

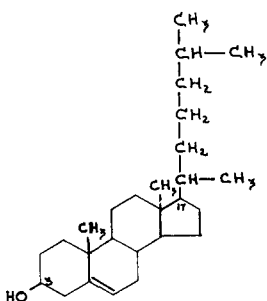
# PHARMACOLOGY SECTION

## Steroid Therapy During Cardiopulmonary Bypass

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It is time someone spoke up in defense of Cholesterol in the diet. Neglecting, for the moment, hypercholesterolemia, the perverse effects of which are all-together too well known to all of us; let us consider the fate of ingested cholesterol. Of the wide variety of sterols daily consumed by the human organism, cholesterol transmits with the greatest facility through the intertinal membrane, It is uniquely soluble in the plasma as an unsaturated fatty acid ester. Most of the esterified product of cholesterol is ultimately converted to bile acids, however a small portion remains as the free alcohol in the plasma.<sup>1</sup> This minute amount of free cholesterol is available for some rather astonishing endocrinological reactions.

Free cholesterol forms the substrate for virtually all steroid synthetic mechanisms within the body. Although the diet provides an adequate, if not over-abundant, supply of cholesterol ordinarily; the body is biochemically equipped to synthesize its own endogenous cholesterolic product should exogenous supplies fail for some reason.<sup>2</sup> Extreme starvation states will induce the organism to "cannibalize" cellular stores if sterols to serve as precursors to endogenous cholesterol synthesis. Moreover, the presence of cholesterol for synthesis of naturally-occurring steroid hormones is essential for the survival and well-being of the human organism and the abrupt removal of same will result in the death of the organism in a matter of hours.



CHOLESTEROL

Figure 1

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## I. STEROID CHEMISTRY AND BIOLOGICAL ACTIVITY

Generally, it can be stated that the steroid hormones function as the mediators of the stress response in the body. Levels of steroid hormone secretion increase immediately in response to any type of somatic or psycho-somatic stress.<sup>3</sup> Stress must first be perceived by the nervous system and then transmitted through a series of poorly understood neuronal pathways to the Thalamus and Hypothalamus. Then a series of protein-related "releasing-factors" are secreted by the Hypothalamus to activate the anterior lobe of the Pituitary to secrete the Adrenocorticotrophic Hormone, (ACTH) also a protein-derived hormone. To this point, all of the hormonal factors are proteins or protein-derivatives. ACTH induces the Adrenal Cortex to secrete the vast array of steroid hormones referred to collectively as the Adrenocortical Hormones. The Adrenocorticotrophic Hormones comprise such famous compounds as: the Androgens and Testosterone, the male sex hormones; the Estrogens and Progesterone, the female sex hormones; and the myriad of steroid hormones responsible for metabolic compensation of stress. The mere description of the awesome number of metabolically-active steroid hormones would be greatly beyond the time and space requirements of this review. Such a breadth and flexibility of physiologic action is made possible by the Corticosteroids as to prompt one to think there is "a steroid for every occasion."

Corticosteroids, like Cholesterol itself, are built upon the Perhydrocyclopentanophenanthrene nucleus or the "steroid nucleus." The nucleus consists of three fused Cyclohexane rings with branched aliphatic chains of varying sizes on Carbon 17. Other compounds, built on the steroid nucleus, and chemically similar to the Corticosteroids are: the Digitalis Glycosides, the Terpenes, and an obscure family of cardioactive substances known as "Toad Poisons."<sup>4</sup>

For purposes of simplicity, the corticosteroids may be divided in two basic categories with regard to their biological activity; the Mineralocorticoids and the Glucocorticoids. The Mineralocorticoids are termed so because of their intense effect upon fluid and electrolyte balance in the body. The major endogenous mineralocorticoid is Aldosterone, and to a lesser degree, Deoxycorticosterone. Aldosterone is responsible for hormonal regulation of renal electrolyte clearance. Aldosterone exerts its major effect by controlling reabsorption of filtered Sodium and Potassium in the Loop of Henle, the distal convoluted tubules, and the urine collecting ducts. The mechanism by which Aldosterone alters permeability of the renal tubules is, as yet, obscure.

Hypersecretion of Aldosterone results in marked retention of Sodium and may, in some cases, reduce daily Sodium loss to a few milligrams. Concomitantly, bodily excretion of Potassium and Hydrogen ion is increased. In severe instances, this may result in Hypokalemia and a generalized metabolic alkalosis with ensuing muscle weakness, convulsions, and finally death due to cardiac failure. Surprisingly, Hyperaldosteronism rarely results in clinical Hyponatremia; seemingly because such an increase in total body Sodium induces a raging thirst in the subject resulting in dilution of the Sodium excess and enhanced urinary output.<sup>5</sup>

In a far more familiar circumstance, Aldosterone-induced Hypokalemia may precipitate the cardiotoxicity phenomenon with its attendant arrhythmogenic and negative inotropic effects.

