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Review Paper

Potential drug–drug interactions and adverse drug reaction associated with dexamethasone currently proposed for COVID-19 treatment in patients receiving other treatments: A review based on drug information resources

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Abstract: COVID-19 is a recently emerged coronavirus, with the majority of cases appearing in the Chinese city of Wuhan in December of 2019 in the form of acute pneumonia. Later this super spreader outbreak was declared as a global pandemic by World Health Organization (WHO) on 11th March 2020. WHO is continuously updating its treatment protocol for COVID-19 by adding new medications that positively impact patients. British scientists have revealed the availability of an effective drug called "dexamethasone," which can cut the threat of death from severe complications of "COVID-19" by a third. This drug is the only drug that has confirmed its effectiveness so far in decreasing the figure of deaths caused by the emerging coronavirus. As dexamethasone is considered the essential drug for treating COVID-19, further studies are required to compare the drug's probable interactions with other medications and adverse drug effects associated with it for public safety. Micromedex® drug interaction tool was utilized to evaluate and identify dexamethasone-related possible drug-drug interactions. Most of the drug interaction happens with CYP3A enzyme inducers like dronedarone, amiodarone, nifedipine, voxilaprevir, ticagrelor, and dihydrocodeine, etc. Finally, it is concluded that dexamethasone should be used under clinical care to emphasize proper screening of comorbid diseases and drugs.

Keywords: COVID-19; Dexamethasone; Micromedex®; CYP3A Enzyme; Drug-Drug interactions.

1. Introduction

COVID-19 is the newly emerged coronavirus whose most cases appeared in the Chinese city, Wuhan, in December of the year 2019 in the form of acute pneumonia (1). Later this super spreader outbreak was declared a global pandemic by World Health Organization (WHO), when more than 118,000 COVID-19 cases had been registered in 114 nations, as well as 4,291 deaths (2, 3). Till the present date, no precise treatment or medicine approved to avoid or to contain the novel coronavirus (2019-nCoV). However, some guidelines have been issued, such as taking proper care to get rid of and improve symptoms and optimizing supportive care. Some specific therapies are being researched and reviewed in a number of clinical trials (4). WHO is continuously updating its treatment protocol for COVID-19 by adding any medications that positively impact patients, following up everything issued by research centers worldwide round the clock. There are currently no vaccines or special drugs to combat corona, but researchers are trying to contain the disease with drugs or vaccines. Vaccines against the novel coronavirus are being rolled out, and across the globe, some four or five vaccines are currently being used.

The hydroxychloroquine (HCQ) clinical trial for the treatment of COVID-19 was halted on June 17, 2020, by WHO. The organization concluded that the anti-malarial drug HCQ did not contribute in reducing mortality rates in hospitals as the new clinical trial data showed its ineffectiveness (5).

Scientists are betting on a steroid treatment and describe it as a major breakthrough in fighting the COVID-19 epidemic (6). British scientists have revealed the effectiveness of dexamethasone which can cut the threat of death from severe complications of "COVID-19" by a third (7).

Dexamethasone (corticosteroid) was first used as a treatment during the 1960s to decrease inflammation in various situations, including certain types of cancers. Since 1977 this drug is available in multiple formulations and has been included in the Model List of Essential Medicines by WHO (8). The drug comes in tablet form, although liquid and soluble alternatives are available. Since it is already used in treating many ailments, it is off-patent and widely available for hospitals and doctors to store. It is also reasonably available in most countries and has low treatment costs (9).

This is the only drug that has confirmed its effectiveness so far in decreasing the number of deaths caused by the novel coronavirus 19. The drug reduced the mortality rate by a third among patients who were placed under respiratory support. Moreover, using this drug reduced the death rate by 20 percent among novel coronavirus patients who needed oxygen (10). Even though many countries included dexamethasone as an essential drug for treating COVID-19, further studies are required to compare the drug's probable interactions with other drugs and adverse drug effects associated with it for public safety.

1.1 Importance of drug-drug interactions

Drug-drug interactions, also termed as DDIs, are reflected as escapable medication-related problems. Drug interactions arise when one or more medications (active pharmaceutical ingredients) interfere with one another, altering the potency or toxicity of the drugs concerned. The chance of developing a DDI is equal to the total amount of drugs taken.

Patients are harmed by drug-drug reactions because the effectiveness of the medication is increased or the clinical usefulness is reduced. According to a review of several trials involving over 370,000 participants, 2.2%t to 70.3% of patients are at risk of drug-drug interactions. According to a report by Nolan and O'Malley, patients who take numerous drugs (ten or more) have a greater than 90% chance of having single or multiple clinically significant drug interactions. Interactions like these are often linked to extended hospitalizations or readmissions (11, 12).

