

## Oral management of a patient with a plasminogen activator inhibitor (PAI-1) deficiency: case report

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### Abstract

*Plasminogen activator inhibitor-1 (PAI-1) deficiency causes a rare bleeding disorder by allowing excessive fibrinolysis to occur. Knowledge of the specific type and severity of the bleeding disorder is crucial in planning a safe and appropriate treatment sequence in conjunction with a hemophilia team. This article reports the oral management of a 9-year-old female with PAI-1 inhibitor deficiency using tranexamic acid (Cyclokapron®). (Pediatr Dent 16:133-35, 1994)*

### Introduction

Many patients routinely receive outpatient dental care when the bleeding diathesis is known and after appropriate medical interventions. Those with more severe or uncommon bleeding disorders may require treatment in a hospital setting under the supervision of a hemophilia team.<sup>1,2</sup> This report describes the dental management of a patient with a rare hemorrhagic disorder involving a complete deficiency of plasminogen activator inhibitor-1 (PAI-1).<sup>3</sup>

### Overview of fibrinolysis and PAI-1

The initiation of vascular fibrinolysis is a complex process. The enzyme plasmin, the primary fibrinolytic protease, is not present in active form in blood and other body fluids, but is formed from an inert precursor, plasminogen, through the proteolytic action of plasminogen activators. Specific inhibitors exist for both plasminogen activators and plasmin — the main in-

hibitors are plasminogen activator inhibitors (PAIs) and alpha-2 antiplasmin, respectively.<sup>4</sup> Decreased fibrinolysis results in a thrombotic tendency (Fig 1).<sup>5</sup> Unopposed fibrinolysis leads to a hemorrhagic tendency as when alpha-2 antiplasmin or plasminogen activator inhibitors are absent.

Two types of plasminogen activators have been identified: tissue-type plasminogen activator (t-PA) and urokinase type plasminogen activators (u-PA). Regulation of plasminogen activator activity occurs in a variety of ways:

- Hormonal regulation of biosynthesis and release
- Proteolytic conversion of plasminogen activators, with altered activities
- Interaction with cell surface receptors or with proteins that function as cofactors in the activation of plasminogen
- Rapid liver clearance of plasminogen activators<sup>5</sup>
- Presence of specific plasminogen activator inhibitors which also control plasminogen activator activity.

At least four immunologically distinct proteins with PAI activity have been identified: Plasminogen activator inhibitor 1 (PAI-1), plasminogen activator inhibitor 2 (PAI-2), proteases nexin (PN), and plasminogen activator inhibitor 3 (PAI-3).<sup>6</sup> However, the precise consequence of in vivo deficiencies of plasminogen activator inhibitors remains to be established.

PAI-1 is found in plasma, platelets, megakaryocytes, the placenta, vascular smooth muscle cells, and hepatocytes. PAI-1 levels are mediated by glucocorticoids, endotoxin, interleukin-1, transforming growth factor, tumor necrosis factor, and thrombin. In normal human plasma, PAI-1 is the primary inhibitor of both tissue-type plasminogen activator and urokinase type plasminogen activator activity.<sup>5</sup>

During platelet aggregation, PAI-1 is released, creating an almost tenfold local increase in PAI-1 levels. The plasminogen activator inhibitor derived from platelets is thought to play an important role in protecting

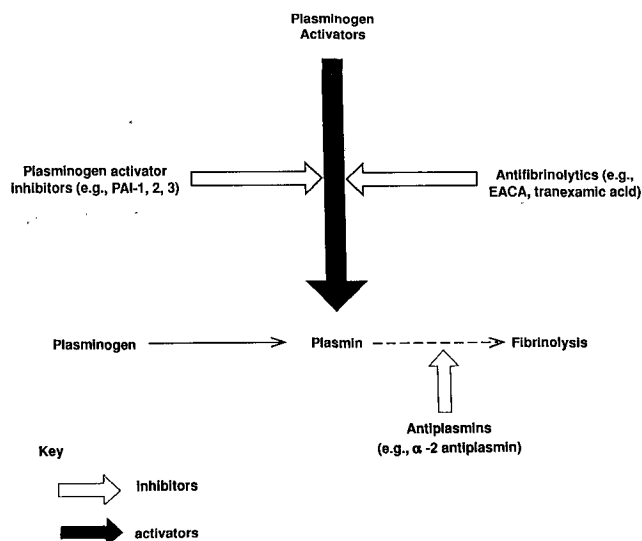


Fig 1. Fibrinolysis.

