DIFFERENT SCHEDULES OF STEROIDS IN I.C.U.

Essay

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DEDICATION

To my late father who I owe to him all I have reached to.

To my husband who greatly supports me, encourage me and stand beside me in the difficult times.

To my son and my family for their support, help and pray.

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ABBREVIATION

ACTH	Adreno-cortico-trophic hormone
AFE	Amniotic fluid embolism
AI	Adrenal insufficiency
ALI	Acute lung injury
ARDS	Acute respiratory distress syndrome
11β-HSD	11 Beta-hydroxysteroid dehydrogenase
CBG	Corticosteroid-binding globuline
CIRCI	Critical illness-related corticosteroid insufficiency
CnI	Calcineurin inhibitor
COPD	Chronic obstructive pulmonary disease
CPB	Cardiopulmonary bypass
CRH	Corticotrophin releasing hormone
CSW	Cerebral salt wasting syndrome
CVP	Central venous pressure
eNOS	Endothelial nitric oxide synthetase
DHEAS	Dihydro-epiandrosterone
FEV_1	Forced expiratory volume in 1 second
GCs	Glucocorticoids
GM-CSF	Granulocyte-macrophage colony stimulating factor

GRE	Glucocorticoid response elements
GR	Glucocorticoid receptor
HAT	Histone acetyltransferase
HDL	High density lipoprotein
HIV	Human immune-deficiency virus
HPA axis	Hypothalamo-pitautry adrenal axis
HSP90	Heat-shock protein 90
ICU	Intensive care unite
IFN	Interferon
IgM & IgG	Immunoglobulin M and G.
IL-10	Interleukin-10
IL-11	Interleukin-11
IL-1β	Interleukin-1beta
LIF	Leukemia inhibitory factor
MAP	Mean arterial pressure
MR	Mineralocorticoid receptor
NF-κB	Nuclear factor-κB
PEFR	Peak expiratory flow rate
PGE2	Prostaglandin E2
PKA	Protein kinase A

PLA2	Phospho-lipase A2
PMNs	Polymorphi-nucleucytes
POMC	Pro-opiomelanocortin
PONV	Post operative nausea and vomiting
PTSD	Post traumatic stress syndrome
RCTs	Randomized controlled trials
rhAPC	Recombinant human activated protein C
ScvO2	Saturation of central venous blood
SIRS	Systemic inflammatory response syndrome
SLPI	Secretory leukoprotease inhibitor
SvO2	Saturation of peripheral venous blood
TGF-β	Transforming growth factor-β
TLR	Toll-like receptor
TNF- α	Tumor necrosis factor-alpha

INTRODUCTION

Steroids are a group of drugs which are chemically related to the hormones produced by the cortex of the adrenal glands (corticosteroids) as a response to adrenocorticotrophic hormone (ACTH) excluding sex hormones. The primary adrenal corticosteroids are cortisol and aldosterone. Cortisol is a glucocorticoid, responsible for carbohydrate, fat, and protein metabolism. Aldosterone is a mineralocorticoid, responsible for regulation of salt and water balance. All corticosteroids, both natural and synthetic share the similar chemical structure, which is based on the structure of cholesterol (***Cavaliere 2004).***

Corticosteroid use has a significant effect on morbidity and mortality in the intensive care unit. There are widespread scales of corticosteroids usage in acute critical illness. Corticosteroids are used therapeutically for relative adrenal insufficiency as well as for the attenuation of the inflammatory and immune response in the critically ill patients ***(Rhen and Cidlowski 2005).***

Early use of corticosteroids has been recommended in sepsis, acute lung injury, acute respiratory distress syndrome and refractory vasodilator shock ***(Annane et al., 2002).***

Corticosteroids are generally safe when used for a short period of time with appropriate monitoring. When used for longer periods, the frequency and severity of adverse effects increases dramatically. Many of these adverse effects are the unavoidable results of the normal actions of

the steroid drugs and must be considered when people decide on a course of long-term corticosteroid therapy ***(Cavaliere et al., 2004).***

Corticosteroids are well known for their broad-ranging immunosuppressive effects, which may place the patient at increased risk of infectious complications.