The change in the pharmacological action or therapeutic response caused by a drug due to another drug's concomitant administration is termed as drug-drug interaction (13). The bulk of these interactions are caused by the pharmacokinetics incompatibility of two drugs/molecules'. Medication errors are caused by drug reactions (14). DDIs may be classified into two categories based on their treatment response:

Synergistic DDIs: Drug synergy is an outcome of di or multi interacting drugs, which (due to similar action) leads to a combined boost of drug efficacy. Drug Synergy is a goal of combinational drug therapy, but sometimes it has toxic effects (15). Synergistic medication interactions are commonly thought to be therapeutically beneficial in combination drug treatments (16).

Antagonistic DDIs: Drug antagonism is an outcome of di or multi interacting drugs which (due to opposite action) lead to an undesirable, reduced efficacy (17).

1.2 Adverse Drug-Reaction Consideration (ADR)

When we talk adverse drug reaction or ADR, it means a negative, unfavorable or unintended reaction to a medication. ADRs affect treatment efficacy and patient's quality of life, often causing sickness and death as a result of which patients lose confidence in or have adverse sentiments toward doctors. Many variables contribute to ADRs, including a rise in the amount of medications available on the market, an ageing population, and an upward spike in polypharmacy, medication reactions, and so on (18).

1.3 Drug Database

Drug Information resources are the databases that consist of critically examined & relevant (current) data about drugs and their utilization information, both clinical & scientific. The efficient use of drug information is an important skill for all healthcare providers. There has been an explosion of information on the Internet for both the health care professional and the consumer. Micromedex® is one such internationally trusted database of clinically useful drug information (19, 20). Some of the drug information sources are represented in table 1.

S. No	Drug Information resources	Access	Developer	Country
1.	DrugDex® System	Subscription	Thomson Reuters MICROMEDEX® 2.0	USA
2.	Martindale		Pharmaceutical Press	UK
3.	Lexi-Drugs®		Lexi-Comp, Inc.	USA
4.	Drug Facts and Comparisons®		Wolters Kluwer Health— Facts &Comparisons™	USA
5.	Epocrates® Online	Free	Epocrates, Inc. www.epocrates.com	USA
6.	A-Z Drug Facts™		WoltersKluwer™ Health www.drugs.com	USA

Table 1: Globally used Clinical Drug Databases

Micromedex® is a tertiary resource designed to provide information to health care professionals about clinical inquires. This resource, commonly used in the hospital or academic setting, provides a variety of information in the areas of drug information, poison information, acute care medicine, and patient education. Information is provided as full-text and is referenced throughout. Although Micromedex® is a large database; the primary literature is readily referenced and easy to access. Therapeutic indications are given a graded evidence rating with usage recommendations. For the clinician, Micromedex® provides prescription information that is detailed, simple to understand, and well-referenced (19, 20).

2. Materials and Methods

We have performed an analysis of dexamethasone drug interactions on Micromedex®. Micromedex® is an international evidence-based website that contains drug-related references. The gathered evidence is further processed for statistical interpretation through Microsoft Excel. Also, we have systematically reviewed the literature on dexamethasone, its pharmacokinetic properties, ADRs, and toxicities associated when dexamethasone drug was placed on PubMed, Google Scholar, CDC database, etc.

3. Results and Discussion

3.1 Micromedex® Drug Interaction Tool Analysis:

Table 2 and Figure 1 and 2 outline the results of the Micromedex® drug interaction tool study to assess and classify dexamethasone-related potential Drug-Drug Interactions. There are around 110 potential drug interactions possible with dexamethasone. Some 5 (4.50%) were contraindicated to severity level. Other 57(51.34%) showed major severity. Some 47(42.34%) were moderately severe, whereas 1(1%) displayed minor severity. Contraindicated severity signifies the drug's potential interactions when used together; major severity signifies the interactions that may impose life hazard and/or require clinical intervention to reduce or safeguard serious adverse effects. In contrast, moderate severity signifies the interactions that could exacerbate the patient's condition and may require a change in treatment.

Table 2: Dexamethasone Drug- Drug Interactions with Severity levels (Micromedex®).

