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Review Article

Clinical pharmacology and adverse effects of Chloramphenicol

AL Prasanna Reddy Syamala[1], Mohammed Sheeba Kauser[1], P Navya[1], P Anusha[1]

[1]Dept. of Pharmacy, Sree Venkateshwara Pharmacy College, Nellore, Andhra Pradesh, India

Abstract

Introduction: Chloramphenicol is a broad-spectrum antibiotic with a well-documented history of efficacy against a variety of bacterial infections. Despite its clinical utility, the use of chloramphenicol has significantly declined due to serious and sometimes fatal adverse effects, most notably aplastic anaemia and gray baby syndrome. This systematic review aims to comprehensively evaluate the current evidence on the clinical pharmacology of chloramphenicol, with a particular focus on its adverse effect profile, risk factors, and mechanisms of toxicity.

Materials and Methods: A systematic search was conducted using PubMed, Scopus, Web of Science, and Cochrane Library databases for studies published between 2000 and 2024. Eligible studies included clinical trials, observational studies, case reports, and pharmacovigilance data that reported on the pharmacokinetics, pharmacodynamics, and adverse effects of chloramphenicol in human subjects. Data were extracted and analysed according to PRISMA guidelines.

Results: A total of 56 studies met the inclusion criteria. Chloramphenicol exhibits excellent tissue penetration and acts by inhibiting bacterial protein synthesis via binding to the 50S ribosomal subunit. However, its metabolism via hepatic glucuronidation and subsequent renal excretion can be impaired in neonates and patients with hepatic dysfunction, increasing the risk of toxicity. The review identified haematological toxicity as the most significant adverse effect, including dose-dependent reversible bone marrow suppression and idiosyncratic aplastic anaemia. Risk factors included prolonged use, high plasma concentrations, and genetic predisposition. Other notable effects included gastrointestinal disturbances, neurotoxicity, and hypersensitivity reactions.

Conclusion: While chloramphenicol remains an effective antimicrobial agent, its use is limited by a narrow therapeutic index and a serious toxicity profile. Clinicians must weigh the benefits against potential risks, particularly in vulnerable populations. Therapeutic drug monitoring and genetic screening may improve safety outcomes. Further research is needed to better understand the mechanisms underlying idiosyncratic toxicities and to identify safer analogues or usage strategies.

Keywords: Chloramphenicol; Clinical pharmacology; Adverse effects; Aplastic anaemia; Gray baby syndrome; Antimicrobial toxicity; Drug safety

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1. Introduction

Chloramphenicol is a broad-spectrum antibiotic first introduced in the late 1940s, notable for its rapid clinical adoption and early success in treating life-threatening infections such as typhoid fever, meningitis, and rickettsia diseases.[1] Its ability to inhibit bacterial protein synthesis by binding to the 50S ribosomal subunit positioned it as a potent agent against both Gram-positive and Gram-negative organisms. Despite its initial promise, the enthusiasm for chloramphenicol waned with the emergence of severe, and sometimes fatal, adverse effects, most notably aplastic anaemia and gray baby syndrome.[2]

Unlike many other antibiotics, chloramphenicol's adverse effects are not limited to gastrointestinal discomfort or hypersensitivity reactions; its hematologic toxicity, particularly the idiosyncratic and unpredictable development of aplastic anaemia, has led to significant caution in its clinical use.[3] This toxicity risk, coupled with the development of safer alternatives, has largely relegated chloramphenicol to a secondary or restricted role in modern antimicrobial therapy, particularly in high-income countries. However, in resource-limited settings where access to newer antibiotics may be restricted, chloramphenicol continues to be used due to its affordability and effectiveness, raising continued concerns about its risk–benefit profile.[4]

From a pharmacological standpoint, chloramphenicol presents unique challenges. It undergoes hepatic metabolism via glucuronidation and is excreted primarily through the kidneys.[5] In neonates, particularly premature infants with

*Corresponding author: Mohammed Sheeba Kauser
Email: Sheebaishaq.doc@gmail.com

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underdeveloped liver enzyme systems, impaired metabolism leads to drug accumulation and the potentially fatal gray baby syndrome. In adults, factors such as prolonged use, high systemic concentrations, and genetic susceptibility contribute to its toxic profile, especially with respect to bone marrow suppression.[6]

Given these concerns, a comprehensive and up-to-date evaluation of the clinical pharmacology and toxicity of chloramphenicol is essential.[7] While much of the early literature on the drug's adverse effects is historical, there remains a need to systematically assess contemporary evidence—particularly from case reports, pharmacovigilance data, and observational studies—that could inform safer prescribing practices and identify populations at greater risk.[8]

This systematic review aims to synthesize current knowledge on the pharmacokinetics, pharmacodynamics, and adverse effects of chloramphenicol, with an emphasis on haematological toxicity. By examining both the historical and recent clinical data, we seek to clarify the mechanisms underlying its toxicities, identify risk factors for adverse outcomes, and evaluate strategies for safer use where chloramphenicol remains a therapeutic necessity.[9]

2. Materials and Methods

2.1. Study design

This study was designed as a systematic review to evaluate and synthesize existing evidence on the clinical pharmacology and adverse effects of chloramphenicol. The review followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines to ensure methodological rigor and transparency.

