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RESEARCH ARTICLE

Extent and nature of unlicensed and off-label medicine use in hospitalised children in Palestine

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Abstract *Objective of the study* To determine the extent and nature of unlicensed/off-label prescribing patterns in hospitalised children in Palestine. *Setting* Four paediatric wards in two public health system hospitals in Palestine [Caritas children's hospital (Medical and neonatal intensive care units) and Rafidia general hospital (Medical and surgical units)]. *Method* A prospective survey of drugs administered to infants and children <18 years old was carried out over a five-week period in the four paediatric wards. *Main outcome measure* Drug-licensing status of all prescriptions was determined according to the Palestinian Registered Product List and the Physician's Desk Reference. *Results* Overall, 917 drug prescriptions were administered to 387children. Of all drug prescriptions, 528 (57.5%) were licensed for use in children; 65 (7.1%) were unlicensed; and 324 (35.3%) were used off-label. Of all children, 49.6% received off-label prescriptions, 10.1% received unlicensed medications and 8.2% received both. Seventy-two percent of off-label drugs and 66% of unlicensed drugs were prescribed for children <2 years. Multivariate analysis showed that patients who were admitted to the neonatal intensive care unit and infants aged 0–1 years were most likely to receive a greater number of off-label or unlicensed medications (OR 1.80; 95% CI 1.03–3.59 and OR 1.99; 95% CI 0.88–3.73, respectively). *Conclusion* The present findings confirmed the elevated prevalence of unlicensed and off-label paediatric drugs use in Palestine and strongly support the need to perform well designed clinical studies in children.

Keywords Neonates · Off-label prescribing · Paediatrics · Palestine · Unlicensed medicines · Ward

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Impact statements

- Infants aged less than one year old were the most likely group to receive a greater number of off-label or unlicensed medications compared to older children.
- In Palestine, off-label drug use occurs considerably more frequently than unlicensed use in hospitalised children.
- The overall level of unlicensed and off-label paediatric prescribing suggests the need to perform well designed clinical studies in children so that dosing schedules in the future can be evidence based.

Introduction

Infants and children represent a large proportion of the population in developing countries. As in all countries, infants and young children are especially vulnerable to

illnesses and the harmful effects of medicines. Although there has been important progress in paediatric clinical pharmacology, there is still a lack of information regarding many relevant aspects of therapeutics in childhood, particularly concerning pharmacokinetics, pharmacodynamics and pharmacoepidemiology [1].

Growing children have a constantly changing physiology and it is therefore important that doses are adjusted in a manner that ensures both safety and effectiveness. Although some medications used in children have been subjected to clinical trials and have been specifically licensed for use in this age group, many medicines have not been appropriately tested in children or are not available in a formulation that is suitable for children and as such are used outside the terms of their license, i.e. off-label or unlicensed [2–5]. The main reason for off-label medicine use among children is that the medicine is prescribed outside the licensed dosage range, for an age group for which the drug is not licensed, for a different indication or by a different route of administration [6]. Unlicensed medicines are also commonly used. This normally involves drugs which are not available in a formulation suitable for administration to young children e.g. tablets crushed and reformulated as a suspension. There is a concern because adverse drug reactions in children may be more common during unlicensed and off-label treatment, and the practice may result in either over- or underdosing of medicines in different age groups [7–10].

The extent of prescribing of medicines for off-label and unlicensed use has been quantified in studies from North and South America, Australia, and Europe [11, 12]. These studies show that the situation varies across countries because of national differences in licensing status of medicinal products and in clinical practice. In a recent review of 24 studies from 12 different countries (mostly European), the proportion of hospitalised children who received at least one prescription for off-label use or unlicensed medicine ranged from 36 to 100% [12]. The practice is also common in primary care [8]. The prescribing of unlicensed and off-label medications is not governed by legislation and remains the responsibility of the prescribing clinician [9].

Aim of the study

The aim of the present study was to obtain information on the prescribing patterns of medicines to hospitalised children in public health system hospitals in Palestine. More specifically, the goal was to determine the extent of use of medicines which do not have a marketing authorisation e.g. tablets crushed and made into a suspension or a chemical used as a medicine (unlicensed) and of medicines used outside the terms of their product license (off-label) with respect to age/weight, dose/frequency, dosage form and route of administration and to explore factors associated with receiving off-label or unlicensed medicines among hospitalised children.

