

## Unlicensed and off-label drug use in paediatric wards

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### ABSTRACT

**Objective:** To determine the proportion of unlicensed &/or off-label prescriptions in paediatric patients.

**Patients & Methods:** This prospective study of drugs administered to children in two paediatric hospital (Ib-Altheer, Al-Kanasaá hospital for pediatrics in mosul city, over 6 months from 1st Nov. 2007 to 1st May 2008. One hundred-forty children were included in this study aged from at birth to 6 years admitted to paediatric medical wards. Drug-licensing status of all prescriptions given to these patients was determined.

**Results:** Of the 1208 prescription given to these children, more than half of all prescriptions 626 (51.8%) were unlicensed or off-label. Where as 582 (48.2%) licensed. The most common category of off-label use 365 (30.2%) was related to age 217 (17.9%), the other off-label uses were related to dose and frequency of administration 77 (6.4%), indication 55 (4.6%) and route of administration 16 (1.3%) and the most common reason of unlicensed preparation was the administration of preparation not licensed for use at all.

**Conclusion:** The use of unlicensed or off-label medicines to treat children was found to be common in paediatric patients, this problem is Widespread in paediatric wards & the clinical pharmacist must take an active role in our hospitals.

### الخلاصة

**الهدف:** لتحديد نسبة الأدوية غير المرخصة أو الأدوية الموصوفة خارج التسمية المعطاة للأطفال الراقدين في المستشفيات.

**الطريقة:** دراسة جماعة بفترة الدراسة الأول من تشرين الثاني 2007 إلى الأول من مايس 2008. المرضى والطرق المستخدمة: كان عدد الأطفال في هذه الدراسة 140 طفل تتراوح أعمارهم ما بين عدة أيام إلى ستة أعوام وقد صنفت الأدوية المعطاة للأطفال الراقدين في ردهات مستشفى ابن الأثير ومستشفى الخنساء للأطفال في مدينة الموصل إذا ما كانت غير مرخصة أو مرخصة خارج التسمية.

**النتائج:** إن أكثر من نصف الأدوية الموصوفة للأطفال الراقدين في الردهات كانت غير مرخص بها أو خارج التسمية (51.8%) وكانت الفئة الأكثر شيوعاً بالنسبة للأدوية الغير مرخصة هي الأدوية الغير مرخصة للاستخدام على الإطلاق بينما الأدوية المرخصة خارج التسمية كانت الفئة الأكثر شيوعاً هي الأدوية التي تعطى خارج العمر المسموح به (17.9%) يليه الجرعة الدوائية وعدد المرات المعطاة (6.4%) والاستطباب وطريقة إعطاء الدواء (1.3%).

**الاستنتاج:** إن استخدام الأدوية الغير المرخصة أو الأدوية خارج التسمية لعلاج الأطفال أصبحت من الأمور الشائعة. وعلى الصيادلة السريري أن يأخذ دوراً فعالاً في المستشفيات.

Many drugs used to treat children in hospital are either not licensed for use in children (unlicensed) or prescribed outside the terms of their product license (off-label prescription)<sup>1,2</sup>. Example of use of off-label drug include salbutamol syrup under 2 years (not licenses for age group) or rectal injection of lorazepam for a child with an acute seizure (route). An example of unlicensed use is the preparation of a solution from a

tablet by the hospital pharmacy. The extent & type of unlicensed & off-label medicine use in paediatric wards in our city is unknown. Several prospective and retrospective studies have been conducted in various health care contexts (general, medical and surgical wards, neonatal and paediatric intensive car units) in the USA, Europe and Australia<sup>3,10</sup>. These studies have brought to light a high proportion of unlicensed and off-label use.



reaching up to 72% of all prescriptions and 93% of all paediatric patients. Furthermore adverse drug reactions in hospitalized children were more frequently associated with unlicensed and off-label drug prescriptions than with the licensed drug (6% vs 3.9%).<sup>4</sup> This study, therefore designed to assess the extent and nature of unlicensed and off-label drug in the different paediatric wards in mosul city.

