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COMPARATIVE STUDY OF EXTEMPORANEOUS MOUTHWASHES FOR MUCOSITIS: WORLD SITUATION AND PERSPECTIVES FOR UKRAINE

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ABSTRACT

Oral mucositis is one of the most common toxicities observed during radiotherapy and chemotherapy for patients with cancer. It is painful and significantly affect nutrition process and mouth care. Painful mucositis impairs the ability to eat and drink fluids and impacts quality of life. Mixed medication mouthwash is commonly used to prevent or treat oral mucositis in world's medical practice. It is typically compounded by a pharmacy and most often contains anticholinergic agents (diphenhydramine), an anesthetic (lidocaine) and an antacid or mucosal coating agent (magnesium or aluminum hydroxide, kaolin, or sucralfate). The mixture may also contain an antibiotic or an antifungal medication (nystatin) and a corticosteroid. In comparison, assortment of compounded topical medications consisted of mostly dosage forms for applications with benzocaine (anestezine) oily solutions, antiseptics (chlorhexidine), antibiotic or an antifungal medication (nystatin), natural additions (infusion of medical herbs) and vitamins.
So, this article presents an analysis of literature data and the assortment of the compounded mouthwashes in Ukraine and in the world. Perspectives for development of new formulas are proposed for Ukrainian pharmacies.

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Introduction. Modern treatment of oncologic diseases includes chemotherapy with radiology. Extensive use of newer radiotherapy and chemoradiotherapy techniques resulted in improved local control and survival. This approach has increased the risk of complications especially mucositis. At present, oral mucositis is considered to be the most serious non-hematological complication of cancer treatment It occurs in up to 40% of patients receiving conventional therapy and as high as 80% of patients receiving high-dose chemotherapy [5, 8, 19].

Oral mucositis is inflammatory or ulcerative lesions of the oral cavity. It is very painful for patients and can compromise nutritional intake. Also increasing risk for local and systemic infection can be causative.

As it is known high dose chemotherapy and localized high dose radiation therapy are the main factors for developing oral mucositis. Such therapy targets the rapidly dividing cancer cells, however, it also affects normal healthy cells that rapidly turnover, for example, the oral mucosa. Speaking, chewing, and swallowing during the food intake may stimulate some damaging of the mouth. And it is sufficient to breakdown the mucosa and formation of painful ulcerations [6, 12, 14, 16].

So, oral mucositis is characterized by damage to the epithelium of the oral mucosa. A reduction of the saliva barrier, disruption of epithelial cells, thinning of the epithelium, ulceration and altered sense of taste also occur [13, 14, 18]. It is reported that sometimes only partial recovery of taste occurs. Pain and the inability to chew, swallow, talk may lead to dehydration, malnutrition. The lack of saliva can cause tooth caries, loss of fillings, mouth ulcers, and pain. These complications make it more difficult to eat. Infection of the sores or ulcerations by a virus, bacterium, or fungus may occur [17]. Moreover, patients affected by a high-grade mucositis have to reduce chemotherapy regimen.

So, mucositis is not an infectious process and cannot be prevented with medications. Management of oral mucositis include nutritional support, pain control, oral decontamination, palliation of dry mouth, management of oral bleeding and therapeutic interventions for oral mucositis [2, 4, 8].

Materials and methods. For presented study the search, analysis, generalization and systematization of compounded topical medications for prevention and therapy of mucositis were carried out. On-line data and some publications were used for the research. It was studied and systematized results from State Register of Medicines of Ukraine, Compendium on-line (A01A Stomatological preparations), Pharmacist's Letter (Internet resource), special sites, literature data and assortment of pharmacies for estimation for Ukrainian compounding practice [3, 5, 9, 11-13, 17].

It must be admitted that the primary symptom of oral mucositis is pain. This pain greatly affects nutritional intake, mouth care and quality of life. Thus, management of mucositis pain is a primary aim of mucositis management strategy. Pharmacists use saline mouth rinses, ice chips and topical mouthrinses containing an anesthetic such as lidocaine. Such agents may provide short-term relief.

So, therapy of mucositis includes such compounded medications as medicinal multipurpose mouthwashes. Prepared by compounding pharmacists, these mouthwashes commonly come in a multitude of formulations.

Results. There are numerous "magic" mouthwash preparations. Most formulations are used every 6-8 hours with instructions to hold in the mouth for 1-2 minutes then spit out or swallow. The mostly used components for topical preparations are presented in the table 1.

