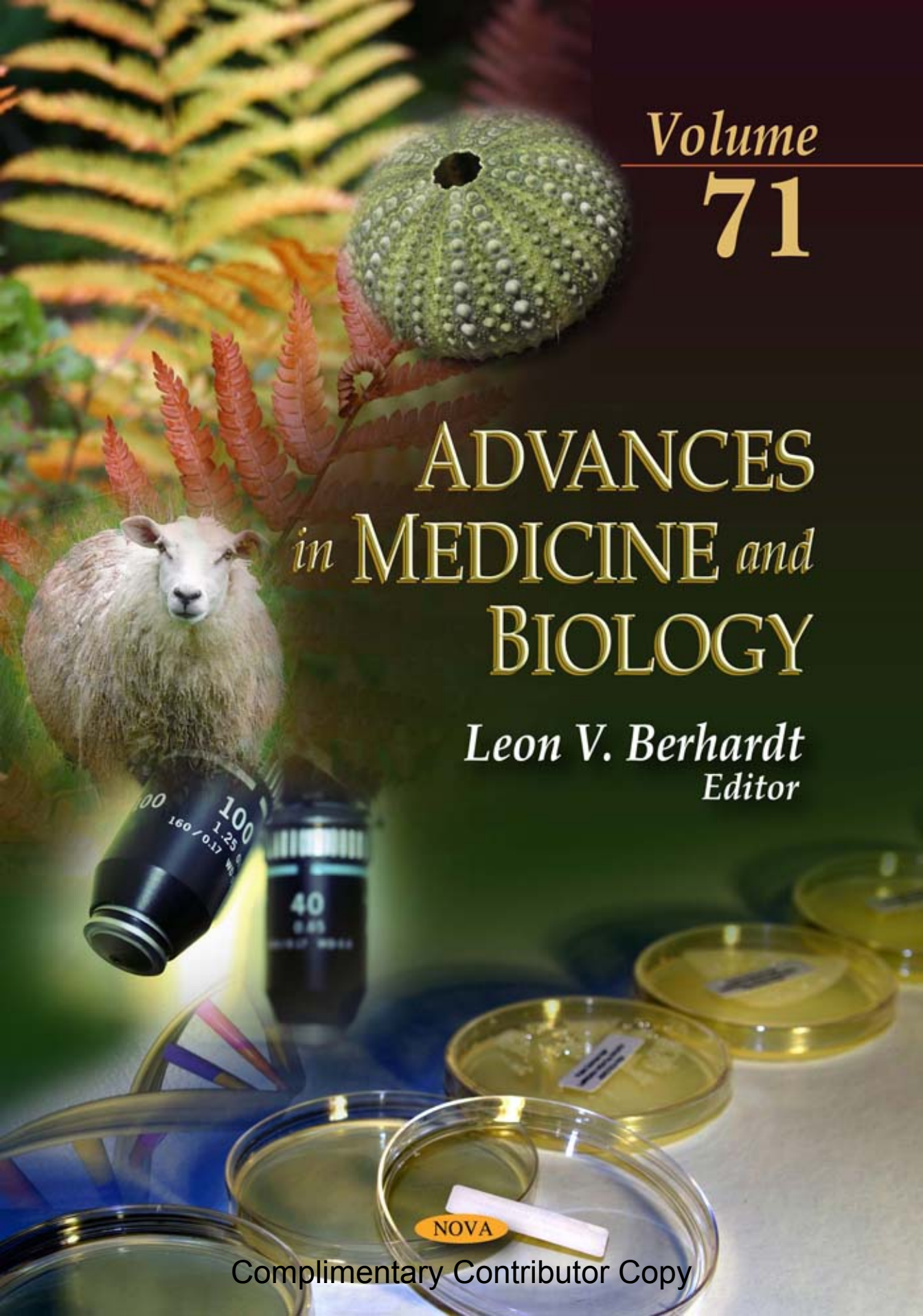

ADVANCES IN MEDICINE AND BIOLOGY

VOLUME 71

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Chapter 10

POTENTIAL SIDE EFFECTS OF METHYLPREDNISOLONE

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ABSTRACT

Methylprednisolone is a synthetic glucocorticoid used mainly as an anti-inflammatory and immunosuppressant agent for hematologic, allergic, inflammatory, neoplastic, and autoimmune diseases [1]. It is generally used via intramuscular, intravenous and oral route; but also it could be applied locally to synovial spaces, the conjunctival sac, skin, and respiratory tract [1]. At the site of inflammation glucocorticoids can inhibit leukocyte infiltration so it interferes with inflammatory response mediators and suppress immune responses [2, 3]. Glucocorticoids like methylprednisolone are used for various conditions such as replacement therapy in acute and chronic adrenal insufficiency, congenital adrenal hyperplasia; also non-endocrine diseases such as rheumatic disorders, renal diseases (nephritic syndrome, glomerulonephritis etc.), allergic diseases, bronchial asthma and other pulmonary conditions; additionally infectious, ocular, gastrointestinal, hepatic diseases, malignancies and cerebral edema [1]. Furthermore it is used for its neuroprotection effects in case of acute traumatic spinal cord injury and graft-versus-host disease [4]. Besides its useful effects on numerous conditions, it has many side effects. Its side effects include hyperglycemia, increased skin fragility, osteoporosis, weight gain, adrenal insufficiency, muscle weakness, menstrual period irregularity, growth failure, delayed puberty [4-6]. Methylprednisolone has somewhat greater glucocorticoid activity and somewhat less mineralocorticoid activity than prednisolone [1]. Its mineralocorticoid effects can cause salt and water retention, hypertension, potassium depletion and metabolic alkalosis [1]. Additionally use of high-dose steroids for more than a week cause in depletion of adrenal glands because of the suppression of hypothalamic corticotrophin releasing hormone and pituitary adrenocorticotropic hormone [1, 6]. Abrupt cessation of glucocorticoids after prolonged therapy can cause adrenal insufficiency due to suppression of the

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hypothalamic-pituitary-adrenal axis, which may be fatal [1]. To prevent this effect treatment should be stopped step by step [6].

INTRODUCTION

Glucocorticoids are one of the most potent and effective anti-inflammatory medication available and widely used in clinical practice [7]. Methylprednisolone is a synthetic glucocorticoid used mainly as an anti-inflammatory and immunosuppressant agent for hematologic, allergic, inflammatory, neoplastic, and autoimmune diseases [1]. Glucocorticoids have numerous effects in carbohydrate, protein and lipid metabolism, effects of glucocorticoids have mainly glucocorticoid effects but also have less mineralocorticoid effects [1].

