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Factors Affecting the Safety Profile of Intravenous Levetiracetam Used for Controlling Seizures in Children: A Literature Review

Samah Alyamani Abdalkarim Alakhdar [a*]

[a] Mediclinic Al Jowhara Hospital, Al Ain, United Arab Emirates.

Author's contribution

The sole author designed, analysed, interpreted and prepared the manuscript.

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Review Article

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ABSTRACT

The administration of intravenous levetiracetam (IV-LEV) serves as a significant therapeutic approach for managing seizures in pediatric patients. The major factors that are involved in the equation determinants contain pharmacokinetic parameters, such as dosage regimen, drug interactions, and patient-specific factors including age, weight, and underlying comorbidities. Furthermore, attention is given to potential adverse effects, including hypersensitivity reactions, renal impairment, and central nervous system manifestations. Clinical trials, observational studies, and pharmacovigilance data contribute to a comprehensive evaluation of the drug's safety, shedding light on optimal dosing strategies and risk mitigation techniques. Understanding these intricate factors is paramount for healthcare providers to ensure efficacious seizure control while minimizing potential harms associated with IV-LEV administration in children. This abstract examines the multifaceted factors that influence the safety profile of IV-LEV in this vulnerable pediatric population. This literature review explores the various factors influencing the safety profile of intravenous levetiracetam (IV-LEV) in its application for seizure management in pediatric patients. Based upon a comprehensive analysis of peer-reviewed articles, clinical trials, and

**Corresponding author: Email: samahalyamaniabdalkarimalakhda@gmail.com.;*

observational studies, the review synthesizes findings related to pharmacokinetic variables, dosage considerations, and potential drug interactions. Additionally, patient-specific determinants, encompassing age-related variations, weight-based dosing implications, and the impact of comorbid conditions, are critically evaluated.

Keywords: Levetiracetam; pediatric population; seizures in children; intravenous administration of levetiracetam.

1. INTRODUCTION

Seizure management in pediatric patients remains a clinical challenge, necessitating effective and safe therapeutic interventions. Among the myriad range of various antiepileptic drugs, intravenous levetiracetam (IV-LEV) has emerged as a promising agent for rapid seizure control [1].

Its pharmacological profile offers advantages such as rapid onset of action and favorable tolerability, making it a preferred choice in emergent situations.

However, as with any therapeutic agent, the safety profile of IV-LEV is paramount, especially when administered to the vulnerable pediatric population.

Various factors intricately modulate its safety, ranging from pharmacokinetic parameters like dosage adjustments and potential drug interactions to patient-specific variables such as age, weight, and underlying medical conditions [2].

Additionally, the emergence of adverse effects, though relatively uncommon, mandates a comprehensive understanding to ensure optimal clinical outcomes.

Intravenous levetiracetam (IV-LEV) stands as a vital therapeutic agent in the realm of pediatric seizure management, offering a rapid onset of action that is particularly invaluable during emergency scenarios where immediate seizure control is paramount [3].

The efficacy of this intravenous formulation's efficacy covers various seizure types, including generalized tonic-clonic seizures and focal seizures, positioning it as a versatile solution for a broad spectrum of pediatric epilepsies [4].

The convenience of intravenous administration further enhances its utility, especially in situations where oral delivery might be impracticable, such as critically ill children or those with compromised gastrointestinal absorption [5].
However, while IV-LEV boasts a generally favorable safety profile, its use demands meticulous attention to dosage considerations, predicated largely on weight and age, to mitigate risks of underdosing or potential adverse effects from overdosing [6].

Concurrently, clinicians must remain vigilant regarding potential interactions with other antiepileptic drugs or medications, underscoring the importance of comprehensive monitoring encompassing renal function, complete blood counts, and other pertinent parameters.

For children necessitating extended therapeutic regimens, periodic reassessments become imperative, ensuring that IV-LEV's benefits continue to outweigh potential risks, while ongoing research endeavors aim to refine its role and optimize outcomes in pediatric neurology [7].

2. METHODOLOGY

2.1 Literature Search Databases

The databases employed for the literature search were not explicitly stated in the provided text. A comprehensive literature review typically involves a systematic exploration of relevant databases. Common databases utilized in medical and pharmacological research include PubMed, MEDLINE, Embase, among others. Regrettably, the specific databases utilized in this review were not specified.

