Editorial

Adverse Drug Reaction Monitoring in Pediatric Practice

An adverse drug reaction (ADR) may be defined as any unwanted consequence of administration of a drug during or following a course of therapy(l). Even though children constitute almost 40% of India's 95 crore populations, information about the ADRs occuring in them is scanty.

Need for ADR Monitoring in Children

Before a new drug is marketed, clinical trials to detect ADRs are conducted in adult patients. These pre-marketing trials can be inadequate to detect the full range of ADRs that can occur(2). If an ADR occurs in 1 in 5000 or even in 1 in 1000 users, it could be missed in these trials. Also, these trials fail to identify ADRs that occur after a latent interval or after prolonged drug use(2).

Children constitute a vulnerable group since a new drug gets released to the market without the benefit of even limited experience in them. Adequate controlled clinical trials in children, with the notable exceptions of pediatric oncology and vaccinations, are lacking because of ethical considerations. Only a vigilant post-marketing surveillance detects ADRs occurring uniquely in children, for example, sulfonamide induced kernicterus in premature infants(3), chloramphenicol induced "gray syndrome "(4), and phenytoin induced movement disorders(5).

Need for ADR Monitoring in Indian Children

Certain conditions peculiar to children in general, and to Indian children in particular, warrant special mention and highlight the need for ADR monitoring:

(a) Children may not voice complaints and ADRs may easily go unnoticed, for example, ethambutol induces visual deficit, phenytoin produces pseudo-dementia and phenobarbitone causes drowsiness. These drugs can lead to impaired learning and deterioration in school performance.

(b) Growth potential may get inhibited by drugs, for example, corticosteroids used for nephrotic syndrome. Also, long-term use of anticonvulsants and sulphonamides can retard growth by inducing secondary hypothyroidism(6).

(c) Children may be more prone to dermal reactions to certain drugs, for example, antimalarials like pyrimethamine-sulfadoxine, chloroquine and quinine(7).

(d) Ethnic and sociocultural variables are known to influence the frequency of ADRs(8). Children in our country represent a wide variety of ethnic and sociocultural groups.

(e) The disease spectrum in Indian children is quite different than that in developed countries. Common diseases in India include tuberculosis, malaria, typhoid fever, recurrent infective diarrhea, scabies, chronic epilepsy kala-azar, *etc.* It is necessary to identify ADRs to drugs used for treating diseases which are endemic in Indian children.

(f) Malnutrition affects drug pharmacokinetics and thus influences

the frequency of ADRs. More than 50% of Indian children are malnourished. To prevent antitubercular drug-induced hepatotoxicity, lower doses of isoniazid and rifampicin have been recommended when treating malnourished children with disseminated tuberculosis(9). Long-term anticonvulsant (phenytoin/ phenobarbitone) therapy can cause osteomalacia and even hypocalcemia. Whether it is necessary to give calcium and vitamin D supplementation to prevent osteomalacia in malnourished children on these drugs remains controversial (l0).

(g) Irrational multiple drug prescriptions are common in pediatric practice. Patients taking a new drug along with other drugs may experience ADRs not revealed during the pre-marketing trials, for example, ventricular arrhythmias can occur when the antihistamine terfenadine is taken in combination with the antifungal agent ketoconazole(ll).

*(h)*Ayurvedic and homeopathic medications are commonly used along with allopathic drugs. An ayurvedic drug ("shankapushpi") used as a memory enhancer has been shown to interact with phenytoin, reducing its blood levels and leading to break through seizures(12).

(i) Certain drugs *(e.g.* ciprofloxacin) not recommended for pediatric use are being widely used in Indian children. On account of its possible adverse effect on growing cartilage, ciprofloxacin is not recommended for routine use in children(13). Since 1990 with the advent of multi-drug resistant typhoid fever ciprofloxacin is being widely used. Such clinical situations offer an opportunity to gather unique data on ADRs in children.

In 1990, we did a survey to detect ADRs to ciprofloxacin in pediatric practice(14). The ADR incidence was 3.1% (104 out of 3341 children). Two new acute ADRs were identified, namely, sudden death after intravenous ciprofloxacin and sinus nodal arrest causing bradycardia. In our survey, ADRs to ciprofloxacin were much lower than that reported by a similar survey done in Germany, wherein 8.3% patients developed ADRs; only 1.1% of their 12,205 patients were less than 18 years of age(15). From 1990-1995, we also received data on 20 children, aged 2-12 years, who developed a ciprofloxacin-related acute reversible arthropathy(16). A minimum 2-year follow-up was achieved in 582 of the 3341 children who had received ciprofloxacin in 1990 and there was no evidence of any delayed arthropathy or any permanent joint damage(16).

Similar ADR surveys need to be done for drugs not routinely recommended but still being used in Indian children, for example, norfloxacin, mefloquine, enalapril, *etc.*

(j) Additives such as colorings, flavorings and sugars are being widely used in liquid formulations prescribed in pediatric practice. These so-called "inactive" ingredients can cause adverse reactions such as rhinitis, urticaria, headache, gastrointestinal dysfunction, asthma and even anaphylactic shock. In India, this problem has received little attention. In India, manufacturers either do not provide clear-cut information of all additives used or they use synonyms making it difficult to identify them(17).

Methods for ADR Monitoring in Pediatric Practice

(a) Spontaneous Reporting System

This is the oldest, most productive and cost-effective method to detect ADRs in children. But it requires a nationwide network of participating pediatricians.

