Dexamethasone or hydrocortisone in COVID-19?

To the Editor: We read with interest the article by Chatterjee et al,[1] who provided an overview of the use of corticosteroids in patients with novel coronavirus disease 2019 (COVID-19). The authors discussed the best available evidence at the time of their writing regarding the outcomes in hospitalized patients with COVID-19 who received corticosteroids. However, with the publication of more randomized trials plus a meta-analysis by the World Health Organization (WHO)[2] on the use of corticosteroids in patients with COVID-19, we wish to complement the authors' discussion to elaborate on the relationship between pharmacodynamic profiles of hydrocortisone and dexamethasone and their respective efficacy in patients with COVID-19.

From the subgroup pooled analysis by WHO to determine the association between corticosteroid use and 28-day all-cause mortality rates in COVID-19 patients, there were no mortality benefits detected from the use of hydrocortisone, whereas dexamethasone significantly reduced the odds of all-cause death at 28 days.[2]

This is consistent with pharmacodynamic observations. Hydrocortisone has a lower affinity for the glucocorticoid receptor compared with dexamethasone. The reported log relative receptor affinities for hydrocortisone and dexamethasone were 0.95 and 2.0, respectively.[3] In addition, hydrocortisone demonstrates less inhibition of proinflammatory transcription factors than dexamethasone. For example, hydrocortisone inhibited tumor necrosis factor alpha-induced nuclear factor kappa B activation less than dexamethasone—the half-maximal inhibitory concentrations [IC50] for nuclear factor kappa inhibition were 15.52 nM and 2.93 nM, respectively.[4] The same is observed for nongenomic activity, for which hydrocortisone demonstrates lower potency: hydrocortisone had less inhibition of the release of prostaglandin E2 (PGE2) compared with dexamethasone (the IC50s for PGE2 release were 750 nM and 20 nM, respectively).[5] Both nuclear factor kappa B activation and PGE2 release play significant roles in the hyperinflammatory and immune responses in COVID-19.

For these reasons, along with its longer biological half-life and lesser mineralocorticoid activity, dexamethasone should be favored over hydrocortisone in patients with COVID-19 who need treatment with systemic corticosteroids.

Chia Siang Kow
School of Postgraduate Studies
International Medical University
Kuala Lumpur, Malaysia

Syed Shahzad Hasan
School of Biomedical Sciences & Pharmacy
University of Newcastle
Callaghan, Australia

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