SAFETY AND EFFICACY PROFILE OF DEXAMETHASONE IN THE MANAGEMENT OF COVID-19: A REVIEW

Vaishali Kailas Ghume[1*], Aarti R. Golhar[1] , Dr. Abhijit N. Merekar[1], Prof. Mahesh D. Dokhe[2], Smita K. Parjane[3]

1. *Department of Pharmaceutics, Dr. Vitthalrao Vikhe Patil Foundation's College of Pharmacy, Viladghat, Ahmednagar-414111.*
2. *Department of Quality Assurance Techniques, Dr. Vitthalrao Vikhe Patil Foundation's College of Pharmacy, Viladghat, Ahmednagar-414111.*
3. *Department of Pharmaceutical Chemistry, Pravara Rural College of Pharmacy, Loni BK, Rahata, Ahmednagar-413736.*

Corresponding Author:

Miss. Vaishali Kailas Ghume

Department of Pharmaceutics,

Dr. Vitthalrao Vikhe Patil Foundation's College of Pharmacy,

Viladghat, Ahmednagar-414111

E-mail: vaishalighume7@gmail.com

ABSTRACT

Dexamethasone is a corticosteroid fluorinated at position 9 used to treat endocrine, rheumatic, collagen, dermatologic, allergic, ophthalmic, gastrointestinal, respiratory, hematologic, neoplastic, edematous and other conditions. Developed in 1957, it is structurally similar to other corticosteroids like hydrocortisone and prednisolone. Dexamethasone was granted FDA approval on 30th October 1958. In a press release for the Randomized Evaluation of COVID-19 Therapy trial on 16th June 2020, dexamethasone was recommended for use in COVID-19 patients with severe respiratory symptoms. Dexamethasone reduced deaths by approximately one third in patients requiring ventilation and by one fifth in those requiring oxygen. Dexamethasone stops two phases of inflammation and exerts both anti-inflammatory and immunosuppressive effects. As dexamethasone is long-acting and has systematic effects, it is about 25-times more potent than other synthetic corticosteroids. Glucocorticoids (a class of corticosteroids) are also stronger than nonsteroidal anti-inflammatory drugs (NSAIDs) like ibuprofen or aspirin. Glucocorticoids stop two phases- i.e., vasodilation and immune cells migration- of inflammation. In contrast, NSAIDs only inhibit the vascular stage. Hence, dexamethasone is both anti-inflammatory and immunosuppressive.

KEYWORDS: Corticosteroids, Dexamethasone, anti-inflammatory and immunosuppressive, COVID-19.

INTRODUCTION:

In March 2020, the World Health Organization (WHO) declared the COVID-19 outbreak a global pandemic. COVID19 is caused by SARS-CoV-2, a variant of coronavirus. As of 10 April 2020, over 1,500,000 confirmed cases have been diagnosed in more than 130 countries and areas, resulting in about 93,000 fatalities thus far. Symptoms of infection are usually nonspecific, and include fever, cough, and myalgia, with diarrhea, with or without the subsequent development of dyspnea. Severe cases that include respiratory distress, sepsis, and septic shock have been increasingly reported.

During the SARS outbreak in 2003, corticosteroid therapy was used to reduce inflammatory-induced lung injury. In Covid-19, too, many countries are investigating the effectiveness of corticosteroid therapy on patients with an acute respiratory infection. Also, the World Health Organization (WHO) has prioritised the evaluation of corticosteroids in clinical trials to assess safety and efficacy.

In interim guidelines on Covid-19 treatment released on May 27, the WHO has recommended “against the routine of systematic corticosteroid” for treatment of viral pneumonia. It said a systematic review and meta-analysis of the impact of corticosteroid therapy on persons with SARS-CoV-2, SARS-CoV and MERS-CoV revealed corticosteroids did not significantly reduce the risk of death, did not reduce

hospitalisation duration, ICU admission rate and/or use of mechanical ventilation, and had several adverse effects.

Corticosteroids have also been investigated for respiratory syncytial virus (RSV) in clinical trials in children with no conclusive evidence of benefit, and are therefore not recommended. Two recent commentaries published in the Lancet between February and March 2020 reported that corticosteroids should not be used for the treatment of COVID-19. However, these assumptions are mainly based on the findings of the met analyses cited above, on disease caused by similar viruses, but not research on COVID-19 specifically. We performed a rapid review of the literature to assimilate the current scientific data on this topic.

What is Dexamethasone?

