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Oral Tranexamic Acid for the Treatment of Melasma: A Case Series and Novel Dosing Regimen

Michael Foss DO,[a] Kevin Nethers MD,[a] Aashni Bhukhan BS,[b] Rajiv Nathoo MD[a]
[a]Kansas City University-GME/ADCS Consortium, Orlando, FL
[b]Nova Southeastern University Dr. Kiran C. Patel College of Osteopathic Medicine, Ft. Lauderdale, FL

ABSTRACT

Melasma is a common disorder affecting millions of people around the world.[1] It is a condition that can disrupt one's self-esteem and overall quality of life.[2] Melasma is characterized by hyperpigmented macules and patches on the face.[1] The pathophysiology of melasma is widely unknown, although multiple triggers have been identified.[3] Among the triggers, sun exposure is considered to be the most important factor.[3] A variety of topical treatments exist for melasma, however most of these options often lead to subpar results. Due to this, novel treatments such as oral tranexamic acid (TXA) have emerged.[4,5] Our case series demonstrates the effectiveness and safety profile of utilizing oral TXA to treat recalcitrant melasma and highlights a possible dosing regimen that can be used for the novel therapy.

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INTRODUCTION

Melasma, characterized by hyperpigmented macules and patches on the face, is a common disorder affecting millions of people across the globe.[1] While it provides no direct health concern, it does pose a considerable cosmetic concern, which can lower self-esteem and overall quality of life.[2]

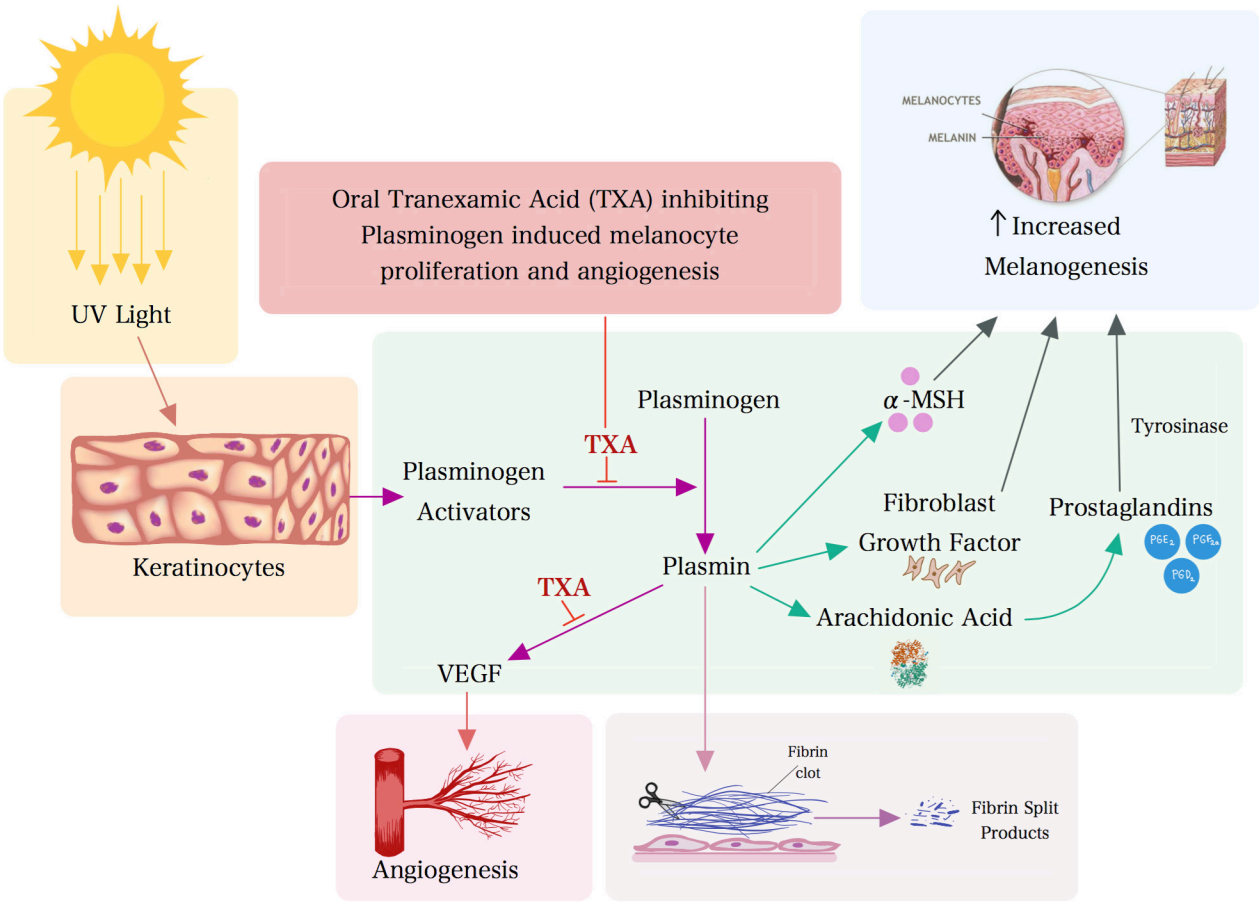
The exact pathophysiology of melasma is unknown, however, certain triggers have been identified. These triggers include sun exposure, pregnancy, use of oral contraceptives/hormone replacement, certain foods, ovarian tumors, photosensitizing drugs, inflammatory processes of the skin, and stressful life events. Familial predisposition has been reported but no Mendelian pattern has been identified.[3] Among the inciting triggers, sun exposure is considered the most important factor.[3]

