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A Brief Report on the Safety and Efficacy of Gentian Violet for Infant Oropharyngeal Candidiasis (OPC) and Maternal Nipple Candidiasis

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Abstract

Gentian violet dye is no longer commonly used for infant oropharyngeal candidiasis (OPC) and maternal nipple candidiasis, largely due to safety concerns, the emergence of modern treatment options, and lack of clarity on dosing. Current treatments for candidiasis include nystatin, azoles such as ketoconazole and fluconazole, and amphotericin B. However, OPC may resist treatment, and mothers may prefer gentian violet as an alternative OTC product. This literature review aims to assess the safety and efficacy of gentian violet in treating OPC and nipple candidiasis. Two search strings in Embase yielded 22 primary research articles, case reports, and commentaries. In terms of efficacy, gentian violet is as effective as standard of care treatments, and functions as a fungicidal agent against *Candida albicans* through biofilm manipulation. Safety concerns include skin and mucosal membrane irritation, airway obstruction, and, most concerning to regulatory agencies, animal carcinogenicity. However, the literature found that there was great variation in the dose and strength of gentian violet applied. Case reports with adverse events usually used high strengths of gentian violet applied more frequently than recommended. A lower strength of gentian violet solution applied as needed is less likely to result in adverse events. Patients may self-select higher strengths of gentian violet or apply more frequently than recommended. If recommended for treatment-resistant OPC and nipple candidiasis, counseling should accompany OTC use of gentian violet.

Significance: Gentian violet is a historical treatment for infant OPC and nipple candidiasis that was popular in the 20th century. It was self-administered by mothers in strengths ranging from 0.5 to 3%. There is currently no consensus on the most effective treatment for OPC and nipple candidiasis. Current treatment options include amphotericin B, clotrimazole, fluconazole, flucytosine, itraconazole, ketoconazole, miconazole, and nystatin. Gentian violet is now readily available for consumer access over the Internet, and self-treatment with herbals has seen a resurgence. It is crucial that gentian violet is used with considerations for both safety and efficacy.

Keywords: Gentian violet; crystal violet; methylrosaniline chloride; oropharyngeal candidiasis; Candidiasis albicans; nipple candidiasis

Introduction

Gentian violet (GV) has a long and varied history as a medicinal agent. Historically, gentian violet has been used as an antibacterial, antifungal, and anti-candidiasis agent. Recent discoveries have found novel targets of GV, namely NADPH oxidase in mammalian cells and thioredoxin reductase 2 in bacterial, fungal, and parasitic cells. Given that gentian violet is well tolerated, effective, and inexpensive, its use in dermatology is predicted to increase [1].

Oropharyngeal candidiasis (OPC) in infants is transmitted during birth from maternal mucosa infected with *Candidiasis albicans*. Less commonly, transmission from the skin of breasts or hands can occur during breast or bottle feeding. In the United States, the peak prevalence of OPC is at four weeks old, and the incubation period ranges from four to 13 days [2]. Infants may present with refusal to feed. New mothers experience nipple candidiasis, typically characterized by bilateral inflammation and severe pain. Pain during breastfeeding, due to any number of reasons, is the leading cause for breastfeeding termination [3]. Successful recognition and treatment of OPC and nipple candidiasis may promote continued breastfeeding and contribute to both infant and maternal well-being.

Historical treatments of OPC with limited efficacy included weak formaldehyde or mercurochrome solutions. Faber and Dickey introduced methylrosaniline chloride (gentian violet 1%) in 1925 as an effective treatment in 14 patients with OPC, but the dye solution has recently fallen out of favor due to the side effects of mucosal irritation and ulceration. As a dye, gentian violet impedes efforts to visualize efficacy as it stains not only clothes, but also mucosal membranes. One benefit of the treatment is that it is not absorbed from the gastrointestinal tract, but more modern treatment modalities also include drugs with limited or no absorption, such as nystatin, amphotericin B, miconazole**,** and clotrimazole. Conversely, agents that are absorbed include flucytosine, ketoconazole, fluconazole**,** and itraconazole [2].

