

Journal homepage: www.mcmed.us/journal/ijner

USE OF NON-FORMULARY DRUGS IN CHILDREN: A DESCRIPTIVE STUDY

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Article Info

Received 25/01/2023
Revised 15/02/2023
Accepted 28/02/2023

Key word: - Non-formulary drugs; pediatric wards; Child

ABSTRACT

We will analyses prescriptions of non-formulary medicines to neonates and children, identify adverse drug reactions (ADRs), identify drug interactions, and identify medications that may pose potential hazards. In January and May 2022, the study hospital conducted a prospective exploratory study at the general pediatric oncology, pediatric wards, neonatal care unit and pediatric intensive care. We discovered that non-formulary drugs and other medicines may interact moderately to severely when we searched electronic health records for adverse drug reactions and consulted Micromedex®. There were 110 non-formulary drugs administered to children or neonates. Children were able to use 45 % of these drugs, 11.1% off-label, and 35.7% not approved for children. ADRs were associated with 5 drugs out of 5 that were potentially nonformulary; 12.5% of prescriptions were nonformulary; 4.8% of drugs had potential interactions. Hospitals that participated in the study frequently prescribed drugs that were not on the formulary and therefore were not approved for use in children. These studies facilitate the assessment of hospital formularies relevant to children's health and Inform patients about the special indications for medicines.

INTRODUCTION

In paediatric patients, the hepatic and renal functions differ as they mature over time due to their gradually maturing bodies. Medicines' pharmacokinetics and consequent effects are affected by these differences. It is due to this immaturity that patients are at risk of developing adverse drug reactions (ADRs), toxicity and drug–drug interactions as well as individual predispositions, hypersensitivity, and polypharmacy in the hospital environment [1,2]. Pharmacists and Therapeutics Committees select medicines in hospitals based on scientific evidence of efficacy and safety, which contributes to rational and safe medication use, especially among children. Providing non-formulary drugs to patients in the hospital, or drugs not approved by the Pharmacy and Therapeutics Committees, can encourage off-label and unapproved use of drugs. Further, medication errors are caused by a information lacking about the effects and use of medicines in pediatric populations [3]. It is common for children receiving oncology or critical care to receive licensed or unlicensed drugs for off-label indications, despite the known risks. The reason for this is the lesser pharmaceutical forms and lacking scientific evidence about the suggested dosages for the paediatric population [4]. Getting medicines that don't have defined parameters of efficacy and safety in children can pose risks to patients as a result of these practices. In some cases, a drug is justified by scientific evidence, but pursuing regulatory approval or conducting studies is not financially feasible [5]. FDA approval is not required for 80% of drugs prescribed to children in the United States. [6]. Thirty percent of medicines sold in Europe are allowed for use in children [7]. Research has shown that in Brazilian hospitals, unlicensed and off-label medication use is prevalent in children [8-10]. Researchers found that the most common conditions in which medicines are used are paediatric oncology, neonatal intensive care

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and paediatric intensive care unit [11].

Unlicensed drugs are associated with adverse reactions, according to some studies. An analysis by Among hospitalized children receiving drugs not approved for paediatric use, Bonatti and Clavenna (2008) found that adverse reactions were 3.6 times more common. [12]. The highest risk of adverse drug reactions is among neonates, due to their severe illness, polypharmacy, low body weight and physiological immaturity, associated with preterm birth [13].

Our primary objective was to categorize the prescriptions of non-formulary drugs in a teaching hospital as unlicensed, licensed and off-label. Also, determine whether this medication may cause adverse reactions, drug interactions, or patient hazards.

METHODS

Between January and May 2022, the study was conducted at a tertiary referral hospital as part of a prospective exploratory study, where neonatal care, paediatric oncology, and paediatric intensive care were available. During the study, pharmacy and therapeutics committees in the region evaluated paediatric patients receiving drugs not included in the formulary. A neonatal care unit with 45 beds, as well as a paediatrics service with 85 beds, which includes a paediatric oncology unit with 20 beds, constitute this 790 -bed hospital. A sample of patients was not included from emergency departments or those being treated there.

Every day, the hospital's electronic records identified patients who received non-formulary drugs. The electronic records were used to characterize prescribing patterns and patient profiles, with the attending professionals consulted as necessary. Anatomical Therapeutic Chemical Classification System was used to classify all drugs based on their Non-proprietary Names. A heterogeneous age range necessitated that patients be grouped according a given FDA classification system: neonates (0 to 25 days), infants (28 days to 2 years), children (2 to 11 yrs), and adolescents (more than 12 yrs) [14].