A variety of treatment options exist for melasma. First-line therapies generally consist of topical skin-lightening agents. These agents include but are not limited to hydroquinone, azelaic acid, mequinol, kojic acid, tranexamic acid (TXA), retinoids, and a variety of combination creams. (ie, hydroquinone combined with a topical retinoid and a low potency topical corticosteroid).[4] Second-line therapies include a variety of chemical peels and laser therapy.[5] Treatment with these first and second line treatments have often led to suboptimal results, therefore, novel treatments such as oral formulations of TXA have emerged. No consensus guidelines on the dosing of oral TXA exist.

Tranexamic acid (TXA) is a synthetic derivative of the amino acid lysine. Its mechanism of action regarding melasma is the inhibition of ultraviolet radiation (UVR)-induced plasmin activity in keratinocytes. Normally, prostaglandins are responsible for stimulating tyrosinase; by blocking the binding of plasminogen, TXA decreases free arachidonic acid, and therefore prostaglandins.[6] As well documented in many dermatologic conditions, tyrosinase is the essential enzyme in melanogenesis and enzymatic browning.[7] Additionally, plasmin is responsible for indirectly leading to angiogenesis, as it converts matrix-bound vascular endothelial growth factor (VEGF) into freely diffusible forms.[6] Oral TXA, therefore, targets melasma by reducing melanin production and decreasing erythema (Figure 1).[6]

Oral TXA is currently FDA approved for cyclic heavy menstrual bleeding (1300 mg PO TID), hemoptysis (500 mg inhalation TID), and tooth extraction in patients with hemophilia (PO or injection 650 mg). Off-label uses include but are not limited to long-term prophylaxis in hereditary angioedema, hip fracture, operative blood conservation, and non-traumatic subarachnoid hemorrhage.[8-11] Treatment for refractory melasma with oral TXA is an off-label indication, yet it has shown promising safety and efficacy data in the limited studies available to date. Our case series demonstrates the efficacy and safety profile of utilizing oral TXA to treat recalcitrant melasma, while also outlining a novel dosing regimen that can be used for this condition.

FIGURE 1. Mechanism of Action of Tranexamic Acid in the Treatment of Hyperpigmentation. Oral TXA inhibits UVR-induced plasmin activity in keratinocytes. By blocking the activation of plasminogen to plasmin, TXA decreases free arachidonic acid, and therefore prostaglandins, resulting in decreased tyrosinase activity. This results in decreased melanin production. Additionally, TXA inhibits angiogenesis indirectly through its negative effects on plasmin activity, which normally converts matrix-bound vascular endothelial growth factor (VEGF) into freely diffusible forms; the result is decreased erythema.

