PRINCIPLES AND PRACTICE OF ENDOCRINOLOGY AND METABOLISM

THIRD EDITION

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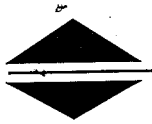

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CHAPTER 78

CORTICOSTEROID THERAPY

LLOYD AXELROD

This chapter examines the risks associated with the use of glucocorticoids and of mineralocorticoids for various illnesses, and provides guidelines for the administration of these commonly prescribed substances.

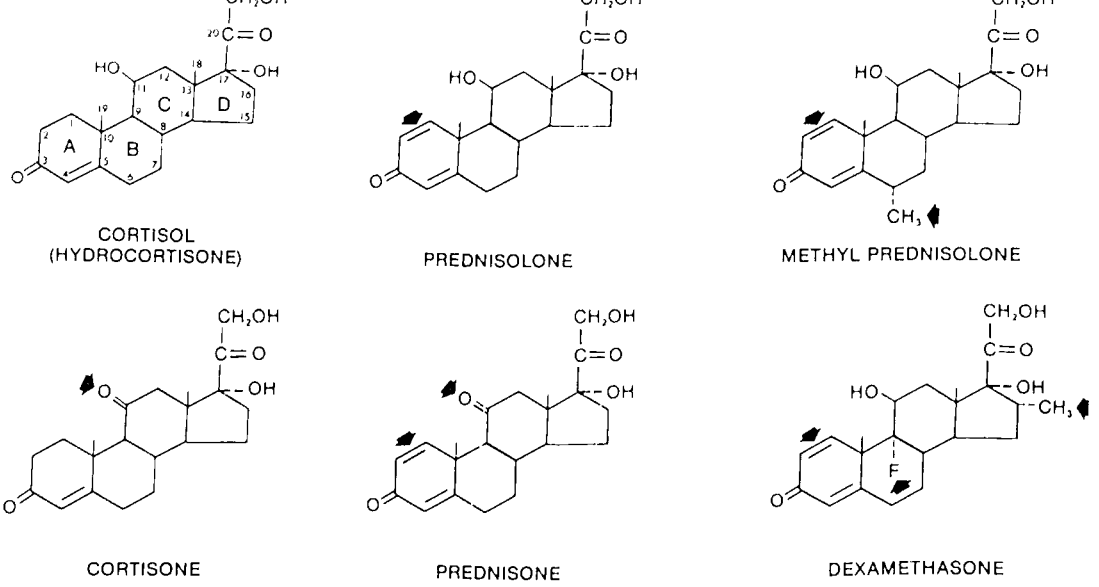

FIGURE 78-1. The structures of commonly used glucocorticoids. In the depiction of cortisol, the 21 carbon atoms of the glucocorticoid skeleton are indicated by numbers and the four rings are designated by letters. The *arrows* indicate the structural differences between cortisol and each of the other molecules. (From Axelrod L. Glucocorticoid therapy. Medicine [Baltimore] 1976; 55:39, and Axelrod L. Glucocorticoids. In: Kelley WN, Harris ED Jr, Ruddy S, Sledge CB, eds. Textbook of rheumatology, 4th ed. Philadelphia: WB Saunders, 1993:779.)

GLUCOCORTICOIDS

STRUCTURE OF COMMONLY USED GLUCOCORTICOIDS

Figure 78-1 indicates the structures of several commonly used glucocorticoids.[1,2] *Cortisol (hydrocortisone)* is the principal circulating glucocorticoid in humans.

Glucocorticoid activity requires a hydroxyl group at carbon 11 of the steroid molecule. Cortisone and prednisone are 11-keto compounds. Consequently, they lack glucocorticoid activity until they are converted in vivo to cortisol and prednisolone, the corresponding 11-hydroxyl compounds.[3,4] This conversion occurs predominantly in the liver. Thus, topical application of cortisone is ineffective in the treatment of dermatologic diseases that respond to topical application of cortisol.[4] Similarly, the antiinflammatory action of cortisone delivered by intraarticular injection is minimal compared with the effect of cortisol administered in the same manner.[3] Cortisone and prednisone are used only for systemic therapy. All glucocorticoid preparations marketed for topical or local use are 11-hydroxyl compounds, which obviates the need for biotransformation.

