

## **Improving Drug Safety Monitoring**

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*Drug safety monitoring is important in children. Young age, polypharmacy, prolonged hospitalization, being critically ill and use of unlicensed and off-label drugs have been identified as risk factors which predispose a child to experience an adverse drug reaction. In our country, the HIV/AIDS epidemic, setting up of intensive care units, increasing availability of imaging studies, and the introduction of several new drugs and vaccines have accentuated the need for improving drug safety monitoring in children. To achieve this aim, establishing in-hospital computerized event monitoring program in major hospitals and an effective national post-marketing drug surveillance network are the need of the hour.*

**Key words:** Adverse drug reactions, event monitoring, off-label medicines, post-marketing surveillance.

An adverse drug reaction (ADR) has been defined as any noxious, unintended and undesired effect of a drug which occurs at a dose used in humans for prophylaxis,

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diagnosis, therapy or modification of physiological functions(1). Children constitute a vulnerable group, since a new drug gets released to the market without the benefit of even limited experience in them(2). Drug safety monitoring, *i.e.*, early detection of possible adverse effects of a drug, especially a newly introduced one is, therefore, crucial in children.

In this article we have reviewed recent data, which highlights the importance of drug safety monitoring in children. We have also discussed the newer situations and insights related to drug safety in Indian children, the safety profiles of certain new drugs being used in Indian children and the steps necessary to improve drug safety in our pediatric population.

### **Importance of Drug Safety Monitoring in Children**

In our country comprehensive information on the safety of drugs used in the pediatric population is meager(2). A recent meta-analysis of 17 prospective studies has shown that ADRs in children are a significant public health issue all over the world(3). The overall rate of pediatric hospital admissions due to ADRs was 2.09% and 39.3% of the ADRs causing hospital admissions were life-threatening reactions. In hospitalized children, the overall incidence of ADRs was 9.53%, with severe (fatal or potentially life threatening) reactions accounting for 12.29% of the total. For outpatient children the overall incidence of ADRs was 1.46%(3).

ADR data in adults cannot be relied upon to predict ADRs in children(2). Recent examples of ADRs detected exclusively in

the pediatric age group include: greenish discoloration of teeth following ciprofloxacin use in neonates(4); gastric outlet obstruction due to prostaglandin infusion in neonates(5); fatal hepatotoxicity following valproic acid use in developmentally-delayed children below 2 years of age(6); benign intracranial hypertension due to recombinant growth hormone therapy in children with short stature(7); and development of depression following isotretinoin use in adolescents(8).

### **Risk Factors for Developing ADRs in Children**

Recent studies have identified risk factors which may predispose a child to develop an ADR:

- (a) *Young age*: Neonates and infants are more likely to suffer an ADR due to their physiological immaturity(9).
- (b) *Polypharmacy*: A consistent relationship has been noted between the number of drugs administered concomitantly and the incidence of ADRs in hospitalized children(10,11).
- (c) *Length of hospital stay*: Longer the duration of hospital stay, more are the chances of a child experiencing an ADR(10).
- (d) *Being critically ill*: Neonates and children in intensive care units are more likely to suffer an ADR, as being critically ill affects drug metabolism(9,11). They also get exposed to a far higher number of drugs that have a narrow therapeutic index, for example, inotropes, vaso-dilators, and anti-hypertensives(11).
- (e) *Use of unlicensed and off-label drugs*: By off-label prescribing is meant using a licensed drug outside the terms of its product license. A recent study from an U.K. hospital has reported that almost 25%

drugs used in its pediatric ward, 40% in its pediatric intensive care unit (PICU) and 55% in its neonatal intensive care unit (NICU) were either unlicensed or being used in an off-label manner(11). ADRs were associated with 95(6%) of the 1574 unlicensed or off-label drug prescriptions, as compared to 112(3.9%) of the 2881 licensed drug prescriptions(11).