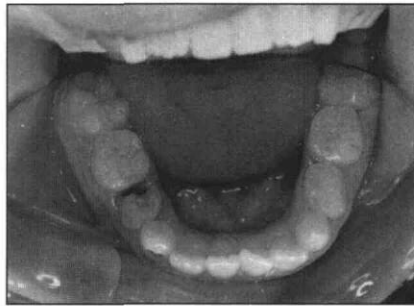
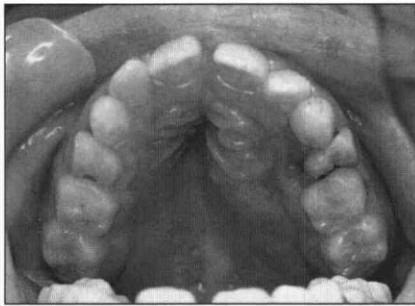


Fig 2. Intraoral views (mirror images) reviewing multiple caries and palatal swelling.

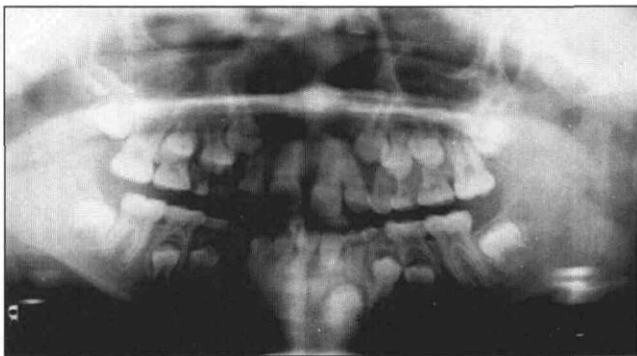


Fig 3. Initial panoramic radiograph of patient's dentition.

the clot against premature lysis. It is possible that the long-term lowering of PAI-1 activity through pharmacologic modulation may be an effective therapeutic approach to thrombolytic therapy.<sup>6</sup> Elevated levels of PAI-1 are thought to be associated with increased risk of coronary artery disease.<sup>7</sup>

### Case report

A 9-year 3-month-old Amish female presented to the dental clinic at James Whitcomb Riley Hospital for Children, Indianapolis, Indiana, with chief complaints of dental caries and a large chronic swelling of the right palate.

Eight months earlier, the patient presented to another institution with a toothache and oral swelling that had recently worsened. At that time, the patient was admitted with the diagnosis of an oral hematoma with an unknown disorder of hemostasis. She was given 1 million units of penicillin G every 6 hr. During the hospital course the patient received 5 units of cryoprecipitate, 15 units of fresh frozen plasma, 4 units of platelets, 588 units of Humate-P™ (Armour Pharmaceutical Co., Collegeville, PA), one unit of packed red blood cells and epsilon aminocaproic acid (Amicar®, Lederle Laboratories, Pearl River, NY) in an effort to control the oropharyngeal hemorrhage.

The patient's medical history included a subgaleal hematoma that resulted from a fall at 5 years of age. The patient's parents and seven siblings were all described as healthy. An aunt, who is a known carrier of

hemophilia A, had two affected sons.

Plasma was obtained from the patient for further evaluation. The patient was subsequently diagnosed with a complete deficiency of plasminogen activator inhibitor-1 (PAI-1).<sup>3</sup>

Intraoral evaluation revealed multiple carious lesions and an abscessed tooth (B) adjacent to an enlarged palatal growth (1 x 2 cm). A full series of radiographs and extra- and intraoral photographs were exposed (Figs 2 and 3). Clinical problems included multiple carious lesions, generalized moderate gingivitis, inadequate arch lengths, and a palatal swelling that was hard and immobile.

Oral hygiene was extremely poor, so thorough instructions for home care, including the use of a 0.12% chlorhexidine mouth rinse (bid), were given to the patient and parents. The patient was also placed on penicillin VK (250 mg q.i.d. for 10 days) for chronic infection in the area of teeth B and L.

Due to the extent of the dental treatment required and the potential for hemorrhagic complications, the patient was treated as an inpatient in the operating room under general anesthesia. Anesthesia was maintained with isoflurane with 65% nitrous oxide and 35% oxygen via oral intubation. Tranexamic acid (Cyclokapron®, Kabi Vitrum, Inc., Franklin, OH), administered orally, was used for control of bleeding, and instructions were given for the initiation of Cyclokapron (500 mg p.o. q8h) two days prior to surgery. Simple extractions of nonrestorable teeth B and L were performed due to extensive caries. A palatal biopsy consisting of two soft tissue specimens was performed. Avitene (Alcon, Inc., Humacao, PR) and 3.0 chromic gut sutures were placed over the biopsy and extraction sites. Preformed space maintainers (Denovo Co., Santa Clara, CA) were cemented onto teeth A and K.

