DEXAMETHASONE USES IN HUMANS AND ANIMALS: PUBLIC HEALTH AND SOCIO-ECONOMIC IMPLICATIONS

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ABSTRACT

Objectives: The importance of dexamethasone is demonstrated by its wide uses in human and veterinary medical practice. Unfortunately, dexamethasone use is prone to abuse. Health authorities have emphasized the importance of increasing knowledge of benefits and potential harmful effects of synthetic glucocorticoids use as a guide to responsible and judicious use of the pharmaceutical. This review provides an overview of the uses of dexamethasone and its consequences on public health *visa vie* socio–economy. **Methodology:** *Source of Data:* The review is based on literature searches using PubMed and MeSH and authors' personal manuscript/abstract files and citations of known references. **Study selection:** The selection of articles reflects the authors' opinion as to originality and importance in the context of the review. The review included human and some aspects of animal study. *Data extraction:* The electronic searches were scrutinized and full manuscripts of all quotes considered relevant to the study were obtained. All the articles whose abstracts were not available were excluded.

Results: Dexamethasone is still one of the most prescribed medicines in human and veterinary medical practice despite over 4-decades of use and its attendant negative consequences. Recently non-medical uses of the drug are also on the increase which greatly contributed to the problems. **Conclusion:** Dexamethasone use has consequences on public health *visa vie* socio-economy. Its indispensability is not unconnected with its broad spectrum pharmacological actions and cost effectiveness. Due to rampant abuses and the attendant adverse effects of dexamethasone, it is recommended that the drug be enlisted as controlled drug.

Keywords: Dexamethasone, Public health, Socio-economy

INTRODUCTION

Like all synthetic therapeutic glucocorticoids, dexamethasone is a derivative of corticosteroids, and having similar 21 carbon steroid skeleton, similar to hydrocortisone. Modifications of this skeleton selectively alter the degree of anti-inflammatory, metabolic and immunosuppressive activities, as well as the protein binding affinity of the resultant compound.^{1,2} Dexamethasone is a

product of such modifications. It is a fluorinated compound derived from corticosteroid and having 21- carbon steroid skeleton with hydroxyl (OH) or methyl (CH₃) group attached at C_{16} ²³ This compound has virtually no mineralocorticoid effect, but remains potent anti-inflammatory and analgesic glucocorticoids with broad significant physiological and therapeutic uses.²³

Dexamethasone has broad pharmacological and

physiological uses in both human and veterinary medical practice. The drug is a glucocorticoid receptor agonist⁴ and therefore has profound effects on nearly all cell types and organ system.^{5,6} The compound has effects on several important biochemical pathways and cellular transport mechanisms including, cellular sodium transport, glycogen synthesis and anti-inflammatory responses.^{7,5} The importance of dexamethasone is demonstrated by its wide application. Therefore, it is used to treat and manage several diseases and other medical conditions in both animals and humans.^{7,5} It has been estimated that approximately 27,000 human prescriptions contained dexamethasone as the active pharmaceutical ingredient were dispensed in the United States alone in 2004.8

Also it was estimated that about 0.9% of all adults population used dexamethasone as therapy for various ailments at any given time point in the United Kingdom.⁹ Thus, dexamethasone is widely used to treat and manage several disease conditions in both humans and animals. Some of these include, but not limited to, arthritis, autoimmune disorders, unresponsive musculoskeletal disorders, thyroiditis, colitis, canine distemper, meningitis, necrotizing enterocolitis, immune mediated hemolytic anemia or thrombocytopenia and some neoplastic conditions.^{7,10,11,12}

Due to its broad pharmacological actions and uses, dexamethasone is prone to abuse as inappropriate chronic or hyper-exposure may cause some serious systemic and psychological side effects and serious social and public health problems. Glucocorticoid hyper-exposure is considered to be one of the major prenatal aetiological factors that might increase the developmental and adult risk of neuropsychiatric disability.^{13,14} Psychic derangements may appear ranging from euphoria, insomnia, mood swings, personality changes, and severe depression to frank psychotic manifestations may occur in hyper exposed subjects.^{13,14} Its use as "performanceenhancing" and "mood elevating", which is tied to its ant-inflammatory and glucogenic properties, is frequently abused in the sporting world.