### **Need to Improve Drug Safety Monitoring in Indian Children**

Children in India comprise a large number (400 million) and a variety of ethnic groups. It is of utmost importance that we have our own comprehensive safety data(2). Also in the last decade or so, pediatric practice in India has undergone changes, which “mandates” that we improve our drug safety monitoring. The HIV/AIDS epidemic, setting up of many intensive care units, increasing availability of imaging studies, increasing awareness of pediatric psychiatric conditions, introduction of newer drugs and vaccines have accentuated the need for improving drug safety monitoring in Indian children. We now review drug safety data in the pediatric population for these newer developments:

#### *HIV/AIDS Epidemic*

This epidemic has led to trimethoprim-sulphamethoxazole (TMP/SMZ) being frequently prescribed in HIV-infected children for the treatment and prophylaxis of *Pneumocystis carinii* pneumonia. Both life-threatening and treatment-limiting adverse events due to suspected delayed hypersensitivity are known to occur after 7 to 21 days of starting TMP-SMZ(12). These include cardiorespiratory arrest, seizures, toxic epidermal necrolysis, hypotension, respiratory distress, liver function abnormalities, azotemia, and gastrointestinal disturbances(12). Also, anti-retroviral drugs have several

adverse effects. Currently, they are not available at affordable rates. In the near future they may become available at concessional rates and HIV-infected children in our country will have to be monitored for their adverse effects.

#### *Intensive Care Units*

Drug safety monitoring is necessary and feasible in intensive care units(11,13). A recent study from U.K. has reported that the drugs most commonly used in a PICU, such as midazolam, are also most likely to cause an ADR(13). Midazolam is being used as a sedative in mechanically ventilated neonates and children. The plasma clearance of midazolam is impaired in children below 3 years of age, who are therefore at increased susceptibility to its toxicity(14). It should be administered cautiously in very low birth weight (VLBW) babies because it can cause hypotension and adverse neurological events such as grade III-IV intra-ventricular hemorrhage(14). Midazolam has also been reported to cause delayed time to become fully alert /abnormal behavior on withdrawal in critically ill children(15).

#### *Imaging Studies*

CT, MRI, 2-D ECHO/Color Doppler, and ultrasonography facilities are now increasingly available in our country. A doctor, nurse or technician who is not well versed in sedating children may administer the sedative drug before the imaging study. A recent study from USA has highlighted that children are vulnerable to adverse events from premedication(16). Nearly 80% of the adverse events presented initially as respiratory compromise. Even chloral hydrate, which is believed to be a very safe drug, was no exception. Adverse sedation events *viz.*, death or permanent neurological injury was associated when 3 or more drugs

were used, despite the fact that each was administered within the recommended dosing limits. This study has recommended that only experienced medical personnel should administer sedatives to children and they should be discharged only after they have recovered fully from the sedation(16).

#### *Pediatric Psychiatry*

A recommended drug, methylphenidate (MPH), is being increasingly used to treat ADHD in Indian children. Its side effects increase linearly with dose, and these include appetite suppression, insomnia, tachycardia, nervousness and headache(17). A small minority of ADHD children on MPH therapy is also at risk for serious growth decrement(18). Pediatricians should therefore closely monitor dose-related side-effects and aim for the lowest effective dose.

#### *(a) Inhaled Corticosteroid (ICS)*

ICS are now the first-line therapy for persistent asthma in children. The use of high doses of ICS (more than 400 micrograms per day) has been shown to cause a significant reduction in growth rate(19). Its dose should therefore be minimized to the lowest effective dose and growth velocity monitored(19). In our country the use of ICS can have another risk. A report from Mumbai has documented that 8 (1.4%) out of 548 patients asthmatics, including adults, developed active tuberculosis following the use of ICS(20).

#### *(b) Nimesulide*

Nimesulide has become popular as a routine antipyretic and anti-inflammatory drug in Indian children. Randomized controlled clinical trials have documented that its antipyretic activity is greater and more rapid than paracetamol(21,22). However, for any drug, it is not just its efficacy that is important, but also its safety. It is believed that

nimesulide is associated with rare (0.1 per 100,000 patients treated), but serious and unpredictable hepatotoxicity *viz.*, increases in serum aminotransferases, hepatocellular necrosis and intrahepatic cholestasis(23).

(c) *Cisapride*

Gastro-esophageal reflux (GOR) is an extremely common and usually self-limiting condition in infants. Cisapride, a pro-kinetic agent, is being commonly prescribed for the symptomatic management of GOR in infants and to reduce feed intolerance in premature neonates in India. Adverse cardiac events (serious ventricular arrhythmias, QTc interval prolongation and sudden death) have been reported in adult patients treated with cisapride, especially with the concomitant ingestion of anti-fungal drugs (fluconazole, miconazole) and macrolides (clarithromycin)(24). A study from USA has suggested that documenting a prolongation of the QTc interval, 3 days following cisapride initiation, would identify infants at risk for adverse cardiac events(25).