### Patients and Methods

This study was prospectively conducted over a 6- month period at Ibn-Altheer and Alkhanasa'a hospital. Data were collected from physician's drug prescription sheets during hospitalization for 140 randomly chosen paediatric (87 male, 53 female). The patient's age ranged from at birth to 6 years (mean±SD 12.12±10.58 months). During the study period, 1208 prescriptions was written for the paediatric patients corresponding to 204 medicines. The details recorded included the patient's name, date of prescription, ward, weight, diagnosis and medicines (with dosage form, dose and frequency of administration and route of administration). The patient's age was classified according to the international conference on harmonization<sup>11</sup>: a) new born infants (at birth - 27days), b) infants, & toddlers (28 days-23 months), c) children (2-11 years). All prescriptions were similarly analyzed to determine whether the medicines were used in a licensed or unlicensed manner. Unlicensed medicines were subdivided into modified preparation & medicines not licensed for use at all & medicines

licensed for paediatric use, but off-label for age; indication; dose & frequency of administration or route of administration. The primary reference source was the British national formulary for children 2007<sup>12</sup>; Nelson text book of paediatrics<sup>13</sup>, data were collected on a data base and summarized using standard descriptive methods.

### Results

Of the 1208 prescriptions, 582 prescription (48.2%) were licensed and 626 prescription (51.8%) were unlicensed and off-label prescriptions, 261 (21.6%) were prescription unlicensed drugs and 365 (30.2%) were off-label prescriptions. All patients received at least one unlicensed or off-label medicine.

Table 1 indicates that the incidence of unlicensed and off-label prescription was higher in the ward (2).

Table 2 Shows the numbers of unlicensed and off-label prescriptions were highest in the age group (1 month-23 months).

Table 3: Indicates the most common category of off-label use was related to age (17.9%), the other off-label uses were related to dose and frequency of administration (6.4%), indication (4.6%) and route of administration (1.3%). The most common reason of unlicensed preparation was the administration of preparations not license for use at all (11.3% of the total prescriptions).

Table 4 Shows the most frequently drugs used either in unlicensed or off-label manner.

Table 1. Unlicensed and off-label prescription in pediatric wards

	Ward(1)*	Ward(2)*	Ward(3)**	Ward(4)**	Total
No. of patient	30	50	35	25	140
No. of prescription	201	530	249	228	1208
Licensed, No. (%)	129(64.1)	220(41.5)	130(52.2)	103(45.2)	582(48.2)
Total unlicensed & off-label, No. (%)	72(35.9)	310(58.5)	119(47.8)	125(54.8)	626(51.8)
Unlicensed, No. (%)	30(14.9)	138(26)	57(22.9)	38(15.8)	261(21.6)
Off-label, No. (%)	42(20.9)	172(32.5)	62(24.9)	89(39)	365(30.2)

\*Ward from Ibn-Altheer hospital

\*\* Ward from alkhansa'a hospital;



Table 2. Unlicensed and off-label prescriptions according to age

	0-28 days	1-23 months	2-6 years	Total
Unlicensed, No. (%)	57(21.8)	131(50.1)	73(27.9)	261(21.6)
Off-label, No.(%)	48 (13.1)	231 (63.3)	86 (23.6)	365(30.2)

Table 3. Categories &amp; frequency (%) of unlicensed &amp; off-label medication use

Category of unlicensed	NO.(%)
Not license for use at all, No. (%)	137(11.3)
Modified preparation No. (%)	124(10.3)
Total number of unlicensed	261(21.6)
Category of off-label drug use	
Inappropriate age No. (%)	217(17.9)
Different dose& frequency No. (%)	77(6.4)
Different indication No. (%)	55 (4.6)
Different route of administration No. (%)	16(1.3)
Total number of off-label use	365(30.2)

Table 4. The most frequently uses of unlicensed&amp; off- label drugs.

