Research Article

Utilization of Off-Label Drug in Children

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ABSTRACT

'Off-label' prescribing occurs when a drug is prescribed for an indication, a route of administration, or a patient group that is not included in the standard product information document for that drug. Prescribing off label is inevitable and very common, especially if the practice involves children, pregnant women or palliative care. The off-label use of drugs has been widespread in treating the paediatric population. In the absence of standard paediatric prescribing information, clinicians often resort to the use of medicines in an off-label way. Many studies have been published across the globe reporting the different rates of off-label use. The Food and Drug Administration (FDA) 'plays a role in almost every sector of the approval, marketing, labeling, advertising, and promotion of both over-the-counter and prescription drugs. The off-label use of FDA-approved drugs is not regulated, but it is legal in the United States and many other countries. The problem is that off-label drug use often does not point towards "standard of care" treatment. Lack of information on off-label drug use may also put patients at a higher possibility for medication errors, side effects, and unwanted drug reactions. Additionally, health care professionals should educate themselves about off-label drug use to understand the risks and benefits and to provide the best possible care for their patients.

Keywords: off-label, unapproved drugs, paediatric, prescribing.

INTRODUCTION

The prescribing pattern of a registered medicine for a use that is not included or disclaimed in the product information is referred to as Off-label (unlabelled or unapproved) prescribing.[1] Prescribing off label drugs is unavoidable and is very common especially in children, pregnant women or palliative care. Off-label use means use of medicine which is outside the product license with respect to route of administration, indication, dose, or age.[2] Off label drug use in children is widely used all over the world.[3] The prevalence of off-label and unlicensed drug use is higher in neonates, infants, premature and low birth-weight babies.[4] Topical preparations such as ear drops, eye drops and dermatological products are also common for much of the off-label and unlicensed drug use. Amongst the systemic drugs, anti migraine preparations, bronchodilators, anti-hypertensive agents, gastro-intestinal agents, oral hypoglycaemic agents, oxymetazoline, antispasmodics, ondansetron and amphotericin B, are commonly prescribed as off-label drugs.[3] The incidence of unlicensed and off-label drug prescriptions appears to be greatest in critically ill neonates and children and lowest in the general population. The risk associated with unapproved and off-label drug use appears to be greater than for prescribing of drugs in accordance with the product license. "Labelled" uses of a prescription drug are approved by regulatory bodies after confirming its safety and efficacy based on its preclinical and clinical data, but medicines are prescribed off-label without undergoing the rigorous regulatory approval process mandatory for getting marketing approval.[5] Prescribing drugs off-label is extremely common worldwide, but unfortunately usually this is done without adequate scientific data evidence.[6, 7]

METHODS

This review work was carried out to study the off label drug use in paediatrics through a comprehensive search of the literature using Pubmed database. The study is eligible only if the articles were written in English. Nearly 31 articles were collected. The search terms used for collecting the articles are off label drug, unapproved drug, paediatrics and unlabelled drug use.

DISCUSSION

Off label drug use classification

As mentioned above, off-label refers to the usage of licensed drugs outside the definition of product license or marketing authorization. It may be used in one of the following reasons:

Dose

Drug is given in dose other than the one recommended. Example is the use of Salbutamol nebulizer dose for children is 60mg or more.

Indication

Drug prescribed for indications outside of those listed. Example is the use of Misoprostol is used off-label for inducing contractions to evacuate the uterus in abortion.

Age

Medicines may be used outside their licensed age group. Some medicines are 'not recommended in children'.

For example the use of salbutamol syrup is not licensed for children less than two years of age, yet it is frequently used in this age group.

Route

The medicines are given by an unlicensed route. For example some of drugs formulated as injection which is given orally for example dexamethasone injection given by mouth in paediatrics for asthma and croup.[8]

Table 1: Category of off-label drug use

S.no	Category	Reason	Example
1	Dose	Dose higher than recommended	• Salbutamol nebulizers are licensed in adults for doses of up to 40 mg daily. In Practice older children may receive up to 60 mg daily.
2	Age	Drug not recommended in the patient below a certain Age	• Diazapam rectal solution is not licensed for children less than one year.
3	Indication	Drug prescribed for indications outside of those listed	• Misoprostol is used off-label for inducing contractions to evacuate the uterus during first trimester medical abortions, and inducing labour for an intrauterine foetal demise (IUFD). It is also used off-label for the treatment of postpartum haemorrhage and cervical ripening.
4	Route of administration	Drug administered by a route not described	• Adrenaline injectable solution used by nebulisation in acute bronchiolitis. • Sodium chloride injectable solution and an eye-drops product (an anti-infective and anti-inflammatory combination), both used as nasal drops.

The advantages of off-label prescribing in paediatrics

Off-label prescribing has been acceptable on several grounds. Firstly, ingenious and flexible use of medications can lead to the discovery of new and important indications. For example, β-blockers were initially approved for the treatment of hypertension but were later found to be beneficial for the treatment of heart failure.[9] Secondly, off-label prescribing has been viewed as crucial in such fields as paediatrics because few drugs have been distinctively tested in children.[10] Finally, off-label prescribing avoids the lengthy and costly process of amending the FDA labelling.