Drugs With Contraindicated Severity To Dexamethasone							
Rotavirus Vaccine	Desmopressin	Rilpivirine	Artemether/Lumefantrine	Praziquantel			
Drugs With Major Severity To Dexamethasone							
Fluoroquinolones	Fentanyl	Dronedarone	Amiodarone	Nifedipine	Thalidomide	Macimorelin	Conivaptan
Nadroparin	Voxilaprevir	Ticagrelor	Bupropion	Dihydrocodeine	Sufentanil	Oxycodone	Darunavir
Fosamprenavir	Cholestyramine	Nilotinib	Etravirine	Hydrocodone	Dual Strong Cyp3A Inhibitors	Telaprevir	Alfentanil
Tacrolimus	Lapatinib	Boceprevir	Hemin	Nimodipine	Sargramostim	Methadone	Tramadol
Pentazocine	Vortioxetine	Meperidine	Nevirapine	Doxorubicin	Vincristin	Velpatasvir	Hormonal Contraceptives
Ubrogepant	Efavirenz	Sunitinib	Lumateperone	Codeine	Ceritinib	Elvitegravi	Strong Cyp3A Inducer
Enzalutamide	Buprenorphine	Daclatasvir	Nsaids	Aldesleukin	Ixabepilone	Piperaquine	Bemiparin
Drugs With Moderate Severity To Dexamethasone							
Ospemifene	Aprepitant	Netupitant	Warfarin	Saiboku-To	Metocurine	Gallamine	Auranofin
Pancuronium	Alcuronium	Aspirin	Licorice	Phenobarbital	Rifapentine	Atracurium	Hexafluorenium
Caspofungin	Fluindione	Aminoglutethimide	Vecuronium	Mifepristone	Tretinoi	Lurasidone	Anthrax Vaccine Adsorbed
Mivacurium	Ma Huang	Glycerol Phenylbutyrate	Doxacurium	Cisatracurium	Amphotericin B Liposome	Ruxolitinib	Amprenavir
Vaccines	Tubocurarine	Pipecuronium	Rocuronium	Selegiline	Delavirdine	Flibanserin	Fluconazole
Sorafenib	Echinacea	Testosteron	Acenocoumarol	Clozapine	Dicumarol	Phenprocoumon	
Drugs With Minor Severity To Dexamethasone							
Albendazole	Tuberculin						

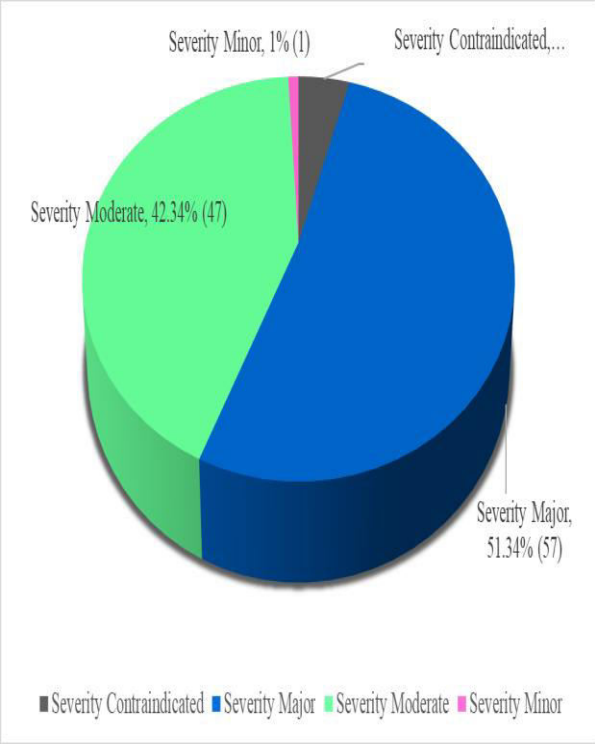

Figure 1 Dexamethasone Drug- Drug Interactions Severity analysis chart (Micromedex®).

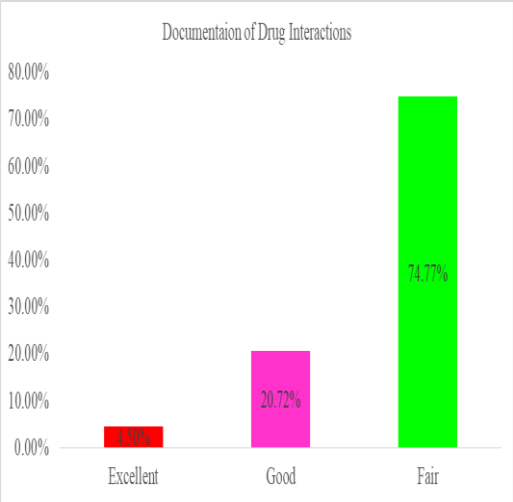

Figure 2 Dexamethasone Drug- Drug Interactions Documentation analysis chart (Micromedex®).

