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Evaluation of Dexamethasone Effects in COVID-19 Treatment

Hamza Khalifa Ibrahim

Department of Pharmacy Higher Institute of Medical Technology - Bani Waleed
Bani Waleed, Libya

Naeimah Ahmeed Ahseen

Faculty of Medicine Tripoli University, Libya

Tousief Irshad Ahmed

Senior resident department of cl. Biochemistry SKIMS, Soura, Srinagar, J&K,
India

Nisreen Ahmeed Ahseen

Department of Pharmacy Higher Institute of Medical Technology - Bani Waleed
Bani Waleed, Libya

Noor-Alhooda M Al-Awkally

Medical Laboratory Department, Higher Institute of Science and Technology,
Sulug

Aejeeliyah Yousuf

Department of Laboratory Higher Institute of Medical Technology - Bani Waleed
Bani Waleed, Libya

Abstract---(COVID-19) Finding a cure for Corona virus sickness in 2019 will be a difficult task for researchers all over the globe, since it is associated with significant lung damage and the potential for multiple organ failure. To far, dexamethasone has shown substantial benefits in COVID-19, reducing mortality while improving recovery. There is a reduction in inflammation due to a reduction in inflammation-related immune responses and a decrease in cytokine production, which prevents COVID-19 from becoming more severe. Dexamethasone's significance in the treatment of COVID-19 is currently unproven. When it comes to combating this pandemic, COVID-19's pathophysiology and dexamethasone's efficacy are the deciding factors.

Keywords---coronavirus, COVID-19, dexamethasone, treatment.

Introduction

Dexamethasone is an intense glucocorticoid with immunosuppressive and calming properties. It is multiple times as intense as cortisol. It is on the List of Essential Medicines by World Health Organization ([World Health Organization, 2019](#)). It was affirmed by FDA in 1958. "It is utilized to treat different problems, for example, endocrine, collagen, rheumatic, unfavorably susceptible, dermatological, gastrointestinal, ophthalmic, respiratory, hematological, edematous, cerebral edema, neoplastic and different conditions." On arising of COVID-19, finding a treatment has become an issue; trying to discover a treatment dexamethasone was tried in hospitalized patients with COVID-19 in United Kingdom National RECOVERY Trial, and found that dexamethasone improves endurance paces of seriously sick COVID-19 for example the individuals who are on mechanical ventilation or requiring oxygen. Likewise, patients without respiratory help were not influenced. Hence, much should be known on how dexamethasone applies its activity and neutralizes COVID-19. Patients taking corticosteroids are in danger of contamination and concealment of hypothalamic-pituitary-adrenal axis ([Ibrahim et al., 2018](#); [Yasir et al., 2018](#)).

Mechanism of action

As an immunosuppressive and anti-inflammatory agent, it is categorised. Changes in gene expression from hours to days might result from the binding of this glucocorticoid receptor to it. Inhibiting neutrophil migration and lymphocyte proliferation are two of the drug's primary mechanisms of action. Capillary membrane permeability has decreased while lysosomal membrane flexibility has increased. Some cytokines (interleukin-1 and interleukin-12, interferon-gamma, and the activation status of cells Almahbbh- macrophages) have been inhibited, and vitamin A molecules have been discovered in larger concentrations in blood ([Johnson et al., 2018](#)). It inhibits pro-inflammatory targets with a varying degree; Cyclooxygenase-2 (CXO-2), interferon-gamma, interleukin -1 α , and interleukin -1 β are strongly inhibited while, C-X-C motif ligand (CXCL1), CC motif ligand 3 (CCL3), interleukin -6, and interleukin -1Ra are less strongly inhibited ([Johnson et al., 2018](#)). Dexamethasone may also improve pulmonary circulation and increase surfactant levels ([Yasir et al., 2018](#)). " Taking corticosteroids in little amounts reduces inflammation but taking them in large amounts reduces immune system function" ([Yasir et al., 2018](#); [Khaliha et al., 2020](#)).

Drug interaction

Dexamethasone as a corticosteroid may interact with some medications whether increase or decrease their effects, among these drugs blood thinners (e.g., Warfarin), as a result the dose need to be adjusted to reach desired levels of blood thinning. Dexamethasone may affect blood levels of mifepristone as well ([Abraham et al., 2006](#)). Enzyme inducers such as, phenobarbital, Phenytoin (Dilantin), ephedrine, what's more, rifampin may expand the breakdown of dexamethasone and diminish its effects.

" Since dexamethasone is a moderate CYP 3A4 inducer, it lessens the effects of concurrent medications that are substrates of this enzyme ([Ogbru, 2020](#))."

