Leading Article

Rational prescribing in paediatrics

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This article focuses on two main areas viz. the process of rational prescribing and the difficulties encountered in practising rational prescribing in paediatrics.

Background

In 1985, the World Health Organization (WHO) defined the rational use of medicines as "patients receiving medications appropriate to their needs, in doses that meet their own individual requirements, for an adequate period of time, and at the lowest cost to them and their community"[1]. A medicine is irrationally used if it is prescribed when there is little likelihood that it will have a beneficial effect or when the anticipated benefit is not worth the potential harm or the cost of the drug. It occurs when the medicine prescribed is incorrect, inappropriate, excessive, unnecessary or inadequate

Medicines should only be prescribed when they are necessary, and in all cases the benefit of administering the medicine should be considered in relation to the risks involved. Bad prescribing habits lead to ineffective and unsafe treatments, exacerbations or prolongation of illnesses, distress and harm to the patient and high cost to the patient and the country.

Approach

In order to guide a prescriber in rational prescribing, the following approach is recommended by the WHO[2]:

1. *Defining the patient's problem*: Prescriber should establish the diagnosis or identify and list the problems based on a detailed history, examination and investigations.

2. *Specifying the therapeutic objectives*: This will prevent unnecessary use of medicines.

3. *Selecting therapeutic strategies*: Four possible therapeutic strategies in rational prescribing are: information or advice, treatment without drugs (non–pharmacological therapy), treatment with a drug (pharmacological therapy), and referral. Often combinations of these strategies are required.

    - *Pharmacological treatment*: The following steps are recommended in choosing the rational pharmacological treatment:

        - Make an inventory of effective groups of drugs for that particular condition.

        - Choose an effective group from the above inventory based on efficacy, safety, suitability and cost data.

        - Choose the correct drug from the chosen group (P –drug). *P drug is a prescriber's personal drug for a particular condition selected through the steps mentioned here*. The choice of P-drug should be based on evidence about maximal clinical benefit for the drug for a given indication with minimum occurrence of adverse reactions. The criteria used in choosing the effective group can be applied to select the P-drug as well.

        - Choose the active substance, dosage form, standard dosage schedule and standard duration of treatment

4. *Verifying the suitability of the chosen pharmacological treatment for each patient*.

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5. *Prescription writing.*

6. *Giving information, instructions and warnings.*

7. *Monitoring (including stopping) treatment.*

It is believed that when these steps are followed, the problem of irrational prescribing will be naturally nullified. However, many studies have documented that the problem of irrational prescribing widely exists in adult and paediatric practice[3]. Most drug utilization studies in children have focused on the issue of unnecessary or inappropriate prescription of drugs; so much so the WHO has claimed that as much as two-thirds of all drugs used by children may have little or no value[4,5].

The problem of irrational use of medicines can no longer be ignored, wished away or dismissed as trivial for it represents not only wasteful expenditure but also a serious hazard to health and life. The most common reasons for irrational use of medicines include lack of knowledge, skills or independent information; unrestricted availability of medicines, overwork of health personnel, inappropriate promotion of medicines and profit motives from selling medicines[2]. However, in paediatrics, the "therapeutic orphan" status of neonates, infants and children has been identified as an important reason for irrational use of medicines which hinder the prescribers who prefer to practise rational prescribing.

Rational prescribing in paediatric practice faces more obstacles than in adult practice. The reasons specific to neonates, infants and children which impede rational prescribing in this age group can be grouped into four main categories[6]:

1. Lack of scientific information in the paediatric age group.

2. Lack of appropriate drug development for neonates, infants and children.

3. Relative market failure.

4. Insufficient staff, knowledge and prescribing information for paediatric healthcare professionals.

Data on the five main criteria used in the process of rational prescribing such as efficacy, safety, suitability and cost of medicines are limited in paediatrics.

Clinical trials in children, paediatric labelling, market failure and extent of unlicensed and off-label prescriptions

The data on efficacy and safety of medicines are obtained from clinical trials conducted by pharmaceutical industries. However, pharmaceutical industries are reluctant to carry out clinical trials in children because of [7]:

- Perceived difficulties in conducting clinical trials in children.

- Difficulty in developing suitable paediatric preparations.

- Unpredictable and smaller paediatric market with limited financial returns.

The pharmaceutical industry avoids applying for licence for paediatric use as insufficient information is available to satisfy the requirements of the Licensing Authority. Hence, many new medicines and the vast majority of older medications have been approved for use in adults for a particular indication, formulation and route of administration, but without labelling for paediatric use even if they have potential use in paediatrics. This situation forces paediatricians to prescribe unlicensed or off label medicines, but without such prescribing, possible effective treatment would be denied to children.