PHARMACODYNAMICS

HALF-LIFE, POTENCY, AND DURATION OF ACTION

The important differences among the systemically used glucocorticoid compounds are duration of action, relative glucocorticoid potency, and relative mineralocorticoid potency (Table 78-1).[1,2] The commonly used glucocorticoids are classified as *short-acting*, *intermediate-acting*, and *long-acting* on the basis of the duration of corticotropin (ACTH) suppression after a single dose, equivalent in antiinflammatory activity to 50 mg of prednisone (Table 78-1).[5] The relative potencies of the glucocorticoids correlate with their affinities for the intracellular glucocorticoid receptor.[6] The observed potency of a glucocorticoid, however, is determined not only by the intrinsic biologic potency, but also by the duration of action.[6,7] Consequently, the relative potency of two glucocorticoids varies as a function of the time interval between the administration of the two steroids and the determination of the potency. In particular, failure to account for the duration of action may lead to a marked underestimation of the potency of dexamethasone.[7]

The correlation between the *circulating half-life* ($T_{1/2}$) of a glucocorticoid and its *potency* is weak. The $T_{1/2}$ of cortisol in the circulation is in the range of 80 to 115 minutes.[1] The $T_{1/2}$s of other commonly used agents are cortisone, 0.5 hours; prednisone, 3.4 to 3.8 hours; prednisolone, 2.1 to 3.5 hours; methylprednisolone, 1.3 to 3.1 hours; and dexamethasone 1.8 to 4.7 hours.[1,7,8] Prednisolone and dexamethasone have comparable circulating $T_{1/2}$s, but dexamethasone is clearly more potent. Similarly, the correlation between the circulating $T_{1/2}$ of a glucocorticoid and its *duration of action* is poor. The many actions of glucocorticoids do not have an equal duration, and the duration of action may be a function of the dose.

The duration of ACTH suppression is not simply a function of the level of antiinflammatory activity, because variations in the duration of ACTH suppression are achieved by doses of glucocorticoids with comparable antiinflammatory activity. The duration of ACTH suppression produced by an individual glucocorticoid, however, probably is dose related.[5]

TABLE 78-1.
Commonly Used Glucocorticoids

Duration of Action*	Glucocorticoid Potency†	Equivalent Glucocorticoid Dose (mg)	Mineralocorticoid Activity
SHORT-ACTING			
Cortisol (hydrocortisone)	1	20	Yes‡
Cortisone	0.8	25	Yes‡
Prednisone	4	5	No
Prednisolone	4	5	No
Methylprednisolone	5	4	No
INTERMEDIATE-ACTING			
Triamcinolone	5	4	No
LONG-ACTING			
Betamethasone	25	0.60	No
Dexamethasone	30	0.75	No

*The classification by duration of action is based on Harter JG. Corticosteroids. NY State J Med 1966;66:827.

†The values given for glucocorticoid potency are relative. Cortisol is arbitrarily assigned a value of 1.

‡Mineralocorticoid effects are dose related. At doses close to or within the basal physiologic range for glucocorticoid activity, no such effect may be detectable.

(Data from Axelrod L. Glucocorticoid therapy. Medicine [Baltimore] 1976;55:39; Axelrod L. Adrenal corticosteroids. In: Miller RR, Greenblatt DJ, eds. Handbook of drug therapy. New York: Elsevier North-Holland, 1979:809; and Axelrod L. Glucocorticoids. In: Kelley WN, Harris ED Jr, Ruddy S, Sledge CB, eds. Textbook of rheumatology, 4th ed. Philadelphia: WB Saunders, 1993:779.)

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