It is an anti-inflammatory drug, commonly used to treat conditions in which the body's immune system does not function properly, and causes inflammation and tissue damage. Dexamethasone reduces the production of the chemicals that cause inflammation and also reduces the activity of the immune system by affecting the way white blood cells function.

Dexamethasone falls in a category called corticosteroids, which closely mimic cortisol, the hormone naturally produced by the adrenal glands in humans. It is commonly used in treatment for rheumatological inflammatory conditions: inflammation of muscles, inflammation of blood vessels, chronic arthritis, and lupus. It is used in lung diseases, kidney inflammation and eye inflammation, and to reduce swelling associated with tumours of the brain and spine. In cancer patients, it is used to treat nausea and vomiting caused by chemotherapy drugs.

LITERATURE REVIEW:

We searched Medline, Google Scholar and MedRxive for studies that included terms for inhaled corticosteroids and COVID-19 and other related acute coronavirus respiratory tract infection. Google Scholar citations were screened. After screening by title and abstract, 10-12 were considered relevant and we were able to obtain full text articles for all but one and systematic review and their full text articles screened by both authors (VG & MD)

PHARMACOLOGY:

As a glucocorticoid, dexamethasone is an agonist of the glucocorticoid receptor (GR). It has no mineralocorticoid activity.

CLINICAL PHARMACOLOGY:

Glucocorticoids, naturally occurring and synthetic, are adrenocortical steroids that are readily absorbed from the gastrointestinal tract. Glucocorticoids cause varied metabolic effects. In addition, they modify the body's immune responses to diverse stimuli. Naturally occurring glucocorticoids (hydrocorti-sone and cortisone), which also have sodium-retaining properties, are used as replacement therapy in adrenocortical deficiency states. Their synthetic analogs including dexamethasone are primarily used for their anti-inflammatory effects in disorders of many organ systems.

At equipotent anti-inflammatory doses, dexamethasone almost completely lacks the sodium-retaining property of hydrocortisone and closely related derivatives of hydrocortisone.

DRUG STRUCTURE AND CHEMISTRY:

Dexamethasone is a synthetic pregnane corticosteroid and derivative of cortisol (hydrocortisone) and is also known as 1dehydro-9α-fluoro-16α methylhydrocortisone or as 9α-fluoro11β,17α,21-trihydroxy-16α-methylpregna1,4-diene-3,20-dione.

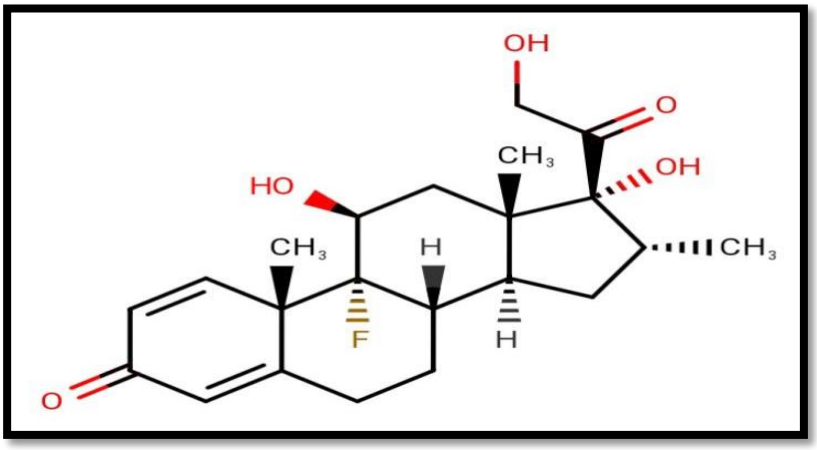

Figure No.1: Structure of Dexamethasone

SYNTHESIS:

To synthesize dexamethasone, 16βmethylprednisolone acetate is dehydrated to the 9,11-dehydro derivative. This is then reacted with a source of hypobromite, such as basic N-bromosuccinimide, to form the 9α-bromo-11β-hydrin derivative, which is then ring-closed to an epoxide. A ring-opening reaction with hydrogen fluoride in tetrahydrofuran gives dexamethasone.

