Review Article

Pharmacovigilance in Paediatric Population: An Evolving Landscape in Drug Safety Monitoring

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ABSTRACT

Adverse drug reactions (ADRs) represent one of the major health problems worldwide which have high morbidity and mortality rates. The risk of ADR is higher in paediatric patients for various reasons. But knowledge about ADR in children is very poor. Adequate recognition of ADR is challenging in paediatric population. Because of their unique physiological and developmental traits, children—from neonates to adolescents – a particularly difficult demographic for drug treatment. When compared to adults, these alterations can have a substantial impact on pharmacokinetics and pharmacodynamics, resulting in changes in drug absorption, distribution, metabolism, and excretion. Historically, paediatric groups have been overlooked in clinical medication studies, resulting in insufficient data on their safety and efficacy. To address this gap, adult research has been extrapolated to children, with changes in body size and maturation, but without an extensive understanding of developmental pharmacology. Therefore, to maximize therapeutic results and reduce harm, adverse drug reactions (ADRs) in children necessitate careful thought, monitoring, and research. Paediatric pharmacovigilance aims to address knowledge gaps and improve drug safety for patients. Health care providers play a critical role in ADR detection and reporting. ADRs can vary in intensity and variety among paediatric age groups, making it challenging to identify, report, and manage them. This review briefly elaborates the historical background of paediatric pharmacovigilance and also physiological peculiarities of pharmacodynamics and pharmacokinetic aspects of drugs in newborns, infants, toddlers and children and the importance of paediatric pharmacovigilance system.

Keyword: *Adverse drug reaction, paediatric population, pharmacovigilance, clinical trial*

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INTRODUCTION

Any substance having the ability to produce a therapeutic effect can also produce unwanted or harmful effects.[1] Drugs are mostly used to alleviate suffering; however, drugs can be fatal and result in ADR; as the saying goes, "Drugs are Double Edged".[2] Adverse drug event (ADE) is one of the healthcare problems that may result in temporary or permanent harm and an increase in healthcare costs.[3] An adverse drug reaction (ADR) is an unfavorable event that is directly linked to the use of a drug.[4] However, the report and much of the subsequent literature about adverse events have focused primarily on medical care for adults.[5] Children are also vulnerable to adverse events and preventable adverse events, and such events have been relatively unstudied in children[5]. The purpose of this article is to introduce paediatric pharmacovigilance, how it differs from pharmacovigilance for adults and what measures could be taken to identify paediatric adverse events.

DEFINITION OF PHARMACOVIGILANCE

Pharmacovigilance comes from the Greek word "pharmakon", which means "drug" and the Latin word "vigilant" which means "to keep watch".[6] Pharmacovigilance is defined by World Health Organization as "the science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other possible drug-related problems".[7]

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The main goals of pharmacovigilance programs are[8,9]:

1) to improve patient care and safety in relation to the use of medications, as well as all medical and paramedical interventions;
2) to improve public health and safety in relation to the use of medications;
3) to contribute to the assessment of benefit, harm, effectiveness, and risk of medications;
4) to encourage safe, rational, and more effective (including cost-effective) use of medications; and
5) to promote understanding, education, and awareness of the importance of medication use.

HISTORICAL BACKGROUND OF PAEDIATRIC PHARMACOVIGILENCE

Research involving children yields valuable information about both children and adults. However, some of the characteristics that make children appealing for study also expose them to unique risks.[9] Historically children were frequently subjected to serious drug related harms, prompting specific measures to improve the safety of paediatric drug therapy.[10] Children were chosen as research participants until the past half century because they were easily accessible. Institutionalized children were a particularly popular type of research subjects in the United States. For instance, Edward Jenner noted at the end of the 18th century that exposure to cowpox appeared to confer immunity against small pox. Then, for testing the small pox vaccine, he chose James Phipps, the eight-year old son of his gardener. Similarly, Joseph Meister, a 9-year old boy, was the first person to receive Louis Pasteur's anti-rabies vaccine in 1885.[12]