Dexamethasone hyper-exposure can occur in the context of the clinical practice of synthetic

glucocorticoid administration for certain obstetric conditions, including pregnancies at risk for premature birth where the dam or the mother is administered glucocorticoid with the aim of increasing foetal lung exposure to glucocorticoid and thereby stimulating lung maturation.¹⁵ Adverse effects are usually manifested in various forms such as adrenal gland depression, immunosuppression, hypertension, psychological disturbances, exogenous syndrome with thin, fragile skin, osteoporosis, muscle atrophy, weight gain and steroid diabetes.^{16,17,18,19} Effects of aquatic pollutants on fish are of increasing concern. The presence of synthetic glucocorticoids within the aquatic environment has been highlighted as a potential environmental concern as they may mimic the role of endogenous glucocorticoids during vertebrate ontogeny.²⁰

Dexamethasone use and its implications in humans

Dexamethasone is commonly used in human medicine for the treatment of wide range of diseases and physiological disorders some of which have been enumerated above. In addition, apart from its famous anti inflammatory effects²¹ dexamethasone is used widely to treat or manage gastrointestinal diseases, spinal cord trauma, shock and edematous states like cerebral edema. Dexamethasone is also used clinically for diagnostic testing of adrenocortical hyperfunction. Dexamethasone has become the drug of choice in neuro-oncology, in part owing to its long half-life and low mineralocorticoid activity.⁹ The drug has other uses such as part of a chemotherapy regiment to reduce swelling of the brain.

Maternal administration of dexamethasone is an important clinical tool used both in the management of pregnant subjects and women at risk of early preterm birth and also in suspected cases of congenital adrenal hyperplasia.²² It has now become routine clinical practice to treat women with threaten preterm delivery with dexamethasone to improve outcomes in premature babies.²³ It has succeeded in reducing neonatal mortality and morbidity from respiratory distress syndrome (RDS). Liggins and Howie²⁴ first described this indication in 1972, when they

reduce the risk of neonatal RDS from 25.8% to 9.0%, masculinization frequently go on to virilize, with and the rate of neonatal mortality dropped from varying degrees of postnatal clitoral hypertrophy. 15.0% to 3.2%.²⁴ Apart from reducing the incidence It is suggested that such individuals are prone to be of respiratory distress syndrome (RDS) and lesbians and homosexuals.²⁹ The modern social mortality in the neonates' dexamethasone has been vices like homosexuality and lesbianism may reported to increased efficiency of blood circulation therefore have their roots from virilization. in both the dam and the fetuses.²⁴

However, since there is no single drug that produces just a single effect without being accompanied with other undesirable effects, dexamethasone is not an exception. Adverse effects in humans are usually manifested in the form of systemic and psychological side effects such as exogenous Cushing syndrome with thin, fragile skin, osteoporosis, muscle atrophy, weight gain steroid diabetes, increased susceptibility to infection and varying degree of psychological disturbances.¹⁸ The programming of physiological, endocrinological, and behavioral functions by pre natal dexamethasone exposure may lead to psychopathologies behavioral problems²⁵. In addition to the well known physical side effects, dexamethasone therapy has been associated with adverse psychological side effects (APSE), ranging from psychotic symptoms to changes in mood and cognition, euphoria, sleep disturbances, psychiatric syndromes. Human studies provide evidence of reduced HPA reactivity in infants, for example,²⁶ and disturbances in neurological and cognitive development.²⁷

Another social implication of dexamethasone usage is in the area of female virilization and male hypervirilization. Virilization is the development of exaggerated masculine characteristics, usually in women, and also in men, often as a result of the adrenal glands overproduction of androgens (testosterone and similar hormones). Virilization is caused by excess production of androgens usually because of enlargement of an adrenal gland (adrenal hyperplasia).²⁸ High androgen levels are most commonly caused by hyperplasia of the adrenal gland as a result of the genetic defects of steroidogenesis, called the virilizing congenital adrenal hyperplasias (CAHs).²⁸ Excessive androgen levels in the female may affect primary sexual diseases and non-specific skin diseases and characteristics by masculinizing the foetal external mastitis.^{36,37,38} Dexamethasone also is used topically

demonstrated that antenatal corticosteroid could genitalia to virilization. Patients with

Dexamethasone treatment has been frequently used pre natally to protect female foetuses from suspected cases of virilization and to treat the virilization associated with congenital adrenal hyperplasia, since it suppresses adrenal function.^{30,22,31} Dexamethasone administered before 10 weeks of gestation in women was reported to be effective in reducing virilization in their offspring.³²

Trends in social cycle now indicate increasing number of parents opting for prophylactic prenatal exogenous glucocorticoids treatments in attempt to mitigate the effects of the fraternal birth order effect on increasing the chances of homosexuality and lesbianism in children, although it raises questions of medical ethics.³

As in animals, numerous evidence indicate that dexamethasone treatment during pregnancy may result in adverse outcomes including intrauterine growth restriction (IUGR), hypertension, glucose intolerance, altered hypothalamo-pituitary-adrenal axis, and decreased foetal and placental weights.^{16,17,19,34,35} These side effects significantly decrease quality of life, life expectancy and increases health care costs and therefore constitute socio economic and public health threats.