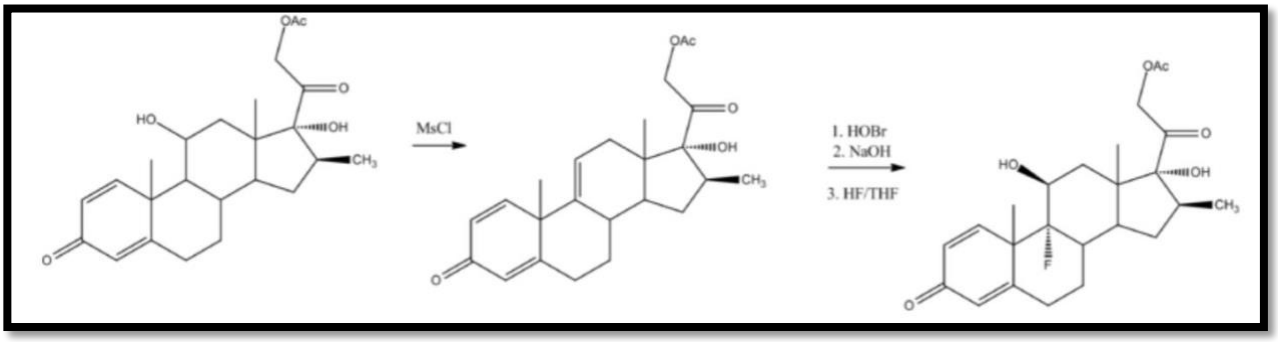

Figure No.2: Synthesis of Dexamethasone

MECHANISM OF ACTION:

The short term effects of corticosteroids are decreased vasodilation and permeability of capillaries, as well as decreased leukocyte migration to sites of inflammation. Corticosteroids binding to the glucocorticoid receptor mediates changes in gene expression that lead to multiple downstream effects over hours to days. Glucocorticoids inhibit neutrophil apoptosis and demargination; they inhibit phospholipase A2, which decreases the formation of arachidonic acid derivatives; they inhibit NF-Kappa B and other inflammatory transcription factors; they promote anti-inflammatory genes like interleukin-10. Lower doses of corticosteroids provide an anti-inflammatory effect, while higher doses are immunosuppressive. High doses of glucocorticoids for an extended period bind to the mineralocorticoid receptor, raising sodium levels and decreasing potassium levels.

Corticosteroids diffuse across cell membranes and complex with specific cytoplasmic receptors. These complexes then enter the cell nucleus, bind to DNA, and stimulate transcription of mRNA and subsequent protein synthesis of enzymes ultimately responsible for anti-inflammatory effects of topical application of corticosteroids to the eye. In high concentrations which may be achieved after topical application, corticosteroids may exert direct membrane effects. Corticosteroids decrease cellular and fibrous exudation and tissue infiltration, inhibit fibroblastic and collagen-forming activity, retard epithelial regeneration, diminish post inflammatory neovascularization and reduce toward normal levels the excessive permeability of inflamed capillaries.

Glucocorticoids are capable of suppressing the inflammatory process through numerous pathways. They interact with specific intracellular receptor proteins in target tissues to alter the expression of corticosteroid-responsive genes. Glucocorticoid-specific receptors in the cell cytoplasm bind with steroid ligands to form hormone-receptor complexes that eventually translocate to the cell nucleus. There these complexes bind to specific DNA sequences and alter their expression. The complexes may induce the transcription of mRNA leading to synthesis of new proteins. Such proteins include lipocortin, a protein

known to inhibit PLA2a and thereby block the synthesis of prostaglandins, leukotrienes, and PAF. Glucocorticoids also inhibit the production of other mediators including AA metabolites such as COX, cytokines, the interleukins, adhesion molecules, and enzymes such as collagenase.

Corticosteroids diffuse across cell membranes and complex with specific cytoplasmic receptors. These complexes then enter the cell nucleus, bind to DNA (chromatin), and stimulate transcription of messenger RNA (mRNA) and subsequent protein synthesis of various inhibitory enzymes responsible for the anti-inflammatory effects of topical corticosteroids. These anti-inflammatory effects include inhibition of early processes such as edema, fibrin deposition, capillary dilatation, movement of phagocytes into the area, and phagocytic activities. Later processes, such as capillary production, collagen deposition, and keloid formation also are inhibited by corticosteroids. The overall actions of topical corticosteroids are catabolic.

PHARMACODYNAMICS:

Corticosteroids bind to the glucocorticoid receptor, inhibiting pro-inflammatory signals, and promoting anti-inflammatory signals. Dexamethasone's duration of action varies depending on the route. Corticosteroids have a wide therapeutic window as patients may require doses that are multiples of what the body naturally produces. Patient’s taking corticosteroids should be counselled regarding the risk of hypothalamic-pituitary-adrenal axis suppression and increased susceptibility to infections.