Aldosterone deficiency will result in exaggerated excretion of sodium with concomitant retention of potassium and hydrogen ions. Hence, a progressive hyperkalemia and metabolic acidosis will ensue causing a generalized systemic muscle weakness, a decrease in circulating blood volume, and finally cardiac asystole. Indeed, it is true that the physiologic preparation acutely deprived of aldosterone will die in a period of a few hours if not vigorously treated with exogenous corticosteroids and massive fluid and electrolyte replacement. Deficiencies in the normal mineralocorticoid balance are routinely treated simply by dietary supplementation of the wasted electrolytes. However, in some instances, it is necessary to compensate aldosterone deficiency by the administration of ACTH, the anterior pituitary hormone that mediates secretion of all adrenocorticosteroids. Additionally, it is possible in some instances to control hypoaldosteronism by the administration of a compound known as synthetic deoxycorticosterone, a biochemical analogue of aldosterone itself.<sup>6</sup>

Glucocorticoids at the other major branch of the adrenocorticosteroid family tree, although the glucocorticoids are chemically quite similar to the mineralocorticoids, they exhibit greatly different physiologic character. Similarly, the major function of the glucocorticoid group is to compensate somatic stress by catalyzing increased utilization of bodily stores of fats, proteins, and carbohydrates. Regrettably, most of the mechanisms by which the glucocorticoids increase availability of metabolic substrate are at the present time unknown.

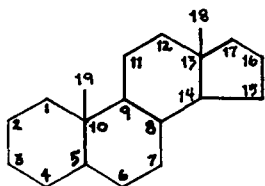
Glucocorticoids seem to exert their most potent effect upon protein metabolism by increasing hepatic protein stores at the expense of protein stores throughout the rest of the body. This is accomplished by a two-fold process, that of increased systemic protein catabolism and by enhanced amino acid transport in the hepatic tissues. Increased availability of amino acid substrate for protein synthesis in the liver provides for more efficient manufacture of the plasma proteins.<sup>7</sup> Hence, the immunologic capability of the organism is enhanced, as well as its ability to regulate plasma fluid volume by adjustments in plasma oncoticity. Additionally, increased availability of amino acids within the liver will necessarily enhance gluconeogenesis, the process of converting amino acids to glucose; providing the organism with an alternate source of cellular metabolic substrate.

Lipid metabolism is also enhanced by the presence of glucocorticoids. Primarily through increased mobilization of fatty acids from adipose tissues of the body.<sup>8</sup> Since plasma fatty acids may also be used as cellular metabolic substrate, such mobilization would tend to increase the organism's ability to combat stress, such as starvation states, and pathological states resulting in depletion of the primary energy substrate, glucose.

Glucocorticoid alterations in protein and fat metabolism are not nearly as all-encompassing as similar glucocorticoid-induced alterations in carbohydrate metabolism.<sup>9</sup> As previously mentioned, glucocorticoids greatly enhance gluconeogenesis in the liver. This steroid group may at times increase the rate of gluconeogenesis by as much as ten-fold.<sup>10</sup> Contrarily, there is also a concomitant decrease in glucose uptake by the cells themselves. Such a decrease in glucose transport and utilization in the extrahepatic cells may play an important role in the protection of the target organs (i.e., the heart, brain, and lungs), during periods of severe stress.

Moreover, each of the aforementioned processes by which glucocorticoids enhance protein, lipid and carbohydrate metabolism has the net effect of increasing

blood glucose levels in response to virtually any type of physiologic stress. Steroid-mediated increases in blood glucose concentration provide the organism with greater discretion in the expenditure of high-energy metabolic substrate. It is postulated that virtually all of the cellular effects of the glucocorticoids are attenuated if not negated in the absence of ACTH.<sup>11</sup> Thus, the interdependence of the glucocorticoids and the anterior pituitary hormones for their biological activity provide for the feedback loop which regulates the secretion of both products in the serum.



## PERHYDROCYCLOPENTANO PHENANTHRENE

Figure 2

Cortisol is the secretory product of the adrenal cortex that is responsible for approximately 95% of the glucocorticoid activity in the body. Cortisol is also known by its medicinal names such as hydrocortisone and compound F. The remainder of glucocorticoid activity is effected by the compound corticosterone to a lesser degree by the compound cortisone. Cortisol secretion is again directly activated by the presence of ACTH and as mentioned previously, ACTH secretion responds immediately to virtually any kind of physical or even mental stress.<sup>12</sup> Regrettably, aside from the above-mentioned metabolic effects of the glucocorticoids, the effect of cortisol on inflammatory process is at this time, mainly conjectural.