The Nuremberg Code was the first international code of research ethics, requiring that all participants in human experimentation provide informed consent, i.e., the voluntary consent of the human subject is absolutely essential. Although the Nuremberg Code did not specifically address the issue of using children as research subjects, the strict need for informed permission appears to have excluded children from taking part in human experiments[11]. The first issue of safety that prompted a pharmacovigilance review was chloroform issues, which were published in the British Medical Journal in 1877. The second issue arose in 1898 with the commercialization of diacetylmorphine, also known as heroin, which became addictive at the beginning of the 1910s (500,000 dependent patients reported only in the US).[13] In 1937, the solubilization of sulfanilamide with diethylene glycol, without any prior toxicology studies, led to a tragic outcome, resulting in 34 paediatric deaths from renal failure out of 103 cases.[14]

The third occurred in the early 1950s when diiodoethyl of tin was added to Stallion, a topical skin product, resulting in 102 deaths from encephalopathy and a hundred patients developing severe, irreversible neurological aftereffects.[13] Several children were born with phocomelia and limb agenesis because of thalidomide during the 1960s.[15] Thalidomide was first marketed as an over-the-counter (OTC) hypnotic/sedative and a safe medication in 1957, and it was later used to treat nausea in pregnant women. The result was over 12,000 cases of teratogenic effects in children (not only limbs malformations).[15] In response to the thalidomide tragedy, the World Health Organization (WHO) launched its Program for International Drug Monitoring in 1968. The WHO-collaborating Uppsala Monitoring Centre, which was established in 1978 to aid the initiative.[7-9] Therefore, the major concerns about teratogenic consequences in children marked the beginning of a new age of pharmacovigilance. In other words, a child disaster led to the creation of PV.[16]

DEVELOPMENTAL ASPECTS OF ADR IN CHILDREN

Childhood has traditionally been a period marked by significant risks and dangers. According to an estimate, children in ancient Egypt had a 30% chance of dying before puberty, whereas a similar estimate in the nineteenth century America was 25%. This dismal statistic has been altered by three major changes: the development of vaccines, public sanitation, and the development of specific pharmacotherapy.[17] Abraham Jacobi, the father of Paediatrics in the United States, stated that "Paediatrics does not deal with miniature men and women, with reduced doses and the same class of disease in smaller bodies, but has its own independent range of horizon".[18] Age related maturation of structure and function of biological system affects absorption, distribution, metabolism, elimination and response to drug. This manifested as variation in potency, efficacy and toxicity of the drug administered to the children.[19]

PHARMACODYNAMIC CHANGES

GABA-A receptors undergo developmental changes during postnatal life, which may affect neurodevelopment and the associated disorders. GABA-A receptors may switch from an excitatory to an inhibitory mode during early development, and this hypothesis may help to explain paradoxical seizures sometimes observed in infants after exposure to benzodiazepines.[20] Channels and transporters go through developmental maturation as well, as transporters are thought to be involved in a dynamic maturation process that is responsible for an enhanced diuretic response to thiazide diuretics in both preterm and full-term babies.[21] Drug-receptor interactions appear to be directly related to age-related developmental changes.[19]

PHARMACOKINETIC CHANGES

Absorption: Developmental changes in absorptive surfaces, particularly the gastrointestinal tract, can affect the rate and extent of a drug's bioavailability. Furthermore, physio pathological factors such as shock cause hypoxia and hypoperfusion, which reduce drug absorption.[22] Paediatric patients' absorption of orally administered medications exhibits some unique characteristics due to the ongoing development of their growing organisms. In newborns, the intraluminal pH of the stomach is relatively higher. It is practically neutral at birth, then decreases to 1-3 in the first 48 hours, then increases again to neutral in the next 10 days. Only after that does it begin to decline, reaching adult levels by 2 years of age.[23] By three years of age, the amount of gastric acid excreted per kilogram of body weight is comparable to that excreted in adults, resulting in the same P^H values (2–3). [22] The effects of these variations in gastric P^H can be profound, with higher peak concentrations of the acid-labile antibiotic penicillin being seen in neonates, whose gastric pH is higher than that of infants and children.[24]

