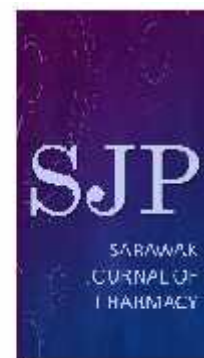




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The use of unlicensed and off-label medications in children

Pan Lee Chee¹, Amanda Koay Su Ling¹

¹*Pharmacy Department, Miri Hospital, Sarawak*

Corresponding author name and email: Pan Lee Chee (panleechee@moh.gov.my)

Abstract

Introduction: In the absence of standard paediatric prescribing information, clinicians often use medicines in an off-label manner. The aim of this study is to provide an insight on the experience and views of healthcare professionals on the use of unlicensed and off-label medicines in children

Methods: A survey instrument composed of 18 questions distributed among healthcare professionals (pharmacist, nurse and prescribers) in Paediatric Medical Ward (PMW), Paediatric Surgical Ward (PSW) and Neonatal Intensive Care unit in Miri General Hospital.

Results: A total of 54 healthcare professionals responded to the questionnaire. Most of the respondents (75.9%) indicated familiarity with the terminology unlicensed medicines while 59.3% indicated they were familiar with the term off-label medicines prior to receiving the questionnaire. About 90% of respondents had come across a dosing error in a paediatric

prescription in their professional practice despite the majority (94.4%) of respondents said they double checked doses of medicines used in children if a calculation required in deciding on the dose.

Conclusion: It is accepted that off-label and off-licence prescribing in paediatric practice is acceptable and essential when no suitable alternative to the required treatment is available

Keywords: Unlicensed, off-label medications, paediatric population, healthcare professionals

Introduction

Globally, there is an increasing demand for research and advancement into developing paediatric medicines. Only a few drugs authorised for sale have been evaluated clinically in the paediatric population. Most marketed drugs are either not labelled, or inadequately labelled for use in the paediatric population (1). The lack of appropriate medication paired with the inadequacy of critical safety and effective information poses significant risks (1). In particular, there is a high likelihood of overdosing or under-dosing where resultant adverse events may occur with the former while the latter leads to mistreating the underlying therapeutic disorder (1).

There are many barriers associated with developing medicines for the paediatric population. First and foremost, conducting clinical trials among children deemed to be unethical, resulting in difficulties in obtaining critical safety data. Moreover, it is established the pharmacokinetic response to a drug such as drug absorption, distribution, metabolism, and excretion are significantly different in children compared with adults (2). These responses change with growth and maturation and hence make it challenging to standardise drug doses between the wide paediatric spectrum, ranging from neonates to children 12-18 years old (2).

Consequently, many of the medicines presently used to treat children based upon data extrapolated from adult clinical trials even though it is well recognised that children are not small adults (2). This refers to the use of off-label medicine where the prescribed medicine is not disclaimed in the approved labelling of the drug with respect to dosage, age, indication or route of administration (3, 4). Off-label medicine used among children represents an important health issue as the effects and health risks may be unexpected (5). Various national and international studies have been published about the amount of and problems associated with off-label

medicines in children (5). On the other hand, unlicensed or unregistered medication is a medicine that has not been assessed nor approved by the drug regulatory body (3).

Methods

A survey instrument composed of 18 questions (Appendix 1) distributed among healthcare professionals (pharmacist, nurse and prescribers) in Paediatric Medical Ward (PMW), Paediatric Surgical Ward (PSW) and Neonatal Intensive Care unit in Miri General Hospital. The objective of the questionnaire was to examine the knowledge and views of healthcare professionals on the use of unlicensed/off-label medicines in children. The questionnaire composed of 3 sections addressing different areas of interest with a separate section including respondent demographics:

a. **Section 1**

Focuses on the experiences and views of healthcare professionals regarding the use of unlicensed and off-label medicines in children

b. **Section 2**

Focuses on information sources that healthcare professionals use when prescribing, dispensing and administering unlicensed/off-label medicines to children

c. **Section 3**

Addresses the dosing issues encountered when prescribing unlicensed and off-label medicines in children

In the questionnaire, terminologies of unlicensed/off-label use of medicines in children defined to facilitate respondents.

Results

Demographics

A total of 80 healthcare professionals approached to participate in this survey, however only 54 (67.5%) healthcare professionals which include paediatrician (7.4%), medical officer (20.4%), houseman (27.8%), paediatric clinical pharmacist (5.6%) and staff nurse (38.9%) responded to the questionnaire.

