International Journal of Medical and Pharmaceutical Case Reports
7(2): 1-6, 2016; Article no.IJMPCR.25476
ISSN: 2394-109X, NLM ID: 101648033

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N-chlorotaurine and N-bromotaurine Combination Regimen for the Cure of Valacyclovir-unresponsive Herpes Zoster Comorbidity in a Multiple Sclerosis Patient

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Authors' contributions

This work was carried out in collaboration between all authors. Author AMK provided the case and the figures, designed the study, performed the clinical application and wrote the protocol. Authors AMK and SL wrote the first draft of the manuscript. Authors JM and MN co-designed the study and corrected the manuscript. Authors AMK, SL and MN managed the analyses of the study. All authors contributed to the literature searches. All authors read and approved the final manuscript.

Article Information

DOI: 10.9734/IJMPCR/2016/25476
Editor(s):
(1) Syed A. A. Rizvi, Department of Pharmaceutical Sciences, College of Pharmacy, Nova Southeastern University, USA.
Reviewers:
(1) Alex Miranda Rodrigues, Instituto Master de Ensino Presidente Antônio Carlos de Araguari- MG, Brazil.
(2) Gustavo Carvalho de Oliveira, Federal University of Rio de Janeiro, Brazil.
(3) Olumayowa Abimbola Oninla, Obafemi Awolowo University, Nigeria.
Complete Peer review History: http://sciencedomain.org/review-history/14421

Case Study

Received 4th March 2016
Accepted 22nd April 2016
Published 3rd May 2016

ABSTRACT

Aims: Skin herpes zoster frequently affects immunocompromised patients including multiple sclerosis patients that belong to a distinct category of autoimmunity. Although considered a manageable condition, non-immunocompetent patients are suboptimally targeted by the gold standard valacyclovir treatment. In the case presented here, a new endogenous antiseptic

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treatment was applied.
Presentation of Case: We describe a recurrent multiple sclerosis patient with herpes zoster skin infection, who was unresponsive to cotreatment with valacyclovir. Topical application of 0.8% N-chlorotaurine twice daily for four days resulted in immediate symptom resolution including loss of pain. Alternating application of 0.8% N-chlorotaurine and 1.0% N-bromotaurine in the next three days led to rapid healing.
Discussion and Conclusion: This is the first case where natural taurine haloamines (N-chlorotaurine and N-bromotaurine), which are involved in innate immunity, were applied in reactivated, painful herpes zoster. The rapid clinical healing observed suggests specific investigations of the therapeutic effect of these compounds in this indication.

Keywords: N-bromotaurine; N-chlorotaurine; herpes zoster; immuno-modulation; valacyclovir; glatiramer acetate.

1. INTRODUCTION

Herpes zoster (HZ) is frequently a complicating disorder in immunocompromised patients [1]. Considerable association between Multiple Sclerosis (MS) and VZV has been described in different parts of the world [2,3], with incidence rates of VZV infection of 6-11 per 1000 patient years [4] and 2 cases of HZ out of 82 MS patients [2]. HZ can be an early manifestation of further VZV-associated neurological complications [5]. Evidence suggests for latent VZV in the form of shingles to participate in the etiopathogenesis of relapsing multiple sclerosis (MS) episodes [6,7]. The course of HZ is generally prolonged during immune-compromisation [8]. MS presents a special case of immune deficiency, i.e. localized immune-mediated lesions [7]. Standard treatment with valacyclovir, although efficiently manages HZ, holds certain disadvantages: (a) increased (and often VZV strain-independent) resistance in non-immunocompetent patients [9], and (b) failure to prevent post-herpetic neuralgia [9]. Persistent and recurrent symptoms and post-herpetic neuralgia, following sub-optimal responsiveness or unresponsiveness, increase disease burden and impair quality of life of non-immunocompetent patients [9]. In worst case scenario, a generalized VZV-reactivation may lead to severe and life-threatening comorbidities [10]. Recent reports mention a higher frequency of developing HZ in glatiramer acetate-treated MS patients (11 vs 6 per 1000 patient-years) [4].

