Clinical Toxicology

Lec:10

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Cardiovascular Toxicology

Angiotensin-converting enzyme inhibitors

ACE inhibitors block angiotensin-converting enzyme, thereby decreasing the formation of angiotensin II, a potent vasopressor, which is critically involved in raising systemic blood pressure. As such, ACE inhibitors are commonly used in the treatment of hypertension. These drugs are also efficacious in the treatment of CHF, left ventricular systolic dysfunction, acute MI, and chronic renal disease.

In general, these drugs are well absorbed from the GI tract, reaching peak serum concentrations within 1–4 hours. Enalapril and ramipril are prodrugs and require hepatic metabolism to produce their active forms.
These drugs are primarily eliminated via the kidneys.
All ACEIs bind directly to the active site of angiotensin-converting enzyme, which is found in the lung and vascular endothelium, preventing the conversion of angiotensin I to angiotensin II.

Because angiotensin II is a potent vasoconstrictor and stimulant of aldosterone secretion, decreased peripheral vascular resistance, decreased blood pressure, increased cardiac output, and a relative increase in renal, cerebral, and coronary blood flow occur.

Hypotension is the most common manifestation in patients with ACE inhibitor overdoses. Adverse effects reported at therapeutic doses include first-dose hypotension, headache, cough, hyperkalemia, dermatitis, renal dysfunction, and angioedema.

The drugs may also cause adverse fetal effects; thus, this class of drugs is contraindicated in pregnancy.

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Toxicity and Treatment

The toxicity of ACEIs in overdose appears to be limited. Hypotension may occur in select patients but deaths are rarely reported in isolated ACEI ingestions. Treatment is supportive and symptomatic.

Activated charcoal alone is sufficient in most cases and should be given as long as no contraindications exist. Intravenous crystalloid boluses are often effective in correcting hypotension, although in rare cases, catecholamines may be required.

Naloxone may also be effective in reversing the hypotensive effects of ACEIs……!!!

Angioedema

Angioedema is an inflammatory reaction in which there is increased capillary blood flow and permeability resulting in an increase in interstitial fluid. If this process is confined to the superficial dermis, urticaria develops, whereas if the deeper layers of the dermis or subcutaneous tissue are involved, angioedema results.

Angioedema most commonly involves the periorbital, perioral, or oropharyngeal tissues. This swelling may progress rapidly over minutes and result in complete airway obstruction and death.

The pathogenesis of acquired angioedema involves multiple vasoactive substances, including bradykinin, and is not IgE-mediated.

One-third of cases may occur at any time after the first few days of therapy, even after years. Because of the propensity to involve the tongue, face, and oropharynx, the airway must remain the primary focus of management. The most important aspect of airway management in patients suffering from ACEI-induced angioedema, however, is early risk assessment for airway obstruction followed by rapid intervention, prior to severe, obstructive swelling developing.

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Therapy typically includes the standard medications used for anaphylaxis, such as subcutaneous epinephrine, intravenous diphenhydramine, and corticosteroids. However, because ACEI-induced angioedema is not an antibody mediated allergic phenomenon, these interventions will probably have limited efficacy so they should not be assumed or relied on to avoid definitive airway protection.

All patients with mild or quickly resolving angioedema should be observed for several hours to ensure that the swelling does not progress or return.

Out patient therapy with a short course of oral antihistamines and corticosteroids is appropriate. Such patients should be instructed to discontinue ACEI therapy permanently and to consult their primary physician about other antihypertensive options.
Because this is a mechanistic and not allergic adverse effect, the use of any other ACEIs is contraindicated.