Distribution: According to a drug's physiochemical characteristics, such as molecular size, ionization constant, and relative aqueous and lipid solubility, a drug is dispersed to different body compartments after absorption. Many of the processes involved in drug distribution differ significantly between neonates, infants, and adults.[22]The volume of the central nervous system (CNS) is relatively large in younger children and does not correlate well with body surface area (BSA) in the paediatric population since CNS volume reaches 80-90% of adult values by age 4-6 years, yet BSA does not reach adult values until about age 16-18 years. This implies that intrathecal therapy would lead to lower concentrations of CFC in younger children compared to adolescents and adults. CFC concentrations after intrathecal methotrexate injection, for example, were found to vary 100-fold, with lower concentrations observed in younger children.[25]

Metabolism: Drug metabolism in neonates, infants, and toddlers undergoes developmental changes as well. The potential increased risk of ADRs in children is consequently determined by the age-related expression of Phase I and Phase II drug metabolizing enzymes, which significantly contributes to pharmacokinetic variations between paediatric and adult patients.[26] Phase I and Phase II metabolic pathways are both underdeveloped at birth. Metabolic enzymes are expressed differently at birth and continue to mature throughout the first few months of life.[27]

Excretion: The glomerular filtration rate (GFR) is reduced in neonates, particularly premature ones, and only gradually increases thereafter, reaching adult levels by 3 months of life. Similarly, tubular secretion in neonates is reduced and undergoes maturation, which is nearly complete by the end of the first year of life.[28]

DRUG RELATED SAFETY ISSUES

Pharmaceutical companies face challenges in conducting medication evaluation studies on neonates, babies, and children due to their high vulnerability and ethical issues.[29] Paediatric patients, particularly neonates and infants, make up a small portion of the pharmaceutical market and have few unique therapeutic indications. As a result, studies and clinical trials in children are often associated with low profit expectations, making them unprofitable investments for the pharmaceutical industry.[30] As a result, unlicensed medications with no paediatric marketing authorization are commonly used, as well as off-label drugs prescribed for other than licensed indications of specific age, dose, and method of administration.[31]

Off-label and unauthorized drug usage has been linked in certain studies to an increased chance of developing adverse drug reactions (ADRs), particularly significant ones.[32] According to a more

recent review of the literature, between 23 and 60 percent of paediatric ADRs were caused by unlicensed and/or off-label medicines.[33] Some diseases only affect children, such as retinopathy of prematurity and bronchopulmonary dysplasia, and the causes and treatments of paediatric diseases differ from those of adult diseases. These disorders might also differ among paediatric age groups (e.g., hypertension, epilepsy).[34] Children are particularly at risk for dosage errors since drug delivery is frequently based on weight or surface area dosage estimations.[35] Numerous studies have shown how susceptible children are to drug errors, which are especially common in neonatal settings.[36]

IMPORTANCE OF PAEDIATRIC PHARMACOVIGILANCE

Paediatric pharmacovigilance starts with the first administration of a medication to a child and continues throughout the treatment process. Off-label and unauthorized use might occur during clinical trials or in clinical practice[37].

Children are more likely to experience ADRs. A major, yet unresolved issue is the insufficient pharmacological and toxicological data available for drugs intended for paediatric use. Children are generally excluded from premarketing clinical trials unless the medicine is specifically designed for them, limiting access to age-specific information on dosing, efficacy, and risks[30,38,39]. Off-label drug use in paediatrics currently ranges between 18 and 65% of prescriptions in hospitals and 11 to 31% in primary care settings[40].

Significant differences in drug absorption, distribution, metabolism, and excretion make it impossible to reliably transfer information obtained in adults to children, infants, and neonates, as the physiological parameters of neonates, infants, children, and adults differ significantly[38,39]. Hence, during research or drug related experiment, the paediatric population might be exposed to drugs with an increased risk of developing unusual drug-related adverse events, which make them a vulnerable group as well[38,39]. Drugs pharmacokinetic and pharmacodynamics property relates to children's body growth, maturation and functioning capacity[23].