In 1952, Dr. Albe Watkins, a general practitioner from California, on his own informed the Food and Drug Administration (FDA) that his 10-year-old son had died of chloramphenicol-related aplastic anemia. He then started driving east. He stopped every few hundred miles, opened the yellow pages and telephoned local doctors to ask whether they knew of any adverse reactions to chloramphenicol. By the time Dr. Watkins reached Washington, he had learned of about a dozen deaths. Dr. Watkin's one-man campaign led to the FDA ordering a national investigation and within days additional cases were uncovered. Eventually in 1953 a Registry on Blood Dyscrasias was established(18). Between 1953-1960 the Registry received 91 reports of chloramphenicol-induced aplastic anemia(18). In 1961, a broader Registry of ADRs was established in the USA(19).

Recently in USA, a new MEDWatch programme has been launched to improve voluntary reporting of ADRs(20). To make ADR reporting easy all relevant data is asked for on a single, one-page reporting form. These forms have been distributed to all health professionals. The informer FAXES the completed form to the FDA and/or to the manufacturer. Both the informer's and patient's identity are kept strictly confidential.

A single spontaneous ADR report may reflect a biased observation. But a number of similar independent observations, spontaneously reported by many health professionals, followed by formal studies can confirm the causality of the ADR. But the spontaneous reporting system cannot estimate the rate of occurrence of the ADR.

(b) Intensive In-Hospital Drug Surveillance System

This is the most comprehensive surveillance scheme available with almost no under-reporting. This prospective method was first tried at the Children's Hospital in Boston, USA in the 1970's and an ADR incidence of 16.8% (280 out of 1669 children) was reported(21). A recent similar study from a pediatric unit in Mumbai has reported an ADR incidence of 1.7% (6 out of 347 children)(22).

Each child's detailed record is kept, *i.e.,* each drug received, its indication for use, dose, route of administration, frequency, duration, dates and reason for stopping. The occurrence of any of a list of specified clinical (or laboratory) "events", *e.g.,* rash, convulsions, gastrointestinal bleed, abnormal liver function tests, hyperglycemia, *etc.* are recorded. This is an expensive and time-consuming method. Now with computer facility, the accumulated data is easily analyzed using an algorithm to determine the causal relationship between the drug and the event(23). Since this method requires multidisciplinary expertise, *i.e.* pediatrician, clinical pharmacologist, nurse, pharmacist, epidemiologist, computer scientist and a biostatistician, it can only be set-up in large hospitals. Such studies give the rate of occurrence of ADRs. They can also generate hypotheses related to previously unrecognized ADRs, *e.g.,* by this method an unexpected association between intracranial hemorrhage and low doses of heparin given to maintain the patency of intra-arterial infusion lines in low-birth-weight infants was detected(24).

Drug surveillance method has also been

applied to the outpatient pediatric setting. Parents are interviewed by telephone a few days after the consultation and ADRs detected(25).

(c) Specific Epidemiologic Studies

These are skilled, carefully designed and controlled studies directed to study a specific ADR(s) occuring to a given drug. They are of two types:

(i) "Cohort Studies": A group of children exposed to a drug are observed prospectively for the development of ADRs, for example, rate of skin rash, vomiting and diarrhea attributable to ampicillin use(26). Cohort studies identify a specific ADR's rate but are expensive to conduct.

(ii) "Case-Control Studies": Children with and without a given adverse event are identified and the frequency of exposure to the drug being investigated is retrospectively ascertained, for example, association between aspirin use and Reye's syndrome was confirmed using this method(27).

Specific epidemiological studies do not provide a comprehensive list of ADRs occurring to a particular drug. Also, they do not consider the potential effects of the concurrent use of additional drugs, the patient's disease state and other risk factors which may affect the risk of ADRs.

Summarizing, no single ADR monitoring method can provide all the answers. A variety of methods are required to improve ADR detection in pediatric practice.

ADR Monitoring in India: Status Today and Recommendations for Future

Unfortunately inspite of its immense need, the concept of ADR monitoring is still new in India. To overcome this shortcoming, the Drug Controller of India has since 1990 started six ADR Monitoring Centers at Calcutta, Chandigarh, Lucknow, Mumbai, New Delhi and Pondicherry(2). One of the main objectives of this project is to gather information on ADRs and also to reciprocally provide data to physicians on the adverse reaction profile of a specific drug, especially a newly-marketed one. The final aim is to aid early detection, prompt treatment and prevention of ADRs. The Indian Council of Medical Research also has an ADR monitoring system consisting of 12 centers spread out in India.

At present there is hardly any spontaneous reporting of ADRs by the pediatricians. All pediatricians should consider this to be their professional responsibility. They should report all serious and unusual ADRs *(i.e.,* ADRs causing death, hospitalization, disability, congenital anomaly or where intervention was required to prevent permanent impairment or damage) to their regional ADR Monitoring Center. In major teaching hospitals, computerized in-hospital intensive drug surveillance systems should be started. To inculcate an "ADR reporting culture", undergraduate medical students should undergo adequate training in ADR detection and reporting skills.

To conclude, the need to identify ADRs in Indian children is acute and steps to initiate such research activities are of vital importance and urgency. In the 1990's with the rapid communication skills available at our disposal it will not be necessary to travel cross-country like Dr. Watkins to confirm the causality of drug-induced reactions. It is important to recognize that dedicated efforts from even a single pediatrician can help save many lives and reduce drug-related morbidity.

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