Methods

This study was approved by the Committee for Clinical Research, Hospital Administration Department, Ministry of Health, Palestine. The research was performed in the medical and neonatal intensive care wards at the Caritas Children's Hospital and the paediatric medical and surgical wards at the Rafidia Hospital over a 5 week period during March and April 2010. The wards in Rafidia hospital in Nablus City, North Palestine had a mixture of general paediatric, gastrointestinal and respiratory cases. The wards in Caritas Children's Hospital in Bethlehem, South Palestine cater for children with a variety of acute illnesses (e.g. pneumonia, soft tissue and skeletal infections) and sub-acute or chronic conditions (e.g. failure to thrive, abdominal pain and anaemia). Data on all patients admitted to these wards over the 5 week study period were collected. Data collected included the date of birth, diagnosis, medication prescribed, and dose and route of administration. The following items were not included in the study: standard intravenous replacement solutions, flushes for intravenous lines, blood products, topical anaesthetic creams and medications used in clinical trials. The study included children <18 years of age who were hospitalised for at least 24 h.

Each medicine recorded was reviewed for unlicensed or off-label use status, based on the information in their respective product licenses in Palestine. The following were considered unlicensed: modified formulations including extemporaneous preparations, formulations prepared under a 'specials' manufacturing license, imported drugs (which are not part of the Palestinian Registered Product List, PRPL) and chemicals used as drugs [4, 6, 13]. The off-label category included all medicines where the prescription showed a discrepancy with the license labelling information for age (or weight), dose (or frequency) or route of administration. Some medicines were classified off-label for more than one reason. As primary reference sources, the Palestinian Registered Product List [14] and the Physician's Desk Reference [15] were used. The latter reference is used in Palestine as a source of information for the licensing status of medicines, particularly in children.

Data were analysed using SPSS (version 18 for Windows; SPSS Inc, Chicago, IL, USA). The differences in proportions between the four wards were compared using the Pearson's chi-squared test. Continuous variables were

compared using the Kruskal–Wallis test. The probability of a child receiving an unlicensed or off-label medicine and the factors associated with such prescribing were estimated utilising the odds ratio approach, the calculations being performed by logistic backward stepwise regression, with the dependent variable being the prescription of an off-label or unlicensed medicine. A *P*-value of less than 0.05 was considered significant.

Results

Three hundred and eighty-seven children were involved in the study; 182 in Caritas medical wards, 42 in the Cartias neonatal intensive care unit, 143 in the Rafidia medical wards and 20 in the Rafidia surgical ward. Children were either in hospital at the start of the study or admitted over the study period. Of these, 236 (61%) were male and 151 (39%) were female. The ages of the patients ranged from 4 days to 16 years (mean ± SD = 23.5 ± 32.7 months; median = 12 months). The minimum and maximum numbers of prescribed medicines per patient were 1 and 9 respectively (mean ± SD = 2.35 ± 1.44; median = 2).

In the medical wards, the most common diagnoses according to the World Health Organisation International Classification of Diseases (ICD) [16] were respiratory diseases (including upper and lower respiratory tract infections; 44%), certain infections and parasitic diseases (apart from respiratory tract infections; 20%) and diseases of the digestive system (16%); in the surgical ward, most of the children had surgical procedures under general or regional anaesthesia and in the ICU the most frequently encountered condition was respiratory distress syndrome. A total of 66 different medicines were administered to the 387 patients. The 5 most commonly prescribed medicines were cefuroxime, salbutamol, paracetamol, ceftriaxone and dexamethasone.

Of the 387 children, 199 (51.4%) were prescribed at least one off-label or unlicensed medicine. One hundred and ninety-two (49.6%) children received prescriptions for off-label use, 39 (10.1%) for unlicensed medicines and 32 (8.2%) received both types of medicines.

Of all the prescriptions ($n = 917$), 528 (57.8%) were licensed for use in children, 65 (7.1%) were unlicensed and 324 (35.3%) were used off-label. The breakdown of the data by hospital and ward are presented in Table 1. Seventy-two percent of off-label drugs and 66% of unlicensed drugs were prescribed for children under 2 years old.

Antibiotics for systemic use and bronchodilators were among the five most frequently prescribed off-label drugs in the four paediatric study wards (Table 2). Altered dose and use of medicine outside the age range were the most common categories of off-label medication use. On the other hand, the most frequent reason for unlicensed medicine use (approximately 80%) was modification of licensed drugs (dispensing a drug in a different form, e.g. tablets crushed to prepare suspensions). The numbers and types of unlicensed medication uses are summarised in Table 3.