Drug-drug interactions were checked through the Micromedex® database for prescriptions containing non-formulary drugs and other medicines before the prescription was filled [15]. A potentially dangerous drugs list identifies drugs that may cause potential harm to patients if taken improperly.

In order to determine the approval status of nonformulary drugs for children, the National Health Surveillance Agency's electronic medicines compendium was used, which provides information about all medicines marketed. As long as the compendia recommended that a medicine be prescribed according to the approved list provided above, these medications were considered "approved" for use in the study population

A drug that has been approved is prescribed at non-official doses or for ages or indications that do not appear in the official information. An off-label use is one that does not comply with the official information. In most cases, unlicensed drugs are imported from abroad, contraindicated in children, or do not have safety and efficacy data obtained from children. When a drug has been modified by the hospital pharmacist or nurse before being administered to a child, it is approved for use in children was considered "unlicensed" [4,17-19]. This classification did not include extemporaneously compounded medicines, which was intended for only commercially available medicines.

Adverse reactions were monitored the patient must stay in the hospital for 30 days or until discharged for patients receiving non-formulary medications. ADRs were actively searched every day. Based on the algorithm, ADRs were categorized as definite, probable, possible, or doubtful when a causal relationship was established between the suspected reaction and the suspected drug. There are 10 questions in the questionnaire that are designed to evaluate the relationship between the cause and effect of a drug and events. According to Rawlins and Thompson, ADRs can also be predicted (Type A) or idiosyncratic (Type B). A Microsoft Excel database was used to store patient and drug data, and SPSS 18.0 software was used to process and analyze them. We conducted a descriptive statistical analysis (standard deviation, means, and relative and absolute frequencies).

RESULTS

It was monitored that 110 patients received non-formulary drugs and were receiving non-formulary drugs during the study period. There was a mean stay of 55 days (SD = 105). Table 1 shows the patient profile. The average number of prescriptions per patient was 11.5 drugs (SD=6.3). 12.5 % of patients received non-formulary drugs, with a mean of 1.7. In general, 40.5 per cent of patients received non-formulary drugs, followed by 42.3 % in oncology, 18.2 per cent in intensive care, and 12.9 per cent in neonatology.

In the 2-11 age group, where approximately 43.15 per cent of patients received non-formulary drugs, the most common prescription was for a nonformulary drug. There were 4.7% of nonformulary drugs considered potentially hazardous since they were on the ISMP list of High-Alert Medications. The interactions between one or more drugs prescribed concomitantly were moderate or severe with 5.3%.

The most common prescription was for a nonformulary drug for people aged 2-11, where 43.15 % received non-formulary drugs. 5 % of non-formulary drugs were deemed potentially hazardous based on the ISMP list, namely topotecan, cladribine, alteplase, melphan and dexmedetomidine. Prescribing concomitantly, fluoxetine, aprepitant, chlortalidone, olanzapine, sotalol and foscarnet

had moderate or severe interactions with each other with 4.9%.

Based on the dosage therapeutic indication and age group, 45% drugs were considered to be "approved" for use in children. Among non-formulary drug prescriptions, 11.1 per cent were written off-label and 35.7 per cent were written for medicines that were not licensed by the FDA. A total of 20 drugs accounted for 12.5 per cent of nonformulary drug prescriptions.

A total of 12 of the 15 medications used off-label had prescriptions at If the doses are lower or higher than the summaries of product characteristics recommend, consult the label. Children's non-formulary drugs were classified as "unlicensed" for use in children because of the lack of scientific evidence of safety and efficacy. There were 30 patients who were given off-label or unlicensed medications during their hospital stay, of which 21 (19.25%) received at least one drug not approved for use in children, and 10 (9.25%) were prescribed at least one medication that was not licensed. As shown in 4, the most commonly unlicensed drugs are listed.

Vitamins, antiemetics, beta blockers and psychotropic drugs, beta blockers, immunobiological drugs (vaccines), and systemic antibacterials and antimycotics were the most common non-formulary drugs prescribed. Most vaccine requests were for neonates and infants, who receive the most immunizations as an age group. About 30% of requests were for vaccines. All three are recommended by the Brazilian Ministry of Health - the 10-valent pneumococcal conjugate vaccine, the pertussis, diphtheria and tetanus vaccine, and the inactivated polio vaccine. Both anti-emetics are used to prevent chemotherapy-induced vomiting and nausea in patients with cancer. A medical evaluation determined that these drugs offer greater therapeutic benefit to patients than formulary anti-emetics, so these drugs were used instead. Systemic antimicrobials have been reported to be the most common class of drugs used off-label [13].