In addition to concerns pertaining to common side effects, gentian violet is also categorized as a carcinogen by several regulatory bodies, including Health Canada, the World Health Organization (WHO), and France's National Centre for Scientific Research (NCSR). Proposition 65 includes gentian violet in the list of chemicals known to cause cancer as of November 23, 2018. Gentian violet is also of concern in the food and cosmetics industries. The Codex Alimentarius Commission, a food safety agency established by the Food and Agriculture Organization (FAO) of the United Nations and WHO, recommends preventing exposure in the meat industry. The French Health Products Agency has prohibited gentian violet in cosmetics.

This brief report aims to evaluate the efficacy and safety of gentian violet solutions for OPC in infants and nipple candidiasis in new mothers. Safety concerns with gentian violet include common adverse effects and severe adverse effects, such as genotoxic and carcinogenic potential. Emerging regulatory data classifies gentian violet as a carcinogen. This report will explore the available data and rationale. Gentian violet will be analyzed as compared to other treatment modalities for OPC and nipple candidiasis in the clinical setting.

Methods

As of January 30, 2021, a literature search of Embase was conducted with two search strings.

Table of search strings

(('crystal violet'/exp OR 'crystal violet' OR 'gentian violet'/exp OR 'gentian violet') AND ('thrush'/exp OR thrush))
OR
(('crystal violet'/exp OR 'crystal violet' OR 'gentian violet'/exp OR 'gentian violet') AND ('nipple'/exp OR nipple))

Inclusion Criteria

Inclusion criteria included articles relating to crystal violet or gentian violet and rash, or crystal violet or gentian violet and nipples.

Exclusion Criteria

Duplicated, irrelevant, and non-English language articles were excluded. Articles were limited to those that focused on gentian violet as treatment for candidiasis as it relates to thrush or nipples in adults and children. Out of the 112 articles returned, 22 articles were extracted for data analysis by three reviewers. The articles were categorized into those discussing efficacy (7), safety (10), or both (5).

Results

Efficacy

Gentian violet has antiparasitic, antibacterial, antiviral, anti-angiogenesis, and antifungal effects, which are hypothesized to be mediated through biofilm manipulation and growth suppression [4]. Gentian violet has efficacy against *Streptococcus, Staphylococcus, methicillin-resistant Staphylococcus aureus, Pseudomonas,* and *Candida* (5. In several experiments at the microbiological level, gentian violet eradicated *Candida albicans*.

Mafojane, Shangase, and Patel [6] found that gentian violet at high concentrations killed *C. albicans,* and gentian violet at subinhibitory concentrations reduced the ability of *C. albicans* to exhibit normal adherence ability and germ tube formation. This is supported by findings from a comparison of gentian violet against tea tree oil, chlorhexidine, povidone iodine, and fluconazole. In AIDS patients, gentian violet was the most potent against 91 *Candida* isolates, with an MIC_{50} (minimum inhibitory concentration) of 0.06 μg/mL and an MIC_{90} of 0.12 μg/mL. Gentian violet was the only agent that was fungicidal (minimum fungicidal concentration = 1 μg/mL) against *C. albicans* isolates and could have a role in treating *C. albicans* resistant to fluconazole [7]. When compared to a control in a separate study, gentian violet significantly decreased *C. albicans'* biofilm mass (1.06 mg versus 2.39 mg for control, $p = 0.00040$) and thickness of *C. albicans* (22 um versus 98 um, $p = 0.008$). Two studies found gentian violet treatment to be comparable to ketoconazole and superior to nystatin in clinical treatment of oral thrush caused by *C. albicans* [4,8]. In addition, gentian violet may be considered in cases where *C. albicans* is resistant to drugs of choice.

Despite promising findings on the biological level, gentian violet's use in real-world populations may not be as clear-cut. In a randomized controlled trial of 90 HIV-positive patients with oral thrush, use of lemon juice for 11 days showed better efficacy than an aqueous gentian violet solution 0.5% for 11 days [9]. In a separate trial, gentian violet prophylaxis was useful for decreasing the prevalence of *C. albicans* in pediatric HIV/AIDS patients. However, there was higher prevalence of other Candida species that cause oral thrush, such as *C. dubliniensis, C. glabrata* and *C. tropicalis* [10].