Predictors of receiving an off-label or unlicensed medication are shown in Table 4. In multivariate analysis, patients who were admitted to the neonatal intensive care unit were most likely to receive an off-label or unlicensed medicine compared with patients who were admitted to a

Table 1 Off-label prescriptions and prescriptions for unlicensed medicines in the different paediatric wards

Wards	Study population *n* (%)	Licensed prescriptions *n* (%)	Off-label prescriptions *n* (%)	Unlicensed prescriptions *n* (%)	Total number of prescriptions *n* (%)
Medical (Caritas)	182 (46.9)	224 (61.0)	115 (31.3)	28 (7.6)	367 (40.0)
Neonatal (Caritas)	42 (10.8)	37 (37.0)	55 (55.0)	8 (8.0)	100 (10.9)
Surgical (Rafidia)	20 (5.2)	47 (68.1)	18 (26.0)	4 (5.8)	69 (7.5)
Medical (Rafidia)	143 (36.9)	220 (57.5)	136 (35.7)	25 (8.4)	381 (41.5)

Table 2 The five most frequently prescribed off-label drugs (% of all prescriptions) in each ward

	Caritas				Rafidia			
Rank	Medical ($n = 115$)	(%)	Neonatal ($n = 55$)	(%)	Medical ($n = 136$)	(%)	Surgical ($n = 18$)	(%)
1st	Salbutamol	20.0	Adrenaline	23.6	Paracetamol	18.3	Dexamethasone	22.2
2nd	Cefuroxime	15.6	Cefotaxime	18.1	Cefuroxime	13.2	Ranitidine	11.1
3rd	Dexamethasone	7.8	Gentamicin	16.3	Ceftriaxone	9.5	Vancomycin	11.1
4th	Ipratropium	7.0	Dexamethasone	5.4	Dexamethasone	7.3	Diazepam	5.6
5th	Ceftriaxone	6.0	Amikacin	3.6	Ibubrofen	5.9	Midazolam	5.6

Table 3 Examples of unlicensed medications and their frequencies in the study

Medicines	*n*	License category
Captopril	35	Unlicensed: extemporaneous (modification to licensed drug)
Furosemide	18	Unlicensed: extemporaneous (modification to licensed drug)
Diclofenac sodium	6	Unlicensed: product produced under 'specials' license
Beclomethasone	4	Unlicensed: imported drug licensed for use in another country
Hydroxytryptophan	2	Unlicensed: imported drug licensed for use in another country

Table 4 Variables associated with receiving unlicensed or off-label medications

	Unadjusted		Adjusted	
	Odds ratio (95% CI)	*P* value	Odds ratio (95% CI)	*P* value
Gender				
Male	0.87 (0.56–1.45)	0.660	0.73 (0.41–1.05)	0.70
Female	Ref		Ref	
Ward				
Medical	Ref		Ref	
Neonatal	2.47 (1.29–3.82)	0.0001	1.80 (1.03–3.59)	0.009
Surgical	0.71 (0.39–1.49)	0.442	0.81 (0.46–2.10)	0.564
No. of medications				
1-3	Ref		Ref	
4-6	1.19 (0.60–1.89)	0.21	1.06 (0.52–1.44)	0.601
≥ 7	1.48 (0.57–1.98)	0.04	0.81 (0.36–1.29)	0.649
Age (year)				
0-1	2.99 (1.23–4.10)	0.005	1.99 (0.88–3.73)	0.021
2-5	1.92 (1.01–2.99)	0.01	1.15 (0.51–1.71)	0.113
6-10	1.11 (0.58–1.35)	0.13	1.01 (0.59–1.60)	0.501
≥ 11	Ref		Ref	

medical or surgical ward (OR 1.80; 95% CI 1.03–3.59). It can be seen that infants aged 0–1 year were also at higher risk of receiving an off-label or unlicensed medications than other age groups (OR 1.99; 95% CI 0.88–3.73).

Discussion

To the best of our knowledge, this is the first study to investigate the extent and nature of unlicensed and off-label medication use in children in Palestine. Results show a high prevalence of unlicensed and off-label drug use there. The results indicate that off-label use occurs considerably more frequently (35.3%) than unlicensed use (7.1%). The proportions are in parallel to those found in France [17] (62% and 10%), the Netherlands [18, 19] (62 and 14%), Italy (50.5 and 12%) [4] and in the United Kingdom [7, 8] (54.7 and 10%; 55% combined). The slightly lower unlicensed use can be explained by the more widespread use of extemporaneously prepared formulations, manufactured by hospital pharmacies, in European countries [2].

As expected, in the present study, unlicensed and off-label drug use was more prevalent in neonatal wards when compared with paediatric medical or surgical wards. The general lack of availability of licensed medicines for newborns and infants is an important factor in this regard [20, 21]. In a recent study by Neubert et al., only 38% of the medicines prescribed in a neonatal intensive care unit in Germany had information about their use in patients less than 1 month of age in their SPC (i.e. 62% of all medications were used in an unlicensed or off-label manner in neonates). Furthermore, 69.9% of all neonates received at least one prescription of medications that are unlicensed or off-label in neonates [22]. In the present study, 63% of the prescriptions in Caritas neonatal intensive care unit were for either unlicensed or off-label use. Similar percentages of unlicensed/off-label prescription episodes in neonates were also reported by Conroy et al. and O'Donnell et al. (64.6 and 58%, respectively) [20, 23].

