SAFETY MONITORING OF PEDIATRIC MEDICATION: A PHARMACOVIGILANCE PROSPECTIVE

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ABSTRACT:

Pharmacovigilance in pediatric medicine is essential due to the distinct pharmacokinetic and pharmacodynamic characteristics of children, which differ significantly from adults. This abstract delves into the importance of pharmacovigilance studies in monitoring and ensuring the safety of medications used in pediatric populations. Children are more susceptible to adverse drug reactions (ADRs) due to factors such as off-label drug use and the limited data available from clinical trials. Effective pharmacovigilance practices involve the systematic collection, analysis, and interpretation of data related to ADRs in children. Recent studies highlight the prevalence of ADRs in pediatric patients, with antibiotics being a common cause. Regulatory bodies, such as the European Medicines Agency (EMA), have developed specific guidelines to address these challenges, emphasizing the need for tailored risk management plans and periodic safety updates. The integration of advanced pharmacovigilance tools and processes, including intensive monitoring and reporting systems, is crucial for improving drug safety in pediatric care. This abstract underscores the necessity for continuous vigilance and collaboration among healthcare professionals, regulatory agencies, and caregivers to enhance the safety and efficacy of pediatric medications.

KEY WORDS: Adverse Drug Reactions (ADRs), Pediatric Pharmacokinetics, Risk Management, Regulatory Guidelines, Safety Monitoring

I. INTRODUCTION

The term “Pharmacovigilance” first appeared in French in the late 1960s, when the term “Pharmacovigilance intensive and Pharmacovigilance spontaneous” were contrasted.1

Pharmacovigilance is the science of detecting, assessing, evaluating, and preventing harmful effects, especially long-term and short-term side effects of drugs. 2

Pharmacovigilance has an important role in the assessment of side effects caused by the drugs whether it is caused by oral drugs, parenteral drugs or I.V. drugs.3

When a pharmaceutical drug is introduced in the market there are still a lot of things that are unknown about the safety of the new drug. These medicines are used by various patients for different diseases who might be using several other drugs and must be following different traditions and diets which may adversely affect the impact of medicine in them. 4

Pharmacovigilance monitors any severe side effects of medications. Boost public safety and health with regards to the use of medications. Encourage the safe, intelligent, and more effective (including cost-efficient) use of medicines by helping to analyses their benefits, harms, effectiveness, and risks.4

Pediatric medication safety is a worldwide concern, and the most important way to promote the safe use of therapeutic agents is to have enough awareness of pharmacovigilance and the spontaneous reporting of adverse drug reactions.

Healthcare professionals’ pharmacovigilance knowledge and adverse drug reaction reporting behaviour and factors determining the reporting rates. 5

The pediatric population encompasses several subsets. The applied age classification of pediatric patients is pre-term and term neonates from 0 to 27 days; infants (or toddlers) from 1 month to 23 months; children from 2 years to 11 years; adolescents from 12 to less than 18 years.[European Commission; Communication From The Commission-Guideline on the format and content of applications for agreement or modification of a pediatric investigation plan and requests for waivers or deferrals and concerning the operation of the compliance check and on criteria for assessing significant studies. 6

The effectiveness and safety of medications in children have been the subject of relatively few clinical investigations.

an increase in the incidence of drug-related adverse events, morbidity, and mortality in the pediatric population, and the overall extent of the drug-related events is considerably high. Studies done in the community confirm that at least one in every 500 children will experience an ADR every year. 7

An adverse drug reaction is a "response to a drug which is noxious and unintended and which occurs at doses normally used in man for prophylaxis, diagnosis, or therapy of disease or for the modification of physiologic function." Adverse drug reaction is different from side effect. 8

Pharmacovigilance in children requires special attention. Drugs are the mainstay of treatment in paediatric practice, yet a high proportion of drugs have not been tested in children. This leads to irrational prescribing, the use of inappropriate doses, the use of age-inappropriate formulations, which may result in underdosing or overdosing, and drug development without due regard for regular development process of a child. Children are more vulnerable to ADRs as the pharmacokinetics and pharmacodynamics of many commonly used drugs vary significantly in paediatric patients 9

An adverse drug event is "an injury resulting from the use of a drug. Under this definition, the term ADE includes harm caused by the drug (adverse drug reactions and overdoses) and harm from the use of the drug (including dose reductions and discontinuations of drug therapy)."