Dexamethasone use and its implications in animals

Clinically, dexamethasone is administered to animals for the treatment of disease conditions such canine distemper, meningitis, necrotizing enterocolitis.^{7,10,11,12,2,4} It is used to manage and treat immune mediated diseases such as immune mediated haemolytic anaemia or thrombocytopenia; some neoplastic diseases; allergic reactions such as asthma, hives and itching; inflammatory diseases and some neurologic

to treat a variety of skin and eye problems.³⁹ In dogs, have tremendous beneficial impacts on cats and horses, dexamethasone is used productivity. In order to ensure profitability and systemically in high doses in emergency situations for anaphylactic reactions, spinal cord trauma, shock and stress³⁷. It is sometimes used systemically as a "performance-enhancing" drug because dexamethasone decreases inflammation, enhance glucose metabolism and may have some mood elevating properties.³⁹ It decreases peripheral utilization of glucose. Hence dexamethasone is usually used as replacement glucose therapy in acute hypoglycaemic conditions like ketosis and acetonaemia. Immediate relief is usually achieved within 8-10 hours following I.V. or I.M dosages of dexamethasone.^{36,40,35} Other uses include treatment and management of prenatal foetal lung malformations and neonatal diseases and management.^{36,38,24,40}

Despite its numerous uses in animals, indiscriminate dexamethasone application unfortunately causes several adverse effects in farm animals and resultant serious consequences on the livestock production and socio economic status of livestock owners. The livestock farmers largely depend on the animals for their livelihood.

The adverse effects range from adrenal gland depression, immunosuppression, decreased foetal growth to abortion.^{16,17,18,19,34} This causes huge damage to livestock economy as a result of reproductive wastages through foetal losses.

Apart from supplementing the food needs of man, animals generate income and play significant role in maintaining a strong agricultural economy, and in maintaining soil fertility and water conservation. In addition, animals provide array of other useful products, e.g. leather, hair, essential enzymes, such as rennin, needed in manufacturing cheese, and insulin use in pharmaceuticals and provides companionship, sports and entertainment.⁴¹ However, the adverse effects are usually caused by irresponsible and inappropriate usage and administration by untrained personnel.

The profitability of livestock depends largely on their management and health⁴². As health is one of the major constraints to efficient livestock production, good health care interventions can

continuity of their stock, producers direct much resources and energy towards management and health of their animals. However, with the low ratio of field veterinarians to livestock population in Nigeria, there is a gross deficit in veterinary services delivery. This compels farmers to indulge in irresponsible self drug administration to their sick animals,⁴³ or employing the services of quacks to attend to these animals. One of such drugs that have great potentials for misuse is dexamethasone due to its wide range of uses. The arbitrary irresponsible and inappropriate usage of dexamethasone may exacerbate the already unfavorable productive situations leading to colossal economic losses with its attendant emotional and psychological trauma to the farming communities. In addition, the maternal treatment with dexamethasone could alter activities at the hypothalamic-pituitary-adrenal axis in the offspring and may have significant consequences on sexual development markers which may interfere with future reproductive function.44

Chronic overdosing of exogenous corticosteroids to animals may trigger long term adaptational effects⁴⁵ which not only violate animal welfare but pose threats to human health by way of treatment drug residue in meat and other animal products. The adverse effects on animals directly translate to man as he eats meat and milk of such animals and also his source of income. However, these effects can be minimized with judicious and responsible application and appropriate treatment by professionals.

Dexamethasone use and its implications on marine life and sea foods

Dexamethasone use in human and veterinary medicine as treatment agents have the potential to contaminate natural watersheds and sea foods via inputs from wastewater treatment facilities and confined animal-feeding operations²⁰. This may impair fish reproduction, growth, and development²⁰ and can pose threats to socioeconomic and public health issues in terms of water pollution and drug residue in sea foods.

synthetic corticosteroids being produced and consumed, the potential exists for these drugs to enter the environment and cause adverse effects in non-target species. In one study, assessment of water samples using a CALUX reporter gene bioassay for glucocorticoid-like activity identified levels ranging from 0.39 to 1.3 ng dexamethasone Eq/L in surface water and 11 to 243 ng dexamethasone Eq/L in industry, hospital, and municipal sewage treatment plant effluents.⁴⁶ Recently, dexamethasone was detected in river water collected downstream from a French pharmaceutical factory at a concentration of approximately 10 µg/L.47 Additionally, studies that detect pharmaceuticals in surface waters, as well as drinking water, at concentrations of parts per trillion to parts per billion ^{20,43} have been presented to the public, making these chemical pollutants a threat to marine life and sea foods and a concern to environment and the public health alike. This unfavorable environmental situation not only causes direct havoc to general ecosystem and marine life, but also indirectly causes huge damage to human and animal health. Behavioral problems, varying degree of respiratory illnesses, damage to vital organs and structures, reproductive wastages through foetal loss and abortions in both humans and animals are amongst myriads of consequences of these pollutants.

