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An Assessment of the Extent of Use of Off-License and Unlicensed Drugs on Children at Parirenyatwa Hospital in Harare, Zimbabwe

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This study was undertaken to assess the extent of use of unlicensed and off-license drugs on children at Parirenyatwa Teaching Hospital in Harare, Zimbabwe. The study was conducted in the two pediatric wards at the hospital. Data on three hundred patients aged 5 years and below was collected prospectively.

Ten percent of the pediatric patients at Parirenyatwa Hospital aged five years and below received at least one drug in an off-license way while 31 % received at least one drug in an unlicensed way. Fifty nine percent of the patients received licensed drugs in a licensed way.

There is a significant amount of unlicensed and off-license use of drugs at Parirenyatwa Hospital in Harare, Zimbabwe. Regulatory authorities and the pharmaceutical industry should re-double their efforts in order to ensure that children receive only well-tolerated and effective medicines.

Key words: Children, off-label medicines, unlicensed drugs, licensing.

INTRODUCTION

Licensing of medicines is essential for rational drug use. The licensing process to which most drugs are subjected gives the best assurance available that the medicines are well tolerated, effective and of a high quality [1]. The gold standard randomized clinical trials supporting adult medicine are unfortunately often not available for a majority of children's treatments. Many of the drug preparations needed in pediatric clinical care do not have a license for use in children [2-3]. There are only a few licensed essential medicines for children on the market owing to a combination of factors including the difficulty in carrying out reliable clinical trials in children due to ethical problems, logistical difficulties and legal concerns [4] and the lack of financial reward for industry [5-6]. Pediatric drug evaluation has often been neglected in the past [7].

There are vast differences between adults and children and even between children of different ages with regard to pharmacodynamic and pharmacokinetic responses to drugs [6]. A large number of medicines used for adults are not necessarily safe and efficacious for use in children. Many drugs used in children are either not licensed for use in pediatrics (unlicensed use), or are used outside their product license (off-label or off-license use). Unlicensed and off-label prescribing is common in children [5-6] resulting in increased risk of medication errors and unanticipated drug reactions [1]. Consequently, there is no guarantee that such use meets the high standards required for patients. This has raised widespread concern worldwide and especially within Europe [7] and the United States [8-9].

Despite concern about the use of unlicensed and off-label drugs on children and infants, little is known about the extent to which this occurs in public hospitals in Zimbabwe. This study was conducted to assess the extent of unlicensed and off-license use of medicines in children at Parirenyatwa Hospital in Harare, Zimbabwe.

METHODS

The study was conducted at Parirenyatwa Hospital in Harare with the permission of the clinical director of the hospital. The study was conducted between 10th February and 10th March 2003.

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All pediatric inpatients aged 5 years and below except those in special wards like the Intensive Care Unit and the neonatal units were included in the study.

Information was collected prospectively by reviewing patient charts and prescriptions in order to pick out any off-license and unlicensed use of medicines. The patient medical records were used to obtain the necessary information including age, weight, sex and diagnosis for each patient. The researchers also observed drug rounds during which drugs were administered to patients.

All drugs administered were assessed for unlicensed and off-license use using previously described classification systems [3], and methods and guidelines used in previous studies [10-14]. The categories were modified including assigning a category on tablet cutting and crushing and capsule opening prior to administration to the patients to cater for the situation in Zimbabwe. For the purpose of this study off-license and unlicensed use were organized into 10 categories while the 11th category represented those children who received licensed drugs used in a licensed way.

The information was recorded using a prescription evaluation form, which was designed for the purpose. Data was entered into Epi Info Version 6.02 statistical package for analysis. Frequencies and means were calculated.

RESULTS

A total of 300 patients of which 142 (47.33 %) were male were included in the study. The majority of patients (47.33 %) were aged between 0 and 12 months and only 12 patients (4 %) were aged between 49 and 60 months.

The majority of pediatric patients studied (54.67 %) were suffering from respiratory conditions. Many of these patients suffered from bronchopneumonia. The second most prevalent diagnosis was gastrointestinal conditions (19.33 %) with the most common condition being gastroenteritis. Other conditions including various cancers and congenital defects were classified as others and constituted 8 % of the diagnosis (Table 2).