(d) *Newer Anti-epileptic Drugs (AEDs)*

Newer AEDs (lamotrigine, oxcarbazepine, and topiramate) are being marketed for pediatric use in India. All over the world there is a lack of systematic pharmacoepidemiological studies investigating ADRs to the newer AEDs, making it difficult to assess accurately their incidence of ADRs(26). The ADRs identified include: hypersensitivity reactions ranging from simple morbilliform rashes to multi-organ failure, psychiatric ADRs and deterioration of seizure control to lamotrigine; hyponatremia and skin rash to oxcarbazepine; cognitive deficits, word-finding difficulties, renal calculi and weight loss to topiramate; and, aphasia, encephalopathy, motor disturbances and late-onset visual field constriction to vigabatrin (26).

(e) *Newer Vaccines*

In India many newer vaccines have been recently marketed *viz.*, Measles Mumps Rubella (MMR) vaccine, Hepatitis B (HB) vaccine, Hepatitis A (HA) vaccine, *Hemophilus influenzae b* (Hib) conjugate vaccine and varicella-zoster (VZ) vaccine. These newer vaccines are not yet on the UIP schedule due to financial constraints. No official post-marketing data is available on the safety of these newer vaccines in Indian children, as pediatricians in the private sector, who usually prescribe these newer vaccines, are not duty-bound to report the adverse events occurring to them.

In the developed world many perceived risks of undergoing immunization have been debated. However current scientific evidence, based on detailed epidemiological studies, does not support a causal association between any vaccine and type 1 diabetes, pertussis or measles vaccines and asthma, HB vaccine and demyelinating autoimmune diseases, and MMR vaccine and autism(27). To fill the gaps in current scientific knowledge of rare vaccine adverse events, the Vaccine Safety Datalink (VSD) project has been started in the USA(28). Computerized immunization registry data has been linked with the computerized medical use data of millions of children who receive vaccines. Currently, studies to determine causal associations, if any, between vaccines and 34 medical outcomes (*e.g.*, autism, autoimmune diseases, asthma, *etc.*) are underway(28).

**Newer Insights**

There have been newer insights into drugs being used in children for many decades which highlight the fact that drug safety monitoring is a continuous process.

(a) *Use of antipyretics*: It is well documented that both paracetamol and ibuprofen are

safe drugs, when used individually, in children. There is presently no scientific evidence that an alternating regimen of paracetamol and ibuprofen is safe, or that it achieves faster antipyresis than either drug used alone(29). However, there is evidence that such a regimen may cause harm. A 14-month-old girl, who was moderately dehydrated, received this regimen for control of fever and developed acute renal failure, which was attributed to the additive and synergistic renal toxicities of paracetamol and ibuprofen(30).

- (b) *Cefaclor-induced serum sickness-like reaction (SSLR)*: Cefaclor, an oral second-generation cephalosporin, is used to treat respiratory and skin infections. Recently this unique ADR, wherein the child develops urticaria, arthralgia and facial edema on receiving a second or third course of cefaclor, has been identified. It occurs in 0.055% of children and its tendency to develop is probably genetically inherited(31).
- (c) *Multiple antibiotic sensitivity syndrome*: This rare but distinct ADR manifests as urticaria, serum sickness-like reaction, anaphylaxis, or Stevens-Johnson syndrome to antibiotics of multiple classes viz., penicillin, cephalosporins, sulfonamides and macrolides. Although its incidence in children is not known it is believed to occur after repeated use of these antibiotics(32).
- (d) *Antiepileptic drug hypersensitivity syndrome (AHS)*: This rare idiosyncratic reaction can occur to aromatic AEDs (phenobarbital, phenytoin, carbamazepine, lamotrigine) within three months of starting therapy. A classic triad of fever, skin rash and hepatic dysfunction should serve as a presumptive diagnosis of AHS

and the offending AED should be promptly omitted. Since there is a high rate of cross-sensitivity between the aromatic AEDs, the child should henceforth receive benzodiazepines, valproic acid, or topiramate for future seizure control(33).