Non-medical use of dexamethasone and its implications

Dexamethasone hyper-exposure can also occur in the context of non-medical application for purposes ranging from cosmetics to moral issues and enhancement of sport performance. Because dexamethasone drastically reduces inflammation and enhance glucose metabolism and have some mood elevating properties, it has also been frequently used with the hope of enhancing sports performance, including race horses.³⁹ Recently, the use of dexamethasone has been banned for sports men and women and also race animals by some sporting bodies. In November 2014, the world's number one badminton player Lee Chong Wei was banned by the Badminton World Federation for testing positive for the drug.⁴⁹ These are some of the socio-economic issues of concern with dexamethasone use.

With the abundance of dexamethasone and similar Synthetic corticosteroids being produced and consumed, the potential exists for these drugs to enter the environment and cause adverse effects in non-target species. In one study, assessment of cosmetics industries exploit this notion to their water samples using a CALUX reporter gene advantage.

The use of dexamethasone under various brand names and marketed as cosmetic products that clean, beautify and promote attractiveness is widespread among commercial sex workers.⁵¹ For example, long term use of dexamethasone under the brand name Oradexon was reported to be a common practice among commercial sex workers and under-age prostitutes in Bangladesh in an attempt to help them easily gain weight and develop fat and increase breast size so that they can be attractive.⁵¹

Abusing dexamethasone use for weight gain and attractiveness by women is detrimental to their health. It is a social complication that has public health implications. Weight gain without increased calorie rich food intake might be a symptom of a serious medical condition. If too much weight is gained as in obesity, serious health side-effects may follow. A large number of medical conditions have been associated with obesity. Health consequences include, but not limited to osteoarthritis, obstructive sleep, apnea, diabetes, some forms of cancer, cardiovascular disease, non-alcoholic fatty liver disease.^{52,53}

In centuries past, a degree of plumpness has been seen as an indicative of personal or family prosperity. In particular, a married woman who was thin was pitied, as her shape showed that her husband could not afford to feed her properly; conversely, having a fat wife was a status symbol, meaning, there was plenty to eat, and she did not need to work hard. Despite the connotations that excess weight had in the past, it has for some time been seen as "unacceptable", in contemporary world.⁵⁴

In Sudan, chemical cosmetic, locally known as "Alnagma", is a commonly used cosmetic that contains high concentrations of dexamethasone in form of creams or tablets.^{54,55} Sudanese women

whiten skin, without care of the side effects.⁵

CONCLUSIONS

Dexamethasone primary efficacy is that of a strong anti-inflammatory, as well as an anti-allergic agent and also to treat autoimmune conditions. Dexamethasone is commonly used in human and veterinary medicine for the treatment of wide range of diseases and physiological disorders. It is considered as one of the most prescribed drugs in recent times due its broad pharmacological action and uses in humans and animals. As a glucocorticoids receptor agonist, it has profound effects on nearly all cell types and organ system. Its uses in animals and humans have affected large scale economic and social life and as well as public health. Although it's IUGR and psychological effects are well documented, it is still the recommended drug of choice in treatment of RDS and in neuro-oncology. Dexamethasone use in animals and fishes has both advantage and disadvantages in terms of economic gains and

abuse this drug as cosmetic for gaining weight and losses and public health implication. Man being a consumer at the top ladder of food chain has the final impacts of the drug abuses and directly affects his socio-economic life and health. Non-medical uses of the drug constitute a major percentage of the drug abuse. However, the recent trend of usage of dexamethasone to mitigate the spread of homosexuality and lesbianism in a society is a welcome development. The indispensability of dexamethasone is not unconnected with its broad spectrum pharmacological actions and uses and that its advantages seem to outweigh the risks. The popularity of dexamethasone and its side effects could represent high percentage of populationattributable risk factor and public health nuisance. However, the adverse effects can be minimized with judicious and responsible application and appropriate treatment by professionals. Although dexamethasone is a non-anabolic steroid, due to its rampant abuses and the attendant adverse effects, it is recommended that the drug be enlisted as controlled drug, probably under Psychoactive Substance Act.

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