Medicines	No. (%)	License category
Salbutamol syrup	102 (8.4)	Off-label for age, dose, indication
Antibiotics	42 (3.5)	Off-label for age, indication, dose
Cough syrup	22 (1.8)	Unlicensed (not license for use at all)
Aminophylline ampule	19 (1.6)	Unlicensed (not license for use at all)
Diclofenac ampule	19 (1.6)	Off-label for route of administration
Metoclopramide ampule	18 (1.5)	Off-label for indication
Adrenaline ampule	17 (1.4)	Off-label for route of administration
Pyridoxine ampule	16 (1.3)	Unlicensed (not license for use at all)
Theophylline syrup	14 (1.1)	Unlicensed (not license for use at all)
Captopril tablet	14 (1.1)	Unlicensed (modified preparation)

## Discussion

In paediatric hospitals of many countries, the use of the unlicensed & or off-label of medicines were frequently found among their patients<sup>14,15</sup>.

Conroy et al.<sup>6</sup> have found 7% unlicensed and 39% off-label medicines in the paediatric medical wards of five European hospitals, and Jong et al.<sup>8</sup> have identified 28% unlicensed and 44% off-label medicines in a paediatrics ward of a general hospital in the Netherlands.

The results of the present study revealed that some pediatrics patients received medications that were not available in liquid form for oral administration and that pharmacy department crushed tablets to make them suitable for children. Bioavailability & stability data are often not available for those preparations. The most common reasons for off-label use were that the medicine was prescribed at a different dose or frequency, in a different

formulation, or in an age group for which it had not been licensed. As found also in the European survey<sup>6</sup> the children in our study received off-label antiasthmatic medications. Like Salbutamol, syrup was prescribed for children under the age of 2 years (off-label for age & dose) combined with salbutamol nebulizer; clinical efficacy of nebulized salbutamol in infants under 18 months is uncertain this is lead to increases incidence of adverse drug reaction.<sup>16</sup>

The exposure of children to unlicensed & off-label medications is common, particularly in neonatal intensive care units (90%) of babies<sup>17</sup> and in pediatrics general intensive care units(70%)<sup>8</sup>. In present study, 51.8% were unlicensed and off-label prescriptions, 21.6% were unlicensed prescriptions and 30.2% were off-label prescription this is similar to that reported by Lampert et al.<sup>10</sup> found 10% unlicensed



and 46% off-label prescription in basal university hospital (Switzerland). Furthermore, a multicenter study of children administered to the general paediatric ward of hospital in Italy found that 1182 (89%) of 1481 hospitalized children received at least 11 drug off-label.<sup>7</sup>

After tragedies of the sulfanilamide-related deaths in the 1930s and the birth defects associated with thalidomide in the 1960s, changes in laws and regulations were introduced for the testing of new drugs to ensure their effectiveness and safety in humans.<sup>19</sup> It is not illegal to prescribe unlicensed or off-label medicines, but their use should be based on scientific evidence, expert medical judgment, or the literature.<sup>14,15</sup>

Many licensed medicines were used in an off-label manner as a result of limited clinical trials in paediatric. Different sources of drug therapy may give different information in relation to off-label, unlicensed and licensed drugs. Unfortunately there is no national formulary which may help our physician for proper treatment. Regarding the other medicines used in an off-label manner, age limitation or doses decided by the manufactures were in contrast with the clinical reality. For example, gentamicin doses in neonates were adapted from results of therapeutic drug monitoring of plasma levels and in such a case, off-label use in an alternative to the doses described in the label.<sup>20</sup>

In our study the extent of off-label drug use in the paediatric wards are not same. This is not astonishing as each of the wards had different physicians and prescribing habits. Unlicensed or off-label prescription were more frequent in the ward<sup>2</sup>, which the highest number of patients with complex therapy in contrast, the proportion was lowest in the ward<sup>1</sup>. This may imply that physicians were inherently conservative before administering drugs to premature and term neonates. Several studies have shown that adverse drug reactions are associated with an important problem in children after unlicensed or off-label drug prescription.<sup>4</sup>

Five out of eight patients with severe adverse drug reactions were associated with the off-label use of medicines<sup>21</sup>. So we need another study to find the incidence of an adverse drug reaction which may associated with off-label drug use & unlicensed drugs.

We need another study to determine the percentage of unlicensed & off-label drug use was significantly associated with the risk of an adverse drug reaction.

In conclusion the use of unlicensed or off-label medicines to treat children was found to be a common in pediatric patients, this problem is widespread in paediatric wards and the clinical pharmacist must take an active role in our hospitals and the ministry of health promote the study of medications in children.

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