MEDICAL USES:

Anti-inflammatory:

- Dexamethasone is used to treat many inflammatory and autoimmune conditions, such as rheumatoid arthritis and bronchospasm. Idiopathic thrombocytopenic purpura, a decrease in numbers of platelets due to an immune problem, responds to 40 mg daily for four days; it may be administered in 14-day cycles. It is unclear whether dexamethasone in this condition is significantly better than other glucocorticoids.
- It is also given in small amounts before and/or after some forms of dental surgery, such as the extraction of the wisdom teeth, an operation which often leaves the patient with puffy, swollen cheeks.
- Dexamethasone is commonly given as a treatment for croup in children, as a single dose can reduce the swelling of the airway to improve breathing and reduce discomfort.
- It is injected into the heel when treating plantar fasciitis, sometimes in conjunction with triamcinolone acetonide.

- It is useful to counteract allergic anaphylactic shock, if given in high doses.
- It is present in certain eye drops particularly after eye surgery – and as a nasal spray, and certain ear drops (can be combined with an antibiotic and an antifungal). Dexamethasone intravitreal steroid implants have been approved by the FDA to treat ocular conditions such as diabetic macular edema, vein occlusion, and central retinal uveitis.
- Dexamethasone has also been used with antibiotics to treat acute endophthalmitis
- Dexamethasone is used in trans venous screw-in cardiac pacing leads to minimize the inflammatory response of the myocardium. The steroid is released into the myocardium as soon as the screw is extended and can play a significant role in minimizing the acute pacing threshold due to the reduction of inflammatory response. The typical quantity present in a lead tip is less than 1.0 mg.
- Dexamethasone may be administered before antibiotics in cases of bacterial meningitis. It acts to reduce the inflammatory response of the body to the bacteria killed by the antibiotics (bacterial death releases proinflammatory mediators that can cause a response which is harmful), thus reducing hearing loss and neurological damage.

Cancer:

- People with cancer undergoing chemotherapy are often given dexamethasone to counteract certain side effects of their antitumor treatments. Dexamethasone can increase the antiemetic effect of 5-HT_3 receptor antagonists, such as ondansetron. The exact mechanism of this interaction is not well-defined, but it has been theorized that this effect may be due to, among many other causes, inhibition of prostaglandin synthesis, anti-inflammatory effects, immunosuppressive effects, decreased release of endogenous opioids, or a combination of the aforementioned.
- In brain tumors (primary or metastatic), dexamethasone is used to counteract the development of edema, which could eventually compress other brain structures. It is also given in cord compression, where a tumor is compressing the spinal cord.
- Dexamethasone is also used as a direct chemotherapeutic agent in certain haematological malignancies, especially in the treatment of multiple myeloma, in which dexamethasone is given alone or in combination with other chemotherapeutic drugs, including most commonly with thalidomide (Thal-dex), lenalidomide, bortezomib (Velcade, Vel-dex), or a combination of doxorubicin (Adriamycin) and vincristine or dexamethasone.

Endocrine:

- Dexamethasone is the treatment for the very rare disorder of glucocorticoid resistance. In adrenal insufficiency and Addison's disease, dexamethasone is prescribed when the patient does not respond well to prednisone or methylprednisolone.
- It can be used in congenital adrenal hyperplasia in older adolescents and adults to suppress ACTH production. It is typically given at night.

Pregnancy:

- Dexamethasone may be given to women at risk of delivering prematurely to promote maturation of the fetus lungs. This administration, given from day to one week before delivery, has been associated with low birth weight, although not with increased rates of neonatal death.
- Dexamethasone has also been used during pregnancy as an off-label prenatal treatment for the symptoms of congenital adrenal hyperplasia (CAH) in female babies. CAH causes a variety of physical abnormalities, notably ambiguous genitalia. Early prenatal CAH treatment has been shown to reduce some CAH symptoms, but it does not treat the underlying congenital disorder. This use is controversial: it is inadequately studied, only around one in ten of the foetuses of women treated are at risk of the condition, and serious adverse events have been documented. Experimental use of dexamethasone in pregnancy for foetal CAH treatment was discontinued in Sweden when one in five cases suffered adverse events.
- A small clinical trial found long-term effects on verbal working memory among the small group of children treated prenatally, but the small number of test subjects means the study cannot be considered definitive.

High-altitude illnesses:

- Dexamethasone is used in the treatment of high-altitude cerebral edema (HACE), as well as high-altitude pulmonary edema (HAPE). It is commonly carried on mountain-climbing expeditions to help climbers deal with complications of altitude sickness.