Table 1. Categories of drug use at Parirenyatwa Teaching Hospital

License Status	Category
A. Off-license use of medicines	1. Outside dosage recommendations (higher or lower doses). 2. Unlicensed indication. 3. Outside the age range. 4. By an unlicensed route.
B Unlicensed use of medicines	5. Modification of a licensed drug. 6. 'Special formulation' of a drug licensed in the solid dosage form. 7. Drug prepared by a special manufacturer. 8. Drug that has been used for many years but has never undergone formal clinical trials. 9. Use of chemicals as drugs 10. Others such as crushing of tablets or opening of capsules.
C. Licensed use of medicines	11. Licensed drugs used in a licensed way.

Table 2. Diagnosis Prevalence

Condition	No. (%) of patients
Respiratory conditions	164 (55)
Gastro-intestinal conditions	58 (19)
Malnutrition	16 (5)
Malaria	14 (5)
Meningitis	10 (3)
Cardiovascular conditions	8 (3)
Neurological conditions	6 (2)
Others	24 (8)
Total	**300 (100)**

Penicillins were the most commonly used drugs (25 %) while other antibiotics and amino-glycosides constituted 15.8 % and 14.9 % of total drug use respectively (Table 3). On average, four drugs were used per patient.

Table 3. Therapeutic classes of drugs utilized

Therapeutic Class	Percentage of total drugs (%)
Penicillins	25
Other antibiotics	16
Aminoglycosides	15
Nutritional supplements	14
Analgesics	6
Antifungals	4
Anti-tuberculosis drugs	4
Anti-inflammatory drugs	3
Drugs acting on the central nervous system	3
Antimalarials	3
Drugs acting on the cardiovascular system	2
Drugs acting on the gastro-intestinal system	2
Anti-cancer drugs	2
Anti-asthmatics	1
Total	**100**

Table 4. License status and category of drugs used

License Status		Category	Percentage (%)
A. Off-license use of medicines	1.	Outside dosage recommendations (higher or lower doses).	7.8
	2.	Unlicensed indication.	0.2
	3.	Outside the age range.	0.6
	4.	By an unlicensed route.	1.2
B. Unlicensed use of medicines	5.	Modification of a licensed drug.	0
	6.	'Special formulation'	0.5
	7.	Drug prepared by a special manufacturer	0
	8.	Drug that has been used for many years but has never undergone formal clinical trials	0
	9.	Use of chemicals as drugs	0
	10.	Others such as crushing of tablets or opening of capsules.	30.9
C. Licensed use	11.	Licensed drugs used in a licensed way	58.8
Total			**100**

Tablet crushing, including the crushing of some enteric coated and sustained release tablets, and capsule opening (category 10) represented the most common form of unlicensed use, accounting for 99 % of all unlicensed use of medicines (Table 4). In most cases, capsule contents were halved; for example when 75 mg of rifampicin was required, a 150 mg capsule was opened and its contents halved before giving it to the child. Drugs that could have been compounded also featured greatly in this category, for example folic acid and vitamin D. The most common category of off-license use of medicines was using drugs outside their dosage recommendations, at higher or lower doses (Table 4).

Thirty patients (10 %) received medication in an off-license way while 93 patients (31 %) received medication in an unlicensed way. Fifty nine percent of the patients received licensed medicines in a licensed way (Table 5)

Patients with respiratory conditions constituted the largest percentage of those receiving medication in off-license (46.0 %) and unlicensed (38.8 %) ways as seen in Table 6.

Table 5. License status of medicines used

License status	No. (%) of patients
Licensed drugs used in a licensed way	177 (59)
Unlicensed use of drugs	93 (31)
Off-license use of drugs	30 (10)
Total	**300 (100)**

Benzylpenicillin was the drug most commonly used in an off-license way. The drug was used outside dosage recommendations (higher or lower doses). Other drugs commonly used in an off-license way were diazepam, gentamicin, amoxycillin and cotrimoxazole. Antibiotics were mostly used in an unlicensed way.

About half of the children at the hospital received drugs that are either unlicensed or off-license (41 %). Our findings were lower than findings by Turner *et al*. [9], Turner S *et al.* [4], T'Jong *et al.* [11] and Conroy, McIntyre and Choonara [15]. According to T'Jong and others, the level of licensed drug use was only 28.4 % while unlicensed and off-license drug use represented 28.0 % and 43.6 % of total drug use respectively. Conroy, McIntyre and Choonara reported 54.7 % and 9.9 % as off-license and unlicensed use of drugs respectively [15]. These findings can be explained by the fact that Parirenyatwa as a central hospital is relatively well funded. The off-license drug use at Parirenyatwa could have been lower if compounding were done at the hospital considering that the necessary facilities are available.