The need to study drugs in children

Several problems has depicted that the dosing regimens are derived from adult studies which cannot be extrapolated to infants and children. The importance of understanding drug metabolism in relation to development is presented by the toxicity of chloramphenicol and sodium valproate.[5] The initial dosage regimen for chloramphenicol was based on studies in adults; however, significantly lower doses are needed to prevent toxicity. Drug toxicity is not restricted to the foetus and the newborn infant; sodium valproate induced hepatotoxicity is related to enhanced omega oxidation. This pathway is enhanced by poly-pharmacy and certain metabolic diseases; it also appears to be enhanced in children younger than 3 years. These examples help in understanding the importance of increasing our knowledge of drug metabolism in children to minimise toxicity while ensuring its efficacy.[8]

Why is off label drug use widespread in children?

For many years children have been excluded from clinical trials which are carried out during market authorization as the society and the law makers thought it was practical not to expose the children to the molecules. This lead to the drugs being marketed without paediatric safety and efficacy data. Paradoxically the societies desire to protect the children has in turn increased their exposure to drugs. Exposure to off label drugs in clinical setting does not generate a data, as physicians do not report off label drug use.[11]

It has been reported that the majority of paediatric patients in hospital care are at risk of receiving at least one drug which is used as off-label drug or a no approved drug. In neonatal hospital care, almost all patients are exposed to at least one off-label or no approved drug.

One of the main reasons for off label drug use is the lack of paediatric formulations .Young children require liquid preparations or dispersible tablets, since many of the drugs are not available in this formulation they resort to crushing tablets or opening capsules.

The disadvantages of prescribing off label drugs in children

When impromptu drug prescription is done, there is little information about the stability and bioavailability of the

drug. [11] It is quite possible that the child may receive an unstable or ineffective drug and if the medium of dispersion is not proper it may lead to adverse drug reaction.

Due to the lack of information about the paediatric dose it may be possible that the physician may calculate the dose according to the adult dose. This is hazardous in nature.[12] In two prospective studies, it has been noted that the incidence of ADRs was higher among children treated with off label drugs or unapproved use of drugs than among those receiving on-label treatment with approved drugs [13, 14].

In children, off-label use of drugs is associated with an increased number and severity of adverse effects [15].

Another problem associated with use of off-label drug is that, it often does not reflect "standard of care" treatment. This could raise concerns about the legal risk to the health care provider if the patients have an unwanted or bad outcome from the treatment.

Priority areas for medicines for children

The therapeutic drug categories most frequently used off-label in hospital care was analgesics and antibiotics.[16-27] Some of the most common drugs used off-label in paediatric hospital care is found to be morphine, paracetamol, salbutamol, caffeine, and heparin. Another area with a high proportion of off-label drug use was that of cardiovascular drugs. [16, 22, 23, 26-28]

The extensive use of insufficiently documented drugs in the Paediatric population strongly supports the need for medicines suitable for children of all age groups with regard to strength, formulation and taste. [18, 20, 23, 29]

Neonates and infants receive the greatest proportion of off-label use of drugs, non-approved drugs in hospital care. Neonates and infants are particularly vulnerable because of their immature renal and hepatic function, and given the need to take their body proportions (weight and surface area) into consideration when determining dosages, the practical difficulties that may be encountered in drug administration, and the incapability of these very young patients to express or report ADRs, hence evidence of both the safety and efficacy of many drugs is urgently needed in these age groups.

A structured documentation of off-label use and the use of no approved drugs, including the clinical outcomes of such treatments, could greatly improve the knowledge in this area. [30]

Drug related problems of off-label drug use in children

Off-label prescribing is not illegal, not necessarily wrong, and is considered in several paediatric guidelines, but remarkably, no reference is made that some drugs are being recommended in an unlicensed or off-label use basis. [31] Quality of drug therapies is not necessarily related to drug license status.[32]However this has several clinical, ethical and safety issues and there is no explicit guide to help clinicians assess the aptness of off-label prescribing.[33] A review that accessed the relationship between off-label and unlicensed medicine use and adverse drug reactions (ADR) in children concluded that good quality of evidence is lacking to answer this question[34] .However, results of previous studies have shown that there might be an association between off-label use and ADR risk.[34]

Santos et al. reported that in an inpatient population, off-label drug use was significantly associated with ADRs (relative risk 2.44; 95% CI 2.12, 2.89) [35].

Respiratory diseases treatments have been reported in several involvements with adverse reactions and off-label prescription. In a retrospective analysis of all ADR reported from the Swedish Drug Information System in 2000, medications used for asthma treatment were the most frequently associated with adverse reactions. Of those, 31% were being used off-label.[36] Several factors interfere in this unknown relationship of off-label medicines and ADR, such as age, type of drug, disease and previous evidence of that medication use. [37]

CONCLUSION

Neonates and infants receive the greatest proportion of off-label use of drugs. Children have all the right to receive safe and effective drugs in proper strength, dosage, route of administration and indication. Off label drug use is significantly associated with adverse drug reactions in children. Critically ill neonates and infants are more vulnerable to development of adverse effects. More clinical trials should be conducted in children. The medicines prescribed to neonates should be licensed whenever possible.

With the development of electronic, computerized patient record systems, the structured documentation of off-label use and the use of non-approved drugs, including the clinical outcomes of such treatments, could greatly improve the knowledge in this area. There is also a need for improved recording of actual drug use in children because it has been shown that drug treatment is insufficiently documented in the medical records of paediatric patients.

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