The documentation of these drug interactions is good with 20.72% drugs and excellent with 4.50% drugs and fair with rest 74.77% drugs their details are available in figure 2. Good documentation signifies that the interaction among drugs exists, but specific clinical studies are missing.

Most of the drug interaction is found to occur with CYP3A enzyme inducers like dronedarone, amiodarone, nifedipine, voxilaprevir, ticagrelor, and dihydrocodeine, etc. that may cause the development of decreased plasma concentrations of the drug and may result in the decreased effect of dexamethasone. Dexamethasone dose was increased in patients receiving the above-mentioned inducers of CYP3A4, and the efficacy of dexamethasone was monitored closely. The results have been presented in table 2. Therefore, this combination is considered deadly in treating COVID-19 conditions (21, 22). However, telaprevir was found to show increased concentration of dexamethasone that may be due to enzyme inhibition. There may be a higher risk of infection with a live vaccine like the rotavirus vaccine as it may enhance the toxic effects or undesirable effects of the vaccine. Growth hormone insufficiency diagnosis with macimorelin and muscle weakness and myopathy with metocurine, gallamine, pancuronium, alcuronium, atracurium, hexafluorenium, etc., were observed. Therefore, such a combination should be avoided. Dexamethasone decreases the level of rilpivirine and praziquantel by affecting the hepatic/intestinal enzymes CYP3A4 metabolism. Increased GI ulceration by pharmacodynamics synergism with asprin was the best example of drug-drug interaction (21, 22).

The use of contraindicated drugs as concomitant therapy should be avoided with dexamethasone to prevent further morbidity. A safer drug regimen should always be preferred under regular clinical monitoring. The patients with comorbidities should be closely monitored, and dose of the drug should be adjusted according to the health condition and contraindications.

Blood pressure, occult blood loss, haemoglobin, serum potassium, glucose, and bone mineral density; weight and height in children; IOP with systemic use >6 weeks should be monitored when taking dexamethasone and also keep an eye on the inhibition of the HPA axis (21).

3.2 Dexamethasone Adverse Drug Reactions:

While a short-term and short dose of drug administration may not cause serious side effects, it could be fatal in moderate to high doses. With therapy for a long duration, it may cause inhibition of adrenal function, Cushing's syndrome, and damaged immune defense (23).

3.3 Adverse Reactions

Corticosteroids are a class of medications that are commonly used in a variety of healthcare settings. Using

them in minimal dose may cause a sub-therapeutic response, and in contrast, using in higher dose may show an adverse effect (24).

Summary Product Characteristics (SmPCs) of dexamethasone injection and tablet highlighted the warnings of possible health hazards associated with the administration of dexamethasone in certain co-morbid and contraindicated patients. When using dexamethasone tablets in diabetics and hypertensive patients, blood glucose and blood pressure may rise during treatment, so regular monitoring should be done for those at higher risk. At high doses, the potassium level in the blood should be monitored. Regular medical checkups, especially with an ophthalmologist, should be done for the patients on long-term treatment (25). Systemic dexamethasone summary of product characteristics (SmPC) or safety summary has been given in the following subtitle (25, 26).

3.4 Contraindication: Hypersensitivity to live virus vaccines

3.4.1 Precautions:

- Manic-depressive illness and previous steroid psychosis
- Acute and chronic bacterial infections
- In a history of tuberculosis
- Osteoporosis
- Severe cardiac insufficiency
- High blood pressure that is difficult to regulate
- Diabetes mellitus that is difficult to regulate
- Psychiatric disorders
- Narrow- and wide-angle glaucoma
- Severe ulcerative colitis
- Diverticulitis
- Enteroenterostomy
- Severe anaphylactic reactions may occur

3.4.2 Warnings:

- Dietary salt restrictions and potassium supplementation may be necessary
- When you stop using corticosteroids after a long period of use, you can have withdrawal symptoms.
- Systemic corticosteroids may be lowered to physiological doses quickly.
- Patients that have received multiple courses of systemic corticosteroids, particularly if they have been taking for more than three weeks.
- Patients who have received multiple courses of systemic corticosteroids, particularly if they have been taking for more than three weeks
- After a year of the end of long-term treatment, a brief course is recommended (months or years),
- Patients that may have causes for adrenocortical insufficiency rather than exogenous corticosteroid treatment,
- Patients taking systemic corticosteroid doses higher than 6 mg dexamethasone daily
- Patients that take their doses in the evening on a regular basis.
- The use of chronic and topical corticosteroids has been linked to visual disturbances.