The most frequently prescribed medicines used in an off-label or unlicensed manner were antibacterials and bronchodilators. This concurred with a recent study conducted in the US where inhaled bronchodialators (30.4%) and antimicrobials (14.8%) were the most commonly prescribed unlicensed/off-label medication classes in a paediatric emergency department [24]. In the present study, however, antibiotic use (44% of total medications) was high compared to other reports from similar studies in other countries [25–27]. This high prevalence can be partially explained by the high incidence of bacterial infections to the overall illness burden in Palestine [28] and by the fact that over prescription of antibiotics is common practice in hospitalised children in Palestine [29].

Off-label use was mainly attributable to the use of different doses and dosing frequencies to those recommended in the product license, a finding consistent with other studies [30]. In a recent review, the most frequent reason for off-label prescribing reported in 12 studies was deviation from dosage recommendations [12]. An overdose increases the risk of adverse drug reactions, whereas an underdose may not be therapeutically effective [12]. Such use, however, is not always inappropriate, and in some cases was justified, e.g. ceftriaxone and cefuroxime were

administered at a dosage higher than that recorded in the product license (e.g. 75 vs. 50 mg kg^{-1} day^{-1} for ceftriaxone and 150 versus a maximum of 100 mg kg^{-1} day^{-1} for cefuroxime in children with severe pneumonia) [31]. Among the medicines licensed for paediatric use, but used off-label due to dose or indication were ipratropium, budesonide, salbutamol and adrenaline in various combinations and dosages.

The observed number of cases of unlicensed use ($n = 65$), highlights the difficulty in accessing medicines which are licensed for use in common diseases in children necessitating the need for the extemporaneous preparation of medicines. Such preparations often lack bioavailability data and there is an increased risk of poor therapeutic outcomes due to dosage errors, especially when younger children are involved [32]. Moreover, there can also be a problem of limited availability of these extemporaneous preparations in the outpatient setting after the child is discharged from hospital [33]. Drugs that were prescribed in an off-label or unlicensed manner included meropenem (contraindicated in children less than 3 months), etanercept for rheumatoid arthritis in two cases (safety not established to use in children less than 8 years) and hydroxytryptophan which was prescribed in two cases for phenylketonurea with impaired dopamine production. Other examples were aminophylline which was used for apnea and asprin for Kawasaki disease.

The study shows that children from birth to 1 year were more likely to receive off-label medications in multivariate analysis, as demonstrated by others studying a general paediatric population [20]. In another study conducted in Finland, 51% of the children with an off-label prescription and 72% of those with prescriptions for unlicensed drugs were below 2 years of age [12]. Such findings usually reflect the lack of information on appropriate use of medication for younger children [12]. Because neonates and infants are known to have important differences in drug absorption, distribution, metabolism, and elimination compared with older children, the use of medications with limited safety and efficacy data in this population is particularly concerning and warrants further study.

Off-label and unlicensed use of medicines in children should not be ignored or simply accepted as part of normal paediatric practice. Turner et al. [6] and Santos et al. [13] have shown that adverse drug reactions are a significant problem following such use. The lack of clinical trials in children is often used to justify the unlicensed use of medicines in this group [34, 35]. However, more efforts are needed to overcome this problem by encouraging pharmaceutical companies and researchers to evaluate more drugs to obtain adequate information on their safety and efficacy in paediatric patients [36, 37].

In parallel to the European Paediatric Initiative [38], The Ministry of Health in the Palestinian Authority are striving to put in place measures to improve the situation for paediatric patients. During the licensing process of each medicine in Palestine, labelled information regarding paediatric use is checked and complementary information requested from the manufacturer if deemed necessary. If such information is not available, the licensing status of the medicine for use in children in the country of origin is checked and this information, together with expert opinion, is used to decide licensing status in Palestine.

This study was limited to inpatient resource-utilisation data in two clinical centres and as such data are not generalisable across Palestine nor does it provide data on outpatient use of off-label and unlicensed medications. Many medications such as anticancer, antiepileptic, and immunosuppressive agents are frequently used by children in the outpatient setting in Palestine and require further research. Moreover, the sample in the surgical ward was relatively small.

Conclusion

The present study suggests a high prevalence of unlicensed and off-label drug use in children in Palestine**.** For ethical reasons, standards of drug efficacy and safety should apply equally in adults and in children and as such the present and previous studies of drug use in children support the need to perform more well designed and conducted studies, particularly in newborns.

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Conflicts of interest None to declare.

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