Contemplations for the collaboration of dexamethasone are sensibly all around archived for corticosteroids with various mitigating and invulnerable administrative exercises that could be answerable for its beneficial outcomes in patients with COVID-19. Solid CYP3A4 inducers or inhibitors can significantly change the convergence of dexamethasone, either diminishing the impacts or raising the danger of toxicity (Florindo et al., 2020).

Dexamethasone itself is a poor CYP3A4 inducer, with most proof proposing that affectability to powerless CYP3A4 substrates is diminished by around 20%. Notwithstanding this helpless enlistment, remedy writing for specific drugs orders dexamethasone as a mellow CYP3A4 inducer, including a few rules for forestalling dexamethasone or changing the portion for simultaneous usage (Florindo et al., 2020).

Contraindication

The main contraindications are systemic infection, administration of live virus vaccine, and hypersensitivity to the components of medication. In certain cases, such as kidney disease, myasthenia gravis, peptic ulcer, diverticulitis, ulcerative colitis, and cirrhosis, dexamethasone should be used carefully (Yasir et al., 2018).

Caution in pregnancy

"dexamethasone can cross placenta, it diminishes respiratory trouble condition danger in untimely newborn child and improves lung development (Kolias et al., 2018; Liggins & Howie, 1972). Considering this impact, the Panel instructs the transient use with respect to dexamethasone in COVID-19 pregnant ladies who need mechanical ventilation (AIII) or who need just strengthening oxygen. (BIII) (Ogbru, 2020). Oral parted developments might be related with dexamethasone use.

Caution in children

"since the safety of dexamethasone use and other steroids for the treatment of COVID-19 in pediatric patients were not evaluated, and RECOVERY Study involved a limited number of pediatric patients, dexamethasone could be successful in pediatric patients with mechanical ventilation, lower mortality rates seen for children with COVID-19 in comparison with adults (Ogbru, 2020)."

Side effects

They are commonly connected with long haul use (over about fourteen days), aside from hyperglycemia. Patients should be checked with respect to the danger of hypertension, hyperglycemia, mental impacts, glaucoma, waterfall, liquid maintenance, osteoporosis Weakness in pathogens (Gyamfi-Bannerman et al., 2016). A drawn out utilization of foundational corticosteroids may increment idle contaminations' reactivation "(e.g.,herpesviruses, strongyloidiasis and, hepatitis B infection)" (Ogbru, 2020).

Effects in treating the emerging coronavirus

Coronavirus is brought about by (SARS-Cov-2) "serious intense respiratory disorder related COVID species 2." it's an "encompassed positive-sense", "single abandoned RNA infection" lead to mellow respiratory illness in human (Calabrese et al., 2020). In beginning stage, patients show introductory viral reaction with mellow manifestations, at that point they may create pneumonic and hyper provocative stage (cytokine storm) having raised incendiary markers, windedness and hypoxia (Corman et al., 2019). This is might be because of enormous arrival of fiery arbiters, including interleukin-1B, interleukin-2, interleukin-8, Tumor defilement factor-alpha (TNF-alpha), ligand 10 subject C-X-C (CXCL10), and ligand 2 topic CC (CCL2) (Siddiqi & Mehra, 2020).

"Pathophysiology of lung during COVID-19 is of two stages, mellow stage described by an irritation, epithelial harm, and safe reaction that are created by cytokine and chemokine discharge, Extreme cycle, generally because of delayed arrival of cytokine inclining to ARDS, kidney harm, other organ disappointment and optional contamination." (Figure 1) (Mehta et al., 2020).

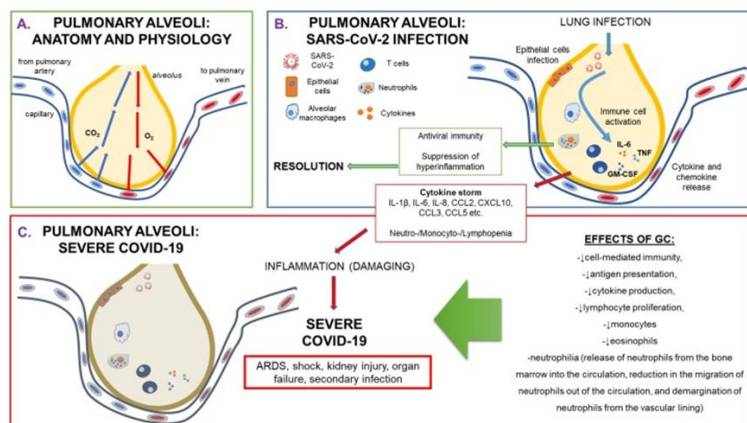


Figure 1.