Cilastatin was administered at an approximately 3.5 g dose above the recommended maximum daily dose of two gram; imipenem with Cilastatin was prescribed at a dose below the recommended minimum. It was also considered off-label to give vitamin C to neonates, as the daily dose prescribed was below thirty milli gram level; Vitamin C is considered a safe supplement, so this specific use was not considered inappropriate. A sodium valproate prescription for encephalopathy is considered off-label because it is approved for treating epilepsy in children up to the age of 10 and for treating epilepsy in children over 10 years old.

Only one prescription of oseltamivir phosphate was extemporaneously altered during the study period, for influenza A prophylaxis. The prescription accounted for 1.8% of all prescriptions for non-formulary drugs. There are few drug-drug interactions identified in the Micromedex® database for nonformulary drugs, all of which can be classed as moderate. It is usually possible to manage such interactions by adjusting dosages or spacing out the administration of the drugs involved. A number of patients with potential drug interactions were tested in this study (in one out of nine patients), One out of nine patients had possible interactions between sotalol and ibuprofen, which blunted the antihypertensive effect of sotalol, and one out of nine patients had a serum level reduction from concomitant olanzapine and sodium valproate.

The patients (4) in general paediatric ward, (2) oncology ward, and (1) intensive care reported symptoms consistent with an adverse drug reaction (ADR). The study identified 6 adverse drug reactions (ADRs), 3 of which were associated with unlicensed drugs, Patients were followed up on average for 7 days (range, 1- 30 days). The drugs involved in suspected adverse drug reactions are listed in Table 5. A statistically significant difference between groups was not found in relationships between unlicensed and off-label prescribing and adverse drug reactions.

Table 1: Profile of paediatric patients given non- formulary drugs

Patients (n=110)	Per cent (n)
Gender	
Female	57 (51.8)
Male	53 (48.2)
Age	
Zero to twenty-eight days	5 (5.5)
Twenty-eight days to two years	29 (27.15)
Two to eleven years	50 (43.15)
More than twelve years	26 (25.15)
Mean age in yrs	7 (s.d=4.3)

Inpatient unit	
General	30 (26.5)
Cancer (oncology)	40 (42.3)
Neonatal (child)	14 (12.9)
Intensive	26 (18.2)
Admission reasons and affected systems	
Tumors cancer	37 (33.9)
Respiratory	16 (14.8)
Premature birth	14 (12.9)
gastrointestinal	10 (9.09)
Other	33 (30.01)
Total	110 (100)

Table 2 – Non-formulary drugs not licensed for use in children.

DRUGS	REASONS	PER CENT OF N
Aprepitant, aripiprazole. cladribine, dexmedetomidine, flunarizine, fluoxetine, melphalan, nitroglycerin, olanzapine, palonosetron, sotalol, tizanidine, topotecan	Safety and efficacy not established	38 (76.0)
Alteplase, factor VIII, foscarnet, pancrelipase	Product not available (imported drug)	6 (12.0)
Oseltamivir	Change in pharmaceutical form	4 (8.0)
Sildenafil	Contraindicated	2 (4.0)

Table 3 – Non-formulary drugs involved in suspected adverse drug reactions.

Drugs which has been suspected	Status	Adr description	Management
Acitretin	Approved	Hypomagnesaemia	Continuation of treatment/ magnesium replacement
Amphotericin B lipid formulation	Approved	Rigors	Diphenhydramine
Cladribine	Un-licensed	Anorexia	Continuation of treatment
Dexmedetomidine	Un-licensed	Periorbital oedema	Continuation of treatment; dose reduction; eventual discontinuation.
Vaccines (DTaP/inactivated polio vaccine/ *haemophilus* B vaccine)	Approved	Hyperthermia	Paracetamol

DISCUSSION

In the hospital where this study was conducted, the Pharmacy and Therapeutic Committee, an interprofessional committee comprised of pharmacists, physicians, and nurses, selects Formularies are formulated for medications and requests are evaluated for medications not on them. Therapeutic indication, dosage, and cost-benefit analysis are all considered before a drug is approved or declined. Children should not be given non-formulary drugs since some do not have paediatric safety data, and formulations do not provide easy dosage adjustments. Generally, non-clinical trials are attributed to off-label and unlicensed prescribing in the paediatric population because pharmacokinetic parameters are heterogeneous and ethical issues are prevalent [1, 8]. There are many countries where these medications are legal and available for prescription, representing the most effective treatment or the only option for many patients. According to Santos et al. (2008), 39.6% of all medications prescribed to children in the same age group were prescribed off-label, and 5.5% were medications that were not approved for children [8]. The facility conducted a study of 2026 formulary drugs prescribed to patients ages 0-14 during the study period, and found that 38.9% were prescribed off-label, while 11.8% were not licensed for use in pediatric patients. There were 49 prescription drugs (2.4% of all prescription drugs) that were not included in formularies [10].

