Steroid pharmacokinetics: An “overlooked” issue of steroid metabolism in acute and chronic disease

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This issue of the Journal of Translational Internal Medicine contains a comprehensive and updated overview of steroid treatment in a wide array of pathologic conditions. Within this scope, we take the opportunity to draw attention to an often neglected, yet very important aspect of steroid metabolism: Steroid pharmacokinetics (PK). The knowledge on PK behavior of steroid drugs such as prednisolone or prednisone has indeed been expanding at a rather slow pace. First, convenient, rapid, and specific determination of plasma levels of these steroids was largely indebted to the breakthrough of high performance liquid chromatography (HPLC). Second, prednisolone is nonlinearly protein-bound. Since unbound prednisolone is the biologically active compound, only the measurement of this free fraction in plasma is relevant. Third, the short half-life of prednisolone precludes to reach steady-state levels and requires determination of the area under the concentration-time curve. Fourth, prednisolone and prednisone are mutually convertible. Intravenous prednisolone, however, is administered as a prodrug ester, which renders comparison and interpretation of reported PK data of both agents unreliable. Finally, total body clearance of prednisolone, and to a lesser extent, only the unbound fraction directly correlates with increasing concentrations of prednisolone. To be valid, steroid PK studies should therefore at least aim at standardization of drug dose, profile and hydrosolubility.

The degree of protein (mainly transcortin and albumin) binding is 77%, 75%, and 65%. Since this does not exceed 80%, all steroids are removed by continuous renal replacement therapy (CRRT) and intermittent hemodialysis (IHD). Volume of distribution is 0.6 L/kg, 1.2 L/kg, and 0.9 L/kg, respectively, remaining within the range of IHD and CRRT removal. Distribution volumes for all given steroids may even be lower because the “older” lipophilic formulas have been replaced by hydrosoluble forms.

The scarce PK data on methylprednisolone point out that 65-70% of the drug is eliminated daily by a normal kidney. From a PK viewpoint, it thus seems appropriate to administer a higher dose for compensating drug loss during CRRT. Though never investigated in vivo, this might significantly challenge interpretation of clinical landmark studies that assessed the effects of methylprednisolone treatment in the critically ill (e.g., the ADRENAL study on adjunctive methylprednisolone treatment in septic shock). In addition, many other PK-related observations may have clinical relevance. To cite a few: PK dose-dependency partly explaining why an alternate-day regimen with prednisone yields fewer biological effects; conversion of prednisone into prednisolone not being a limiting factor, even when liver function is severely impaired; hypoproteinemia in se not enhancing unbound concentrations of prednisolone in vivo; patients with hepatic or renal failure, elderly subjects, and renal transplant recipients showing increased unbound prednisolone concentrations.

Importantly, PK values are also influenced by dose magnitude (e.g., the distribution

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volume of methylprednisolone significantly augments with increasing dose). Finally, transcortin and albumin levels may considerably vary between patients thereby producing divergent free steroid concentrations despite the use of similar dose regimens.[4]

Considerable attention has been accorded to endogenous steroid PK. However, the exogenous metabolism and in particular the elimination route of steroids has been poorly studied.[1,2] The liver plays a preponderant role in steroid metabolism. Yet, several studies also divulged a key role for the kidney.[4-6] Unfortunately, we are confronted with a lot of uncertainty. Different types of steroids indeed have highly different elimination routes. Virtually no data exist regarding renal handling of steroids in chronic kidney disease and as mentioned earlier,[1,2] on steroid elimination or metabolism during IHD and CRRT. The PK of methylprednisolone and prednisolone was evaluated in 24 healthy male subjects treated with single or multiple doses orally for 3 days. For each drug, six different dose regimens (ranging from 1 to 80 mg of methylprednisolone and 1.25-100 mg of prednisolone) and administration intervals ranging from 3 to 24 h were investigated.[3] Plasma was assayed using a normal phase HPLC method. Methylprednisolone expressed linear PK with no apparent dose- or time-dependency. In contrast, prednisolone showed marked dose-dependency with higher clearance and volume of distribution for higher doses. The latter is explained by its saturable plasma protein binding because clearance and distribution volume of unbound drug were not dose-dependent. After multiple dosing, prednisolone displayed a time-dependent PK profile with increased unbound clearance and volume of distribution.[3] Such complex pharmacokinetic behavior obviously thwarts any attempt to reliably determine prednisolone doses needed to obtain a desired target concentration in the presence of AKI and/or extra-renal epuration. With concentrations proportional to the given dose, the PK of methylprednisolone is more predictable. Thus, assessment of methylprednisolone plasma protein binding is less important in patients undergoing IHD or CRRT.

Methylprednisolone PK and its direct suppressive effects on cortisol secretion and cell trafficking were compared in six patients with chronic renal failure (CRF) and in six healthy controls.[6] Intravenous administration of 0.6 mg/kg methylprednisolone produced similar PK in both groups. Clearance approximated 280 mL/h/kg, and volume of distribution, \( V_d \), and unbound fraction were respectively 1.1 L/kg, 2.7 h and 0.20 h.[4] Treatment with methylprednisolone may thus offer a therapeutic advantage in CRF patients since all other corticosteroids display altered PK characteristics in this condition. Other processes besides renal elimination may be responsible for an observed decrease in plasma steroid concentrations. A study in patients with rheumatoid arthritis and systemic lupus erythematosus demonstrated that inadequately low serum levels of adrenal androgens and cortisol were not due to increased renal clearance and daily loss of these hormones but resulted from decreased adrenal production or increased conversion or conjugation to downstream hormones.[7]

CONCLUSION

A poignant lack of awareness and knowledge regarding catabolism, clearance mechanisms and elimination route of steroids fuels the ongoing controversy that surrounds adjunctive corticosteroid therapy in patients with chronic[8] or acute[9] inflammatory disease. This particular patient population also is more prone to develop early and significant kidney dysfunction, necessitating extra-renal support. A better understanding of steroid PK, preferentially guided by HPLC measurement of plasma steroid concentrations, likely will have direct clinical implications, for instance by adapting steroid doses in IHD or implementing higher dose regimens during CRRT.

REFERENCES


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