When corticosteroids are given in injection form, extreme care is needed in people with affective disorders, especially when they are on a higher dose. Corticosteroids given systemically may worsen the fungal infections. It may cause retention of salt and water; in such cases, dietary salt restriction and a potassium supplement may be necessary (24).

Some adverse reactions mentioned below may not be specifically for dexamethasone but reported for the drugs from the same category.

3.5 ADR reported with Dexamethasone (Figure 3)

Cardiovascular: Bradycardia, cardiac failure, cardiomegaly, circulatory shock, edema, embolism (fat), hypertension, vasculitis, syncope, hypertrophic cardiomyopathy (premature infants), thrombophlebitis, cardiac arrhythmia, myocardial rupture (post-MI), tachycardia, thromboembolism.

Central nervous system: Neuropathy, paresthesia, increased intracranial pressure, emotional lability, insomnia, malaise, vertigo, myasthenia, pseudotumor cerebri (usually following discontinuation), psychic disorder, seizure, euphoria.

Dermatologic: allergic dermatitis, alopecia, atrophic striae, diaphoresis, ecchymoses, erythema, facial erythema, fragile skin, hyperpigmentation, skin

atrophy, acne vulgaris, ,hypopigmentation, perianal skin irritation (burning, tingling, itching; after IV injection), petechiae, skin rash, suppression of skin test reaction, subcutaneous atrophy, urticaria, xeroderma, hypertrichosis.

Endocrine & metabolic: Cushing syndrome, diabetes mellitus, decreased glucose tolerance, carbohydrate intolerance, fluid retention, hirsutism, decreased serum potassium, adrenal suppression, sodium retention, glycosuria, menstrual disease, growth suppression (children), hyperglycemia, hypokalemic alkalosis, moon face, weight gain, HPA-axis suppression, negative nitrogen balance, protein catabolism, redistribution of body fat.

Gastrointestinal: Abdominal distention, gastrointestinal hemorrhage, gastrointestinal perforation, pruritus ani (after IV injection), hiccups, ulcerative esophagitis, increased appetite, nausea, pancreatitis and peptic ulcer.

Neuromuscular & skeletal: Amyotrophy, aseptic necrosis of bones, bone fractures, myasthenia, myopathy, osteoporosis, rupture of tendon, steroid myopathy, vertebral compression fracture

Miscellaneous (19, 20): Genitourinary: Defective (increased or decreased) spermatogenesis; **Hematologic & oncologic:** Kaposi sarcoma, petechial, tumor lysis syndrome; **Hepatic:** Augmented serum transaminases hepatomegaly; **Hypersensitivity:** Anaphylactic reaction, anaphylaxis, angioedema, hypersensitivity; **Local:** Post-injection flare (intra-articular use); **Ophthalmic:** Glaucoma, sub-capsular posterior cataract, exophthalmos, increased intraocular pressure.

There are various factors that affect the development of ADRs, such as age, sex, drug dose, co-morbidity, etc. Careful evaluation of these factors could prevent and reduce the incidence of unwanted & undesired ADRs. Counseling, health education & reconciliation of medications are essential which must be performed by health care providers (HCPs). For example, drug information resources should also be utilized in the evidence-based medication decision-making process, making aware HCPs about advancement in the medical field and basics such as drug-dosing, lethal drug interaction, possible adverse events. Relevant clinical information is a mandatory requirement to prescribe medication for the optimum therapeutic outcome. The Benefits of medical therapy must always outweigh the risks associated with it (27).

According to a study, the GI system was the most affected system with dexamethasone, followed by the cardiovascular system. Each patient's relative costs and advantages must be carefully considered before corticosteroids are started (28). Adolescent patients experience more ADR with oral dexamethasone than children. The ADR is also affected by the co-administered drugs (29). The use of these corticosteroids should not be stopped abruptly, and it should be done gradually (30)

4. Conclusion

COVID-19 is a pandemic disaster and a health emergency of prime focus for all the world economies. Various options for COVID-19 treatment are currently available, such as the use of chloroquine, hydroxychloroquine, azithromycin, dexamethasone, remdesivir, plasma therapy, etc. and many others are in the pipeline. The major proportions of patients are asymptomatic; therefore, blind use of dexamethasone should be prohibited. Most of the drugs are CYP3A4 enzyme inducers or inhibitors; their use should be carefully monitored considering DDIs and ADRs associated with dexamethasone. It should be used under clinical care by emphasizing proper screening of comorbid diseases and drugs.

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6. Author's Contributions

All authors are equally contributed in the preparation of the manuscript.

7. Conflict of Interest

The authors declare that there is no conflict of interest.

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