### How to Improve Drug Safety in Pediatric Practice?

Various efforts are being taken in the USA and in Europe to improve drug safety in children. We now describe these efforts and discuss their feasibility in our country:

- (a) *By conducting clinical drug trials*: The well-intentioned protectionist belief that children should not be exposed to potentially harmful side effects of a medicine until more is known about its effects in adults, has ironically led to pediatric drug evaluation getting neglected(34,35).

In recent times in the USA and in Europe, there has been an increasing demand by pediatricians and clinical pharmacologists for conducting well designed drug trials in children. Guidelines to conduct drug trials in children, without compromising on the ethical issues, have already been published(34,36). Since 1994, the Federal Drug Administration (FDA) in the USA has introduced new regulations, which "require" the drug manufacturer to re-examine existing information on marketed drugs, in order to determine whether the labeling of the drug can be modified for permitting its licensed use in children. All information relevant to children, on the basis of adult studies and available pediatric data, needs to be re-examined. If any such information is available then the drug manufacturer will be "required" to submit an application to the FDA for

### Key Messages

- ADRs in children are a significant public health issue.
- Young age, polypharmacy, prolonged hospital stay, being critically ill, and use of unlicensed and off-label drugs are risk factors for ADRs to occur.
- ADRs in children cannot be extrapolated from adult ADR data.
- Ethical drug trials in children are possible to conduct and are needed to improve drug safety.
- An in-hospital computerized event monitoring program can help reduce ADRs in hospitalized patients.
- An effective national post-marketing drug surveillance program is the need of the hour.

supplemental pediatric labeling within two years of marketing the new drug(35). Legislation passed in 1997 offers the drug manufacturer a major financial incentive, in the form of a 6-month extension to patent exclusivity, on the condition that a drug trial to determine its efficacy and safety in children will be completed within that period(37). This legislation has led to a dramatic increase in the number of pediatric clinical trials being conducted in the USA(37). It is hoped that such trials will result in children, like adults, having access to safe and effective medicines. As yet in our country, clinical drug trials are not permitted in the pediatric age group, except for newer vaccines. Unless there is a change in this policy by our drug regulatory authorities, this method of improving drug safety in Indian children is not feasible.

(b) *By using computerized pre-recorded data to assess causality of adverse events:* In many developed countries all patient data (clinical history, symptoms and signs, laboratory and radiological investigations done and treatment being given) is recorded using computers. With the

advent of computerization, identifying “adverse events” occurring during hospitalization has become relatively easy(38). Another advantage is its ability to assess the causality of each “adverse event” within a reasonable time frame(38). In some tertiary care hospitals in our country where computers are already being used to record data of patients, such intensive surveillance studies are feasible.

(c) *By implementing pro-active measures to improve spontaneous ADR reporting:* The spontaneous reporting system is the most productive and cost-effective method to detect ADRs in children(2). Questionnaire-based postal surveys have been conducted to gather information on ADRs occurring to ciprofloxacin in Indian children(2). However this method has still not been well established in India(2).

Two recent studies have shown the way to achieve an active ADR reporting system(39, 40). In Italy a network of family pediatricians was developed by properly presenting the project to them and then training them in ADR reporting(39). Each week, for a year, the

participating pediatricians sent, by e-mail, a detailed report of each observed ADR to the central authority. Although ADR reporting was mandatory in Italy, till then, only 4 ADRs per 100 000 children were being reported annually. After this project was started, 15 ADRs per 1000 children have been recorded annually(39). In U.K., a similar pro-active project involving doctors working in tertiary centers and smaller district general hospitals has proved successful(40). In the U.K project, in addition, a monthly reminder letter was sent to each participating doctor to stimulate ADR reporting for newer drugs. Examples of ADRs mentioned in the reminder letter included: skin reactions to lamotrigine, arrhythmias to cisapride, visual field defects to vigabatrin and systemic adverse reactions to inhaled or nasal corticosteroids(40). This has resulted in obtaining substantial data on specific ADRs occurring to newly introduced drugs. In both studies, the motivation of the participating doctors was maintained by giving them prompt feedback and acknowledging their valuable support(39,40). Such pro-active measures to improve spontaneous ADR reporting are feasible in major cities, towns and districts headquarters in our country, as internet services are now easily available.

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