Nausea and vomiting:

- Intravenous dexamethasone is effective for prevention of nausea and vomiting in people who had surgery and whose postoperative pain was treated with long-acting spinal or epidural spinal opioids.
- The combination of dexamethasone and a 5-HT_3 receptor antagonist such as ondansetron is more effective than a $5HT_3$ receptor antagonist alone in preventing postoperative nausea and vomiting.
- Dexamethasone, when used as an anti emetic during surgery, does not appear to increase rates of wound infection and it is unclear if it has an effect on wound healing.

Sore throat:

- A single dose of dexamethasone or another steroid speeds improvement of a sore throat.

CONTRAINDICATIONS:

Contraindications of dexamethasone include, but are not limited to:

- Uncontrolled infections
- Known hypersensitivity to dexamethasone
- Cerebral malaria
- Systemic fungal infection
- Concurrent treatment with live viruses vaccines (including smallpox vaccine)

ADVERSE EFFECTS:

The exact incidence of the adverse effects of dexamethasone are not available, hence estimates have been made as to the incidence of the adverse effects below based on the adverse effects of related corticosteroids and on available documentation on dexamethasone.

Common:

- Acne
- Insomnia
- Vertigo
- Increased appetite
- Weight gain
- Impaired skin healing
- Depression
- Euphoria
- Hypertension
- Increased risk of infection
- Raised intraocular pressure
- Vomiting
- Dyspepsia
- Confusion
- Amnesia

- Irritability
- Nausea
- Malaise
- Headaches
- Cataract (in cases of long-term treatment it occurs in about 10% of patients)

Withdrawal:

Sudden withdrawal after long-term treatment with corticosteroids can lead to:

- Adrenal insufficiency
- Hypotension
- Fever
- Myalgia
- Arthralgia
- Rhinitis
- Conjunctivitis
- Painful itchy skin nodules
- Weight loss
- Death

DRUG INTERACTIONS:

Known drug interactions include:

- Inducers of hepatic microsomal enzymes such as barbiturates, phenytoin, and rifampicin can reduce the half-life of dexamethasone.
- Cotreatment with oral contraceptives can increase its volume of distribution.

CONCLUSION:

This article provides valuable information regarding the safety and efficacy profile of Dexamethasone in the management of COVID-19. It is more useful reference for the research scientist. Considering the low cost, safety and efficacy criteria, easy availability of Dexamethasone should be prescribed to COVID-19 patients under medical supervision.

ACKNOWLEDGEMENT:

The authors are thankful to Dr. Vitthalrao Vikhe Patil Foundation's college of Pharmacy and Medical College for ceaseless encouragement during the study and for all time guidance and encouragement.

BIBLIOGRAPHY:

1. Dexamethasone Use During Pregnancy" . Drugs.com. Archived from the original on 17 May 2016. Retrieved 9 June 2016. "Dexamethasone is only recommended for use during pregnancy when there are no alternatives and benefit outweighs risk."
2. World Health Organization. Coronavirus Disease 2019 (COVID-19): Situation Report, 45 (2020). Available online at: https://www.who.int/emergencies/ diseases/novel-coronavirus-2019/situation-reports (accessed April, 10 2020).
3. Rankovic, Zoran; Hargreaves, Richard; Bingham, Matilda (2012). Drug discovery and medicinal chemistry for psychiatric disorders . Cambridge: Royal Society of Chemistry. p. 286. ISBN 9781849733656. Archived from the original on 2016-03-05.
4. Fischer, Jnos; Ganellin, C. Robin (2006). Analogue-based Drug Discovery . John Wiley & Sons. p. 485. ISBN 9783527607495.
5. Chan JF, Yuan S, Kok KH, To KK, Chu H, Yang J, et al. A familial cluster of pneumonia associated with the 2019 novel coronavirus indicating personto-person transmission: a study of a family cluster. Lancet. (2020) 395:51423. doi: 10.1016/S0140-6736(20)30154-9
6. Chen Y, Liu Q, Guo D. Emerging coronaviruses: genome structure, replication, and pathogenesis. J Med Virol. (2020) 92:418–23. doi: 10.1002/jmv.25681
7. Zumla A, Chan JF, Azhar EI, Hui DS, Yuen KY. Coronaviruses—drug discovery and therapeutic options. Nat Rev Drug Discov. (2016) 15:32747. doi: 10.1038/nrd.2015.37
8. Shang L, Zhao J, Hu Y, Du R, Cao B. On the use of corticosteroids for 2019-nCoV pneumonia. Lancet. (2020) 395:683–4. doi: 10.1016/S0140-6736(20)30361-5
9. Stewart LA, Clarke M, Rovers M, Riley RD, Simmonds M, Stewart G, et al. Preferred reporting items for a systematic review and meta-analysis of individual participant data: the PRISMA-IPD statement. JAMA. (2015) 313:1657–65. doi: 10.1001/jama.2015.3656
10. Stroup DF, Berlin JA, Morton SC, Olkin I, Williamson GD, Rennie D, et al. Meta-analysis of observational studies in epidemiology: a proposal for reporting. JAMA. (2000) 283:2008–12. doi: 10.1001/jama.283.15.2008
11. "Dexamethasone" . The American Society of Health-System Pharmacists. Archived from the original on 2017-08-31. Retrieved July 29, 2015.

