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Nitrofurantoin as an intracanal medicament in endodontic Therapy -A Narrative Review

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Abstract

Nitrofurantoin has been one of the most effective and popular antibiotics used in medicine for decades, it's mainly used to treat urinary tract infections. Over the past few years, its clinical significance in the field of dentistry has become a boon. It is widely used as an intracanal medicament in treating Dental abscess, cellulitis etc. It is seen that nitrofurantoin is highly effective against Enterococcus faecalis which is the most common bacterial microorganism encountered in root canals. This article aims to review the beneficial aspects of nitrofurantoin in the field of pediatric dentistry.

Keywords- Nitrofurantoin, Pulpectomy, Intracanal medicament, Enterococcus faecalis, Postoperative pain

Introduction

Infections of the pulp, periapical, and/or intra-radicular tissues may result from dental caries, a progressive disease of the dental hard tissue if left untreated in its early stages.[1] A persistent peri-radicular infection following root canal treatment can result from various factors, including intra-radicular infections, extra-radicular infections, foreign body reactions, and the presence of cysts. These infections occur due to bacterial invasion of the root canal, ultimately leading to reinfection and the failure of root canal treatment.[2] Enterococcus faecalis (EF), a resilient facultative bacterium, is the most prevalent and resistant microorganism responsible for persistent peri- radicular lesions and, ultimately, the failure of endodontic procedures. Enterococcus faecalis is detected in root canal failures in a range of 24% to 70% through culturing methods and 67% to 77% through molecular methods. In some studies, it constitutes a significant portion, approximately 90%. [3]This microorganism possesses several distinctive characteristics that facilitate its survival within the root canal and its capacity to induce reinfection. These characteristics include the ability to endure periods of nutrient scarcity, penetrate deeply into dentinal tubules, exhibit resistance to antimicrobial agents, and adapt to changing environmental conditions. [2]

The first step in eliminating intracanal bacterial invasion is chemomechanical root canal preparation. This process reduces endodontic infection but doesn't ensure complete disinfection due to microorganisms hiding within the complex root canal anatomy. To achieve comprehensive disinfection, intracanal medicaments are crucial supplementary measures.[4]

Local intracanal medicaments have been a longstanding choice in endodontics, offering a more effective approach than systemic antibiotics. They are preferred due to their ability to prevent the potential adverse side effects associated with systemic antibiotic use.[5] Calcium hydroxide (CH) is commonly employed as an intracanal medicament in teeth with necrotic pulp. However, its effectiveness against certain bacterial species, particularly Enterococcus faecalis, is known to be limited. In response to this challenge, a combination of

treatment options has been explored for primary necrotic pulp canals. These options include Triple antibiotic paste (TAP) and chlorhexidine 2% (CHX), either used individually or in combination with chlorhexidine (CH).[1] Triple antibiotic paste (TAP) is a combination of three antibiotics—metronidazole, ciprofloxacin, and minocycline—used as an intracanal medicament due to its strong antimicrobial properties However, there's an ongoing debate among studies regarding its effectiveness in completely eradicating Enterococcus faecalis (EF) from the root canal system This controversy could be attributed to the emergence of bacterial resistance. Another drawback of TAP is the potential for crown discoloration, primarily due to minocycline.[6]

In response to these challenges, a modified version of TAP called modified triple antibiotic paste (MTAP) has been developed, with minocycline replaced by clindamycin. MTAP has demonstrated effectiveness equal to that of TAP in reducing EF within the root canal system.[6] Given the limitations of TAP and its modification to MTAP, there has been a demand for a novel medicament with reduced resistance risk, comparable potency against EF, simpler preparation, cost-effectiveness, and the use of a single drug rather than a combination. To overcome this disadvantage a need for a new medicament was essential in the field of dentistry which lead to the introduction of nitrofurantoin.

Nitrofurantoin (Nit) is a synthetic nitrofuran compound with broad-spectrum antibacterial properties. It demonstrates effectiveness against a wide range of both gram-positive and gram-negative microorganisms. [8]This well-established antibacterial agent is commonly prescribed for the treatment of urinary tract infections (UTIs) and is particularly favored for its efficacy in combating infections caused by multidrug-resistant pathogens.[9]

HISTORICAL PERSPECTIVE

Nitrofurantoin, originally developed by prominent pharmacologists and researchers Dr. William L. Elion and Dr. George H. Hitchings, made its debut on the market in the early 1950s under the trade name "Furadantin." It was primarily introduced as a treatment for urinary tract infections (UTIs) caused by susceptible bacteria. The first US patent on the synthesis of nitrofurantoin was awarded in 1952 to Kenyon J. Hayes at the long-defunct Eaton Laboratories1 (Norwich, NY). The drug was introduced in 1953. In his 2015 book Basic Principles of Drug Discovery and Development, Benjamin E. Blass called nitrofurantoin “a surprisingly successful drug” because of its market longevity.[13]

Notably, in a study involving 300 isolates of Enterococcus, none exhibited resistance to Nit, including Enterococcus faecalis (EF). Several research studies have confirmed the high efficacy of Nit against EF.[10,11] Because of its high efficacy against anaerobic bacteria that are abundant in such infections, considering the prevalence of anaerobic bacteria in the root canals of individuals with irreversible pulpitis, this medication has demonstrated significant antimicrobial properties. Moreover, recent literature has suggested that Nitrofurantoin is effective in combating Enterococcus faecalis and has demonstrated pain-relieving qualities in endodontic cases, as supported by a recent study.[2,12] But there is a lack of research investigating the impact of Nitrofurantoin (Nit) as a novel intracanal medicament in the root canal system's efficacy against Enterococcus faecalis (EF) in endodontics.

