

Bismuth subgallate and cervico-vaginal disorders

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ABSTRACT

Bismuth subgallate represents a salt which has been widely used in the last decades in gastroenterology and otorhinolaryngology for hemostatic, astringent, anti-inflammatory and antibacterial purposes. The product seems to be efficient also in terms of inducing a more rapid wound healing stimulating all the key points of this process. Once the benefits of bismuth subgallate administration have been widely demonstrated in topical administration at the level of the postoperative wounds in oto- rhinolaryngology, it was further investigated in treating other mucosal lesions such as cervico-vaginal ones especially due to the fact that the two types of mucosa present similar features. Therefore, this bismuth salt was successfully associated in the composition of vaginal topical products with promising results. The aim of the current paper is to discuss the properties, mechanisms of action and benefits of adding bismuth subgallate in topic vaginal products.

Keywords: bismuth subgallate, cervical lesions, vaginal disorders, inflammation, wound healing

INTRODUCTION

The yellow, insoluble and poorly absorbable substance is the heavy metal salt of the gallic acid which is widely known for the protective effect of different surfaces such as gastric mucosa. Meanwhile, it is associated with poor systemic absorption when administrated orally allowing in this way to be kept at the level of the gastrointestinal tract and to prevent excessive bacterial development [1]. In cases in which it is administrated orally, when coming in contact with clorhidric acid bismuth subgallate is transformed into other bismuth salts such as citrate or oxychloride which have the capacity of bounding to proteins from the level of the gastrointestinal ulcers and inducing a protective effect. Meanwhile it stimulates the local secretion of prostaglandins and mucosal bicarbonate diminishing the action of pep-

sin and having a protective effect on the gastro-intestinal mucosa [2].

When it comes to the rates of systemic absorption, it is estimated to be lower than 0,04% of the total ingested amount and it occurs at the level of the upper part of the small intestine [2]. However, this percent can vary depending the patients diet [2]; once absorption takes place bismuth salts are found in the systemic circulation bound to the plasma proteins and trend to concentrate at the level of the liver, spleen, lung, muscle and even brain [1]. As for bismuth salts excretion, it usually occurs via the renal pathway while less than 10% of the amount is eliminated via digestive pathway. Therefore, whenever renal function impairment occurs there is a significant risk of systemic accumulation of bismuth subgallate leading to the apparition of nephrotoxicity, encephalopathy, hepa-

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totoxicity, osteoarthropathy, gingivitis or stomatitis [2].

PROPERTIES

Bismuth subgallate is widely recognized for the astringent, anti-inflammatory and hemostatic properties. The hemostatic effect is mainly explained through the action on the coagulation factor XII and further activation of the intrinsic coagulation mechanisms leading to the development of a fibrin cloth [3]. The phenomenon was intensively studied after surgical procedures in oto-rhinolaryngology and results have shown that local application of bismuth subgallate improves the local hemostasis and the process of wound healing especially in the case of open wounds; meanwhile decreased surgical time and decrease intraoperative blood loss was observed in cases in which this salt was used [4-6]. The method seems to be particularly efficient in patients with hematological disorders [5].

The astringent effect of the salts of bismuth such as bismuth subgallate is explained through the capacity of attraction and further precipitation of the protein matrix; therefore, once the bismuth subgallate products are placed at the level of the open wound, a protective film containing bismuth salts and precipitated proteins will be created at this level and will prevent bacterial adherence and colonization [7]. This property has been widely demonstrated in head and neck surgery; however, due to the fact that oral and vaginal mucosa present a significant series of similarities, experience gained in in oto-rhinolaryngology was successfully implemented in gynecology; therefore both types of mucosa are covered by unkeratinized stratified squamous cell epithelium and present a rich vascularization system while their permeability is similar [8]. Meanwhile, this property has been also used in treating rectal disorders such as hemorrhoids, the main benefit being related to the astringent effect [1].

Another significant property which has been attributed to bismuth salts such as subgallate is represented by the antibacterial effect, the most commonly investigated species being those from the gastrointestinal tract such as Salmonella, Shigella, Campylobacter jejuni, Helicobacter pylori, Vibrio cholera or viruses such as rotavirus. The main mechanism of action which is responsible for the antibacterial effect of bismuth subgallate are related to the capacity of creating complexes with the bacterial wall, inhibiting bacterial enzymes and blocking adenosin triphosphate synthesis [2].