In-depth consideration of alternative anti-HZ treatments to manage immunocompromised patients is an emerging option. Importantly, HZ is associated with increased risk of MS occurrence and of relapsing MS episodes [6,7]. Moreover, HZ is a side-effect of the first-line recurrent MS treatment, glatiramer acetate (GA) [11,12]. A recurrent MS patient presenting with HZ is a problematic case as he is prone to VZV [6], less certain to adequately respond to standard antiviral therapy, and more in need for continuation of the anti-MS immunomodulatory regimen [13]. We describe such as case of valacyclovir-unresponsive relapsing MS patient with painful HZ comorbidity, and his rapid symptomatic cure by repurposing taurine haloamines (i.e. low cost, broad spectrum, anti-inflammatory investigational drugs, currently in phase II clinical trials [14-16]) against VZV reactivation. Importantly, composite rate of pain intensity [17] scored to 7 was immediately resolved.

2. PRESENTATION OF CASE

A 35-year-old male chronic MS patient presented with HZ after 8 months of adverse event-free GA-monotherapy (10 mg daily, intramuscular). Serious initial headaches were followed, within 3 days, by typical papules development at the front-upper thoracic area (region T2-T4) extending to both sides, with two lesion niches localized on the left (Fig. 1a). He experienced 37.8℃ fever and strong local pain extending to the back of the thorax, where no dermal eruption could be noticed. A modified Zoster Brief Pain Inventory (ZBPI) [16] questionnaire for thorough determination of herpetic pain and post-herpetic neuralgia [18] was completed. As acute herpetic pain was diagnosed, the composite rate of pain intensity [17] was considered the most suitable pain assessment scale, where the patient scored 7. Sleep deprivation (rated 9 points of maximum 10 on the ZBPI scale) became evident. General activity, mood, relations with other people, and enjoyment of life were significantly impaired (5 points of maximum 10). High IgG and low IgM anti-VZV blood titers (IgG 3614 mIU/mL, normal limits 135-165 mIU/mL; IgM 0.4, negative when

<0.9) were consistent with VZV-reactivation. Computed tomography scans showed activity indicating a relapse of MS. Oral valacyclovir (500 mg every 8 h) was initiated two days after papule occurrence, as per Center for Disease Control guidelines for immuno-modulated patients [19]. Upon lack of any response to therapy for three weeks and pain persistence, valacyclovir was discontinued with patient's consent. Lidocaine cream (2%) did not relieve the herpetic lesion-induced neuropathic pain.

N-chlorotaurine (NCT) and N-bromotaurine (NBT) option was favored given unresponsiveness and no clear evidence of efficacy for prolonged acyclovir/valacyclovir treatment against latent VZV reactivation [7,13], especially in this case of an immuno-modulated recurrent MS patient [7]. Moreover, the sustained moderate pain, the poor night sleep quality and the possible need of GA discontinuation required the consideration of an alternative rapid and effective therapy. At this point, investigational NCT/NBT topical application was suggested. The patient was handled according to the Declaration of Helsinki guidelines and gave written informed consent. NCT and NBT solutions at 0.8% and 1.0% concentrations, respectively, were each freshly prepared in water-for-injection, as previously described [20]. Each solution was put into a sterile spray bottle, releasing approximately 130 µL per single puff. The patient was instructed to spray topically 15 puffs on the affected skin area at each application and to keep the solutions at 4℃ throughout the treatment period.

Four days after previous anti-herpetic treatments' discontinuation, application of 0.8% NCT directly onto the herpetic lesions every 12h for the first four days was initiated. Before application, in the composite rate of pain intensity [17] the patient scored 7. Upon first application (Fig. 1b), a moderate, short-term (1-minute) burning sensation was experienced as a type of discomfort distinguishable from herpetic lesion-induced pain. Subsequent applications induced no discomfort, while the neuropathic pain was immediately resolved based on the modified ZBPI questionnaire [18]. The score regressed from 7 to 1 after one day of application and to zero after three days. Sleep became undisturbed as early as from the first night of application and quality of life improved accordingly. The erythema around the lesions intensified after the first application, but the papules regressed rapidly from the second day of (Fig. 1c). On day 4, papules completely shrunk (Fig. 1d, e) and were evaluated as cured.

For the prevention of HZ reactivation, NCT therapy was continued. NBT, which presents strong immune-modulatory effects *in vitro* [21], was added to potentiate NCT anti-inflammatory activity and induce re-epithelialization [16,21]. Therefore, on day 5, treatment was modified to one 0.8% NCT spray in the morning and one 1.0% NBT spray in the evening. On day 7, the scabs were shed and the affected tissue was largely re-epithelialized (Fig. 1f). Patient still declared being free of pain (score zero). NCT/NBT combination regimen was continued for one more month upon patient's request to preclude re-occurrence. No subacute herpetic pain, itching, other discomforts or adverse events occurred throughout this treatment period. No signs of lesion or postherpetic neuralgia were observed for the following period of eight months. It has also contributed to the patient's compliance with immunomodulatory therapy.