Some elements of cortisol's effect in the acute inflammatory reaction in the body are presently being elucidated. Firstly, cortisol seems to exert a stabilizing effect on the capsular membranes to be more resistant to rupture within the cells during periods of acute inflammation. Specifically, cortisol appears to exert a direct effect upon the lysosomal membrane. Since the lysosomes contain the major portion of the hydrolytic enzymes of the cell, such a stabilizing effect would tend to reduce the incidence of lysosomal rupture and subsequent digestion of the lysis of the cell itself.<sup>13</sup> Secondly, cortisol attenuates the effects of such compounds as bradykinin and histamine which are found in large concentrations in inflamed tissue and cause marked vasodilation and interstitial edema. Contrarily, cortisol potentiates the effects of the alpha adrenergic agents in the plasma, such as epinephrine and norepinephrine thus allowing greater vasoconstriction in affected tissues. This supression of bradykinin and histamine in concert with the induction of increased local sympathetic tone as the effect of markedly decreasing capillar permeability. Hypothetically, local decreases in capillary permeability, mediated by cortisol, would ameliorate the "plasma-leak" phenomenon seen in inflamed tissues.<sup>14</sup>

If, indeed, the "plasma and plasma protein-leak" circumstances is reduced by cortisol, then it can be assumed that the plasma oncotic gradient will not become severely unbalanced in inflamed tissues and hence, fulminant interstitial edema will not ensue. It should be noted that these postulated effects of cortisol relate primarily to the acute inflammatory response of the body and do not necessarily extend to pathological states in which tissues are chronically inflamed. Formed elements of the

blood are affected in a number of ways by cortisol. Large concentrations of cortisol in the tissues immediately induce a marked decrease in the number of circulating polymorphonuclear leucocytes, specifically, the eosinophils, monocytes, and lymphocytes. Furthermore, the biological efficiency of the remaining leucocytes is decreased by the presence of cortisol thus decreasing the effectiveness of the entire acute cellular immunity response. Additionally, cortisol invades the integrity of the hormonal immunity system of the body by causing wide-spread atrophy of the lymphoid tissues. Thus, with chronic administration, cortisol may cause a loss of active or passive acquired immunity due to insufficient production of cellular antibodies. Chronic cortisol therapy will also result in clinical polycythemia by a method which is yet, still quite mysterious. Overall, these cortisol-induced effects upon formed elements of blood may, in severe instances, precipitate the death of the subject from what would otherwise be a sublethal infection.

## II. STEROID TREATMENT IN THE CARDIAC PATIENT

Elucidation of the basic biochemical mechanisms of the protective effect of corticosteroid therapy upon cellular integrity is the subject of vigorous on-going research. With this sketchy background of the activities of endogenous corticosteroids; let us consider the supposed effects of administration of exogenous corticosteroids, specifically their synthetic analogues. With cortisol as the molecular model many synthetic departures have been taken. By way of categorizing the effects of these synthetics let us speak of their "mineralocorticoid" equivalent and their "glucocorticoid" equivalent. The most familiar product is synthetic hydrocortisone (Sole-cortef) which is an equimolar equivalent to endogenous hydrocortisone in both its mineralocorticoid and glucocorticoid activity. The established clinical application for hydrocortisone is the treatment of a variety of endocrine disorders including acute and chronic manifestations of adrenocortical insufficiency resulting from a chronic pathological state such as Addison's disease and post-traumatic or post-surgical management where a balanced regimen of mineralocorticoids and glucocorticoids activity is desirable. The administration of hydrocortisone as an adjunctive in the treatment of ischemic myocardial syndromes is controversial and probably contraindicated in most subjects as the specific glucocorticoid activity of hydrocortisone is weak relative to other synthetic analogues. The glucocorticoid agent presently enjoying the greatest clinical application in the treatment of acute myocardial insufficiency is the agent methylprednisolone-sodium succinate (Solu-Medrol).<sup>15</sup> Upon comparison of the steroid potency of methylprednisolone when compared to hydrocortisone it is evident that, irrespective of the route of the administration, methylprednisolone exerts approximately four times the glucocorticoid effect of hydrocortisone and roughly the same anti-inflammatory potency of the non-methylated product prednisolone.<sup>16</sup> The mineralocorticoid activity of methylprednisolone is roughly equivalent in equimolar dose to hydrocortisone and slightly less potent than prednisolone. Thus with this four-fold increase in glucocorticoid activity, methylprednisolone would necessarily reach higher serum and tissue levels in shorter periods of time than would hydrocortisone and remain biologically effective for a longer period of time. The next agent in the hierarchy of steroid potency is betamethasone. The glucocorticoid activity of betamethasone is roughly ten times that of synthetic hydrocortisone and hence, relatively 2.5 times the glucocorticoid potency of methylprednisolone. The mineralocorticoid activity of betamethasone is, however,