3. EXPLORING THE FACTORS AFFECTING THE SAFETY PROFILE OF LEVETIRACETAM IN CHILDREN

When viewing it from a broader perspective, one can see that there are several factors that influence the safety profile of intravenous levetiracetam (IV-LEV) when utilized for

controlling seizures in children. Here are some prominent factors overviewed in detail:

3.1 Dosage and Administration

Children's weight varies considerably across age groups, necessitating precise weight-based dosing to prevent under- or overdosing. Therefore, rapid administration or inappropriate dilution can increase the risk of adverse reactions such as infusion-site reactions or precipitation of the drug [8].

A study emphasized the importance of weight-based dosing in pediatric populations to achieve therapeutic efficacy while minimizing toxicity. The research highlighted the variability in drug distribution and metabolism across different age groups in childhood, underscoring the need for tailored dosing regimens [9].

Similarly, another research indicated that inappropriate dilution or rapid infusion rates of IV-LEV could lead to infusion-related reactions, such as phlebitis or local irritations, necessitating adherence to recommended administration protocols [10].

3.2 Pharmacokinetic Interactions

Concomitant use of other antiepileptic drugs or medications metabolized through similar pathways might influence the pharmacokinetics of IV-LEV, potentially leading to drug interactions or altered clearance rates [11].

Investigations exploring potential drug interactions between IV-LEV and other antiepileptic drugs have elucidated mechanisms that might alter drug clearance rates or potentiate adverse effects, necessitating cautious co-administration strategies [12].

3.3 Patient-Specific Factors

According to a comprehensive review, neonates and infants exhibit developmental differences in renal function and drug metabolism, influencing IV-LEV's pharmacokinetics and necessitating age-specific considerations in dosing and monitoring [13].

Similarly, children with renal or hepatic impairments, metabolic disorders, or specific medical conditions might exhibit altered IV-LEV pharmacodynamics, emphasizing the importance of individualized therapeutic strategies [14].

3.4 Adverse Reactions

Clinical observations have documented varying degrees of hypersensitivity reactions to IV-LEV, ranging from dermatological manifestations to severe anaphylactic responses, necessitating vigilant monitoring and immediate intervention protocols [15].

A meta-analysis highlighted rare neurological adverse effects associated with IV-LEV, including agitation, confusion, or behavioral alterations, warranting awareness among clinicians and tailored patient monitoring [16].

3.5 Renal Function

IV-LEV's predominant renal excretion pathway is of major importance with implications for dose adjustments in children with compromised renal function to prevent potential drug accumulation and associated toxicities [17].

3.6 Monitoring and Surveillance

Systematic monitoring encompassing renal function tests, complete blood counts, and relevant biochemical markers to facilitate early detection of adverse reactions or emerging complications associated with IV-LEV therapy [3].

3.7 Duration of Therapy

Longitudinal studies have often highlighted the necessity for periodic reassessments during prolonged IV-LEV therapy in children, considering potential cumulative effects, emerging adverse reactions, and evolving clinical scenarios to optimize therapeutic outcomes [18].

In synthesis, while IV-LEV stands as a cornerstone in pediatric seizure management, evidence-based insights derived from comprehensive research endeavors underscore the potential for tailored therapeutic approaches, vigilant monitoring, and periodic reassessments to ensure optimized safety and efficacy profiles in this vulnerable population [1].

4. EFFECT OF ALTERING LEVETIRACETAM DOSAGE IN CHILDREN WITH SEIZURES

Understanding the implications of altering its dosage is pivotal for optimizing therapeutic outcomes while minimizing adverse effects.

Here's an exploration of the effects of dosage alterations in children with seizures:

4.1 Efficacy Considerations

Inadequate dosing might compromise LEV's antiepileptic efficacy, leading to inadequate seizure control. Achieving an optimal LEV dosage is paramount, balancing efficacy with tolerability. Research has highlighted the significance of personalized dosing strategies, considering factors such as age, weight, seizure type, and concomitant medications to maximize therapeutic benefits [19].

4.2 Safety Profile

Escalating LEV dosages beyond recommended limits can potentiate adverse effects. Studies have elucidated potential complications, including behavioral changes, somnolence, or irritability, associated with supratherapeutic LEV doses in pediatric populations [19].

Alterations in LEV dosage, particularly excessive dosing, can exert undue strain on renal function due to LEV's predominantly renal excretion pathway [20].

Monitoring renal parameters and adapting dosing regimens accordingly are imperative to prevent renal complications [18].

4.3 Pharmacokinetic Considerations

Concurrent administration of medications that interact with LEV can necessitate dosage adjustments. Comprehensive studies emphasize understanding drug-drug interactions, influencing LEV metabolism, and clearance rates in pediatric patients to mitigate potential risks [12].