2.2. Data sources and search strategy

A comprehensive literature search was conducted in the following electronic databases such as PubMed, Scopus, Web of Science and Cochrane Library.

The search included articles published from January 2000 to March 2024. The search terms used were a combination of Medical subject headings (MeSH) and keywords, including: "Chloramphenicol," "clinical pharmacology," "adverse effects," "toxicity," "aplastic anaemia," "gray baby syndrome," "drug safety," "haematological toxicity," and "pharmacokinetics."

Boolean operators (AND, OR) were used to combine terms appropriately. Manual screening of reference lists from selected articles was also performed to identify additional relevant studies.

2.3. Inclusion criteria

In this study original research articles, clinical trials, observational studies, case series, and case reports, articles published in English, studies involving human subjects (adults and children) and studies reporting on pharmacokinetics, pharmacodynamics, or adverse effects of chloramphenicol was included.

2.4. Exclusion criteria

In this study In vitro or animal-only studies, Reviews, editorials, and commentaries (though reference lists were screened) and Studies not reporting clinical outcomes or pharmacological data related to chloramphenicol was excluded.

2.5. Study selection

Two independent reviewers screened the titles and abstracts for relevance. Full-text articles were obtained for potentially eligible studies. Discrepancies between reviewers were resolved through discussion or consultation with a third reviewer.

2.6. Data extraction and management

Data were extracted using a standardized form, which included the following parameters:

1. Study design and location
2. Patient population and demographics
3. Chloramphenicol dosage and route of administration
4. Reported pharmacokinetic/pharmacodynamics data
5. Type, frequency, and severity of adverse effects
6. Risk factors associated with toxicity
7. Clinical outcomes and recommendations

Data were entered into Microsoft Excel for organization and further analysis.

2.7. Quality assessment

The methodological quality of the included studies was assessed using Newcastle-Ottawa Scale (NOS) for observational studies, Joanna Briggs Institute (JBI) critical appraisal checklists for case reports and case series and Cochrane Risk of Bias Tool for randomized controlled trials. Each study was rated as low, moderate, or high quality based on bias, completeness, and clarity.

2.8. Data synthesis

A qualitative synthesis of findings was performed due to heterogeneity in study design, populations, and outcome measures. Where applicable, data were grouped by adverse effect type (e.g., haematological, hepatic, neurologic), age group, and dosage. Quantitative pooling or meta-analysis was not performed due to the variability in data formats and outcome measures.

3. Results

3.1. Study selection

A total of 612 articles were identified through database searches, with an additional 23 articles retrieved through manual searches of bibliographies. After removing 98

duplicates, 537 unique articles were screened based on titles and abstracts. Of these, 88 full-text articles were assessed for eligibility, and 56 studies met the inclusion criteria and were included in the final qualitative synthesis. Reasons for exclusion included lack of pharmacological or clinical toxicity data (n=12), non-human studies (n=10), and insufficient methodological quality (n=10).

3.2. Characteristics of included studies

The 56 included studies comprised 12 clinical trials, 18 observational studies, 14 case reports and 12 pharmacokinetic/pharmacodynamics (PK/PD) studies. Geographically, studies were distributed across Asia (n=21), Europe (n=14), North America (n=10), and other regions (n=11). Patient populations ranged from neonates and children to adults and elderly individuals, covering various indications including typhoid fever, meningitis, and rickettsia infections.

3.3. Pharmacokinetics and pharmacodynamics

Chloramphenicol demonstrated high oral bioavailability (~90%), extensive tissue distribution, including cerebrospinal fluid (CSF), hepatic metabolism via glucuronidation, renal excretion of inactive metabolites and PK variations were notable in neonates and patients with hepatic dysfunction, both of whom exhibited reduced clearance and increased plasma concentrations. Several studies emphasized the importance of therapeutic drug monitoring to avoid toxicity in these populations.

3.4. Adverse effects

Adverse effects were reported across a wide range of studies, categorized into the following:

1. Haematological Toxicity: Aplastic anaemia (idiosyncratic, rare but often fatal): reported in 9 case reports and 4 observational studies and Dose-related reversible bone marrow suppression: observed in 15 studies, usually reversible upon discontinuation

2. Neonatal Toxicity (Gray Baby Syndrome): Reported in 6 case series and 5 pharmacological studies and Caused by underdeveloped liver enzyme activity leading to drug accumulation and cardiovascular collapse

3. Hepatotoxicity and Neurotoxicity: Mild elevations in liver enzymes noted in 6 studies and Neurotoxicity (e.g., confusion, optic neuritis) was rare but observed in 3 reports

4. Hypersensitivity Reactions: Rash, fever, and angioedema were reported in isolated cases

Risk factors for adverse effects included are Prolonged therapy (>7 days), High plasma levels (>25 mcg/mL), Genetic predisposition (e.g., poor metabolizers) and Co-administration with other bone marrow-suppressing agents

In quality assessment Of the 56 studies: 42 were rated as high quality, 10 as moderate quality, 4 as low quality and The most common limitations were small sample sizes, retrospective designs, and lack of control groups.

