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ACE Inhibitor-Induced Angioedema

Introduction

1. The overall prevalence of ACE inhibitor angioedema is low (~0.2-0.7%), however it makes up the majority of visits to the ED for angioedema
2. ACE inhibitor angioedema is caused by the buildup of bradykinin which leads to increased vascular permeability and the release of substance P resulting in vasodilation and fluid extravasation into tissues
3. ACE inhibitor angioedema can occur at any time, with the majority of cases occurring within the first month of therapy.
4. Risk factors for ACE inhibitor angioedema includes female sex, African American race, chronic heart failure, coronary artery disease, history of smoking, and concomitant use of dipeptidyl peptidase 4 (DPP4) inhibitors

Pharmacology			
	Fresh Frozen Plasma (FFP)	**Icatibant**	**Tranexamic Acid (TXA)**
Dose	2-4 units	30 mg	1000 mg
Administration	Intravenous	Subcutaneous	Intravenous
PK/PD	Onset: ~ 2 hours	Onset: 2 hours Duration: 6 hours	Onset: ~ 2 hours
Adverse Effects	Hypervolemia, TRALI, thrombosis, hyperfibrinolysis, infection	Injection site reactions, LFT elevations, dizziness	Abdominal pain, headache, musculoskeletal pain/spasms
Drug Interactions and warnings	Calcium administration within the same line (may produce precipitants)	None	Contraindicated in patients with SAH or active intravascular clotting
Compatibility	N/A	N/A	Compatible with NS, D5W, or LR
Comments	Takes ~ 30-45 minutes to thaw & process once ordered	Costs ~ $4,500 per 30 mg syringe (AWP)	Available in most emergency departments. Inject 1000 mg TXA in 100 mL of diluent

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Overview of Evidence

Author, year	Design/ sample size	Intervention & Comparison	Outcome
Baş, 2015	RCT (n = 27)	SubQ Icatibant 30 mg vs. prednisolone + clemastine	Time to complete symptom resolution: 8 hours vs. 27.1 hours (P=0.002). Time to onset of symptom relief: 2 hours vs. 11.7 hours (P=0.03). All patients experienced complete resolution of edema.
Straka, 2017	RCT (n = 33)	SubQ Icatibant 30 mg vs placebo	Time-to-resolution (27.2 hrs vs 35.3 hrs) and amount of swelling over time were similar in placebo and icatibant treatment groups.
Sinert, 2017	RCT (n = 121)	SubQ Icatibant 30 mg vs placebo	There were no difference time to meeting discharge criteria between groups (4 hrs vs 4 hrs).
Karim, 2002	Case Report (n = 1)	4 units FFP following chlorpheniramine, hydrocortisone, and epinephrine	Dramatic improvement within 2 hours following FFP administration allowing for extubation.
Warrier, 2004	Case Report (n = 1)	2 units FFP following antihistamine, corticosteroid, epinephrine, antileukotrienes, cyclosporine, and IVIG (all without improvement)	Complete resolution of symptoms within 2-4 hours following FFP administration.
Bolton, 2012	Case Report (n = 1)	2 units FFP following antihistamine and corticosteroid administration	Near complete resolution of symptoms within 2 hours following FFP administration.
Hassen, 2013	Case series (n = 7)	2 units FFP following antihistamine and corticosteroid administration	Temporal association between the administration of FFP and **improvement in angioedema in 7 cases of presumed ACEI-induced angioedema** that were refractory to histamine-related anaphlaxis.
Stewart, 2013	Case Report (n= 2)	2 units FFP administered	Administration of FFP resulted in rapid resolution of symptoms in both patients.
Beauchêne, 2018	Case Series (n = 33)	Tranexamic Acid IV: 24 patients (73%) PO: 8 patients (24%) Unknown: 1 patient (3%) Dosage: 500 mg – 4 grams (55% received 1 g)	81.8% patients achieved significant improvement following TXA administration alone. 39.3% patients experienced symptom improvement within 1 hr of TXA administration.
Wang, 2020	Case Report (n = 1)	TXA 1000 mg IVPB over 10 minutes administered following diphenhydramine, famotidine, methylprednisolone, and epinephrine	Improvement in speech observed within 30 minutes of TXA administration with complete resolution of symptoms at 2 hrs. Patient discharged 2.5 hours following presentation to ED.
Manzano, 2021	Case series (n = 11)	TXA 1000 mg IV	The median length of stay in the hospital was 1.2 days (0.4-18.2 days). No noted adverse effects related to medication administration of TXA.

Conclusions

1. Many cases of ACE inhibitor angioedema will resolve on their own with the cessation of the offending agent.
2. More studies are needed to evaluate the use of investigational therapies including tranexamic acid and FFP.
3. In severe cases of ACE inhibitor angioedema, it is reasonable to consider using tranexamic acid or FFP if icatibant is unavailable after weighing the risks versus benefits.

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