Most of the clinical support for gentian violet use in thrush comes from case reports and commentaries. In one clinic, a registered nurse was responsible for the initial application of gentian violet in a strength of 0.5% or 1%, and patients were concurrently sent home with nystatin oral suspension (infant) and nystatin cream (mother). From there on out, the patients could choose to return to the clinic for the second application, or self-administer a second application of gentian violet, which was considered the "final" application [11]. This indicates a shorter duration of treatment than other case reports or commentaries. Barrett et al. [12] recommends an over-the-counter (OTC) gentian violet solution of 0.5% applied once a day for up to seven days. This application is to the infant's mouth and to the mother's breast. Utter's instructions are for patients to "swab all white patches with 1% gentian violet every fourth day". Utter (13) does raise several questions for the practical use of gentian violet: What is an effective but safe strength? Should a healthcare provider apply the gentian violet? To both mother and infant? How often should it be applied and for how long? Should physicians inform mothers of its OTC availability? These questions have no distinct answers in literature. In

addition, Barrett et al. [12] posits that "gentian violet can be a safe medication and may be particularly effective in cases of thrush that are resistant to nystatin treatment".

Several commentaries concede that it is actually difficult to evaluate the clinical results of gentian violet due to it staining mucosal membranes. Gentian violet is, in fact, a dye, and this can interfere with "visualization" and "clinical assessment" (2,14). The messy application of gentian violet results in staining of mouth, skin, and clothes. Staining is the most common side effect and can deter patients from using gentian violet [2,5,12,14].

Safety

Skin and mucosal membrane irritation are also common side effects, often, but not always, associated with prolonged use (>seven days) or higher concentrations (3% preparations). Specific reports of irritation include irritant contact dermatitis, oral ulceration, mucous membrane lesions, stinging, and even necrosis [4,5,12]. In one case study, an infant who received a high dose of 2% gentian violet (10 to 12 times per day for four days) presented with refusal to breastfeed and a swollen, irritated tongue [15]. In another case report, an infant prescribed 2% gentian violet dosed twice a day to oral thrush lesions for 14 days presented with tongue and oral mucosal ulcerations, in addition to inability to feed and weight loss. Utter [16] suggests that 0.25% or 0.5% gentian violet solutions might be safer and retain the same efficacy. A third case report found an infant to have "brownish patches, gelatinous-like in appearance, on the right boreal mucosa near the mandibular maxillary junction" with "similar lesions […] present on the undersurface of the tongue [17]. Finally, a startling six cases of oral ulceration occurred in six infants with oral candidiasis treated with gentian violet 0.5% or 1% twice daily [18]. It is unclear what the severity in each case was, but the side effects of mucosal irritation seem to range from self-resolving ulcers or dermatitis to severe necrosis. Irritation can extend beyond the region of the oral cavity into "glossitis, esophagitis, laryngitis, tracheitis, superficial necrosis of the glans penis, and hemorrhagic cystitis" [19]. The irritation may be so distressing that infants refuse to feed.

Infants with difficulty breastfeeding could have airway obstruction, trouble breathing, and internal irritations. Some examples of less easily visualized irritations include esophagitis, laryngitis, or pharyngitis. It especially is not advisable to apply gentian violet to infants with oral lesions or open wounds, as there have been reports of "difficulty feeding and obstructive laryngotracheitis" due to increased absorption of gentian violet [4,20]. A detailed case study of an infant treated with 1% gentian violet reports that the infant "developed cough and difficulty feeding, and had to be intubated for airway obstruction secondary to gentian violet use" [21]. Other side effects reported include epistaxis, hypothyroidism, keratoconjunctivitis, and infection after surgery [4,19].

Potential carcinogenicity based on animal studies remains the most concerning safety question for gentian violet. Studies in mice receiving oral gentian violet have found increased rates of liver and thyroid cancer [5]. In a study where 720 male and 720 female mice received lifetime doses of gentian violet at 0, 100, 300, and 600 ppm, there were dose-related trends for liver neoplasms, hepatocellular carcinomas, and sarcomas at several organ sites. The gentian violet was dosed orally through a spray method into the mouse feed. Mice received gentian violet dosed food beginning at the age of four to five weeks old to 12, 18, or 24 months of age. Females ingested 0, 500, 250-275, and 100 mg of gentian violet/ kg/ body weight/ week at each of the respective dose levels (0, 100, 300, and 600 ppm), and males ingested 0, 450-475, 225-250, and 75-100 mg gentian violet at the respective dose levels. At time of sacrifice at 24 months old, female mice exhibited liver neoplasm rates of 4%, 5%, 32%, and 75% in the 0, 100, 300, and 600 ppm trial groups. Male mice had rates of 15%, 17%, 18%, and 35% in the respective groups [22].