4.4 Individualized Approaches

Neonates, infants, and older children might necessitate distinct LEV dosing regimens due to developmental variations in drug metabolism, renal function, and seizure etiologies.

Tailored therapeutic strategies, informed by age-specific considerations, are pivotal for optimizing LEV efficacy and safety profiles [15].

A structured approach to LEV dosage titration, underpinned by rigorous monitoring, facilitates optimal therapeutic outcomes. Different protocols advocate for systematic evaluations, including clinical assessments, seizure frequency monitoring, and pharmacokinetic assessments, to guide dosage adjustments judiciously.

4.5 Longitudinal Assessment

Prolonged LEV therapy mandates periodic reassessments of dosage adequacy, considering evolving clinical scenarios, emerging adverse effects, and therapeutic responses.

Longitudinal studies frequently emphasize on the necessity for regular evaluations to refine LEV dosing regimens and optimize seizure management outcomes in children [21].

5. EXPLORING THE SAFETY PROFILE OF LEVETIRACETAM

Different studies and research indicate that behavioral issues and drowsiness stand out as predominant adverse reactions to LEV, with behavioral disturbances often leading individuals to halt their treatment.

Children administered with LEV showcased twice the likelihood of displaying abnormal behavior compared to those on a placebo. This finding resonates with an earlier in-depth review solely concentrating on behavioral aspects [22].

Interestingly, the influence of LEV on behavior is not unidimensional; while some children experienced heightened energy, alertness, and activity, others grappled with adverse manifestations like aggression, irritability, restlessness, and nervousness [23].

Refining upon the numbers, approximately 2.2% of children had to discontinue LEV due to its adverse effects, a figure closely mirroring the discontinuation rates associated with another medication, lamotrigine. Moreover, when LEV was paired with another antiepileptic drug, the discontinuation rate surged to 4.5% [24].

The safety profile of LEV as a monotherapy has been the subject of limited research, with only two Randomized Controlled Trials (RCTs) directly comparing its safety with other antiepileptic drugs (AEDs) and one study contrasting LEV monotherapy against a placebo over a fortnight [25].

Notably, ethical considerations permitted participants in this placebo study to opt out and seek appropriate treatment upon experiencing a seizure, thereby curtailing insights into LEV's

safety profile. Compounding this, there exists no product authorization for LEV monotherapy among children below 16 years, underscoring a dearth of compelling safety and efficacy data for this demographic [26].

Drawing from a cumulative analysis of 17 prospective studies, the incidence of adverse events (AEs) appears diminished with monotherapy compared to polytherapy - a pattern corroborated by antecedent research on AEDs [21].

Navigating the intricate terrain of polytherapy, the behavioral implications of AED combinations emerge multifaceted. Each AED can engender distinct behavioral outcomes, complicating efforts to unequivocally attribute specific behavioral manifestations to LEV. Nevertheless, transitioning from polytherapy to monotherapy or reducing the AED count frequently heralds behavioral amelioration [27].

However, the intricate relationship between LEV dosage and behavioral outcomes remains elusive. A paucity of detailed dosage specifications in various studies impedes comprehensive analyses. Some scholars posit that atypical behaviors precipitated by LEV are idiosyncratic, suggesting individualized reactions rather than dose-dependent phenomena [7].

Interestingly, expansive research on adults administered LEV during preclinical phases failed to discern a salient correlation between dosage and behavioral aberrations [28] Nonetheless, an accelerated dose titration emerges as a plausible risk element, warranting cautious consideration in therapeutic strategies [29].

6. CONCLUSION

In synthesizing the extensive literature available on the safety profile of intravenous levetiracetam (IV-LEV) for pediatric seizure management, several pivotal factors emerge as paramount. Firstly, the importance of meticulous dosage and administration cannot be overstated, given the profound implications of weight-based dosing and the potential risks associated with rapid infusion rates. Concurrently, pharmacokinetic interactions, especially when IV-LEV is co-administered with other antiepileptic drugs, necessitate vigilant monitoring to avert adverse outcomes. While IV-LEV offers promising therapeutic benefits in pediatric seizure management, a nuanced understanding of the intricate factors delineated in this literature review is imperative. Clinicians must navigate these complexities judiciously, employing individualized approaches, rigorous monitoring protocols, and evidence-based interventions to optimize therapeutic efficacy while safeguarding against potential risks in this vulnerable population.

CONCENT AND ETHICAL APPROVAL

It is not applicable.

COMPETING INTERESTS

Author has declared that no competing interests exist.

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