THE INFLUENCE OF BISMUTH SUBGALLATE ON THE HEALING PROCESS

The healing process includes multiple mechanisms such as hemostasis, inflammation, wound contraction and remodeling. Therefore, it seems that bismuth subgallate is particularly efficient in promoting all these processes due to the capacity of facilitating the hemostatic process, stimulating the action of macrophages as well as the synthesis of growth factors and decreasing in this way the surface of the wound. In the meantime it seems that bismuth subgallate provides an increased collagen synthesis, an increased process on angiogenesis and a decreased level of nitric oxide synthesis [9]. Therefore, while angiogenesis accounts for 60% of the healing process, it is mandatory to identify a product which is able to accelerate it; once tissue injury occurs, local macrophages are activated and produce enzymes which digest the basal membrane; furthermore endothelial cells are stimulated and new vascular structures develop invading the wound.

When it comes to the effect of bismuth subgallate on the quality healing process, another positive aspect has been demonstrated; therefore, although initially after placing the salt on a wound a higher number of macrophages will be found at this level when compared to wounds in which saline solution is placed, seven days later gigantic cells were not observed due to the fact that the salt of bismuth did not create an effect of foreign body [10].

THE RATIONALE OF USING BISMUTH SUBGALLATE IN TOPICAL VAGINAL PRODUCTS

When it comes to the rationale of using bismuth subgallate as part of topical products used as part of the treatment of cervico-vaginal disorders, it seems that the principal benefits are related to the hemostatic, anti-inflammatory and antibacterial effect. Meanwhile bismuth subgallate as part of topical vaginal ovules plays a central role in order to provide an efficient hemostasis effect after limited cervical procedures such as loop resection or trachelectomy. Therefore, it has been demonstrated that bismuth subgallate is efficient in stopping bleeding from capillaries during surgery for limited lesions of the uterine cervix and stimulating wound healing [11,12]. Meanwhile, the anti-inflammatory effect of bismuth subgallate is related to the fact that this product is able to decrease the nitric oxide and prostaglandin E synthesis at the level of the stimulated macrophages [13-15].

Therefore, although screening tests for human papilloma virus detection have been widely implemented in our country, a significant number of

cases are still diagnosed with preneoplastic and neoplastic lesions of the uterine cervix [16-18]. In such cases, once the lesion is detected, it is widely recommended to be treated by performing a local excision; after excision local administration of topical products with hemostatic, anti-inflammatory and antibacterial effect significantly improves the process of healing, a more rapid healing of the postoperative wound being obtained [11,12,19,20]. Meanwhile, topical administration of bismuth subgallate products decreases the risk of postoperative bleeding and shortens the time to discharge; during the next postoperative days, local placement of bismuth subgallate based products will induce a more rapid healing of the postoperative wound as mentioned before. Last but not least, bismuth subgallate seems to create a protective film and to prevent local infection of the wound. This aspect plays a crucial role especially due to the fact that vagina is an organ presenting a proper microbiota which suffers permanent modifications depending on the age of the patient [21]. The most commonly encountered bacteria in the human vaginal microbiota is represented by *Lactobacillus* species, a microorganism which is responsible for the maintenance of a slightly acid pH at this level. Once the amount of *Lactobacilli* decrease the local vaginal pH increases inducing the apparition of a basic medium which will further favor the development of different pathogenic micro-organisms including bacteria, viruses and fungi. Other factors which might influence the development of different pathogenic species at this level are represented by hormonal modifications such as the modification of the estrogen amounts, intercourse, menstruation or the use of certain antimicrobial agents [21,22]. In cases in which other pathogenic agents develop, significant increase of interleukin 1, 4, 8 and 10 occur inducing a greater pro-inflammatory response [23-26].

Meanwhile, increasing the value of pH will further create the adequate conditions for the development of viral infections such as HPV and therefore will increase the risk of cervical cancer development. Therefore, topic administration of bismuth subgallate might decrease the risk of HPV infection by contributing to the maintenance of a normal vaginal microbioma; furthermore, if this infection develops and neoplastic or preneoplastic diseases occur local resection is mandatory. Even though local administration of bismuth subgallate compounds will further decrease the length of hospital in stay as well as the risk of developing wound complications [11,23-25].

SIDE EFFECTS OF PROLONGED USAGE OF BISMUTH SUBGALLATE

In case of prolonged usage of bismuth subgallate or increased amounts of the administrated salt certain dermatological side effects such as allergies have been reported; however, in cases necessitating topic intravaginal administration of this salt the systemic absorption of the product is minimal [1,2].

CONCLUSIONS

Topic agents containing bismuth subgallate proved to have multiple benefits when it comes to cervico-vaginal lesions; therefore the product seems to provide a better healing process, a more efficient hemostasis and in the meantime creates a protective film preventing the development of wound infection. Meanwhile due to the fact that the systemic absorption is much reduced, the risk of general side effects is rather null.

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