The physiology and pathophysiology of lung alveoli during infection with SARS-CoV-2 (Mehta et al., 2020)

(A) The life structures and elements of solid alveoli. Gases are shipped when oxygen arrives at the blood and leaves carbon dioxide in the lung's little air spaces. The air shows up at the lungs through internal breath, experiences bronchi, bronchioles, and finally through alveoli. Carbon-dioxide-loaded air is pushed out of the alveoli into comparative areas during exhalation. (b) Pathophysiology of aspiratory alveoli during SARS-CoV-2 pollution. Covid Infection, SARS-CoV-2 called builds up an invulnerable reaction set off by a chemokine and cytokine discharge, just as an epithelial injury. This can prompt the enactment of resistant cells, coming about in one or the other goal or extraordinary COVID-19 and finishing in and the disappointment of different organs intense respiratory pain condition. (C) Severe COVID-19: Biological parts of safe frameworks. A tireless cytokine discharge incites aggravation that wounds alveolar epithelial, and bringing about optional contamination, stun, ARDS, and multi-organ disappointment (Mehta et al., 2020).

“With respect to, dexamethasone being a mitigating arbiter can lessen this irritation and forestalls tissue harm; as indicated by the RECOVERY Trial dexamethasone was found to have benefits for patients requiring respiratory help, it diminished passings by 33% in patients on mechanical ventilation (proportion 0.65 [95% certainty stretch 0.48 to 0.88]; $p=0.0003$) and by one-fifth in other oxygen-just patients (0.80 [0.67 to 0.96]; $p=0.0021$). Furthermore, it was not successful for patients without respiratory help (1.22 [0.86 to 1.75; $p=0.14$ ”).

In a test study researched the "mitigating impacts of dexamethasone" on mice, it was discovered that those impacts are mostly reliant on (DUSP1) "double explicitness phosphatase 1" (an individual from phosphatases has a capacity in articulation of fiery go between at both transcriptional and posttranscriptional level); its enlistment is a novel calming component of Glucocorticoids. This protein (DUSP1) was instigated by LPS (liposaccharides) and "portion conditionally expanded" by dexamethasone (Johnson et al., 2018). If these outcomes are material it can propose fundamental comprehension of dexamethasone activity all in all, and against COVID-19 also. That is dexamethasone restrains certain provocative targets(for example Cyclooxygenase-2{COX-2}, interferon-gamma, interleukin - 1 α , interleukin - 1 β , C-X-C theme ligand 1{CXCL1}, CC theme ligand 3 {CCL3}, interleukin - 6, interleukin - 1Ra, tumor rot factor, interleukin - 12p40 mRNA, and Colony invigorating variable 2 mRNA) (Ogbru, 2020). Also, a large portion of those objectives occur in COVID-19 (Siddiqi & Mehra, 2020).

As seen toward the start of other COVID scourges, for example, SARS in 2002 and MERS in 2012. (Momattin et al., 2019), the quest for helpful mediations for COVID infection in 2019 was escalated (COVID-19) The absence of a proper antibody, treatment routine and the board suggestions for COVID-19 are answerable for quick spread and raised death rates. Coronavirus related passings in extraordinary structures were generally ascribed to respiratory breakdown, conceivably because of deadly pneumonia brought about by wild inflammation. (Huang et al., 2020), “The SARS-CoV-2 disease is described by an expansion in favorable to incendiary and abatement in calming cytokines bringing about a condition of cytokine storm disorder, which thusly prompts the improvement of intense respiratory misery condition (ARDS), stun, numerous organ disappointment and resulting demise of the individual” (Huang et al., 2020).

Despite the fact that the utilization of corticosteroids has been accounted for as normal treatment of COVID-19 to lessen irritation related with injury. (Huang et al., 2020), their utilization is disputable and approval through clinical preliminaries is profoundly justified. It has taken thus long, with a total of 14 preliminary clinical trials, before it could be said that dexamethasone (corticosteroid) is safe and effective for the treatment of SARS-CoV-2 infection According to the findings of the Oxford University-led Rehabilitation trial (NCT04381936), Dexamethasone was previously believed to be one of the most effective medications on the world for reducing the risk of mortality among COVID-19 patients. World's greatest preclinical study. Rehabilitation, a preliminary randomized, double-blind, and open-label study for patients in hospitals, began in March 2020 (Mahase, 2020). The risk of mortality in COVID-19 ventilation and oxygen patients was shown to be reduced by up to 35% and 20%, respectively, when given dexamethasone. Accordingly, dexamethasone was

approved by the UK Government for use in the treatment of COVID-19 patients who remain ill. Regardless, there were no therapeutic benefits to COVID-19 patients with mild, major, or hospitalized COVID-19 patients (Ledford, 2020).

