

Review Article

A brief review of muco-protective agent in the treatment of recurrent aphthous ulcer and behcet's syndrome: Rebamipide

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Abstract: Recurrent aphthous stomatitis (RAS) is an inflammatory condition of unknown etiology commonly affecting non keratinised oral mucosa. Various topical and systemic drugs had been used for its treatment since decades. Rebamipide is a well-known gastro- protective drug that has been successfully used since 1980 for treating gastric ulcers. Its therapeutic use in management of RAS was not known before. But now the efficiency of this drug had led to its secured position in oral physician and dermatologist's drug armamentarium for treatment of RAS and Behcet's disease. Present review here by takes an effort to highlight various aspects of Rebamipide.

Keywords: Rebamipide, recurrent aphthous ulcer, behcet's syndrome.

INTRODUCTION

Patients with mucositis usually complain of severe burning sensation in the mouth, inability to eat, drink, speak and sleep which eventually affects the patient's quality of lifestyle. The exact etiology of the disease is still unknown. Many researchers had attributed some causes of RAS like herpes virus infection; autoimmunity; vitamin deficiencies (B1, B2, B12, zinc, and folic acid); drugs (Captopril, Gold salts, Nicorandil, Phenobarbitol, Piroxicam) and most importantly stress (Kudur, M.H. *et al.*, 2013). Many treatment options have been carried out which includes antibiotics (Tetracycline, Minocycline), anti-viral, anti-inflammatory agents (Topical and Systemic Corticosteroids), immune-modulatory drugs (Thalidomide), analgesics (Lidocaine, benzocaine), zinc, vitamin B complex, vitamin C, but none of them gives complete cure. Rebamipide is an amino acid analog of 2 (1H)-quinolinone. Behcet's disease is a chronic inflammatory disease involving RAS, uveitis, skin lesions and genital ulcers.

Rebamipide is not only used for long term treatment of RAS, but also for behcet's syndrome cases. Kudur, M.H. *et al.*, (2013) in their study found Rebamipide to be a well-tolerated drug with easy route of administration which improves both the aphthae count and the pain score.

MECHANISM OF ACTION

Rebamipide (muco-protective agent) acts by: (Kudur, M.H. *et al.*, 2013)

- **Enhancing the preservation of existing epithelial cells.**

This affect is attributed by increasing the content of soluble mucus, increasing the gastric concentrations of PGE2 and PGI2, down regulation of 15- hydroxyprostaglandin dehydrogenase, increasing mucosal blood flow through enhanced nitric oxide synthase activity, decreasing the expression of neutrophil adhesion molecules (CD11b/CD18),

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inhibiting the secretion of TNF- α by inhibiting the synthesis of inflammatory E-selectin and has a free radical scavenging effect on reactive oxygen species.

- **Replacement of the lost tissues.**

By increasing the expression of epidermal growth factor and EGF receptors. This eventually leads to angiogenesis, increased production of granulation tissue and epithelisation of ulcer healing.

PHARMACOKINETICS

The effective concentration of Rebamipide is in the range of 1-1000 μm .

For 100 mg Rebamipide: (Arakawa, T. *et al.*, 1998)

C_{max} is 280 $\mu\text{m/ml}$

T_{max} is 2 hours

$T_{1/2}$ is 1.5 hours

Up to 98.4% ingested Rebamipide is found to be bound with plasma proteins. Rebamipide is metabolized in the liver by enzyme namely cytochrome P450. This enzyme acts through hydroxylation and glucuronidation which results in the formation of 6-hydroxy and 8-hydroxyrebamipide (Koyama *et al.*, 2002). The role of glucuronidation in the metabolism of the drug is very low and non-significant. Drug interactions of Rebamipide are generally found to be safe (Sakurai, K. *et al.*, 2004).

DOSAGE

The recommended adult dose is 100 mg orally three times daily.

- *RAU*: 3 tablets/day for 7-14 days.
- *Behcet's syndrome*: 3 tablets/day for 2 months.

INDICATIONS

Genta RM (2003) in their review article quoted the indications of Rebamipide in the management of:

- Stomatitis
- RAS
- Behcet's syndrome

Matsuda, T. *et al.*, (2003) conducted a multi-centric, double blind, placebo controlled study in which they had compared Rebamipide 300 mg/day with placebo in 35 patients of Behcet's disease for 12-24 weeks and concluded that Rebamipide is a very effective and safe drug in treatment of RAS and reducing the pain score when compared to placebo with a significant 'P' value.

Bruce, A. *et al.*, (2007) in their review quoted that there are no more randomized, placebo-controlled studies of Rebamipide in the treatment of RAS. However; Parvathi Devi, M. K. *et al.*, (2014) carried out

a comparative study in between Levamisole and Rebamipide in treatment of RAS. They diagnosed 100 patients with RAS; out of which they assigned 50 patients randomly to each of the two treatment groups. In patients with high scores of pain, aphthae count, ulcer size and frequency of occurrence, they found after 3 months of follow up that both drugs showed better results and recommended to use in RAS & Behcet's disease.

Sun, A. *et al.*, (2003) had also assessed the efficacy of Rebamipide in patients with Behcet's disease whose main symptom were oral aphthosis.

