***Case report***

**AMITRIPTYLINE INDUCED THROMBOCYTOPENIA AND SUBCONJUNCTIVAL HEMORRHAGE**

**ABSTRACT**

Amitriptyline, a widely used tricyclic antidepressant, is commonly prescribed for major depressive disorder and some off-label conditions. Although it generally has a favourable safety profile, there are case reports and studies linking amitriptyline with platelet dysfunction. Research suggests that bleeding events related to this drug are more likely in individuals who are vulnerable due to platelet dysfunction, inhibition of platelet monoamine oxidase (MAO), or, in rare cases, an idiosyncratic reaction. One case of thrombocytopenia accompanied by subconjunctival hemorrhage occurred in a patient taking amitriptyline at a dose of 25 mg/day, which resolved after discontinuing the drug. This rare side effect exercises the need for caution when using amitriptyline in certain patients.

**INTRODUCTION**

Subconjunctival hemorrhage is typically a harmless, self-resolving condition, usually caused by ocular trauma. Its prevalence has risen with increased rates of systemic hypertension, diabetes, hyperlipidaemia, and the use of anticoagulants.1 In most cases, the condition doesn’t result in pain or vision changes, and do not require specific treatment. In this report, we discuss a case of subconjunctival hemorrhage potentially induced by amitriptyline.
Amitriptyline, a tricyclic antidepressant, functions by inhibiting the reuptake of norepinephrine and serotonin, enhancing the availability of these neurotransmitters in the central nervous system (CNS).2 It affects both presynaptic and postsynaptic receptors, along with neurotransmitter transporters,3 influencing signal transduction and secondary signaling pathways. Long-term use can lead to changes in enzyme and receptor function.4 It’s commonly used for treating depression, anxiety disorders, PTSD, insomnia, somatoform disorders, premenstrual dysphoric disorder, nocturnal enuresis, migraine, and neuropathic pain.2,5
Amitriptyline can also lead to thrombocytopenia and thrombocytopenic purpura.6 However, subconjunctival hemorrhage linked to its use has not been previously reported. The mechanism behind this side effect remains unclear, but the possibility of idiopathic thrombocytopenia should be considered.7-9 The temporal relationship between starting the medication and the onset of thrombocytopenia leading to subconjunctival hemorrhage suggests more than a mere coincidence. This mechanism, although rare, has been discussed in existing literature.10

**CASE REPORT**

A 28-year-old female with Asian descent presented to the ophthalmology OPD with a history of redness in both eyes since 2days. She had no history of trauma, no history of pain or visual disturbances or photophobia or watering or discharge or any other associated symptoms. She had no history of fever, weakness or loss of appetite. She was not any antiplatelet agents.

She was a known case of migraine treated with amitriptyline 25mg for 2 months prescribed by a physician. No other drug intake

**OCULAR EXAMINATION:** Visual acuity in both eyes was 6/6, N6 with normal colour vision and Extraocular movements.

On anterior segment examination: In the right eye diffuse subconjunctival hemorrhage noted in the inferotemporal area in 5’o clock position about 3\*5mm in size and in the left eye a strip of diffuse subconjunctival hemorrhage noted at the junction of inferior bulbar and inferior palpebral conjunctiva along whole length. Lids, cornea, pupil were clinically normal.

Posterior segment examination was unremarkable. Her hemogram was done including other blood parameters.

**Blood Test Results:**

* Haemoglobin: 12.9 g/dL
* Packed Cell Volume: 41.4%
* RBC count: 4.85 x10^6/μl
* Mean Corpuscular Volume: 85.4 fl
* WBC count: 4.9 x10^3/μl (normal differential counts)
* Platelet count: 98,000 with mean platelet volume 6.5 fl
* Coagulation Profile:
	+ Prothrombin Time (PT): 13.6 s (normal range: 12-15 s)
	+ Partial Thromboplastin Time (PTT): 26.5 s (normal range: 22-32.6 s)
	+ INR: 1.05 (normal range: 0.8-1.2)

The patient never had a history of Thrombocytopenia/Subconjunctival hemorrhage/other bleeding manifestations. Complete ocular examination and systemic examination was normal. Platelet count gradually increased after stopping the drug and subconjunctival hemorrhage gradually resolved.

She was started on oral flunarizine and oral propranolol for migraine.

 

**FIGURE 1:** This is an image of both eyes showing subconjunctival hemorrhage marked in arrows.

**DISCUSSION**

Amitriptyline is a tricyclic antidepressant which blocks the reuptake of both serotonin and norepinephrine neurotransmitters and, desensitizes presynaptic auto receptors and heteroreceptors, producing long-lasting changes in monoaminergic neurotransmission on chronic use.11

Platelets resemble monoaminergic neurons in several respects, in terms of uptake of 5-HT and its inhibition, the subcellular storage and, release of 5-HT, and the metabolism of aromatic amines brought about by monoamine oxidase. Previous reports suggest that tricyclic antidepressants inhibit platelet monoamine oxidase (MAO) activity both in vitro and in vivo. And the sedative-hypnotic effects of the tricyclic antidepressant drugs closely correlate with the magnitude of platelet MAO inhibition and are mediated through alterations in the metabolism of both serotonin and/or the phenylethylamines.12

Treatment with amitriptyline tends to be associated with elevated platelet counts. The cause for this is not known, but relevant in terms of patients with long-term thromboembolic risk.13 And the possible effect of amitriptyline on [platelet function](https://www.sciencedirect.com/topics/medicine-and-dentistry/thrombocyte-function) and [sphingolipid](https://www.sciencedirect.com/topics/medicine-and-dentistry/sphingolipid) metabolites may represent a possible role of the [acid sphingomyelinase](https://www.sciencedirect.com/topics/medicine-and-dentistry/acid-sphingomyelinase) in the [hypercoagulability](https://www.sciencedirect.com/topics/medicine-and-dentistry/hypercoagulability) especially after a brain injury.14 Amplification of platelet aggregation can be altered by antidepressants that inhibit serotonin reuptake, in particular selective 5-HT reuptake inhibitors (SSRIs), because of depletion or decrease in intraplatelet 5-HT levels.

On the contrary, amitriptyline is associated with antiplatelet actions. This attributed to the inhibition of protein kinase C activity, by reducing the phosphorylation of proteins within platelets induced by thrombin. 15

Also, the release of arachidonic acid and its associated metabolites induce platelet aggregation under the influence of thrombin. The thromboxane’s which are transformed form the released arachidonic acid reacts with certain membrane receptors of the platelets coupled with further activation of phosphoinositide cycle and increase in calcium levels. Amitriptyline induces inhibition of this thromboxane’s which inhibits amplification of platelets.16-21. The overall impact of amitriptyline on platelet activity is likely a combination of these various mechanisms.

Evidence suggests that such bleeding episodes and thrombocytopenia occurs in vulnerable individuals, due to various direct and indirect mechanisms. It is vital to understand these mechanisms for a proper management of patients treated with amitriptyline.

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