Table 1. Composition of compounded topical preparations for mucositis in Ukraine and in the world

Foreign pharmacy	Ukrainian pharmacy
Diphenhydramine hydrochloride	Dexamethasone
Chlorpheniramine	Hydrocortisone
Lidocaine hydrochloride	Prednisolone
Dyclonine hydrochloride	Benzocaine
Coating agent (Hydroxpropyl cellular gel, Polyvinylpyrrolidone/sodium hyaluronate gel)	Procaine (Novocain)
Magnesium hydroxide, aluminium hydroxide (Maalox)	Tannin
Sucralfate*	Borax
Dexamethasone*	Sulfadimezine
Hydrocortisone*	Tetracycline hydrochloride
Prednisone	Norsulfazol
Tetracycline hydrochloride	Rifampicin
Misoprostol*	Doxycyclin
Chlorhexidine	Chlorpheniramine
Benzydamine hydrochloride	Nystatin
Clotrimazole	Vitamin B2
Nystatin*	Tocopherol
Tocopherol	Vitamin A
Vitamin A	Methyluracil
Aloe plant	Hydrogenous peroxide
Allopurinol	Propolis
Pentoxifylline	Sea buckthorn oil
Ketamine	Medical plants (decoctions, infusions)
Morphine	Nitrofuran (furacilin)

* Ingredient has not been shown to be effective in treating oral mucositis or has not been adequately studied

Analysis of Ukrainian extemporaneous drugs revealed mostly used oily solutions, suspensions for applications and spreading. Among active components benzocaine, antibiotics, antifungals, vitamins are prescribed the most frequently. Besides, compounded medications may include glucocorticoid, antiseptics and agent for trophic improving in tissues.

In comparison, foreign pharmacy presented different formulas. It has been admitted that combination of ingredients may vary, but the most common products often include antihistamines (diphenhydramine, chlorpheniramine) for creating an anesthetic or pain relieving effect; corticosteroids (hydrocortisone, dexamethasone, clobetasol) for reducing inflammation and aids in healing; antibiotics (tetracycline) to stop bacterial infections; anti-inflammatory agents to reduce inflammation; topical anesthetics (tetracaine, lidocaine) to reduce pain and irritation; liquid antacid to help the medication coat the tissues of the mouth. Other common ingredients include misoprostol (anti-inflammatory and protective activity); sucralfate (a protective coating for the healing process); ketamine or morphine for pain relief. Chan A. and Ignoffo R. (2005) determined the top five medical agents used to compound the magic mouthwash: diphenhydramine, viscous lidocaine, magnesium hydroxide/aluminum hydroxide, nystatin and corticosteroids [3].

Some ingredients of the mouthwashes have negative or discordant data about their efficacy. The Aloe plant contains multiple pharmacologically active compounds which have healing and anti-inflammatory effects. Puataweepong, et al. (2009) revealed that Aloe vera did not delay the onset of severe mucositis compared with the placebo [15]. But it was also confirmed that receiving Aloe vera patients had less mucositis than the placebo group. However, Su, et al. (2004) showed that oral Aloe vera was not a beneficial adjunct to head and neck radiotherapy compared with placebo [18]. Some author (2012) combined these differences with more time of exposure to the cavity and due to its dosage form, its preparation Puataweepong, et al. used fresh Aloe vera gel prepared under well-controlled technique of enzyme deactivation [1].

Misoprostol is a synthetic prostaglandin E1 analogue, it has anti-inflammatory and mucosa-protecting properties. There are limited data presented by Hanson, et al., 1995, to suggest that its topical administration may benefit patients receiving head and neck radiotherapy [7]. In a Radiation Therapy Oncology Group (RTOG) (1996-2007) phase II trial of misoprostol in 33 patients receiving radical dose radiotherapy, the incidence of mucositis was compared with that in historical controls and misoprostol was not only ineffective but might have also resulted in worse toxicity. Veness et al. (2006) provided with the negative results of topical misoprostol in reducing the severity of radiation-induced mucositis when given before daily radiotherapy [20]. Results of study presented by Lalla et al. (2011) receiving high-dose chemotherapy, misoprostol rinse was safe, but we did not find a beneficial effect on severity of oral mucositis, mouth pain severity, duration of hospital stay, and need for total parenteral nutrition [10]. But authors marked some limitation because accrual was terminated before the planned sample size was achieved.

Presented data allows to predict a possibility of development new formulas for topical treatment of mucositis using conception of foreign pharmacy, for example, adding water-soluble topical anesthetics, antihistamines, antacids if viscous liquid dosage forms.

Conclusions. Treatment of mucositis is an actual problem for modern oncology. Compounded topical drugs give the opportunity to combine different components for meeting the needs of individuals. Taking into account the experience of other countries, development of new compositions, study of efficacy and stability mouthwashes have significant perspective for scientific researches.

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