Knowledge and views about unlicensed/off-label medicines

Majority of the respondents, 41 (75.9%) indicated that they were familiar with the term 'unlicensed' medicines while 32 (59.3%) indicated they were familiar with the term 'off-label' medicines prior to receiving the questionnaire. Regarding the familiarity with unlicensed/off-label prescribing among the different sectors of healthcare professionals, paediatricians and paediatric clinical pharmacist being most familiar with the term unlicensed medicines and off-label medicines. Majority of the respondents reported neonates (preterm and term from birth to 28 days) to be the most likely to receive unlicensed (44.9%) or off-label (42.3%) medicines. On the other hand, infant (1 to 23 months of age) was, according to the respondents, less likely to receive unlicensed (11.7%) or off-label (13.5%) medicines (Table 1).

Table 1: Unlicensed and off label medicine prescribing, dispensing and administration to children by different healthcare professionals

	Paediatrician		Medical officer		Houseman		Paediatric Clinical Pharmacist		Nurse	
	UL	OL	UL	OL	UL	OL	UL	OL	UL	OL
Neonates including preterm and term from birth to 28 days	100%	75%	27.3%	36.4%	6.7%		66.7%	66.7%	23.8%	33.3%
Infants from 1-23 months of age		25%	9.1%	9.1%	6.7%		33.3%	33.3%	9.5%	
Children 2-11 years of age			18.2%	27.3%	26.7%	53.3%			19%	23.8%
Children 12-18 years of age			45.5%	27.3%	60%	46.7%			47.6%	42.9%

UL: unlicensed medication

OL: off-label medicine

Views about safety and efficacy of unlicensed/off-label medicines

Majority of the participants had concerns regarding safety (96.3%) and efficacy (85.2%) with the use of unlicensed and off-label medications use in children. Safety and efficacy concerns among medical officers, houseman, paediatric clinical pharmacist and nurses were relatively consistent across the participant groups. With regards to individual practice, approximately 29.6% of the participants admitted having experience adverse drug reactions while 31.5% experienced treatment failure.

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Dosing-related issues and information sources

Vast majority (94.4%) of the respondents said they double checked doses of medicines used in children if a calculation required in deciding on the dose. Interestingly, 88.9% of respondents had come across a dosing error in a paediatric prescription in their professional practice. More than half of respondents (66.7%) felt that licensing more medicines for use in children would decrease dosing errors in children. When asked about the various information sources they used when dealing with medicines in children, respondents reported the reference manual was the most commonly used, followed by previous experience with medicine (Table 2).

Table 2: Information sources used by healthcare professionals when prescribing, dispensing or administering unlicensed and off-label medicines to children

Information sources	Regularly	Often	Sometimes	Rarely	Never
Reference Manual	53.7%	24.1%	18.5%	3.7%	-
Published research	7.4%	24.1%	42.6%	20.4%	5.6%
Unpublished research		3.7%	24.1%	33.3%	38.9%
Prescribing information	42.6%	25.9%	27.8%	-	3.7%
Previous experience with the medicine	20.4%	55.6%	22.2%	-	1.9%
My group/hospital/facility/office's experience with the medicine	35.2%	50%	13%	-	1.9%
Peer recommendations	9.3%	38.9%	27.8%	13%	11.1%
Information from pharmaceutical representative	37 %	24.1%	27.8%	3.7%	7.4%
Patient/guardian suggestion	5.6%	-	16.7%	29.6%	48.1%
Patient/guardian request	1.9%	1.9%	16.7%	35.2%	44.4%

Discussion

In this present survey, the levels of knowledge and views on unlicensed/off-label medicines in paediatric population among healthcare professionals (prescribers, pharmacists and nurses) evaluated. Majority of the participants in the survey were familiar with the terminology of unlicensed/off-label prescribing.

In Malaysia, it is necessary for medications that marketed to be licensed by the Drug Control Authority (DCA) to ensure they meet requirements for efficacy, safety and quality. Due to paucity of clinical trials among the paediatric population, prescribing in this population remains a challenge.

Off-label use of drugs has been extensive in treating the paediatric population. Although off-label prescribing is not illegal and may occasionally clinically indicated (e.g. exceptional use in an informed patient with serious disease, when there are no suitable alternatives and potential benefits outweigh potential risks), it raises several clinical, safety and ethical concerns. This study shows, with regards to personal experience, participants admitted seeing adverse drug reactions and treatment failure. This may expose children to ineffective treatment regimens and to unknown risks of adverse events by extrapolation of adult data (6).

Overall, the research indicated that still much remains to be achieved both managing off-label and unlicensed medicine use and in creating an environment in which research in children to improve the evidence base is integrated into routine practice (6).

Despite having available data on paediatric pharmacology, there is still a lack of alternative approved medications for children and a limited availability of paediatric formulations. As a result, off-label and unlicensed prescribing continues to be a central theme in today's paediatric practices (6). Although the ultimate legal responsibility lies with the prescriber, the prescription of these treatments does not constitute a breach of duty as long as the prescriber can depend on information and guidance from a respected body of medical opinion (7).