12. "Prescribing medicines in pregnancy database" . Australian Government. 3 March 2014. Archived from the original on 8 April 2014. Retrieved 22 April 2014. "Drugs which have been taken by a large number of pregnant women and women of childbearing age without any proven increase in the frequency of malformations or other direct or indirect harmful effects on the fetus having been observed."
13. World Health Organization (2019). World Health Organization model list of essential medicines: 21st list 2019. Geneva: World Health Organization. hdl: 10665/325771 . WHO/MVP/EMP/IAU/2019.06. License: CC BY-NC-SA 3.0 IGO.
14. "Dexamethasone for Accelerating Lung Maturation in Preterm Babies" (PDF). Archived (PDF) from the original on 22 December 2015. Retrieved 29 July 2015.
15. "The Top 300 of 2019" . clincalc.com. Retrieved 22 December 2018.
16. Till J. "Paramedic Clinical Training Aid" . Archived from the original on 31 March 2012. Retrieved 30 August 2011.
17. Brouwer MC, McIntyre P, de Gans J, Prasad K, van de Beek D (September 2010). Van De Beek D (ed.). "Corticosteroids for acute bacterial meningitis". The Cochrane Database of Systematic Reviews (9): CD004405. doi:10.1002/14651858.CD004405.pu b3 . PMID 20824838 .
18. Roila F, Ballatori E, Ruggeri B, DeAngelis V (May 2000). "Dexamethasone Alone or in Combination with Ondansetron for the Prevention of Delayed Nausea and Vomiting Induced by Chemotherapy". N Engl J Med. 342 (21): 1554–9. doi:10.1056/NEJM20000525342210 2 . PMID 10824073 .
19. Holte K, Kehlet H (November 2002). "Perioperative single-dose glucocorticoid administration: pathophysiologic effects and clinical implications". J Am Coll Surg. 195 (5): 694–712. doi:10.1016/s10727515(02)01491-6 . PMID 12437261 .
20. Dan L. Longo, Anthony Fauci, Dennis Kasper, Stephen Hauser, J. Jerry Jameson and Joseph Loscalzo, Harrison's Principles of Internal Medicine, 18th edition, p.3055.
21. Bloom SL, Sheffield JS, McIntire DD, Leveno KJ (April 2001). "Antenatal dexamethasone and decreased birth weight". Obstet Gynecol. 97 (4): 48590. doi:10.1016/S00297844(00)01206-0 . PMID 11275014 . S2CID 33601749 .
22. A Prenatal Treatment Raises Questions of Medical Ethics Archived 2016-08-31 at the Wayback Machine.
23. "Decadron, Dexamethasone Intensol (dexamethasone) dosing, indications, interactions, adverse effects, and more" . Medscape Reference. WebMD. Archived from the original on 12 December 2013. Retrieved 11 December 2013.

24. "PRODUCT INFORMATION DEXMETHSONE (dexamethasone)" (PDF). TGA eBusiness Services. Aspen Pharmacare Australia Pty Ltd. 10 August 2010. Archived from the original on 28 January 2017. Retrieved 11 December 2013.
25. "PRODUCT INFORMATION DEXMETHSONE INJECTION" (PDF). TGA eBusiness Services Aspen Pharmacare Australia Pty Ltd. Aspen Pharmacare Australia Pty Ltd. 2 March 2011. Archived from the original on 29 January 2017. Retrieved 11 December 2013.
26. "DEXAMETHASONE tablet [ECR Pharmaceuticals]" . DailyMed. ECR Pharmaceuticals. December 2010. Archived from the original on 13 December 2013. Retrieved 11 December 2013.
27. "Dexamethasone" . Drug Information Portal. U.S. National Library of Medicine.