There is recent evidence that potential ADEs may be more common in pediatrics, suggesting that the epidemiologic characteristics of medication errors may be different between children and adults.10

Post marketing surveillance (PMS) of medications is the process by which marketed medicines are monitored for adverse drug reactions (ADRs) post clinical trials.11

Use of Pharmacovigilance in Pediatric Patients

1. Monitoring ADRs: Tracking adverse drug reactions to identify safety issues early.
2. Data Analysis: Collecting and analyzing data to detect patterns and trends.
3. Risk Management: Implementing tailored risk management plans to minimize risks.
4. Regulatory Compliance: Adhering to guidelines and submitting safety reports.
5. Education: Training healthcare professionals on recognizing and managing ADRs.
6. Technology: Using electronic health records and decision support systems to enhance ADR detection.
7. Collaboration: Facilitating communication among healthcare providers, regulatory bodies, and caregivers.
8. Post-Marketing Surveillance: Performing research to collect empirical safety data.

9. Patient Involvement: Encouraging reporting of ADRs by patients and caregivers.12,13

The history of Pharmacovigilance

1. **Early Beginnings (1848)**:
   The origins of pharmacovigilance can be traced back to 1848, following the tragic death of a young girl due to chloroform anesthesia. This incident highlighted the need for safer drug practices and led to the adoption of alternative anesthetics
2. **Thalidomide Tragedy (1961)**:
   The formal inception of pharmacovigilance occurred in 1961 in Great Britain after the severe birth defects caused by the drug Thalidomide, which was prescribed to pregnant women for morning sickness. This disaster underscored the importance of systematic drug safety monitoring
3. **Establishment of WHO Programme (1968)**:
   In response to the Thalidomide tragedy, the World Health Organization (WHO) established the International Drug Monitoring Programme in 1968. This program aimed to enhance global drug safety through the collection and analysis of adverse drug reaction (ADR) reports
4. **Development of Regulatory Frameworks**:
   Over the years, various countries developed their own pharmacovigilance systems and regulatory frameworks. The European Medicines Agency (EMA) and the U.S. Food and Drug Administration (FDA) have been instrumental in setting guidelines and standards for drug safety monitoring

5. Modern Pharmacovigilance:

Today, pharmacovigilance involves advanced technologies and methodologies, including electronic health records (EHRs), big data analytics, and artificial intelligence (AI) to detect and assess ADRs more efficiently. The focus has expanded to include proactive risk management and continuous improvement of drug safety practices14,15

II. PNEUMONIA IN PEDIATRIC PATIENTS-

Pneumonia is an infection of the lung tissue. When a person has pneumonia the air sacs in their lungs become filled with microorganisms, fluid and inflammatory cells and their lungs are not able to work properly. Diagnosis of pneumonia is based on symptoms and signs of an acute lower respiratory tract infection, and can be confirmed by a chest X-ray showing new shadowing that is not due to any other cause (such as pulmonary oedema or infarction). 16

Pneumonia is the single largest infectious cause of death in children worldwide. Pneumonia killed 740 180 children under the age of 5 in 2019, accounting for 14% of all deaths of children under 5 years old but 22% of all deaths in children aged 1 to 5 years. Pneumonia affects children and families everywhere, but deaths are highest in southern Asia and sub-Saharan Africa.

Pneumonia remains a significant health issue in India, particularly affecting children. Here are some key points about its severity:

1. Mortality Rate: Pneumonia is responsible for about 14% of under-five mortality in India
2. Incidence-According to WHO estimations, India has an annual incidence of 0.37 cases of clinical pneumonia per kid. This indicates that pneumonia poses a serious risk to health, especially for young children.
3. Severe Cases: India accounts for 36% of the total burden of clinical pneumonia in the WHO South-East Asia region. Severe episodes of pneumococcal pneumonia are estimated to be around 0.56 million annually[3].
4. Risk Factors: Key risk factors include malnutrition, lack of exclusive breastfeeding, indoor pollution from cooking fuels, and inadequate vaccination17,18

III. COMMON PRESCRIBED MEDICINES IN PNEUMONIA FOR PEDIATRIC PATIENTS

1) Amoxicillin-

Amoxicillin is a penicillin-class, effective broad-spectrum antibiotic, which is commonly prescribed to children for treatment of pneumonia and other illnesses, including other bacterial infections of the ears, sinuses, throat, urinary tract, skin, abdomen, and blood. In 2014, WHO published its recommendations for home treatment of pneumonia, establishing amoxicillin as the recommended treatment for pneumonia in children under age five19. WHO recommends amoxicillin 250 mg dispersible tablets as the most convenient formulation to treat childhood pneumonia in community settings, and especially in remote areas where no reliable sources of clean water and electricity are available.20