Unlicensed use: Use of medicines which have not gone through the rigorous process of pre-clinical and clinical trials and the registration procedures[7].

Off label use: Use of licensed medicines outside the conditions of the license[7].

Many studies have documented the extent of the use of unlicensed and off label drug preparations in children. A study comprising five European countries reported that 67% of hospitalized children were receiving an unlicensed or 'off label' drug preparation[8]. About one quarter of prescriptions in hospitalised children, two thirds in neonatal intensive care units and one-tenth given for children under primary care in the UK is either unlicensed or off label [9-11].

"Children are not small adults"

In the absence of such specific trial based data in children, in most instances, adult data are extrapolated to obtain paediatric data. This extrapolation is often inappropriate and irrational

because children have a different range of diseases, metabolize medications differently, respond to treatment that is unpredictably different to adults, experience age-specific adverse drug reactions, and continue to grow and develop[12]. Adult experience with the medicinal products may not predict accurately the minimum effective dose, maximum titrated dose, therapeutic effect or adverse reaction in the child even when dosage has been adapted to body weight or surface area. This not only makes the choice based on efficacy and safety irrational, it also leads to irrational choice of dose as well.

Quality assurance of pharmaceuticals and bioequivalence of paediatric medicines

Quality assurance of medicinal products is crucial in developing countries, because economical pressure may force them to procure multi-source (generic) pharmaceutical products. When multi-source pharmaceutical products are evaluated, the Regulatory Authority needs to consider not only the quality, efficacy and safety of such products, but also their interchangeability. Regulatory Authorities should therefore require documentation of a generic pharmaceutical product to meet three sets of criteria relating to[13]:

- Manufacture (GMP) and quality control.
- Product characteristics and labelling.
- Therapeutic equivalence.

The WHO guides the Regulatory Authorities about instances where therapeutic equivalence studies should be requested as eligibility criteria for registration[13]. Many paediatric formulations (e.g.; solutions for oral use, powder for re-constitution, parenteral products, etc) do not require equivalence studies if they meet the first and second criteria.

Practical difficulties in administering medicines to children and suitability criteria

Children are a special group; even if we improve safety, efficacy and quality of their medicines, the practical difficulties (parental anxiety, difficulty in obtaining a good history, difficulty in performing a thorough examination, bitter taste of liquid preparations, poor compliance, dosing difficulties with teaspoons and liquids, cost of paediatric dosage forms) encountered in managing them prevent the doctors from choosing the most appropriate medicine based on efficacy, safety and quality. However, the "suitability" clause in the rational prescribing approach permits accommodation of the practical difficulties in choosing the most appropriate medicine for a child.

Paediatric formulations

Rational use of medicines is not limited to selecting the most appropriate drug for a condition, but extended to choosing the dose, dosage form, route of administration, frequency and duration. There are limitations in determining the dose, dosage form and route of administration in children. There are no suitable paediatric formulations for many of the medicines which have beneficial therapeutic efficacy in children. Of the 284 medicines listed on the 14th edition (2005) WHO Model Essential Medicine List (EML) core list, 119 were judged as requiring an oral paediatric formulation. Of these 119, there were 59 medicines without paediatric formulations. Of these 59, 29 had an appropriate formulation and licensed indication in the reference country (USA, UK, or Australia)[14]. Of the 293 medicines listed in the recent edition of Sri Lankan EML, 114 were judged as requiring an oral paediatric formulation. Of these 114, there were 76 medicines without an appropriate paediatric formulation. This leads to irrational use of dosage forms and route of administration in children.

Dose determination in children

Drug dosing remains one of the most urgent considerations in off–label prescribing. This happens when there is no licensed paediatric dose. Many paediatric dose reference sources are available, but they tend to be based on local practice and experience, not hard evidence gained from properly conducted clinical trials.

Other areas which need to be addressed to promote rational use of medicine in paediatrics

1. *Perinatal medicine*: Profound changes in the development and the maturation of neonates' organs and organ systems potentially place neonates at increased risk and/or at different risks compared with adults or older children on exposure to pharmaceutical agents. Off label and unlicensed use of medicines are more in neonatal units and neonatal intensive care units than the general paediatric wards and paediatric intensive care units[8-11]. Limited market for medicines used only in neonates putting off the pharmaceutical industries in investing in these medicines is an added problem.

2. *Rare diseases and orphan drugs*: Most children with rare metabolic disorders are given unlicensed medicines that are often supplied by chemical rather than pharmaceutical companies.