According to studies, medication errors in children were three times more common than in adult populations. Due to the wide variations in body mass, paediatrics presents a complex and distinct set of dangers that necessitates to be assessed individually based on patient age, weight or body surface area, and clinical state.[41] Several reports of reactions in children differed from those in adults, not only in terms of the reactions and drugs involved, but also in that they were more concentrated around a smaller set of reaction types and drugs.[42]

GLOBAL BURDEN OF ADR IN PAEDIATRIC PATIENTS

Since pre-marketing clinical trials are typically conducted on adults, information on the frequency, severity and drug classes are most frequently linked to adverse events in the paediatric age range is particularly relevant.[43] The pediatric population is one of the most vulnerable groups to adverse drug reactions (ADRs). According to the WHO Global Individual Case Safety Report (ICSR) database (VigiBase), 7.7% of children aged 0 to 17 years experienced ADRs.[44] However, these figures appear to be underestimated, as another study showed a higher incidence of ADRs, totaling over 7000 serious or fatal ADR reports in children, mostly under the age of two[30]. A recent systematic review showed that the reported incidence of ADR in hospitalized children were ranging between 0.6% and 16.8%.[45] Another systematic review of seventeen prospective studies showed that in hospitalized children, the overall incidence of ADRs was 9.53% severe reactions accounted for 12.29% of the total. The overall rate of paediatric hospital admissions due to ADRs was 2.09%.[46]

There were 19 ADRs recorded from a total of 1083 hospital admissions from a prospective cross-sectional study conducted Mexico. Incidence of ADR was 1.7%. All newly admitted patients were observed by active monitoring.[47] In another prospective observational cohort study conducted in the UK, a total of 5,118 children were included, with 17.7% experiencing at least one ADR. Over half of the drugs involved in these ADRs were opiate analgesics and medications used in general anesthesia (GA). 0.9% of these ADRs caused permanent harm or necessitated admission to a higher level of care. Children who had GA were more than six times more likely to develop an ADR than children who did not have GA.[48]

PAEDIATRIC PHARMACOVIGILANCE METHODS

Major problems with pharmacovigilance in the paediatric population include: i) a lack of clinical trials in children or a small number of them, which results

in inadequate safety and pharmacokinetic data as well as the unavailability or limited availability of paediatric adequate formulations; ii) drug-related issues that are specific to children or a particular paediatric age group, which makes adult safety data unreliable; iii) a unique and increased susceptibility to certain excipients like ethanol and iv) frequent use of off-label and unlicensed medications, which leads to underreporting of ADRs due to legal concerns.[49]

Paediatric signal evaluation and identification are advanced techniques in paediatric pharmacovigilance. Both necessitate knowledge of paediatric clinical practice, risk reduction, and paediatric safety specifications.[37] The paediatric signal detection process considers the drug's present safety specification and regularly examines available safety data for potential new dangers or changes in risk factors, severity, or outcomes. Pooling safety data from paediatric clinical trials is recommended wherever possible.[37] Meanwhile, paediatric signal evaluation considers how ADRs manifest in children and how childhood development can influence them. The approach is based on knowledge of paediatric disorders, comorbidities, prevalent co-medications, and obstacles in identifying and treating children. This includes studying how developmental factors affect the assessment and treatment of paediatric disorders.[37]

CONCLUSION

The difficulties of paediatric pharmacovigilance and medication safety require joint efforts from society and key stakeholders. To address the lack of paediatric formulations and age-group-specific Pharmacokinetic and Pharmacodynamics data for both patent-protected and off-patent medicines, pharmaceutical industry and regulatory authorities may collaborate with academic researchers, regardless of labelling status (off-label/unlicensed). Creating an open-source, evidence-based paediatric formulary that is available in several languages and updated as needed can significantly reduce dose-related toxicities and lack of efficacy in children. It might have sections for parents, nurses, and children. Additional chapters may cover medication adaptations for low-income settings and recommended practices to prevent medication errors. To achieve this, paediatricians, pharmacologists, drug safety experts, and pharmacists worldwide should work together and establish an independent authority. Children, like adults, have the right to obtain safe and effective pharmaceuticals in the appropriate dose, mode of administration, indication, and duration, together with accurate information and medical supervision.

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