4. Discussion

This systematic review highlights the dual nature of chloramphenicol as both a highly effective antimicrobial agent and a drug with significant toxicity risks. Despite its broad-spectrum activity and excellent tissue penetration—including effective cerebrospinal fluid levels—its use has dramatically declined in many parts of the world due to concerns over rare but severe adverse effects.[10-13] Nevertheless, in resource-limited settings where newer antibiotics are often unavailable or unaffordable, chloramphenicol continues to play a critical therapeutic role. This underscores the need for a nuanced understanding of its pharmacological properties and toxicity profile.[14-15]

4.1. Clinical pharmacology

The pharmacokinetic properties of chloramphenicol, including high oral bioavailability and wide tissue distribution, make it effective for treating serious infections such as meningitis and typhoid fever.[16] However, its metabolism via hepatic glucuronidation and renal excretion of inactive metabolites makes certain populations particularly neonates, elderly patients, and those with hepatic dysfunction more susceptible to drug accumulation and toxicity. The evidence suggests that therapeutic drug monitoring, though not widely practiced, could significantly reduce the incidence of adverse outcomes, especially in settings where pharmacokinetic variability is common.[17-19]

4.2. Adverse effects

Hematologic toxicity remains the most concerning and well-documented adverse effect of chloramphenicol.[20] Reversible, dose-dependent bone marrow suppression is relatively common but manageable with drug discontinuation. However, the idiosyncratic development of aplastic anemia, which is often fatal and unpredictable, has led to widespread restrictions on the drug's use. The mechanism behind this effect is not fully understood, although genetic susceptibility and immune-mediated responses are suspected contributors.[21]

Gray baby syndrome, once a frequent and devastating complication in neonatal use, is now largely preventable through improved understanding of neonatal pharmacokinetics and avoidance of use in this population. Nevertheless, the syndrome continues to be reported sporadically in under-resourced settings, highlighting the need for better clinical guidelines and awareness.

Liver enzyme abnormalities and rare neurotoxic effects such as optic neuritis were noted in several studies but appear to be infrequent and often reversible. Hypersensitivity

reactions, while typically mild, further complicate chloramphenicol's safety profile.

5. Risk-Benefit Considerations

Given the severity of its adverse effects, chloramphenicol should not be a first-line agent in areas where safer alternatives are available. However, it remains a viable option in specific clinical situations—such as life-threatening infections with limited treatment options or in settings constrained by cost or availability. In these contexts, the benefits of chloramphenicol may outweigh its risks, provided that appropriate dosing, monitoring, and patient selection are prioritized.[22]

6. Limitations of the Review

The findings of this review are subject to several limitations. First, there is a reliance on observational studies and case reports, which are inherently prone to bias and lack the methodological rigor of randomized controlled trials. Second, heterogeneity in study designs and outcome measures limited the ability to perform meta-analyses. Finally, the quality and availability of data from low-income countries—where chloramphenicol is most commonly used—were variable, potentially underestimating or overestimating both efficacy and toxicity rates.

7. Future Directions

Further research is needed to elucidate the mechanisms behind idiosyncratic aplastic anemia and to identify genetic or biochemical markers that may predict susceptibility. Development of safer chloramphenicol analogues or formulations with reduced toxicity potential is another area worth exploring. Additionally, the implementation of standardized therapeutic drug monitoring protocols in clinical settings could mitigate adverse effects and allow for safer use of the drug in high-risk populations.

8. Conclusion

Chloramphenicol remains a historically significant and pharmacologically potent antibiotic with broad-spectrum efficacy. However, its clinical use has been overshadowed by the risk of serious, and in some cases life-threatening, adverse effects—most notably aplastic anaemia and gray baby syndrome. This systematic review underscores the importance of cautious and judicious use of chloramphenicol, particularly in vulnerable populations such as neonates, the elderly, and patients with impaired liver function.

While reversible bone marrow suppression is relatively predictable and manageable, the idiosyncratic nature of aplastic anaemia highlights the urgent need for better risk stratification and monitoring strategies. In resource-limited settings, where therapeutic alternatives may be scarce, chloramphenicol continues to serve as an essential treatment option. Its use in such contexts should be guided by strict clinical protocols, appropriate dosing, and, where possible, therapeutic drug monitoring.

9. Conflict of Interest

Nil.

10. Source of Funding

Nil.

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