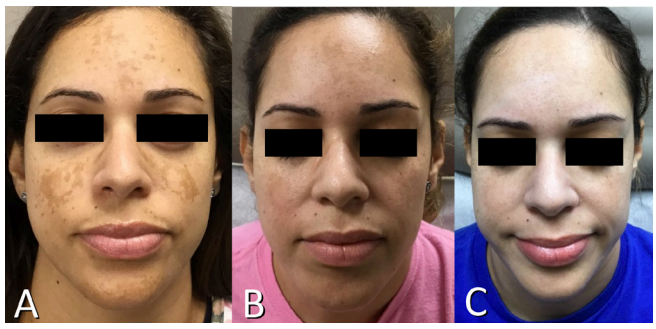


CASE 1

A 39-year-old Hispanic female without significant medical history presented for a chief complaint of discoloration located on the chin, bilateral cheeks, upper cutaneous lip, and forehead. The patient stated that the discoloration had been present for approximately seven years and worsened with previous pregnancies and sun exposure. Of note, the patient denied any medication use including oral contraceptives. Previous treatments included strict sun protection, hydroquinone, fractional laser resurfacing, salicylic acid pads, kojic acid/hydroquinone compound, and a series of three Jessner's peels (salicylic acid, lactic acid, and resorcinol) without improvement. Physical examination demonstrated well demarcated blotchy hyperpigmentation over the central forehead, glabella, malar cheeks, upper cutaneous lip, and chin (Figure 2).

Given the failure of various topical modalities, the patient was started on oral TXA, 325 mg twice daily. The patient demonstrated significant reduction of hyperpigmentation within three months (Figure 2). She experienced no adverse effects of the oral TXA. Given the high rates of recurrence of melasma after abruptly

FIGURE 2. Case 1. (A) Prior to initiation of oral TXA. Hyperpigmented patches on the face. (B) After 6 months of therapy, significant improvement of hyperpigmentation. (C) After completing 6 months of maintenance therapy with oral TXA 325 mg QD.



discontinuing oral TXA, the decision was made to taper oral TXA from 325 mg twice daily to 325 mg once daily after 6 months of therapy. The patient was able to maintain the same level of melasma clearance at the once daily dosing schedule (Figure 2). As such, she was continued on daily sun protection and oral TXA 325 mg once daily indefinitely and reported no unwanted side effects.

CASE 2

A 47-year-old Hispanic female with past medical history significant for hypothyroidism and female hormonal acne presented with the chief complaint of a long-standing history of discoloration located around her eyes, cheeks, and forehead. Current medications included spironolactone, levothyroxine, and progesterone. She denied any prior treatments.

On exam, ill-defined hyperpigmented macules and patches were appreciated on her bilateral periorbital areas, malar cheeks, and forehead, consistent with melasma.

Due to her concurrent use of progesterone and lack of prior therapy it was decided to start treatment with topical agents. She was initially treated for 6 months with a combination topical cream consisting of adapalene 0.3%/desonide 0.05%/hydroquinone 4% without significant improvement. After completing 3 months of treatment, with the guidance of her gynecologist, she discontinued oral progesterone, which was thought to be contributing to the melasma. She continued the combination cream for another 3 months, for a total of 6 months of therapy, with no appreciable change from baseline (Figure 3). Due to lack of improvement with the topical regimen alone, she was initiated on oral TXA 325 mg twice daily, while continuing adapalene 0.3%/desonide 0.05%/hydroquinone 4% cream nightly, in combination with strict photoprotection using a tinted mineral based sunscreen. After 6 months of this regimen, the patient demonstrated a significant reduction of hyperpigmentation (Figure 3). At that time her oral TXA dose was down titrated to 325 mg daily, with no evidence of relapse of her melasma at 9 months on this regimen (Figure 3).

FIGURE 3. Case 2. (A) Prior to initiation of oral TXA. Hyperpigmented patches on the face consistent with melasma. (B) After completing 6 months of oral TXA 325 mg BID. (C) After completing 9 months of maintenance therapy with 325 mg QD.

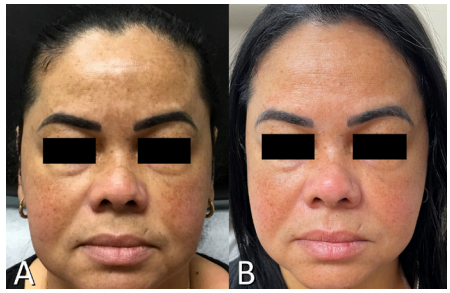
CASE 3

A 41-year-old Hispanic female with a past medical history of type 2 diabetes mellitus and hypothyroidism presented with a chief complaint of discoloration located on her periorbital areas, malar cheeks, and forehead that worsened with sun exposure and had been present for several years. Her medications included levothyroxine and insulin glargine. She denied any prior treatments for this concern.

