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Roles of Antifibrinolytics in Cosmetics and the Absence of Aprotinin Additives as a Consumer-Bought Anti-Aging Agent

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ABSTRACT

Plasmin is a "skin aging" enzyme that contributes to the production of wrinkles and inflammation, which is produced from plasminogen. This study examines the roles of antifibrinolytics in inhibiting plasminogen through the medium of cosmetic products, primarily dominated by tranexamic acid (TXA) and epsilon-aminocaproic acid (EACA), as established antifibrinolytic agents. Because aprotinin is a powerful antifibrinolytic agent not found in cosmetic products, a disparity was observed. To resolve this, the mechanisms and properties of each antifibrinolytic were analyzed. TXA and EACA were found to be lysine analogs, and aprotinin is a bovine polypeptide derived from lung tissue that serves as a serine-protease inhibitor. Because aprotinin is banned in the United States, is difficult to isolate, and has too large a molecular weight to penetrate the skin, it was found that aprotinin is unlikely to function for "anti-aging" properties on the epidermis.

INTRODUCTION

The rapid growth of the skincare industry and the desire for "anti-aging" products have led to an increase in the number of new chemicals and compounds used by pharmaceutical companies. Many consumers are not always aware of the dangers posed by some products they use, so comparing antifibrinolytics, compounds used in cosmetic products, is important to assess their cosmetic potential and evaluate consumer safety. Wrinkles are among the most common signs of aging. A thinning of skin layers and a lack of collagen in the skin create these creases, which are often viewed as unappealing (1). Many efforts over time have been made to reduce the visual effects of aging. Some examples include wearing sunscreen, maintaining a healthy diet, using Botox, and using skincare products. Campiche et al. demonstrated that plasmin is a skin-aging enzyme that contributes to inflammation by upregulating the production of inflammation and other damaging enzymes. Free plasmin is defined as an enzyme in the blood that breaks down blood clots. Plasmin is regulated by plasminogen activator inhibitors (PAIs), which in turn are regulated by antifibrinolytics such as tranexamic acid (TXA) and aminocaproic acid (EACA) (2). TXA and EACA block the plasminogen activation binding sites (called lysine binding sites) to prevent the blood clot from being broken down. However, TXA's main role as an anti-inflammatory and an inhibitor of melanogenesis is a core reason why it is found in skincare products (3).

Antifibrinolytics are a class of medications used to reduce bleeding and blood clotting during heart procedures, surgeries, and other procedures. However, some are also used in skincare products to tighten wrinkles and brighten the complexion. The known types of antifibrinolytics include aprotinin, tranexamic acid, and aminocaproic acid. Although they all serve similar purposes in cardiac surgery, only tranexamic acid is found in multiple skincare products.

Ferguson et al. conducted a study to investigate the differences between various antifibrinolytics used in cardiac surgery from 2002 to 2007. The demographic chosen was “cardiac surgical patients” who used the three different types of antifibrinolytics to help with post-operative bleeding. This study revealed that aprotinin had the highest death rates in patients who were administered it in surgery, caused by increased rates of cardiovascular and cerebrovascular complications, renal failure with short- and long-term mortality compared with other antifibrinolytic agents (4). The study was concluded early because the 30-day mortality rate was the highest in the aprotinin group, and was relatively the same in the tranexamic acid and aminocaproic acid groups. This study concluded that aprotinin leads to problems with patients' liver, kidneys, and brain, and caused more deaths than tranexamic acid and aminocaproic acid in cardiac surgery patients.

MECHANISMS OF ACTION OF APROTININ, TRANEXAMIC ACID, AND AMINOCAPROIC ACID

Aprotinin is a serine protease inhibitor that is used to prevent blood loss during major surgeries like cardiac surgery and liver transplantation (5). Its mechanism of action consists of blocking the activated thrombin (enzyme that helps create clots) receptor on platelets (blood cells that help to create clots) and activating the protease-activated receptor 1 (PAR1), while leaving other parts of the platelet untouched. This helps prevent dangerous blood clots and reduces excessive bleeding after surgery (6).

Tranexamic acid’s mechanism involves blocking the lysine binding sites of plasminogen to keratinocytes, thereby reducing the production of inflammatory mediators, which are also melanocyte stimulators. This mechanism of TXA helps to reduce inflammation and melanin production, which is a primary reason why it is used in skincare. TXA also inhibits the activation of protease-activated receptor 2 (PAR2) by serine protease and calcium influx in keratinocytes, leading to an improved permeability barrier function in rosacea patients. Several studies have been conducted specifically to examine the effect of TXA on melasma and acne. Estcourt et al. formulated a study on melasma involving TXA. Seventy-four women in Hangzhou, China, were administered oral TXA at a dose of 250 mg twice daily over a 6-month period. The results showed a gradual reduction of melasma in most patients. There was an overall improvement rate of 95.9% (7). In a study on acne, a randomized, double-blind, placebo-controlled design was employed. The efficacy of 10% TXA serum was analyzed. Eighteen patients with mild to moderate acne applied the 10% serum to one side of their face and a placebo to the other side, twice a day. After 8 weeks

of use, acne was significantly reduced on the TXA side. It also reduced skin redness. These studies provide further evidence that TXA has a significant effect on acne and melasma (7).