Conclusion

For now, off label and off licence prescribing in paediatric practice is generally acceptable and essential when no suitable alternative to the required treatment is available. Until such times as more licensed medications are available for the paediatric population, clear guidance should be established to allow consistency in practice across the healthcare professionals who are involved with such medicines in their routine practice.

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APPENDIX 1.**THE USE OF UNLICENSED AND OFF-LABEL MEDICINES IN CHILDREN**

Definition: The International Conference on Harmonisation (ICH) has defined children to be individuals of both sexes who range between 0 and 18 years of age. This age range has been used in this questionnaire.

For each question please circle the option which you agree with, unless the question tells you to choose more than one option.

I. Experiences and views regarding medicines for children

Unlicensed drug : Use of medicines without a product license or marketing authorisation

Off-label drug : Use is defined as the use of licensed medicines outside of the terms of their product license or marketing authorisation with regards to the dose, indication, age, and route of administration, as well as contraindicated drug use

1. Before completing this questionnaire, were you familiar with the definition for unlicensed medicines?

(a) Yes

(b) No

2. Before completing on this questionnaire, were you familiar with the definition for off-label medicines?

(a) Yes

(b) No

3. Regardless of your own practice area, which of the following age groups of children in general are most likely to receive unlicensed medicines? (please tick one box only)

Age Group	
Neonates, including preterm and term from birth to 28 days	
Infants from 1 to 23 months of age	
Children 2 to 11 years of age	
Children 12 to 18 years of age	

4. Regardless of your own practice area, which of the following age groups of children in general do you feel are most likely to receive off-label prescriptions? (please tick one box only)

Age Group	
Neonates, including preterm and term from birth to 28 days	
Infants from 1 to 23 months of age	
Children 2 to 11 years of age	
Children 12 to 18 years of age	

5. In your own clinical experience, have you used:

5.1. A dose lower than the recommended dose? (e.g. extended dosage interval to take into consideration possible decreased elimination in children)

(a) Yes

(b) No

5.2. A dose higher than the recommended dose use? (e.g. the use of a higher dose in attempt to improve effectiveness)

(a) Yes

(b) No

5.3. A medicine which is licensed for use in older children in younger aged children? (e.g. use of medicines in infants when the medicines are only licensed for use in older children)

(a) Yes

(b) No

5.4. A medicine via a different route of administration? (e.g. Oral administration of intramuscular preparations due to non-availability of an oral liquid formulation)

(a) Yes

(b) No

5.5. A medication for a different indication from the licensed indication?

(a) Yes

(b) No

6. In general, do you have concerns about the efficacy of unlicensed and off-label medicine use in children?

(a) Yes

(b) No

7. In general, do you have concerns about the safety of unlicensed and off-label medicine use in children?

(a) Yes

(b) No

8. In general, would unlicensed and off-label medicines increase the likelihood of adverse drug reactions (side effects) when compared with licensed medicine use in children?

(a) Yes

(b) No

9. Have any children that you have previously dealt with, to your knowledge, ever experienced an adverse drug reaction following the use of unlicensed or off-label medicines?

(a) Yes

(b) No

10. Have any children that you have previously dealt with, to your knowledge, ever experienced treatment failure following the use of unlicensed or off-label medicines?

(a) Yes

(b) No

II. Information sources

11. When prescribing/dispensing/administering medicines for children, to what extent do you use the following information sources:

Regularly : I perform this activity > 75% of the time

Often : I perform this activity > 50% but < 75% of the time

Sometimes : I perform this activity > 25% but < 50% of the time

Rarely : I perform this activity < 25% of the time

Never : I do not perform this activity

References	Regularly	Often	Sometimes	Rarely	Never
Reference Manuals					
Published research					
Unpublished research					
Prescribing information					
Previous experience with the medicine					
My group/hospital/facility/office's experience with the medicine					
Peer recommendations					
Information from pharmaceutical representative					
Patient/guardian suggestion					
Patient/guardian request					

III. Dosing Issues

Medicine use in children may require extrapolating the dose based on the weight or surface area of the child, from the dose used in adults.

12. Do you routinely double check doses of medicines used in children if a calculation was required in deciding on the dose to be given?

- (a) Yes (b) No

13. Have you ever come across a dosing error in a paediatric prescription?

- (a) Yes (b) No

14. Would licensing more medicines for use in children will decrease dosing errors in paediatrics?

- (a) Yes (b) No

IV. General information about yourself

15. Age group:

- a) 21-30
- b) 31-40
- c) 41-50
- d) 51-60
- e) Over 60

16. Sex

- (a) Male (b) Female

17. You are a:

- a) Paediatrician
- b) Medical officer
- c) Houseman
- d) Hospital pharmacist
- e) Nurse

18. How long have you been a qualified healthcare professional?

_____ Year

THANK YOU VERY MUCH INDEED FOR ASSISTING WITH THIS RESEARCH