On exam, ill-defined hyperpigmented macules coalescing into patches were noted distributed on her bilateral periorbital areas, malar cheeks, and forehead, consistent with melasma (Figure 4). As she was treatment naïve, the decision was made to start her on a combination cream consisting of hydroquinone 6%/tretinoin 0.5%/fluocinolone/ascorbic acid in combination with strict photoprotection with tinted mineral based sunscreen. She was treated on this regimen for 6 months without satisfactory improvement.

Due to lack of improvement with the topical regimen alone, she was initiated on oral TXA 325 mg twice daily, while continuing her previously prescribed combination cream daily and strict photoprotection. After 6 months of this regimen, the patient demonstrated a significant reduction of hyperpigmentation. She was then tapered to oral TXA 325 mg daily, while continuing the above measures, demonstrating continued clearance of her melasma (Figure 4). She reported no unwanted side effects throughout the course of her therapy.

FIGURE 4. Case 3. (A) Prior to initiation of oral TXA. Hyperpigmented patches on the face consistent with melasma. (B) After completing 6 months of oral TXA 325 mg BID, followed by 3 months of maintenance therapy with 325 mg QD.



CASE 4

A 49 year old Hispanic female with past medical history of hypertension presented with a chief complaint of persistent periorbital discoloration, present for years and worsened by sun exposure. She had previously treated the area with both topical hydroquinone 4% and topical tretinoin 0.25% without significant improvement.

On exam, hyperpigmented macules were noted distributed on

her bilateral periorbital consistent with melasma.

The decision was made to start oral TXA 325 mg BID. The patient continued this regimen for 6 months with significant improvement in her melasma. The patient reported no side effects. After that time she was tapered to 325 mg QD of oral TXA and a compounded cream of consisting of hydroquinone 10%/kojic acid/ascorbic acid/hydrocortisone was added to her regimen. The patient has remained on this regimen for over 1 year, and at the time of writing has no evidence of relapse.

DISCUSSION

Oral tranexamic acid (TXA) is a relatively novel agent for recalcitrant melasma. A variety of dosing strategies have been proposed and tested in small trials. A retrospective analysis comparing 500 mg, 750 mg, 1000 mg, 1500 mg daily dosing showed no significant difference in melasma area and severity index (MASI) or melanin index.[12] According to our literature review, a regimen of 250 mg BID has been most commonly used.[5, 13-15] This dosing regimen appears effective and safe.[16] Alternatively, a review by Bala et al summarizes that 500 mg daily over 12 weeks is safe and efficacious.[17] In the United States, however, oral TXA is most commonly dispensed in 650 mg tablets, therefore 325 mg BID dosing is commonly used.

Oral TXA is a renally eliminated drug with reported oral bioavailabilities ranging from 34% to 45%.[18-20] Plasma concentrations of TXA reach minimum effective levels (≥5 µg/ml) within 1.5 hours and a peak concentration within 3 hours, with a half-life of 2-11 hours.[20-22] At therapeutic concentrations it is minimally bound to plasma proteins and negligible accumulation is observed after repeated dosing to steady-state conditions.[18] Oral TXA has shown to be effective and superior to many other treatment modalities in the management of melasma. Twelve studies from 2011 to 2019, most without placebo groups, reported improved MASI scores and patient ratings during therapy, but relapse has been common.[23] One of these studies reported 69% improvement in MASI score, however, 72% experienced relapse within two months of stopping oral TXA.[23] One placebo-controlled study with Hispanic white women showed 49% improvement in MASI scores after three months of oral TXA compared to 18% in the placebo group and no adverse events; again, relapse occurred within three months of discontinuation.[13] Colferai et al conducted a placebo-controlled trial and found that oral TXA was associated with 50% improvement at 12 weeks compared to 5.9% in the placebo group.[24] In another randomized controlled trial involving 47 patients, an improvement of 50%was shown on 250 mg BID vs. 5.9% on the placebo.[24] At least seven studies have tested oral TXA in Asian populations with promising results and minimal adverse effects.[16, 25-30] Superiority was seen with oral TXA and triple combination cream versus triple combination cream monotherapy.[29] Relapse after therapy remains a concern in virtually all publications.

Safety data at this point is limited, but Zhang et al. performed a systemic review and meta-analysis, which included 1563 adults and 21 studies.[31] Ten trials were related directly to adverse effects.[31] The daily systemic doses of TXA in this analysis ranged from 500 mg to 700 mg.[31] The main adverse effects

TABLE 1.