In a 2021 study conducted by Abbasi H et al, it was established that Nitrofurantoin is a viable alternative to conventional intracanal medicaments for relieving immediate post-operative pain in individuals with symptomatic irreversible pulpitis, particularly when compared to calcium hydroxide and Nitrofurantoin can serve as a practical substitute for the currently established standard intracanal medicaments.[14]

NITROFURANTOIN FORMULATION

Nitrofurantoin belongs to the nitrofuran family, characterized by a furan ring (a five-membered aromatic ring with four carbon atoms and one oxygen) directly linked to a nitro group (-NO2). This synthetic compound can be prepared from 1-aminohydantoin sulfate or hydrochloride and 5-nitro-2-furaldehyde diacetate in isopropyl alcohol, as detailed in the 1987 IARC report. It is manufactured in various countries, including China, India, Italy, the Netherlands, and Spain, as documented by Chemical Information Services in 1989-90. In Sweden,

the sales of nitrofurantoin in 1988 amounted to 0.09 defined daily doses per 1000 inhabitants, as reported by Apoteksbolaget in 1988 and 1989.[15]

Notably, Nitrofurantoin is available in different pharmaceutical forms, including 50 mg and 100 mg tablets and a suspension. Tablets may contain impurities like calcium pyrophosphate, magnesium stearate, starch, and sucrose. Suspensions may include impurities such as carboxymethyl cellulose, sodium citric acid, glycerine, magnesium aluminium silicate, methylparaben, propylparaben, saccharin, sodium citrate, and sorbitol, as reported in the 1987 IARC publication.[16]

Mechanism of Action

For the antimicrobial effects of nitrofurantoin to be felt, the nitro group on the medication must be reduced by bacterial nitroreductase enzyme activity and this activity by bacterial flavoproteins modify or inactivate bacterial micro- and macromolecules.[17]

At three different points in the citric acid cycle, nitrofurantoin inhibits certain enzymes involved in the bacterial metabolism of carbohydrates, preventing the production of vital ATP. Additionally, the reactive intermediates attack/inhibit the start of ribosomal protein translation, completely halting protein synthesis. They also attach to DNA, which increases the risk of DNA damage and strand breaks.

Since the bacteria are damaged in various ways and are unable to repair the damaged processes at the same time, the reactive chemicals' low resistance rates are caused by their interference in multiple biochemical processes. This also helps explain why there aren't any instances of resistance to different antibiotic classes.

Antimicrobial Spectrum

Nitrofurantoin has the greatest effect against uropathogens and a wide and broad spectrum of action. mainly against gram-positive Staphylococcus and Enterococcus and Gram-negative bacteria such as Klebsiella and Citrobacter. It is also seen that this gram-positive E. faecalis is the main causative organism found in infected root canals.[18]

General Application

Nitrofurantoin action is against infections caused by anaerobic bacteria mainly Enterococcus Faecalis, which is found in UTI infections.

Dental Considerations

In recent years, Nitrofurantoin has a wide range of applications in the field of dentistry. Due to its action against anaerobic bacteria, it is used in conditions like -Dental Cellulitis, Abscess, and Intracanal Medicament in infected root canals.

An experimental study done by Alrahman et al in the year 2020 showed the biocompatibility action of nitrofurantoin when used in rats and its effects were found to be equal to the routinely used mixed triple antibiotic paste.[19]

In a 2021 study conducted by Abbasi H et al, it was established that Nitrofurantoin is a viable alternative to conventional intracanal medicaments for relieving immediate postoperative pain in individuals with symptomatic irreversible pulpitis

An in-vitro study done in the year 2022 by Mann, N. S. et al, showed the effectiveness of nitrofurantoin against Enterococcus Faecalis[20]

Administration

Nitrofurantoin in the powdered form is mixed and then normal saline was mixed in this powder (liquid: powder 1ml:100mg) to prepare 100mg/ml Nitrofurantoin paste. [21]

Adverse Effect

Nitrofurantoin is, overall, a relatively safe drug. The overall experience after more than three decades of extensive use shows a very low reported side-effect incidence of less than 0.001 per cent based on total courses of therapy and there is no reported side effect of nitrofurantoin in its application in dentistry.

Conclusion

The resistant microbes mainly Enterococcus faecalis are associated with the root canal, most of which showed moderate to high resistance against the antibacterial agents used, viz clindamycin, doxycycline, and metronidazole. Due to the high level of microbial resistants newer drugs are advocated.

In that aspect Nitrofurantoin has better efficacy in treating Enterrococcus Faecalis, However, further studies need to be advocated to determine their efficacy with a few modifications like altering drug delivery modes or combining to target maximum pathogenic microbes and reducing catastrophic therapeutic failures.

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