The correlation to human carcinogenicity has not been established but is certainly of concern to several countries and regulatory bodies, including the WHO, Health Canada, Codex Alimentarius Commission, and the California Environmental Protection Agency. France, in particular, recommends the duration of use be no more than seven days with no refills on existing prescriptions [20]. Proposition 65 from the California Environmental Protection Agency includes gentian violet in the list of chemicals known to the state to cause cancer as of November 23, 2018 [23]. The specific mechanism of action for carcinogenicity is not established. It may be due to a combination of effects, including gentian violet's genotoxic role as an electrophile that reacts with DNA and re-

sults in free radicals. Gentian violet also induces oxidative stress through the formation of reactive oxygen species [4]. Although there are no human case reports of gentian violet carcinogenicity, it is difficult to establish the causality and timeline if there are later occurrences of cancer in an infant's life. As discussed, exposure rates may vary greatly due to strength (0.25% to 3%), alcohol vs. aqueous formulations, duration of use, application technique, and the age and size of the neonate.

Discussion

Gentian violet should not be recommended for self-administered, OTC treatment of oral and nipple candidiasis without proper counseling. It is sometimes used as a second-line agent when infants are resistant to nystatin. Multiple regulatory bodies have dissuaded against the use of gentian violet for nipple candidiasis and OPC due to safety concerns, mainly in animals. Although some common adverse events may self-resolve, even the most innocuous-appearing reactions can be difficult to visualize due to the staining capacity of gentian violet. Infants are not capable of self-reporting adverse events or discomfort but can express these through refusal to breastfeed and weight loss. Gentian violet has been associated with more severe reactions, including ulcers, necrosis, and airway obstruction.

As stated previously, the regulatory concerns primarily rely on mouse mutagenicity studies. The minimum lethal dose of gentian violet for humans is 50-500 mg/kg, falling within or above the oral doses given non-naïve mice. In fact, the naïve mice who did not receive any gentian violet had neoplasm rates as high as 15%. A typical 0.5% "topical" dose of one [1] mL exposes mothers and infants topically to a dose of 5 mg (0.125 mg/kg for mothers and 1.25 mg/kg for babies).

In the 2016 Update of the Clinical Practice Guideline for the Management of Candidiasis, the Infectious Disease Society of America notes that common treatments and doses in neonates include amphotericin B deoxycholate (1 mg/kg) and fluconazole (12 mg/kg). Capspofungin (25 mg/m^2/day) and micafungin (10 mg/kg/day) are both approved for use by the Food and Drug Administration (FDA) for oral candidiasis in pediatric populations [24].

No cases of cancer, after a century of use, have definitively been linked to gentian violet, and the FDA allows the sale of gentian violet OTC. Counseling patients in proper administration of all antifungals and medication adherence is crucial to treatment success. There may be patients or healthcare providers who because of preference, easier availability, cost, or other risk-benefit factors may choose to use gentian violet. As gentian violet is applied in the office in several case reports, healthcare providers should demonstrate the application of gentian violet before patients self-administrate. Dr. Jack Newman of Mother & Child Health has provided guidelines for well-informed and proper use of gentian violet [25].

The authors accept regulatory bodies' decision in limiting the use of gentian violet but do not preclude its use when there is in-office counseling, including demonstration and initial application of gentian violet and the guidelines of Newman are utilized.

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Conflicts of Interest

Not applicable

Ethics Approval

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Consent to Participate

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Consent for Publication

The authors consent to publication of this brief report

Availability of Data and Material

The authors agree that, subject to requirements or limitations imposed by local and/or U.S. Government laws and regulations, any materials and data that are reasonably requested by others are available from a publicly accessible collection or will be made available in a timely fashion, at reasonable cost, and in limited quantities to members of the scientific community for noncommercial purposes.

The dataset associated with our work can be accessed by contacting the corresponding author at his email address.

Code Availability

Not applicable

Authors' Contributions

Three authors extracted data for the literature review.

Author Acknowledgements

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