Of note, antibody titers against VZV remained unaltered (high IgG, low IgM), at least for 8 months after the treatment period.

3. DISCUSSION

Taurine haloamines (NCT and NBT) are naturally occurring components of the innate immune system that act as endogenous antiseptics. They are endogenously, transiently and rapidly produced in tissues undergoing oxidative stress (infection/inflammation) by activated neutrophils and eosinophils, the cells showing extremely high concentration of taurine. Taurine reacts with HOCl and HOBr in cytosol to produce taurine haloamines, less toxic anti-microbial and anti-inflammatory agents [21]. *In vitro* NCT is effective against herpes simplex virus 1 and 2, adenoviruses and other viruses [14,22]. Importantly, topically applied exogenous taurine haloamines (NCT/NBT) in pharmaceutical quality are clinically effective against bacterial and fungal skin infections [14,15,23]. Due to their clinically demonstrated high tolerability and safety, broad-spectrum microbicidal/anti-inflammatory activity, absence of systemic side effects and drug interferences, and lack of resistance development, they have drawn increasing attention as possible advantageous alternatives, especially in cases where conventional antimicrobial regimens are inefficient or insufficient [21,24].

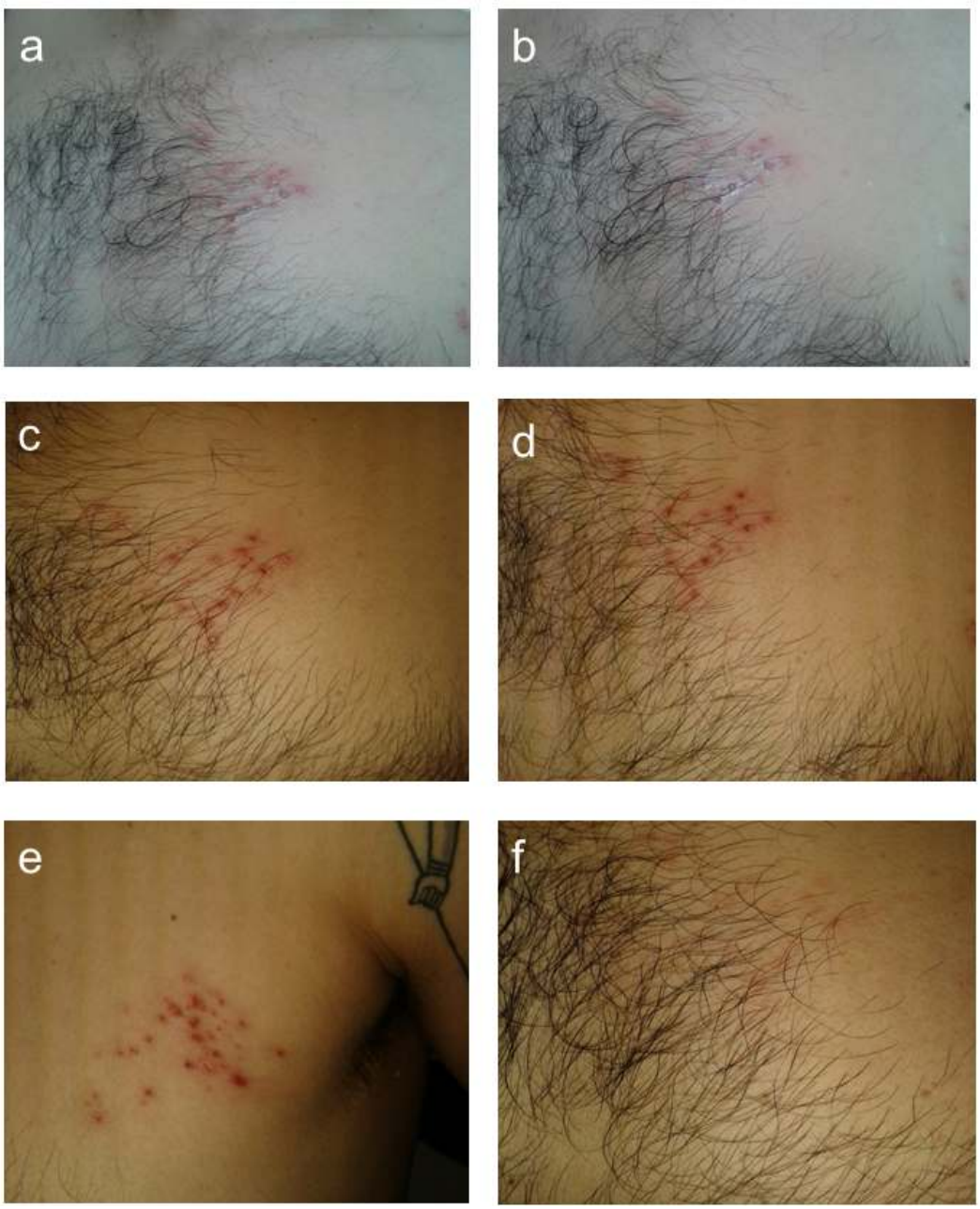

Fig. 1. 7-day period course of the patient's herpetic lesions upon treatment with N-chlorotaurine and N-bromotaurine

*(**a**) Typical niche of herpetic papules at the upper thoracic frontal area before treatment with 0.8 % NCT, (**b**) intensification of erythema around the papules immediately after application of 0.8% NCT, (**c**) rapid regression of herpetic papules on day 2 of treatment with 0.8% NCT, (**d**) complete regression of herpetic papules on day 4 with 0.8% NCT at the same area as (**e**) the same regression as the one described in (**d**) was observed in herpetic papule niches at another, distal area of the upper thoracic area, (**f**) extensive re-epithelization of the skin at day 7 at the lesion of the upper thoracic frontal area, after inclusion of 1% NBT in the treatment regimen from day 4*

In lack of established therapeutic alternatives against valacyclovir-unresponsive HZ and due to adequate NCT/NBT experimental and clinical record on favorable efficacy, tolerability and safety profile, we efficiently combined intramuscularly injected GA with topical administration of NCT, followed by NCT/NBT for the cure of herpetic comorbidity in an MS case.