Corticosteroids use are associated with increased rate of infection, increased ICU and ventilator length of stay (L.O.S) and a trend toward increased mortality. ICU physician must be cautious when prescribing corticosteroids keeping in mind their indications, risks and benefits ***(Schumer 2006).***

AIM OF THE WORK

The aim of this work is to highlight the different uses of steroids in ICU and assessment of the risk/benefit ratio when we decide to use them.

Also it discusses the duration of steroids use and the expected complications which challenge us for proper use of steroids in ICU.

PHYSIOLOGY OF STEROIDS

Cortisol (hydrocortisone) is the major endogenous glucocorticoid secreted by the adrenal cortex. Over 90% of circulating cortisol is bound to corticosteroid-binding globulin (CBG) with lesser than 10% in the free biologically active amount form. During acute illness, particularly sepsis, CBG levels fall by as much as 50% resulting in a significant increase in the percentage of free cortisol ***(Dimopoulou et al. 2007)***.

The circulating half-life of cortisol varies from 70 to 120 min with a biological half-life of approximately 6 to 8 h. The adrenal gland does not store cortisol; increased secretion arises due to increased synthesis under the control of ACTH (Fig.1) ***(Arlt and Stewart 2005).***

Activation of the HPA axis and the interaction with the inflammatory response

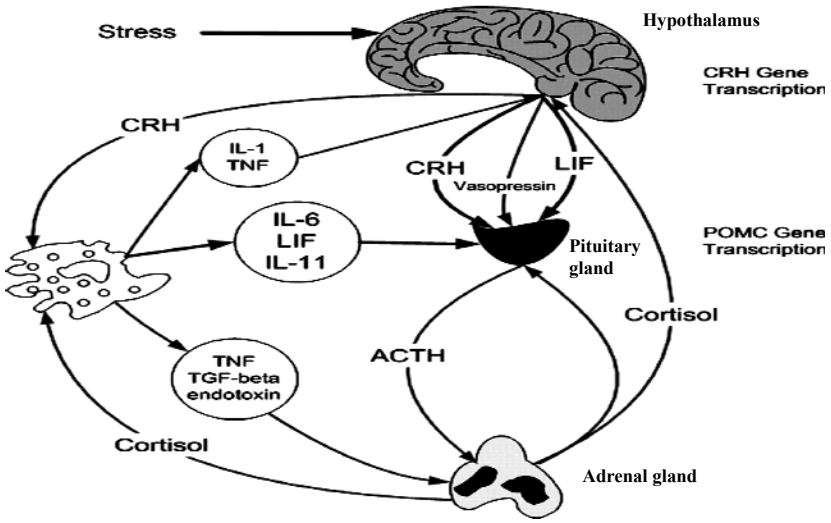

Fig. (1): IL-11 = interleukin-11; LIF = leukemia inhibitory factor; POMC = pro-opiomelanocortin; TGF-β = transforming growth factor-β ***(Marik et al. 2008).***

Cholesterol is the principal precursor for steroid biosynthesis in steroidogenic tissue (Fig. 2). In a series of sequential enzymatic steps cholesterol is converted to pregnenolone and then to the end products of adrenal biosynthesis (aldosterone, DHEAS and cortisol) in the 3 zones of the cortex as the following:

1. From zona glomerulosa: 2 mineralocorticoid hormones (aldosterone & deoxycorticosterone).
2. From zona fasciculata: 2 glucocorticoid hormones (cortisol & corticosterone).
3. From zona reticularis: sex hormones mainly androgens (DHEA & androstenedione) ***(Arlt and Stewart 2005).***