Summary of Patient Characteristics Treated With Oral Tranexamic Acid

	Demographics	Prior Treatments	Oral TXA Dosing Regimen	Side Effects	Outcome
Case 1	39-year-old Hispanic Female, Fitpatrick type III	Strict sun protection, hydroquinone, fractional laser resurfacing, salicylic acid pads, kojic acid/hydroquinone compound, Jessner's peels (x3)	Oral TXA 325 mg BID for 6 months, followed by 325 mg QD indefinitely	None	Significant improvement from baseline, no evidence of relapse with tapered dose.
Case 2	47-year-old Hispanic female, Fitzpatrick type III	Adapalene/hydroquinone/ desonide combination cream	Oral TXA 325 mg BID for 6 months, followed by 325 mg QD indefinitely	None	Significant improvement from baseline with no evidence of relapse on maintenance dosing. Used combination cream throughout treatment with TXA.
Case 3	41-year-old Hispanic female, Fitpatrick type IV	Hydroquinone/Tretinoin/ Fluocinolone/Ascorbic acid combination cream	Oral TXA 325 mg BID for 6 months, followed by 325 mg QD indefinitely	None	Significant improvement from baseline with no evidence of relapse on maintenance dosing. Continued to use compounded cream during treatment.
Case 4	49-year-old Hispanic female, Fitpatrick type III	Tretinoin 0.25%, Hydroquinone 4%, Hydroquinone 10%/kojic acid/ascorbic acid/hydrocortisone combination cream	Oral TXA 325 mg BID for 6 months, followed by 325 mg QD indefinitely	None	Significant improvement from baseline, no evidence of relapse with tapered dose.

were gastrointestinal symptoms such as heartburn, nausea, abdominal pain, and epigastric discomfort.[31] Oligomenorrhoea, hypopigmentation, urticarial rash with angioedema, moderate myalgias, transient headache, anxiety, and depression were also reported.[31] Kim et al conducted another systematic review of eleven studies with up to 667 participants and determined that side-effects of TXA were minor and similar to the effects documented by Zhang.[32]

The primary safety concern with oral TXA is the potential risk of clotting. The risk of clotting is highest in patients with co-morbidities such as clotting disorders, history of pulmonary emboli, prolonged immobility, hormone therapy, drug interactions, active bleeding, cancer, and surgery.[17] A long-term study conducted by Muse et al utilized TXA to treat menorrhagia at doses of 3.9 g to 4 g for up to 5 days per month over 29 menstrual cycles.[17] Only mild side effects were reported, such as headache and back pain. Significant adverse effects were not noted. As stated above, doses of TXA utilized to treat melasma are much less, generally ranging from a total dose of 500 to 1500 mg daily. Moreover, studies determined that even in the setting of hemorrhagic conditions, TXA was found to only have minor side effects like nausea and diarrhea. At this point, data does not suggest that TXA causes a significant risk for thromboses, likely equivalent to the risk associated with oral contraceptive pills.

While the risk of serious adverse effects is low, screening patients for the risk of developing these potential adverse reactions is imperative. The oral formulation is contraindicated in patients with a history of active thromboembolic disease or with an intrinsic risk of thrombotic events. Concomitant use with procoagulant agents, including anti-inhibitor coagulant complex/factor IX complex concentrates, oral tretinoin, and/or oral contraceptives can increase the risk of thrombosis and therefore must be used with caution.

In conclusion, no consensus guidelines exist for the off-label use of oral TXA for the treatment of recalcitrant moderate to severe melasma. Multiple studies have shown this treatment modality to be safe and effective, however, the dosing regimen varies in the literature. We propose that oral TXA can be used safely and effectively at a dosing regimen of 325 mg twice daily for 6 months for initial clearance of melasma. Due to the fact that melasma often recurs after treatment discontinuation, maintenance therapy is usually necessary, however, effective dosing regimens utilizing oral TXA as maintenance therapy for melasma have not been established. As seen in this limited case series, continuation of oral TXA 325 mg once daily after initial clearance on twice daily dosing is an effective regimen to consider. It appears that, based on oral TXA's pharmacokinetics, steady state dosing of the medication is not required to maintain efficacy in preventing melasma relapse after clearance. As such we recommend once daily dosing indefinitely for maintenance therapy to reduce incidence of side effects without compromising efficacy. Further studies are required to validate this novel regimen.

DISCLOSURES

The authors have no conflicts of interest to declare.

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AUTHOR CORRESPONDENCE

Michael Foss DO
E-mail:..... Michael.Foss@ADCSclinics.com