COVID-19 Therapeutics & Toxicities

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Key Article

- *Chary M, et al. COVID-19: Therapeutics and Their Toxicities. J Med Toxicology. 2020. Epub ahead of print.*

Introduction

- Currently, there is no approved treatment or proven therapy for COVID-19.
- As researchers and pharmaceutical companies race to develop antiviral medications and vaccines, many have turned to treatments with little to no supporting evidence.
- Social media has seemingly propagated some misinformation.
- This article provides information on the toxicities of potential therapies used in the management of patients with COVID-19.

Viral Entry Inhibitors

- Chloroquine
    - Used primarily to treat malaria – prevents Plasmodia from crystallizing heme to hemozoin leading to buildup of heme that becomes toxic to the parasite
    - Alters glycosylation of ACE2 – decreases affinity of ACE2 for the coronavirus spike protein, reducing entry in vitro; may also inhibit pro-inflammatory cytokine signaling
    - Overall it is thought that it may reduce infectivity
    - Toxicity/Clinical manifestations
        - Doses > 5 gms are associated with mortality
        - Cardiovascular
            - Ventricular dysrhythmias
            - QRS widening due to sodium channel blockade
            - Profound hypotension
        - Neurologic
            - Seizures
            - CNS depression
        - Hypokalemia
            - Likely due to intracellular shifts

        - Values < 3.0 mmol/L correlate with mortality
        - Total body potassium stores may not be depleted
    - Treatment of Toxicity
        - Epinephrine infusion and high dose diazepam
        - Hypokalemia – be sure to monitor very closely for rebound hyperkalemia as toxicity resolves
        - QRS prolongation – sodium bicarbonate – may worsen hypokalemia
        - Lipid emulsion and ECMO can be considered in individual cases
- Hydroxychloroquine
    - A derivative of chloroquine; considered less toxic
    - Minimum fatal dose is not well known
    - Toxicities/Clinical manifestations
        - Hypotension
        - Hypokalemia
        - Ventricular dysrhythmias
    - Treatment of toxicity is the same as for Chloroquine toxicity

Nucleoside Analogs

- Remdesivir
    - A prodrug metabolized to an adenosine nucleotide analog
    - Has demonstrated efficacy against COVID-19
    - Toxicity extrapolated from toxicity of other nucleoside analogs – thought to reflect mitochondrial dysfunction
        - Metabolic acidosis with elevated lactate – associated with high mortality
        - Peripheral neuropathy
        - Bone marrow suppression
        - Pancreatitis
        - Myopathies
    - Treatment: no specific antidote; mitochondrial cofactors (thiamine, riboflavin, vitamin C) may help but is not proven

Azithromycin

- Thought to have modulatory effect on immune cells; reduces RSV release by decreasing interferon signaling in vivo and inhibits proinflammatory cytokine release in airway smooth muscle and epithelial cells
- Main toxicity is QTc prolongation leading to cardiac dysrhythmias
- If patients ingest combination of chloroquine or hydroxychloroquine and azithromycin may be more likely to have cardiac dysrhythmias

ACE Inhibitors & Ibuprofen

- Concern that ACE inhibitors may increase susceptibility to COVID-19
- ACE inhibitors can increase ACE2 expression in human tissue potentially creating more binding sites for COVID-19

- The receptor binding domain of COVID-19 has a high affinity for the ACE2 receptors
- Alveolar cells infected with COVID-19 express less ACE2 on their cell surface than normal cells
- As a result of these, some feel that patients taking ACE inhibitors may benefit from stopping these meds
- **No direct evidence of the impact of ACE inhibitors on the trajectory of those with COVID-19**.
- **A recent consensus statement recommends that patients taking ACE inhibitors and ARBs continue to take them**.
- Do not abruptly discontinue these meds
- Though ibuprofen increases ACE2 expression, no current organizations recommend withholding ibuprofen for the symptomatic treatment of COVID-19