3. *Vitamins, minerals and other nutrients*: Vitamin and mineral supplementation for premature babies, malnourished children, children with specific mineral or vitamin deficiency, and children affected by HIV/AIDS faces many issues such as lack of a product, lack of suitable formulation, lack of appropriate dosing combination and lack of evidence.

4. *Paediatric clinical pharmacology*: It is very important to have trained paediatric clinical pharmacologists who can contribute to promote rational use of medicines in children, and advise on many other issues related to prescribing in paediatrics.

Rational use of medicine is the best tool to provide the optimal evidence based care to any age group of patients. However, some urgent issues need to be addressed before rational use of medicines can be fully implemented in children. Some recent global developments with regard to paediatric medicines and some recommendations to address the issues mentioned in this article are given below.

Some global developments with regard to paediatric medicines

This problem of children remaining therapeutic orphans is now globally recognised. In order to alleviate children's sufferings and to promote their status, in April 2006, the World Health Organization recommended activities under[15]:

1. *Rational use* (ensuring that paediatric medicines are administered appropriately in the right doses and formulations).

2. *Quality and safety* (ensuring paediatric medicines meet international requirements for quality, safety and efficacy).

3. *Access* (increasing production, procurement and supply of paediatric medicines).

For example, after 30 years of drafting the first Essential Medicine Model List in 1977, the WHO has produced a draft Paediatric Essential Medicine Model List in 2007. The WHO is also working on availability, accessibility and cost of paediatric medicines. In the USA, the FDA introduced the voluntary Paediatric Exclusivity (PE) clause within the Modernization Act (FDAMA). PE provides exclusive rights to the company to market a drug for an extended period of six months if the company undertook paediatric clinical trials. The Paediatric Rule (PR) introduced by FDA in 1999 mandated manufactures to submit safety and effectiveness data on relevant paediatric age groups before approval. The Best Pharmaceuticals for Children Act (BPCA) was signed into law on 4 January 2002 in the USA shortly after the PE provision of the FDAMA expired on 1 January 2002. Similarly, many changes are taking place to improve availability and accessibility of paediatric medicine and describing all of them is beyond the scope of the article.

Some recommendations to address the issues mentioned in this article in the Sri Lankan setting

1. *To assure the efficacy and safety of medicines used in children*

    - Registration should ensure that only safe, efficacious and good quality medicines are available in the market and that unsafe non-efficacious medicines are banned.

    - Regulatory authority should be advised by a paediatric subcommittee on efficacy and safety of medicinal products (both new and old) in children.

    - Pharmacovigilance in paediatrics needs to be strengthened.

    - Doctors should be aware that many medicines may not have been tested in children and should assess the risk-benefits before prescribing for children.

2. *To assure the quality of paediatric medicines used in Sri Lanka*

    - The Authority should be independent with command powers of enforcement backed by legal provision for penal sanction against offenders. To retain public confidence and respect, the Authority must be seen to undertake its tasks in an independent, authoritative, and impartial manner.

- Advisory bodies: The responsible officer must have access to a standing paediatric advisory committee for advice on technical issues regarding paediatric medicines.

3. *To make paediatric formulations available, Joint WHO-UNICEF consultation on Essential Medicines for children held in August 2006 decided to take these up*[14]:

    - Establish a "formulation working group" to develop, review and consolidate guidelines for regulators and manufacturers on appropriate formulations for children (including consideration of cost-effective formulations, dosing device, pack size and volumes appropriate for children).

    - Develop guidelines for extemporaneous formulations for children in the setting/environment of the developing world.

    - Develop suitability criteria for paediatric formulation development with particular reference to the developing world.

4. *To have evidence based data on dose for children*

    - To develop a local neonatal and paediatric formulary (includes orphan drugs, chemicals used as medicines, vitamins, minerals).

    - Developing a "dosing" tool to administer oral liquid preparations to children.

    - Availability of therapeutic drug monitoring.

    - Surveillance of paediatric medicines available in Sri Lanka for their paediatric labelling.

5. *Other areas for improvement*

    - Perinatal pharmacology group to support the neonatologists.

    - Paediatric essential medicine list and ensuring these medicines are accessible to all the children in Sri Lanka.

    - Developing the orphan drug list and guiding the clinicians on how to get these medicines.

    - Drugs and therapeutic committees with paediatric focus on big hospitals and at regional level.

    - Training prescribers in rational use of medicines in children.

    - Training slots in paediatric clinical pharmacology.

    - Training pharmacists, nurses and other paramedical staff in rational use of medicines in children

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