Glucocorticoids generally used via intramuscular, intravenous and oral route; but also it could be applied locally to synovial spaces, the conjunctival sac, skin, and respiratory tract [1]. At the site of inflammation glucocorticoids can inhibit leukocyte infiltration so it interferes with inflammatory response mediators and suppress immune responses [2, 3].

Glucocorticoids like methylprednisolone are used for various conditions such as replacement therapy in acute and chronic adrenal insufficiency, congenital adrenal hyperplasia; also non-endocrine diseases such as rheumatic disorders, renal diseases (nephritic syndrome, glomerulonephritis etc.), allergic diseases, bronchial asthma and other pulmonary conditions; additionally infectious, ocular, gastrointestinal, hepatic diseases, malignancies and cerebral edema [1]. Furthermore it is used for its neuroprotection effects in case of acute traumatic spinal cord injury and graft-versus-host disease [4].

Besides its useful effects on numerous conditions, it has many side effects. Its side effects include hyperglycemia, increased skin fragility, osteoporosis, weight gain, adrenal insufficiency, muscle weakness, menstrual period irregularity, growth failure, delayed puberty [4-6]. Methylprednisolone has somewhat greater glucocorticoid activity and somewhat less mineralocorticoid activity than prednisolone [1]. Its mineralocorticoid effects can cause salt and water retention, hypertension, potassium depletion and metabolic alkalosis [1]. Additionally use of high-dose steroids for more than a week cause in depletion of adrenal glands because of the suppression of hypothalamic corticotrophin releasing hormone and pituitary adrenocorticotropic hormone [1, 6]. Abrupt cessation of glucocorticoids after prolonged therapy can cause adrenal insufficiency due to suppression of the hypothalamic-pituitary-adrenal axis, which may be fatal [1]. To prevent this effect treatment should be stopped step by step [6].

ENDOCRINOLOGIC SIDE EFFECTS

Glucocorticoids regulate the production of gluconeogenic substrates and activity, also they reduce the glucose utilization by peripheral tissues and increase the oxidation of fats for energy production [8, 9]. Glucocorticoids stimulate hepatic gluconeogenesis from amino acids and glycerol; inhibit glucose uptake in adipose tissue; in peripheral tissues they reduce

glucose usage and increase gluconeogenesis [1, 6, 9]. So glucocorticoids cause increased carbohydrate intolerance and hyperglycemia [4].

Glucocorticoids also cause adrenal suppression, amenorrhea, Cushing's syndrome, diabetes mellitus, hypokalemia, hypokalemic alcalosis, growth suppression in children, hyperlipidemia, irregular menstrueal cycle, pituitary-adrenal axis suppression, protein catabolism, sodium and water retention [1, 4, 6].

