EDITORIAL

OFF-LABEL PAEDIATRIC PRESCRIPTIONS

Off-label prescribing refers to use of drugs for an unapproved indication in an unapproved age group or unapproved dose regimen. The terms off-label and off-licence are used interchangeably. Off-label prescribing carries a negative connotation but it is not illegal. It is estimated that one out of five outpatient prescriptions written in the USA is off-label. It is assumed that practitioners always use their best professional judgement, based on available information or experience, in prescribing off-label drugs. It is more prevalent in paediatrics because less than 20 % of medicines are approved by national regulatory bodies for use in children because they lack evidence of safety and efficacy in this age group.

It is a mandatory requirement that before drugs are approved for use, they must be registered by national regulatory authorities. The process involves reviewing data from clinical trials. It also ensures that the manufacturing and quality assurance procedures meet acceptance criteria. The validated information must be displayed on the label attached to the immediate medicine container. As long as the prescriber does not deviate from the label specifications regarding the use of the medicine, he/she is legally protected in case of litigation arising from the use of the medicine. The pharmaceutical company which carried out research and development and the regulatory authority which registered the product are held accountable. Most research-based pharmaceutical companies jealously guard their reputation and it is common to find on the label a disclaimer cautioning that the safety of the medicine has not been established in children below a certain age. However, small pharmaceutical companies often do not exercise such caution.

Paediatricians who prescribe off-label medicines are not protected in case of litigation. He/she has no credible defence since personal opinion, as opposed to scientifically-generated clinical trial data, count for little. Because of this consideration, paediatricians are more likely to err on the side of caution and prescribe an under-dose. It is often difficult to monitor changes in disease conditions especially in neonates. Again, the paediatrician is more likely to insist on hospitalization of the child for close monitoring. There is an unacceptable tendency to regard children as "small adults" and use body weight to calculate off-label doses. According to Clarke's rule, the dose of a child is obtained from the equation: dose (child) = adult dose × weight (kg)/70. The assumption is that the average weight of an adult is 70 kg which is certainly not correct for Africans. Children differ from adults in a fundamental way because their metabolizing enzymes and excretion functions are not fully developed. In neonates, calculation based on body weight often leads to an over-dose, while in school going children, the calculation often leads to an under-dose. Paracetamol and chloramphenicol off-label doses tend to be toxic to neonates.

In prescribing off-label medicines, it is often necessary to split adult solid dosage forms (i.e., tablets). This may be possible where such splitting was anticipated by the manufacturer and there are clear break lines allowing division of the tablet into halves or quarters. In other cases such as sugar-coated tablets, splitting may be difficult or impossible. Unlike in adults where the dose range is defined, the paediatrician is dealing with a wide spectrum of age groups ranging from the neonates (less than 6 months) to children aged 12 years. This means the dose has to be individualized, further complicating the process of preparing the off-label medicine from the adult dosage forms. In the course of splitting the tablet, a significant error may occur and this can lead to serious consequences for drugs with low therapeutic index such as digoxin.

The medicines split from adult dosage forms have to be formulated into liquid dosage forms such as solutions and suspensions. Most liquid formulations are unstable which means they have to be prepared just before use, or have a very short shelf-life of a few days. The diluents used including water, sugar

syrup and methylcellulose may not give a homogeneous product and the compatibility between drug and the diluents may be problematic. Many liquid formulations have to be stabilized or adjusted for pH. There are no established guidelines in preparing off-label medicines because of the many inherent variables.

Another factor is that paediatricians operate in unfavourable environment hardly conducive for rational thinking. He/she has to deal with restless emotionally unstable parents (usually mothers) with unrealistic expectations. In effect, the paediatrician is dealing with two patients. When an infant cries for whatever reason, may it be pain, discomfort or hunger, the mother gets unduly worried. Even when the infant is calm and sleeping, the mother still worries, imagining that it is slipping into a coma. A comical narrative is told of a first-time mother who returned the baby to hospital a few hours after being discharged because it was crying incessantly. The paediatrician pointed out the baby was crying because the mother had wrapped the baby with too much covering. On removing the excess covering, the baby calmed down and even smiled as if to say "thank you".

More recently, regulatory bodies have begun to advocate for some form of limited clinical trials in children. There are some ethical issues to be settled especially with neonates where changes in disease condition may be difficult to monitor. Ibuprofen used as an antipyretic in children carried no dosing information for children younger than 2 years until recently. Following studies, safe and effective dose for children 6 months to 2 years is now available. For drugs which have been used for a long time, the clinical trials in children amount to validation of established doses and should not be difficult. For example, use of amphetamine in hyperkinetic children suffering from attention-deficit hyperactivity disorder (ADHD) is well established even though this is an example of off-label use of drugs.

An article in this issue of the journal by *Bilakhia et al.* highlights some of the problems associated with preparation of paediatric liquid dosage forms including off-label doses from adult solid dosage forms such as tablets and capsules.

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