reduced somewhat below that of methylprednisolone and hydrocortisones. This reduction in mineralocorticoid activity is not quantitated in the same manner that glucocorticoid activity is, it is rather said to be somewhat less potent in causing sodium and fluid retention. The agent thought to be of the greatest glucocorticoid potential that is commonly in chemical use is dexamethasone. Although several other synthetic steroid preparations have been isolated which exhibit a greater glucocorticoid potential than dexamethasone, these agents are not routinely available at this date. Synthetic dexamethasone exhibits approximately forty times the glucocorticoid potential of hydrocortisone and approximately ten times the glucocorticoid potential of methylprednisolone. The mineralocorticoid activity of dexamethasone is said to be "negligible." Thus it would seem that all of the synthetic steroid preparations, dexamethasone would be the agent of choice when a strictly glucocorticoid potential is of the greatest therapeutic value.<sup>17</sup>

Adverse reactions stemming from the use of synthetic corticosteroid preparations are unfortunately many and not quite varied. It can, however, be said that the more severe systemic adverse reactions to the corticosteroid therapy are largely encountered during chronic administrations and much less frequently encountered during acute administration, such as those dosage regimens administered to the cardiac patient only in the perioperative. Aside from the fluid and electrolyte abnormalities cited earlier the most common adverse reactions of the corticosteroid therapy are as follows:

*I. Neurological*

convulsions, vertigo, and headache, especially in the presence of known organic brain syndrome.

*II. Musculoskeletal*

muscle weakness, also known as steroid myopathy, pathological fracture, loss of muscle mass, vertebral compression syndrome, and early onset of osteoporotic changes.

*III. Endocrine*

carbohydrate intolerance, precipitation of latent diabetes mellitus, suppression of growth and failure to thrive in children, induction of acute Cushingoid syndrome, menstrual irregularities, and exacerbation of symptoms in previously isolated diabetic patients.

*IV. Gastrointestinal*

generalized abdominal distention, ulcerative esophagitis, perforation of previous peptic ulcer, and acute pancreatitis.

*V. Ophthalmic*

increased intraocular pressure, glaucoma, and formation of cataracts.

*VI. Metabolic*

systemic nitrogen loss due to protein catabolism.

*VII. Psychological Disorders*

exacerbation of previous psychotic tendencies of emotional disturbance, acute psychotic event, and acute psychoneurotic depression.

Gratefully, the vast majority of the above mentioned adverse reactions are short lived and resolve spontaneously upon withdrawal of the medication.

### III. CORTICOSTEROID EFFECTS UPON MYOCARDIAL MORPHOLOGY

Steroid effects upon the individual myocardial cell are best viewed through specific effects upon the plasma membrane, intracellular organelles and inclusions, and the metabolic processes indigenous to each specific organelle. Beginning with the out-lying structure and moving inward towards the nucleus, first let us consider the specific effects upon the myocardial sarcolemma. The mysterious "stabilization" effect of the corticosteroids upon the sarcolemma has been demonstrated by a reduction in swelling brought about by steroid treatment in the sarcomere that is traumatized or rendered ischemic. Generalized cellular swelling is one of the most graphic and demonstrable effects of ischemic stress on the myocardium. Swelling or increase in intracellular water contents following ischemia is greatly reduced by pre-treatment with corticosteroids. The initial event in ischemic cellular swelling must necessarily be increased sarcolemmal permeability which is thought to result from dysfunctional sodium-potassium ion pumps within the plasma membrane itself. Maintenance of function of these ion pumps is an extremely high energy-requiring process, in as much as, the cellular membrane requires a dense concentration of high energy phosphates to continue to actively extrude sodium from the cell while retaining potassium within the cell during normal function. Thus, with the onset of ischemia rapid depletion of high energy compounds within the cellular membrane would almost immediately result in failure of the ionic pumps to extrude necessary amounts of sodium and other osmotically-active substances from the cell; allowing the cell to engorge with fluid. It is at least unlikely that the glucocorticoids act in any way to forestall the depletion of high energy phosphates, however, they may act directly upon the structure of the plasma membrane, with its large phospholipid contingent, to maintain basal rates of permeability during periods of ischemia.

### DOSEAGE SCHEDULE AND ROUTE OF ADMINISTRATION

Administration of synthetic Corticosteroids in the Cardiopulmonary Bypass patient may be accomplished by several methods. The most popular method is to add the steroid compound directly to the prime during recirculation. In the case of methylprednisolone the systemic dosage schedule of thirty milligrams per kilogram of patient body weight may be administered by I.V. injection fifteen to thirty minutes prior to institution of Cardiopulmonary Bypass. Dexamethasone, however, is best administered in the priming contents as prior administration by I.V. injection is associated with moderate to severe hypotension in some patients.

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