CARDIOVASCULAR SIDE EFFECTS

Cardiovascular side effects of methylprednisolone mainly result from mineralocorticoid effects of corticosteroids [1, 10]. They may also induce hypokalemia by transcellular potassium shift caused by several mechanisms such as increased Na^+/K^+- ATPase pool in skeletal muscle, steroid induced hyperinsulinemia and hyperglycemia [11-13]. As a result corticosteroids can cause arrhythmias, bradycardia, cardiac arrest, cardiomegaly, circulatory collapse, congestive heart failure, edema, hypertension, hypertrophic cardiomyopathy in premature infants, myocardial rupture (post MI), syncope, tachycardia, thromboembolism, vasculitis [1, 6].

CENTRAL NERVOUS SYSTEM SIDE EFFECTS

Effects of methylprednisolone on central nervous system (CNS) could be divided as direct effects like effects on mood, behavior and brain excitability and indirect effects on CNS by effecting blood pressure, plasma concentrations and electrolyte concentrations [1]. Side effects depends on the dose and the duration of the treatment [14]. The effects could be as follows; delirium, depression, emotional instability, headache, hallucinations, insomnia, increased in intracranial pressure, malaise, nervousness, personality changes, psychotic disorders, seizure and vertigo [15, 16]. In a prospective study; 50 patients received 75-100 mg of prednisone or equivalent for longer than a week for ophthalmologic treatments, 30% of the patients suffered from hypomanic symptoms and 10% from depressive symptoms, but psychosis, dementia and delirium didn't observed [17].

IMMUNE SYSTEM SIDE EFFECTS

Glucocorticoids have immunosuppression potential resulting with increased risk of infections. They inhibit both acquired and innate immunologic functions [18]. Immunologic effects of glucocorticoids are sometimes dose-dependent but also the underlying diseases, co-morbid illnesses and other immunosuppressive therapies give additional risks for immunosuppression [19].

Systemic glucocorticoids causes a dose-dependent increase risk of infection especially with bacterial, viral and fungal pathogens [20]. Older patients have higher risk for infection [21]. Additionally patients receiving glucocorticoids may not show symptoms and signs of infection clearly because of the inhibition of cytokine release and associated reduction of

inflammatory and febrile responses [19]. Chronic steroid use can cause increased infection risk in rheumatologic and autoimmune disorders [20, 22].

Live virus vaccines may be applied to patients using prednisone or its equivalent in doses of less than 20 mg/day for 14 days or less; in long term physiologic replacement therapy of glucocorticoids; also in topical (aerosol, intraarticular, bursal or tendon injection) use of them [6]. MMR, Zoster and other live virus vaccines shouldn't be used for one month after cessation of higher doses of glucocorticoids [6].

Table 1. Major side effects associated with glucocorticoid therapy

Dermatologic and soft tissue	**Renal**
Skin thing and purpura	Hypokalemia
Cushingoid appearance	Fluid volume shifts
Alopecia	**Genitourinary and reproductive**
Acne	Amenorrhea / infertility
Hirsutism	Intrauterine growth retardation
Striae	**Bone**
Hypertrichosis	Osteoporosis
Eye	Avascular necrosis
Posterior subcapsular cataract	**Muscle**
Elevated intraocular pressure/glaucoma	Myopathy
Exophtalmos	**Neuropsychiatric**
Cardiovascular	Euphoria
Arrhytmias (with intravenous pulse therapy)	Dysphoria / depression
Hypertension	Insomnia / akathisia
Perturbations of serum lipoproteins	Mania / psychiosis
Premature atherosclerotic disease	Pseudomotor cerebri
Gastrointestinal	**Endocrine**
Gastritis	Diabetes mellitus
Peptic ulcer disease	Hypothalamic-pituitary-adrenal insufficiency
Pancreatitis	**Infectious disease**
Steatoheptitis	Heightened risk of typical infections
Visceral perforation	Opportunistic infections
	Herpes Zoster

* Saag KG, Furst DE. Major side effects of systemic glucocorticoids. Wolters Kluwer; 2012 [cited 2013 February 20]; Available from: UpToDate.

DERMATOLOGIC SIDE EFFECTS

Dermatologic side effects of glucocorticoids include acne, allergic dermatitis, alopecia, dry scaly skin, skin atrophy, erythema, sterile abscess, urticaria, edema, hirsutism, hyperpigmentation, hypopigmentation, hypertrichosis, impaired wound healing, petechiae, ecchymoses, rash, skin test reaction impaired, striae [1, 23].

Other major side effects of glucocorticoids also have major side effects on other systems are given in Table 1.

CONCLUSION

Methylprednisolone is used mainly as an anti-inflammatory and immunosuppressant agent but also it has many side effects. We have to know its potential side effects and inform patients about them.

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