The fact that these medicines are new on the market may be a contributing factor could explain why unlicensed drugs were used more frequently in our sample than off-label use. Consequently, therapeutic indications, dose and administration data are limited to those determined by adult clinical trials when applying to the National Health Surveillance Agency for marketing authorization. Palonosetron and aprepitant, for example, do not have definitive efficacy and safety data for paediatric

populations. Science, however, supports their use in recent years. It was found that palonosetron was an effective alternative to ondansetron in paediatric oncology patients, with no adverse effects throughout the study period. Prepitant was well tolerated and associated with improved treatment efficacy in a randomized double-blind clinical trial that enrolled 11 and 19-year-old oncology patients. In comparison to dexamethasone and ondansetron alone, dexamethasone, ondanetron and aprepitant were well tolerated and associated with increased treatment efficacy. A significant difference between groups was not observed. Probably because of the small sample size, the authors concluded. Patients receiving oncological care are usually the majority of those receiving unlicensed or off-label medicines, primarily because of childhood physiological conditions, malignant nature of their diseases, and ethical considerations. According to a study, 87% of patients receiving a prescription for an unlicensed medicine over a 2-week period were classified as off-label users; 43% were off-label drugs. The study population in the UK was found to have 45% of prescriptions that were off-label or unlicensed.

Off-label use is also most commonly attributed to dosage, which is most commonly cited as the main reason for placing prescriptions in this category [8]. A common reason for off-label use, however, is therapeutic indications that are often different from those approved. It is consistent with the literature that off-label prescribing rates were higher in general paediatric wards and neonatal care units in this sample [8, 9, 11].

There is a very common practice of modifying dosage forms so as to allow or facilitate use in paediatric patients. Our facility modified oseltamivir despite it being commercially available for oral suspension for children over the age of 1 year, although it may affect pharmacokinetic parameters. Products modified in our facility may affect pharmacokinetic parameters, and thus their use is considered unlicensed. Due to a temporary unavailability of the oral suspension, an extemporaneous preparation of oseltamivir capsules was made based on the recommendations of the Ministry of Health. A product manufacturer provided instructions for compounding oral solution in this particular case, but most extemporaneous oral preparations lack any such information.

Furthermore, some drug interactions which are harmful can enhance or antagonize the desired pharmacological effects, but others can improve response to therapy or decrease the incidence of adverse events associated with concomitant use. The results of this study revealed a number of therapeutically beneficial interactions, including the combination of dexamethasone and aprepitant, which improved nausea and vomiting associated with chemotherapy, as well as the combination of captopril and chlortalidone, which improved hypertension control thanks to its additive effects.

The use of concomitant drugs can enhance or antagonize pharmacological effects, while other drugs can improve the response to therapy or reduce the incidence of adverse reactions. There are a number of therapeutically beneficial interactions reported in this study, including the combination of aprepitant and dexamethasone, which improved chemotherapy nausea and vomiting. Additionally, combining captopril and chlortalidone, which improved hypertension control as a result of their additive effects, improved hypertension control.

A review examined, that studies has been carried out in hospitals that used drugs included in their formularies. ADRs were most common among patients aged 0 to 24 months and females.

Adverse drug reactions are more likely to occur in children who use potentially hazardous medications, or "High-Alert" medications. As a result of their frequent involvement in medication errors, these drugs are more likely to cause harm to patients. As such, they require more intensive monitoring by attending professionals. About 58% of high-alert medication-induced injuries occur in the hospital setting according to the Institute of Health Care Improvement [10]. Due to a 30-day follow-up period, delayed ADRs could not be detected in this study; ADRs were underreported, resulting in an understated incidence of ADRs; there were only patients receiving non-formulary drugs enrolled near the end of the study, so the study had a small sample size; the study was short in duration because only patients enrolled at the end of the study were included. Despite these limitations, the study is valid for providing inputs and supporting some decisions that are not covered by standard formularies.

CONCLUSIONS

Paediatric pharmacotherapy relies heavily on extrapolation, using the same data used for adult marketing approvals. There is no scientific evidence to support the safety and efficacy of many non-formulary drugs in children. Off-label and unlicensed prescriptions may cause adverse reactions. Additionally, these practices can lead to medication errors and drug interactions. In addition to making recommendations on which medicines should be included in hospital formularies, Pharmacy and Therapeutics Committees watch over medication use and protect patients.

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