Dexamethasone (fabricated pregnan corticosteroid; cortisol subordinate) is an eminent life-saving medicine that is extensively used to treat easily affected and safe framework ailments (Figure 2). It is normally used for the balance and control of rheumatic issues, skin conditions, asthma, various kinds of excessive touchiness, steady obstructive aspiratory issue, cerebrum edema, eye torture related to eye an operation and bronchospasm. Corticosteroids smother the action and enunciation of explicit particles related with the searing response related with pneumonia. Likewise, a couple of sub-nuclear pathways are connected with corticosteroids which incorporate transactivation by extending the quality record of various quieting cytokines (Rhen & Cidlowski, 2005).

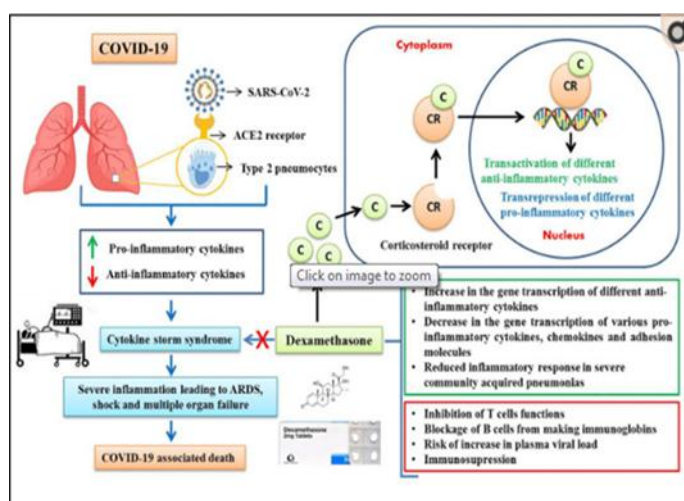


Figure 2. An outline of dexamethasone and its method of activity in COVID-19 patients (Ibrahim et al., 2018)

Furthermore, by diminishing quality record of different supportive of incendiary cytokines, chemokines, and grip atoms, corticosteroids can prompt trans-articulation (Rhen & Cidlowski, 2005). Furthermore, research center tests indicated a diminished provocative reaction in outrageous network procured pneumonia following corticosteroid organization (Sibila et al., 2008). Dexamethasone is indicated to counter the cytokine storm caused by the SARS-CoV-2 sickness, protecting the lungs and therefore lives, in this specific case, detailed investigations are necessary for the mitigating effect of dexamethasone.

Corticosteroids, on the other hand, may be helpful in treating COVID-19 in conjunction with immunoglobulins (IV-IG) and interferon (IFN-). Early use of dexamethasone with IV-IG and IFN- may reduce the harmful consequences of thiamine shortage in patients with COVID-19, according to a study. This study (IRCT20120225009124N4; <https://www.irct.ir/>) is now in its basic stages. It has been shown to be almost ten times more potent than cortisone and to last twice as long as the corticosteroid as a result of the FDA's approval as an

immunosuppressant that may be used for a wide variety of conditions. Provocative cytokines are suppressed by dexamethasone, which is also recommended for this purpose. It is still possible that the increased viral load in plasma might be caused by the obstruction of immunoglobulin assembly on T and B cells, which is a serious worry that warrants additional investigation (Sibila et al., 2008).

The earth shattering disclosure of dexamethasone as the main life-sparing medication is truly encouraging. It reveals insight into the expectation of lessening passing of basically sick medical clinic patients. It has been shown to be effective only in patients on ventilators or oxygen, but the overall effects on mortality reduction would be significant, since individuals with chronic illnesses are the major supporters of COVID-19's demise. Besides the generally low cost and worldwide flexibility of medications would prompt the disposal of the pandemic concerns. The medication would demonstrate valuable to low-and center pay nations where a fruitful yet exorbitant medication will be external the monetary control of the overall population (Sibila et al., 2008). However, the disclosure of more effective medications, for example, dexamethasone could change the worldwide effects of the COVID-19 pandemic on life and the economy. The objective has not yet been reached, in any case, and a fruitful antibody and fix are likewise expected to handle this pandemic.

Conclusion

For the treatment of COVID-19, dexamethasone has a critical role, which we explore in this study. Dexamethasone reduces morbidity and mortality in COVID-19 patients requiring respiratory support, as it prevents tissue damage and attenuates the severity of inflammation. Taking the short-term drug dexamethasone in a timely manner may help prevent the progression of the respiratory system caused by hypoxia in moderately to severe patients, and help to speed up the healing of those affected, and it is a relatively low-risk and low-cost drug.

The contribution of dexamethasone to the treatment of COVID-19 depends to a large extent on its mechanism of action that contributes to the pathophysiology of COVID-19. Although, known information about dexamethasone side effects, drug interaction, age and sex variation as well as COVID-19 comorbidities should be considered when using dexamethasone. Further studies about the levels of dexamethasone action against COVID-19, recognizing whether it is dose-dependent or not, and the safety of its use with other medication and COVID-19 comorbidity all are needed.

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