The findings in our study are higher than those in the study by Craig, Henderson and Magee who reported 3.4 % unlicensed and 19.4 % off-license drug use [12]. This high incidence of unlicensed use of medicines in our study is related to the rampant practice of tablet crushing and capsule opening at the hospital. Tablets, including the enteric coated and sustained release types, are crushed and capsules are opened before administration. This practice takes responsibility away from the manufacturer in case of adverse drug reactions.

DISCUSSION

The most common use of penicillins (25 %), aminoglycosides (14.9 %) and other antibiotics (15.8 %) shows a similar trend to that obtained by summers who also conducted a study at a teaching hospital in a developing country. Summers reported that antibiotics were the most commonly used class of drugs (30 %) followed by supplements, analgesics and respiratory drugs [10].

The use of drugs outside their dosage recommendations, especially at higher doses, is the most common off-license use of drugs. In many of the studies reviewed, off-license use of medicines accounted for the greater proportion of drug use when compared to unlicensed use. In our study unlicensed use was more than off-license use in the ratio of 3 to 1.

Children diagnosed with respiratory conditions were found to be more susceptible to off-license and unlicensed use of medicines than other patient groups in the study.

The occurrence of both unlicensed and off-license drug use at Parirenyatwa Teaching Hospital exposes children to higher risks of adverse events in line with findings by Impicciatore and Choonara [3]. The continued occurrence of unlicensed and off-license drug use at Parirenyatwa and indeed in the public sector in Zimbabwe calls for immediate and urgent attention. Measures need to be taken to enhance the availability and regular supply of pediatric dosage forms especially in the public sector in developing countries. Governments should give incentives to local pharmaceutical companies to invest more into research and development of pediatric formulations. In addition, the Essential Drug Lists should be more accommodative to the needs of children.

Table 6. Diagnosis versus license status of the drug

Condition	Off -license Use (%)	Unlicensed Use (%)	Drugs used correctly (%)
Respiratory conditions	45	39	57
Meningitis	5	4	4
Gastro-intestinal conditions	12	16	16
Malaria	2	10	5
Malnutrition	4	12	4
Neurological conditions	8	2	1
Cardiovascular conditions	5	8	2
Others	19	9	11

CONCLUSION

There is a significant amount of unlicensed and off-license drug use at Parirenyatwa Hospital. Regulatory authorities and the pharmaceutical industry need to ensure a more rational use of drugs in children and infants to avoid exposing them to risk.

REFERENCES

[1] S. Conroy, Paediatr. Drugs 4 (2002) 353-9.

[2] J.T. Gilman and P. Gal, Clin. Pharmacokin. 23 (1992) 1-9.

[3] P. Impicciatore and I. Choonara, Br. J. Clin. Pharmacol. 48 (1999) 15-18.

[4] S. Turner, A. Longworth, A.T. Nunn and I. Choonara, Br. Med. J. 316 (1998) 343-345.

[5] A. Bush, Expert Opinion on Drug Safety 2 (2003) 109-112.

[6] L. Cuzzolin, A. Zaccaron and V. Fanos, Fund. Clin. Pharmacol. 17 (2003) 125-131.

[7] I. Choonara and J. Dunne, Arch. Dis. Child. 78 (1998) 402-403.

[8] I.J. Cote, R.E. Kauffman, G. J. Troendle and G.H. Lambart, Pediatr. 98 (1996) 118-123.

[9] S. Turner, A. Gill, T. Nunn, B. Hewitt and I. Choonara, Lancet 347 (9000) (1996) 549-550.

[10] R.S. Summers, Ann. Trop. Paediatr. 6 (1986) 129-133.

[11] G.W. T'Jong, P.D. van der Linden, E.M. Bakker, N. van der Lely, I.A. Eland, B.H.C. Stricker *et al*. Eur. J. Clin. Pharmacol. 58 (2002) 293-297.

[12] J.S. Craig, C.R. Henderson and F. A. Magee, Iran. Med. J. 94 (2001) 237-240.

[13] S. Conroy and V. Peden, Paediatr. Anaesth. 11 (2001) 431-436.

[14] S. Conroy, I. Choonara, P. Impicciatore, A Mohn, H. Arnell, A. Rane *et al*. Br. Med. J. 320 (2000) 79-82.

[15] S. Conroy, J. McIntyre and I.Choonara, Arch. Dis. Child. 80 (1999) F142-148.