2) Azithromycin-

Azithromycin is often used to treat pneumonia in children, particularly when the infection is suspected to be caused by atypical bacteria like *Mycoplasma pneumoniae* or *Chlamydia pneumoniae*. Here's

how it is typically administered. This erythromycin derivative offers protection against numerous gram-positive species and has significantly increased efficacy against gram-negative bacteria, including Enterobacteriaceae.It is more beneficial because of Shorter Course: A five-day course of azithromycin is often as effective as a longer course of other antibiotics and having Good Tolerance: It is generally well-tolerated by children, with fewer gastrointestinal side effects compared to other antibiotics 21

3)Ceftriaxone-

Ceftriaxone for injection, USP is a sterile, semisynthetic, broad-spectrum cephalosporin antibiotic for intravenous or intramuscular administration. This substance is used to treat a number of diseases that are acquired in the community, including those caused by Salmonella typhi and Neisseria gonorrhoeae. Ceftriaxone is commonly used to treat severe bacterial pneumonia in children, especially when oral antibiotics are not suitable or when the child requires hospitalization. Here's how it is typically used. The Benefits of Ceftriaxone is in Broad-Spectrum Activity: Effective against a wide range of bacteria, Once-Daily Dosing: Simplifies treatment regimens and improves compliance and also has Good Tissue Penetration: Reaches high concentrations in body fluids and tissues, ensuring effective treatment.22

4)Cefotaxime-

Cefotaxime is a drug used to treat pneumonia and cervicitis/urethritis. A beta-lactam antibiotic that belongs to the third generation of cephalosporins is cefotaxime. The sensitive strains of bacteria that impact the lower respiratory tract, Genito-urinary tract, central nervous system, intra-abdominal infections, bone and joint infections, skin infections, gynaecologic infections, and septicaemia can be treated with its broad-spectrum antibacterial activity. Broad-Spectrum Activity: Effective against a wide range of bacteria Good Tissue Penetration: Reaches high concentrations in body fluids and tissues, ensuring effective treatment 23

IV. SIDE EFFECTS OF COMMON PRESCRIBED MEDICINES IN PNEUMONIA FOR PEDIATRIC PATIENTS

1. Side effects of Amoxicillin-

Allergic reactions of Amoxicillin is skin rashes, itching, hives, face swelling, lips, tongue, or throat, Skin irritation, blistering, peeling, or loosening, including within the mouth, severe fever, diarrhoea, Itching, unusual vaginal discharge, or Typically, side effects don't need to be treated by a doctor;

however, if they persist or become troublesome, let your care team know. Headache, nausea, vomiting, and diarrhoea Amoxicillin: Applications & Adverse Reactions 24,25,26

2. Side effect of ceftriaxone

Allergic reactions like skin rash, facial, lip, tongue, or throat swelling, itching, or hives, Perplexity Feeling sleepy Gallbladder issues include fever, nausea, vomiting, and excruciating stomach discomfort. Reduced urine production and oedema in the hands, feet, or ankles are signs of kidney damage. Kidney stones can cause lower back or side pain, blood in the urine, or difficulty passing pee. Low red blood cell count—atypical exhaustion or weakness, headache, light-headedness, and difficulty breathing Fever, nausea, vomiting, and intense stomach pain that radiates to your backor worsens after eating or when touched are all signs of pancreatitis. Convulsions severe fever with diarrhoea unusual exhaustion or weakness.27,28,29

3)Side effects of azithromycin-

These common side effects of azithromycin happen in more than 1 in 100 people. There are things you can do to help cope with them: feeling seek , diarrhea, vomiting ,loose appetite headache ,feeling dizzy , faster or irregular heartbeat, eyes turn yellow, or your skin turns yellow, temporary hearing loss, or you feel unsteady on your feet , severe pain in your stomach or back, Allergic reactions, which may be severe and include: Skin rashes, itching or hives, Swelling of the throat, tongue or face Shortness of breath or wheezing Skin rash or peeling, or mouth ulcers breathing problems Nausea, sudden weight loss ect.30,31,32