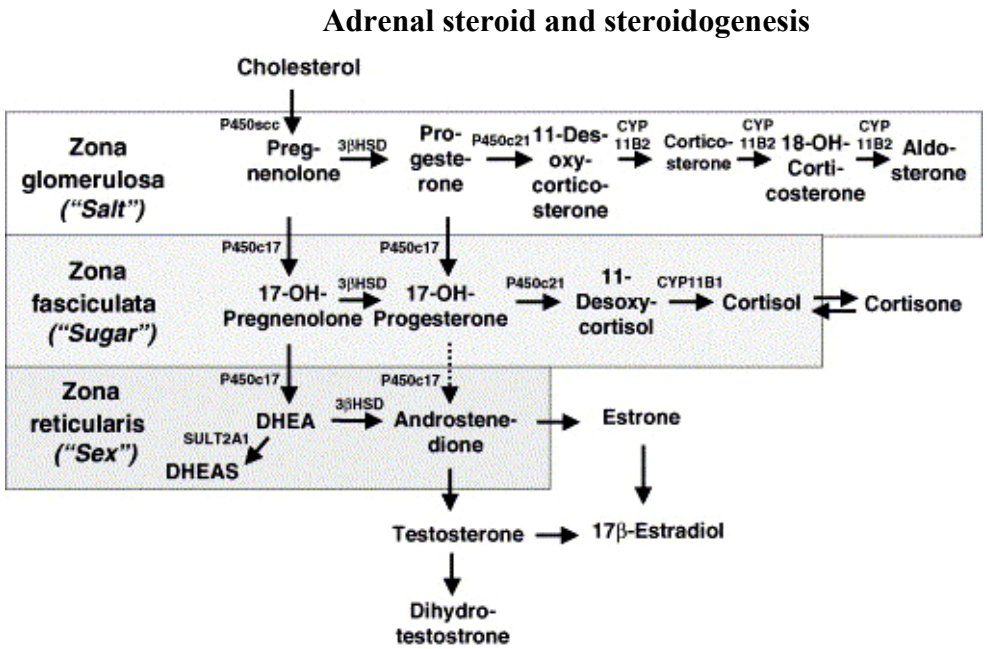

Fig. (2): Steroidogenesis in the human adrenal. Following the uptake of cholesterol into mitochondria within adrenocortical cells, aldosterone, cortisol, and adrenal androgen precursors are synthesized through the coordinated action of a series of steroidogenic enzymes in a zone-specific fashion- DHEAS: Dihydro-epiandrosterone ***(Arlt and Stewart 2005).***

At rest and during stress approximately 80% of circulating cortisol is derived from plasma cholesterol with the remaining 20% being synthesized in situ from acetate and other precursors. Experimental studies suggest that high-density lipoprotein (HDL) is the preferred cholesterol source of steroidogenic substrate in the adrenal gland ***(Yaguchi et al. 1998).***

The activity of glucocorticoids is mediated by both the glucocorticoid receptor (GR) and mineralocorticoid receptor (MR). The GR and MR share both functional and structural homology, both aldosterone and glucocorticoid hormones bind to both the GR and MR ***(Rogerson and Fuller 2003).***

The 11 beta-hydroxysteroid dehydrogenase (11β-HSD) enzyme plays an important role in preventing glucocorticoid access to cells that express the MR. This enzyme has two isoforms, a NAD-dependent form (11β -HSD-2) and a NADP-dependent form (11β -HSD-1). 11β -HSD-2 is found in tissues with high levels of MR activity such as the kidney, sweat and salivary glands, placenta, and colon. 11β -HSD-2 converts cortisol to cortisone, its inactive reduced metabolite which is unable to bind to the GR and MR.

11β -HSD-1 is found in glucocorticoid target tissues and catalyzes the conversion of cortisone to the active glucocorticoid cortisol (Fig.3). Pro-inflammatory cytokines modulate the activity of the 11β -HSD enzymes, with interleukin-1beta (IL-1β) and tumor necrosis factor-alpha (TNF- α) increasing the activity of 11β -HSD-1 while decreasing that of 11β -HSD-2 ***(Tomlinson et al. 2001).***