Chaitanya, B. *et al.*, (2017) in their clinical research had found that Rebamipide gargles are effective means to prolong the onset of oral mucositis and it also reduces the severity of oral mucositis in the patients undergoing chemo-radiotherapy. Similar findings were also noticed by Takashi, Y. *et al.*, (2011) in their study on oral cancer patients. Shinohara, A. *et al.*, (2015) had also conducted a study on Rebamipide and found Rebamipide gargles effective against chemotherapy induced oral mucositis

CONTRAINDICATION

Rebamipide is contraindicated in the patients with a known history of drug hypersensitivity.

PRECAUTIONS

Pregnancy and lactation

It is a category C drug (Kim, Y.J. *et al.*, 2010). It should be used with caution only when therapeutic benefits outweigh any potential risk. Avoid lactation when Rebamipide is administered.

Use of Rebamipide in children

Clinical evidence to support the use of Rebamipide in children is insufficient.

SIDE-EFFECTS

Adverse drug reactions to Rebamipide is not common, side effects seen are mild and can be corrected with dose adjustment. The main side-effects noticed is constipation (Park, S.H. *et al.*, 2007), bloating, diarrhoea, nausea and vomiting. Hypersensitivity and rashes were seen in less than 1% of patients.

CONCLUSION

The new drug Rebamipide is a muco-protective drug with ulcer protective functions. Rebamipide is orally administered, safe, well tolerated and effective drug when used for the treatment of RAS and Behcet's disease. Rebamipide does not have any specific adverse drug reaction. Even dermatologist had also started using this drug for treatment of mucositis. It is highlighted that oral physicians should prescribe

Rebamipide in treatment of recurrent aphthous ulcer and Behcets's disease.

REFERENCES

1. Kudur, M.H., & Hulmani, M. (2013). Rebamipide: A novel agent in the treatment of recurrent aphthous ulcer and Behcet's syndrome. *Indian J Dermatol*, 58, 352-4.
2. Arakawa, T., Kobayashi, K., Yoshikawa, T., & Tarnawski, A. (1998). Rebamipide: Overview of its mechanisms of action and efficacy in mucosal protection and ulcer healing. *Dig Dis Sci*, 43, 5S-13.
3. Koyama, N., Sasabe, H., & Miyamoto, G. (2002). Involvement of cytochrome P450 in the metabolism of rebamipide by the human liver. *Xenobiotica*, 32(7), 573-586.
4. Sakurai, K., Sasabe, H., Koga, T., & Konishi, T. (2004). Mechanism of hydroxyl radical scavenging by rebamipide: Identification of mono-hydroxylated rebamipide as a major reaction product. *Free Radic Res*, 38, 487-94.
5. Genta, R.M. (2003). Review article: The role of rebamipide in the management of inflammatory disease of the gastrointestinal tract. *Aliment Pharmacol Ther*, 18(Suppl 1), 8-13.
6. Matsuda, T., Ohno, S., Hirohata, S., Miyanaga, Y., Ujihara, H. & Inaba, G. (2003). Efficacy of rebamipide as adjunctive therapy in the treatment of recurrent oral aphthous ulcers in patients with behcet's disease: A randomised, double-blind, placebo-controlled study. *Drugs R D*, 4, 19-28.
7. Bruce, A., & Rogers, R.S. 3rd. (2007). New and old therapeutics for oral ulcerations. *Arch Dermatol*, 143, 519-23.
8. Parvathi Devi, M. K., Ramesh, D. N. S. V., Shrinivas, K., Amit, R.B. , Thriveni R., & Aditi, A. B. (2014). Efficacy of Rebamipide and Levamisole in the Treatment of Patients with Recurrent Aphthous Ulcer - A Comparative Study. *Journal of Clinical and Diagnostic Research*, 8(11), 119-122.
9. Sun, A., Chang, Y.F., Chia, J.S., & Chiang, C.P. (2003). Levamisole and Chinese medicinal herbs can modulate the serum interleukin-6 levels in patients with recurrent aphthous ulcerations. *J Oral Pathol Med*, 32, 206-14.
10. Chaitanya, B., Paki, K.M., Yathiraj, P.H., Fernandes, D., Chhapparwal, Y. (2017). Rebamipide gargle in preventive management of chemo-radiotherapy induced oral mucositis. *Oral Oncol.*, 72: 179-182.
11. Takashi, Y., Hiroshige, C., Takafumi, S., Akira, M., Tadayoshi K., Daichi C., Hironobu M. J. (2011). Preventive effect of Rebamipide gargle on chemotherapy-induced oral mucositis in patients with oral cancer: a pilot study. *Oral Maxillofac Res.*, 2(4): e3.
12. Shinohara, A., Nakamura, M., Onikubo, T., Nakamura, K. (2015). Efficacy of Rebamipide gargle against chemotherapy-induced oral mucositis. *Yakugaku Zasshi.*, 135(8): 937-41
13. Kim, Y.J., Cheon, J.H., Lee, S.K., Kim, J.H., & Lee, Y.C. (2010). Rebamipide may be comparable to H2 receptor antagonist in healing iatrogenic gastric ulcers created by endoscopic mucosal resection: A prospective randomized pilot study. *J Korean Med Sci*, 25, 583-8.
14. Park, S.H., Cho, C.S., Lee, O.Y., Jun, J.B., Lin, S.R., & Zhou, L.Y. (2007). Comparison of prevention of NSAID-induced gastrointestinal complications by rebamipide and misoprostol: A randomized, multicenter, controlled trial-storm study. *J Clin Biochem Nutr*, 40, 148-55.