Extubation and recovery were unremarkable and during the hospital course the patient had no postoperative bleeding, maintained stable vital signs, and denied oral discomfort. The patient had some emesis on the evening of surgery but tolerated feeding well thereafter. She was discharged the following day on Amoxicillin (Smith Kline Beecham Pharmaceuticals, Philadelphia, PA) (250 mg p.o. t.i.d. for 10 days), Cyclokapron (500 mg p.o. q. a.m., 750 mg p.o. q. p.m., and 500 mg p.o. q.h. for 7 days), and Tylenol® (McNeil Consumer Products, Fort Washington, PA) (325 mg q6h p.r.n. pain).

A diagnosis of dense fibrous connective tissue and hyperplastic periostitis was made. At the 2-week postoperative visit, the patient and parents reported no problems. The intraoral examination revealed a healing biopsy site. Chronic generalized gingivitis and intact restorations and appliances were also noted. Due

to the poor level of oral hygiene, guidelines for oral hygiene were reiterated to the parents and patient.

The 6-week postoperative evaluation showed significant improvements in oral hygiene and slight decrease in size of the palatal swelling. The band and loop appliances were removed due to premolar eruption.

The 4-month recall examination revealed no caries, adequate oral hygiene, slight deficiency in the maxillary arch, and minimal changes in the palate (Fig 4).

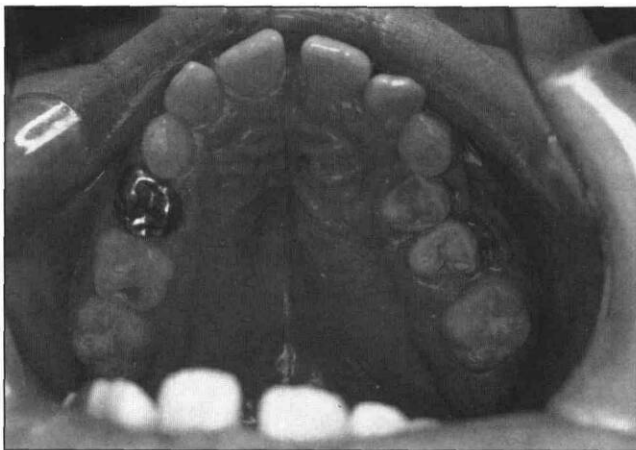
## Discussion

A patient with an unusual bleeding disorder (PAI-1 deficiency) presented with multiple carious lesions and chronic swelling of the right palate. The absence of PAI-1 leads to excessive fibrinolysis, resulting in a bleeding diathesis.

Tranexamic acid is an inhibitor of fibrinolysis and is often used to prevent clot lysis in the oral cavity in patients with a hemorrhagic diathesis (Fig 1). This antifibrinolytic agent acts by inhibiting the conversion of plasminogen to plasmin. Tranexamic acid inhibits the fibrinolytic system via two mechanisms. It decreases plasminogen activation (by competition with plasminogen activators) at serum concentrations achieved by oral administration. It also decreases the activity of plasmin, however, at levels that are not achievable through the oral route.<sup>8</sup> Therefore, tranexamic acid (Cyclokapron) was used in this patient to serve as an inhibitor of fibrinolysis, essentially fulfilling the function of the deficient coagulation factor PAI-1.

Prior to general anesthesia, oral hygiene instruction and chlorhexidine mouth rinses were used to decrease the severity of the patient's gingivitis, promote healing, and minimize oral gingival bleeding.

Treatment was performed under general anesthesia and consisted of extractions, space maintenance, and



**Fig 4.** Palatal view (mirror image) at 4-month postoperative visit showing minimal improvement in the area of swelling. Note the ectopic eruption of tooth 5.

palatal biopsy. After the extraction, direct topical application of Avitene powder (microfibrillar collagen) was used to help with local hemostasis. The results of the palatal biopsy indicated hyperplastic periostitis, a condition resulting from mild irritation, trauma, or infection. It should resolve over the next few years after extraction of the chronically infected tooth. The decision to place the patient on antibiotics was made after consulting the patient's hematologist. Amoxicillin was selected due to the patient's complex medical and oral condition.

This case report demonstrates the appropriate and safe dental care of a patient with a rare bleeding disorder completed in the hospital setting. The patient now has no dental symptoms and is followed on an outpatient basis for routine preventive care and monitoring.

Dental treatment of a patient with a bleeding disorder requires a thorough understanding of the patient's coagulopathy. Knowledge of the specific type and severity of the bleeding disorder is crucial in planning a safe and appropriate treatment sequence. The invasiveness of the procedure and the need for replacement therapy should be discussed with the patient's hematologist to develop a plan to prevent or control hemorrhage prior to initiating treatment.<sup>1</sup>

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