Lastly, aminocaproic acid is a lysine analog like tranexamic acid, which means it also blocks the lysine binding sites on plasminogen. Blocking these sites inhibits plasmin and, therefore, inhibits fibrinolysis, which prevents the blood clot from being broken down immediately.

After considering the above antifibrinolytics, several questions have arisen regarding their use in skincare products. In the study conducted by Ferguson et. al from 2002 to 2007 involving "cardiac surgical patients" and the effects of the different antifibrinolytics, the effect of aprotinin is more dangerous than that of tranexamic acid and aminocaproic acid (4). However, all antifibrinolytics have the same function: to reduce bleeding. This continuity in utility posed a larger question about the use of aprotinin on the epidermis for anti-wrinkle and anti-inflammatory purposes.

Some widely available products that contain tranexamic acid include "iNNBeauty Bright and Tight," "The INKEY List Tranexamic Acid Serum," and "Allies of Skin Tranexamic & Arbutin Advanced Brightening Serum." These products claim to "treat dark circles for all skin tones & under-eye concerns, hydrate & visibly plump fine lines and wrinkles, reduce dark circles & crow's feet in just 5 days, dull hyperpigmentation, uneven patches and dark spots, fade the appearance of dark spots, strengthen skin and reduce dullness" (8, 9, 10). Therefore, this study aims to investigate the potential understudying of aprotinin in various cosmetics and beauty products to enhance their anti-wrinkling effects compared to tranexamic acid.

METHODS

This paper is a literature-based narrative review. The results of this research were compiled from a search of various medical journal articles and peer-reviewed websites that compared each of the antifibrinolytics. The inclusion criteria primarily consisted of review articles and case studies. Non-peer-reviewed articles, blogs, and other websites were excluded from consideration, except for exemplar cosmetic websites. These resources were used to determine a possible explanation for why tranexamic acid is the only antifibrinolytic agent found in skincare products, rather than other antifibrinolytics. Using the resources available online, insight into the mechanisms of each antifibrinolytic was gained. The resources were also utilized to connect skincare products with the compounds and elements they are composed of. This information was also obtained from commercial sources by producing physical skincare products and evaluating their appearance, texture, and whether they deliver the claimed benefits. Through various online studies, information was collected and analyzed regarding which antifibrinolytic is more harmful to patients undergoing cardiac surgery. These studies helped gather background information to examine each type of antifibrinolytic and its mechanism separately.

RESULTS

The study began with the inquiry into aprotinin's ability to be used in skincare and other beauty products, but after researching specific types of these products and discovering that only one type of antifibrinolytic (TXA) is seen in commercially available cosmetics, the study was expanded to aminocaproic acid to investigate its ability to be used successfully in skincare products.

When reviewing the ingredient lists of products mentioned to contain antifibrinolytics, almost only tranexamic acid was identified. This is because of TXA's mechanism of action, which involves reducing inflammation and melasma.

The only source of aminocaproic acid-containing cosmetics was on a foreign, difficult-to-use website. The product found from this company, Hada Labo, was a "skin conditioner" and was displayed in Japanese, but the rest of the website was in English and difficult to navigate. It includes 6-aminocaproic acid to prevent acne and for smooth skin (11). Aminocaproic acid and aprotinin did not appear to be present in significant quantities in commercial cosmetics, but a substantial number of products containing tranexamic acid were identified. In fact, Sephora has a search result for "Tranexamic Acid Skincare" (12) with brightening patch products, creams that claim to "resurface and hydrate," "dark spot" toners, and more.

Aprotinin is a broad-spectrum serine protease inhibitor. Because serine protease inhibitors can be used to reduce inflammation, aprotinin could be used in skincare. However, aprotinin functions via the same mechanism as PAI-1, "the main physiological inhibitor of plasminogen activators" (13), which has the same function of limiting the breakdown of blood clots as the lysine analogs TXA and EACA, but a different mechanism, which could have an impact on its usage on the epidermis. PAI-1 blocks the plasminogen activators (u-PA and t-PA) by binding to them and forming a stable complex, so they cannot work. This is a more direct approach to stopping the breakdown of blood clots, compared to the mechanisms of EACA and TXA (14).

Another significant difference between aprotinin and the small molecules TXA and EACA is that aprotinin is a polypeptide, which will have a larger size in solution compared to TXA and EACA. Aprotinin has a molecular weight of 6,511 Da (g/mol) (15), while TXA has a molecular weight of 157.21 Da (16), and EACA has a molecular weight of 131.17 Da (17). According to the 500 Dalton rule for skin penetration of chemical compounds and drugs, "the molecular weight of a compound must be under 500 Dalton to allow skin absorption" (18). This review suggests that because TXA and EACA's molecular weights are below 500 Da, they are not limited by this rule and can penetrate the skin. However, with a molecular weight of 6,512 Da, aprotinin exceeds the size limit established by the 500 Da rule.