V. PHARMACOVIGILANCE STUDY CONSIDERATION OF ADVERSE DRUG REACTION

1. Monitoring Adverse Effects

Continuous monitoring of adverse drug reactions (ADRs) is essential to identify any new or rare side effects that may not have been evident during clinical trials. This involves collecting data from various sources, including healthcare providers, patients, and clinical studies, to ensure comprehensive surveillance.33,34

***Example**:* A child receiving antibiotics for bacterial pneumonia develops a severe allergic reaction. This adverse event is reported to a pharmacovigilance database, which helps in identifying similar cases and assessing the risk associated with the antibiotic.35

2. Reporting Systems

Effective pharmacovigilance relies on robust reporting systems that allow healthcare professionals and patients to report ADRs easily. These systems can be national or international databases, such as the FDA's MedWatch in the United States or the WHO's VigiBase. Reporting can be done through online portals, phone calls, or paper forms.36

***Example**:* Healthcare providers use systems like the FDA's MedWatch or the WHO's VigiBase to report adverse drug reactions (ADRs) in pediatric patients. These systems facilitate the collection and analysis of data on medication safety in children.37

3. Data Analysis

Following collection, ADR data must be examined for trends or indicators that might point to a safety issue. This involves statistical analysis and data mining techniques to identify trends, such as an increase in a particular side effect or a new side effect emerging in a specific population.38

***Example**:* Data from multiple reports of ADRs in children treated for pneumonia are analyzed. If a pattern of increased gastrointestinal side effects with a particular antibiotic is detected, this information can lead to updated treatment guidelines to minimize these risks.39,40

4. Regulatory Compliance

Pharmaceutical companies and healthcare providers must comply with regulatory requirements and guidelines set by health authorities, such as the FDA, EMA, or WHO. This includes timely reporting of ADRs, conducting post-marketing surveillance studies, and updating product labels with new safety information.

Pharmaceutical companies must comply with regulations by submitting periodic safety update reports (PSURs) and risk management plans (RMPs) for medications used in pediatric pneumonia. These documents help regulatory authorities monitor and manage the safety of these medications.41

5. Risk Management

Developing and implementing risk management plans (RMPs) is crucial to mitigate identified risks. RMPs outline strategies to minimize the impact of known risks, such as additional monitoring, restricted use, or educational programs for healthcare providers and patients.

***Example**:* If a specific antibiotic is found to cause severe side effects in children, a risk management plan might include recommendations for alternative treatments, dosage adjustments, or additional monitoring for high-risk patients.42,43

6. Communication

Effective communication of safety information is vital to ensure that healthcare providers, patients, and the public are aware of potential risks. This can include safety alerts, updated product labels, educational materials, and public health advisories. Clear and timely communication helps prevent harm and promotes informed decision-making.44

***Example**:* When new safety information about a pneumonia treatment is discovered, regulatory agencies issue safety alerts and update product labels. This ensures that healthcare providers and caregivers are informed about the potential risks and how to manage them.45

7. Education and Training

Ongoing education and training for healthcare professionals on the importance of pharmacovigilance and how to report ADRs are essential. This can include workshops, online courses, and continuing medical education (CME) programs. Educated healthcare providers are more likely to recognize and report ADRs, contributing to overall drug safety.46

***Example**:* Hospitals and clinics provide training sessions for healthcare professionals on recognizing and reporting ADRs in pediatric patients. By enhancing the identification and reporting of adverse events, this education advances pharmacovigilance.47

VI. PHARMACOVIGILANCE STUDY OF AMOXICILLIN IN PNEUMONIA FOR PEDIATRIC PATIENTS:

1. Short-Course vs. Standard-Course Therapy

Study: The SAFER Randomized Clinical Trial

Details: This study aimed to determine if a shorter course of high-dose amoxicillin (5 days) was as effective as the standard 10-day course in treating community-acquired pneumonia in children aged 6 months to 10 years. The trial found that the shorter course was not inferior to the standard course in terms of clinical outcomes. This suggests that shorter antibiotic courses can be effective, potentially reducing the risk of antibiotic resistance and minimizing adverse effects. For example, fewer days of medication can lead to fewer gastrointestinal disturbances like diarrhoea and nausea.48

2. Dose and Treatment Duration

Study: The CAP-IT Randomized Clinical Trial

Details: This trial investigated the efficacy of different doses and treatment durations of amoxicillin in children with community-acquired pneumonia. The study compared lower doses (35-50 mg/kg per day) and shorter durations (3-5 days) with higher doses (70-90 mg/kg per day) and longer durations (7-10 days). The findings indicated that the lower doses and shorter durations were just as effective as the higher doses and longer durations. This is significant because it suggests that effective treatment can be achieved with less medication, reducing the risk of side effects and the burden on patients and caregivers.