We propose that the success of NCT/NBT regimen against VZV-infection in our patient relies on the nature of the disease [7,25] with several combined factors: a) its antiviral activity; b) its ability to prevent further inflammatory responses; c) its ability to support cell-mediated immunity, which is considered a prerequisite for protection against VZV reactivation [19]; d) the way of administration since its topical use leaves the GA systemic effects unaffected in all other places of the body; e) its rapid action. NBT effectiveness in topical treatment of HZ seems to be related to its anti-inflammatory properties. Previously, we have described that topical application of NBT in acne vulgaris produced significant reduction of inflammatory skin lesion counts (papules/pustules) [15]. We concluded that NBT is a good candidate for treatment of various skin inflammatory diseases. In the present case, we hypothesize that NBT supports the effect of NCT and ameliorates skin symptoms. As it is typical for case reports, we cannot exclude that the clinical course of the patient could have been similar without the new treatment. The prompt response of HZ, on the other hand, indicates a therapeutic effect. The rapid resolution of pain is most intriguing and suggests further preclinical and clinical studies.

A polyspecific IgG response against Measles, Rubella and Varicella-Zoster Virus known as the MRZ reaction is generally noticed in the CSF of patients developing MS [26]. This finding for our patient may predict for a well stated establishment of MS during this period of IgG against VZV evaluation as high antibody titers against VZV are isolated from bloodstream. Moreover, MRZ antibody positivity is more evident in patients with relapsing MS episodes, which also coincided in our patient supported by radiological findings (CT scans).

4. CONCLUSION

In immunocompromised patients, HZ as an alerting sign for VZV-reactivation requires rapid and efficient elimination of virulent particles to prevent possible complications. For GA-immuno-modulated MS patients who present HZ comorbidity and either low or no response to valacyclovir, a suitable alternative therapeutic option is needed. The combination of systemic GA plus topical NCT/NBT is a conceivable option. Based on this case report and on the already demonstrated clinical advantages of taurine haloamines, we suggest further clinical studies of NCT and NBT efficacy against HZ.

CONSENT

The patient gave written informed consent to the treatment and answered and signed a complete ZBPI form.

ETHICAL APPROVAL

All authors hereby declare that the study has been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki. Special approval from a committee was not applicable.

ACKNOWLEDGEMENTS

We thank the staff of the Euroclinic Microbiology Department, Athens, Greece, and Dr. Nikos Kostalas, Navy Hospital, Athens, Greece.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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Peer-review history:
The peer review history for this paper can be accessed here:
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