Lastly, aprotinin is difficult to obtain. In addition to its banned status in the United States (19), it is largely obtained through an extensive and expensive process that involves processing ground tissue from bovine or porcine lungs (20). These tissues are prepared by buffer extraction, clarification (removal of solid debris), precipitation, and then pH-balanced column chromatography. This review suggests that the

combination of these two restricting factors has, in turn, resulted in increased clinical use of the alternative TXA and EACA (21).

Overall, TXA, EACA, and aprotinin, as antifibrinolytics, all inhibit plasmic activity but differ in mechanism, molecular weight, and cosmetic relevance. Both TXA and EACA's mechanisms of action involve blocking the lysine-binding sites on plasminogen at the keratinocyte surface, thereby inhibiting plasmin, fibrinolysis, and the production of inflammatory mediators. Aprotinin's mechanism differs from the others, as it acts more directly to prevent the breakdown of blood clots. As a broad-spectrum serine inhibitor, aprotinin can reduce inflammation and functions similarly to PAI-1, sharing the goal of TXA and EACA to limit the breakdown of blood clots, but in a different way that could affect its safety on the epidermis. PAI-1's mechanism involves blocking plasminogen activators (u-PA and t-PA) by binding to them and forming a stable complex, preventing their activity. The weight of these different compounds also affects their impact on the epidermis. Aprotinin has a molecular weight of 6,512 Da, exceeding the 500 Dalton rule for skin penetration of chemical compounds and drugs, meaning that, unlike TXA and EACA with molecular weights of 157.21 Da and 131.17 Da, aprotinin is too large to penetrate the skin. Aprotinin is also less accessible than TXA and EACA due to its banned status in the US and the expensive process that involves processing ground tissue from bovine or porcine lungs required to obtain it. These differences help explain why TXA is more frequently used in cosmetics than EACA and especially aprotinin.

DISCUSSION

Research into the roles of antifibrinolytics resulted in a clearer mechanistic understanding of aprotinin, tranexamic acid, and aminocaproic acid. Aprotinin may not be considered a strong contender for anti-wrinkle efficacy in cosmetics due to its banned status in many countries, its bulky specific volume, which prevents the protein from penetrating the epidermis, and its difficulty in replicating the protein itself.

An article from the Market Research Community on aprotinin states, "Plasma-derived aprotinin, though historically significant, faces challenges related to source variability and potential viral transmission" (22). In addition to these challenges, to ensure the same quality and cleanliness of bovine lung tissue for aprotinin's use, it would be very costly to manufacture in the quantities required for cosmetic use.

Additional possible reasons why aprotinin is not suitable for cosmetic use include that it functions with the same mechanism as PAI-1, which is a more direct inhibitor of plasminogen than other antifibrinolytics. The lysine analogs TXA and EACA have mechanisms of action that prevent the breakdown of blood clots, which are more indirect than the mechanism of PAI-1 and therefore differ from aprotinin. This could be a reason why aprotinin is more dangerous in certain cardiac surgery procedures.

Another reason why aprotinin may not be used in skincare is that it did not affect inflammation during a coronary artery bypass surgery. During a study dedicated to analyzing aprotinin's effect on inflammation during cardiac surgery, the results showed that aprotinin only prevented bleeding during the surgery, not any inflammation that occurred (23). Due to this finding, it is unlikely that aprotinin would be effective in limiting inflammation, hyperpigmentation, and wrinkles on the epidermis through cosmetic products.

Although many assertions can be drawn from medical journal articles and peer-reviewed websites, it should be acknowledged that the biggest limitation of this study is the absence of direct dermatological or skin-penetration studies to prove exactly why aprotinin and EACA are not found in skincare as commonly as TXA.

CONCLUSION

This study has examined the role of antifibrinolytics, specifically their use in cosmetics. One way this was done was by acknowledging and comparing each mechanism in TXA, EACA, and aprotinin. TXA and EACA are both lysine analogs, which means that they block the lysine binding sites on plasminogen. This process reduces the breakdown of blood clots and is particularly useful during cardiac surgeries. However, this process also reduces the production of inflammatory mediators and melanocyte stimulators, making TXA an especially good candidate for reducing inflammation and hyperpigmentation. Aprotinin is a broad-spectrum serine protease inhibitor with a mechanism similar to that of PAI-1; it forms a stable complex with the plasminogen activators (u-PA and t-PA), thereby preventing them from functioning. Aprotinin has a more direct mechanism of action, reducing the breakdown of blood clots, which has a more severe effect on patients when examined in cardiac surgery patients. Due to this, aprotinin is banned in many countries, including the US, which may make it especially difficult to use in skincare products, even if its dangerous effects in surgery translate to the epidermis. Aprotinin's mechanism has the same effect as TXA and EACA in terms of inhibiting plasminogen, but aprotinin prevents the breakdown of blood clots by directly blocking the plasminogen activators instead of blocking the lysine binding sites on plasminogen. Aprotinin is also a polypeptide, and its molecular weight is too large to penetrate the skin. Additionally, because it is derived from bovine sources, it's challenging to replicate. Due to these reasons, aprotinin is unlikely to be as effective as TXA and EACA in these cosmetic products.

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