3. Comparative Efficacy

Study: Comparative study of amoxicillin and penicillin V

Details: This study compared the efficacy of amoxicillin with penicillin V in treating pediatric pneumonia. The results showed that amoxicillin was more effective, with better clinical outcomes and no increase in severe complications. This supports the recommendation of amoxicillin as a first-line treatment for pediatric pneumonia. For instance, children treated with amoxicillin had faster recovery times and fewer hospital readmissions compared to those treated with penicillin V.

4. Adverse Effects and Safety Monitoring

Details: Across various studies, adverse effects of amoxicillin in treating pediatric pneumonia were monitored closely. Common side effects included gastrointestinal issues such as diarrhea and nausea, as well as allergic reactions like rashes. Severe adverse effects were rare. For example, in the CAP-IT trial, the incidence of severe allergic reactions was very low, and most side effects were manageable with supportive care. Continuous monitoring and reporting of these adverse effects are crucial for ensuring the safety of pediatric patients.49,50,51,52

VI) Current Challenges

- Limited Data: Pediatric populations are often underrepresented in clinical trials, leading to a lack of comprehensive safety data for many medications1.
- Differences in Drug Response: Children's metabolic and physiological differences from adults can lead to different drug responses and adverse effects.
- Reporting Gaps: Adverse drug reactions (ADRs) in children are often underreported, making it difficult to identify and address safety issues promptly.

VII). Technological Advancements

- Artificial Intelligence (AD): AI and machine learning are being increasingly used to analyze large volumes of data, such as electronic health records and spontaneous reporting databases, to identify potential safety signals

- Natural Language Processing (NLP): NLP can help in extracting relevant information from unstructured data sources like social media and patient forums, providing real-time insights into drug safety
- Data Mining Algorithms: These algorithms can detect patterns and trends in data that might indicate emerging safety issues

VIII). Regulatory Changes

- Enhanced Regulations: Regulatory bodies are considering the role of advanced technologies in PV to improve the efficiency and effectiveness of safety monitoring
- Global Collaboration: Increased collaboration between regulatory authorities, healthcare

providers, and pharmaceutical companies can lead to better data sharing and more comprehensive safety monitoring.

IX) . FUTURE DIRECTIONS

- Real-Time Monitoring: The use of real-time monitoring systems can help in the early detection of ADRs and timely intervention.

• Patient-Centric Approaches: Engaging patients and their families in the PV process can provide valuable insights and improve reporting rates.

- Education and Training: Continuous education and training for healthcare professionals on the importance of PV and how to report ADRs can enhance the overall safety monitoring system.

CONCLUSION-

In this review, the safety profile of amoxicillin in pediatric patients with pneumonia has been extensively evaluated from a pharmacovigilance perspective. Amoxicillin remains a cornerstone antibiotic in the treatment of pediatric pneumonia due to its efficacy, broad-spectrum activity, and generally favorable safety profile. However, like all medications, its use is not without potential risks, particularly in young children.

Pharmacovigilance data reveals that amoxicillin is generally well-tolerated, with common adverse effects being mild and self-limiting, such as gastrointestinal disturbances and skin rashes. Severe reactions, such as anaphylaxis or Stevens-Johnson syndrome, though rare, highlight the importance of vigilant monitoring, especially in patients with known allergies or a history of hypersensitivity to penicillin-based drugs.

The findings underscore the necessity for continuous surveillance and reporting of adverse drug reactions (ADRs) in pediatric populations. By enhancing pharmacovigilance systems and encouraging healthcare professionals and caregivers to report any adverse events, it is possible to better understand the safety of amoxicillin and optimize its use in pediatric

pneumonia treatment. Furthermore, individualized treatment plans, considering underlying health conditions and risk factors, are essential for minimizing adverse outcomes. Ultimately, while amoxicillin remains a highly effective and safe option for the management of pediatric pneumonia, ongoing pharmacovigilance efforts are crucial to ensure that any emerging safety concerns are promptly identified and addressed, maintaining a balance between therapeutic efficacy and patient safety.

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