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Mini Review

Is Dexamethasone a Substrate, an Inducer, or a Substrate-Inducer of CYP3As?

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Abstract

Dexamethasone is a steroidal agent used in the treatment of many different clinical conditions. As such, it is often combined with several drugs from various pharmacological classes. The clinical significance of potential drug-drug interactions involving dexamethasone either as a substrate or as an inducer of cytochrome P450 3As (CYP3As) is not well established due to conflicting results. *In vitro* studies conducted with human microsomes, primary cultures of human hepatocytes, and clinical studies using various dexamethasone concentrations and doses are reviewed to provide valuable information. Results from these studies demonstrate that CYP3As are clearly involved in the metabolism of dexamethasone, a substrate with weak affinity. However, the potential mechanism for CYP3A induction by dexamethasone remains unclear. Combining results from clinical studies employing different doses, different treatment durations along with evaluation of the baseline CYP3A enzyme activity suggests that dexamethasone could increase *CYP3A4* gene expression by 25-30%, a marginally clinically significant effect.

Keywords: CYP; Drug-drug interactions; Drug metabolism; Victim drugs; Substrates; Inducers; *In vitro; In vivo*

Abbreviations: CYP: Cytochrome P450; mRNA; Messenger RNA; C_{max}: Max Concentration

Introduction

Dexamethasone is a steroidal anti-inflammatory agent widely used in the treatment regimen of many different conditions such as chronic inflammatory diseases, autoimmune diseases, and cancer [1]. The initial dosage of dexamethasone varies from 0.5-40mg a day depending on the condition being treated. Low doses (0.5-2mg every 6 hours for 2 days) are usually used to test for Cushing's syndrome[1]. Higher doses (30mg for up to 1 week) can be used for the treatment of acute exacerbations of multiple sclerosis[1]. In cancer patients, dexamethasone (1-40mg administered intravenously or orally daily) is frequently used as either an anti-inflammatory, antiemetic, or anti-neoplastic agent [1].

Use of dexamethasone for multiple indications in patients with multiple diseases increases the risk of significant drug-drug interactions. Whether dexamethasone is a substrate of CYP450 isoforms, and if so, whether it is a perpetrator or victim drug due to competitive inhibition is not yet established. Furthermore, there are *in vitro* [2], *in vivo* [2] and clinical [3] studies supporting the possibility that dexamethasone is an inducer of CYP3A. However, there is an ongoing debate about the clinical significance and the potency of dexamethasone as an inducer of CYP3A. The objective of this minireview is to provide information about the enzymes involved in the metabolism of dexamethasone (with a special look at CYP3As) and discuss whether the drug induces CYP3A activity in clinically meaningful manner.

Dexamethasone as a substrate of CYP3As

Evidence from *in vitro* studies

Based on studies conducted in animal and human liver microsomes (HLM), hydroxylation and side chain cleavage were found to be primary pathways for dexamethasone metabolism [4]. Hydroxylation, producing major metabolite 6β-hydroxy dexamethasone, and minor metabolite 6α-hydroxy dexamethasone, is mediated by CYP3A4, with an epimer formation ratio of 1:3

for 6α-hydroxy dexamethasone and 6β-hydroxy dexamethasone respectively. Other *in vitro* studies using specific human CYP3A4 antibodies4 showed that the 6-hydroxylated dexamethasone metabolite formation correlates with CYP3A4 levels. In addition, Gentile, et al. [4] studied dexamethasone metabolisms in the presence of low micromolar concentrations of ketoconazole, a selective human CYP3A4 inhibitor. They showed that both 6α-and 6β-hydroxy dexamethasone formation decreased in parallel with almost complete inhibition at 3μM [4].

These findings are in line with the role of CYP3A4 in the 6-hydroxylation of endogenous glucocorticoid cortisol. Indeed, this relatively simple metabolic pathway led to the suggestion of using dexamethasone as a probe for CYP3A4 in both *in-vivo* and *in vitro* studies [4]. In addition to the CYP3A4 metabolic pathway, dexamethasone side chain cleavage was suggested to be mediated through CYP17A, but this pathway is reported to be insignificant *in vivo* [5].

Evidence from *in vivo* pre-clinical studies

Dexamethasone pharmacokinetics have been reported in dogs, horses, camels, rats and cattle [6]. However, *in- vivo* studies evaluating the metabolic pathway of dexamethasone transformation are limited and do not provide details of CYP450 isoforms involved in metabolism. Katheeri, et al. [6], studied the metabolism of dexamethasone in camels using both *in vivo* and *in vitro* techniques; a fraction of parent dexamethasone was eliminated unconjugated and as a phase II glucuronide conjugate [6]. Additionally, there was significant metabolism of dexamethasone, and at least two phase I metabolites were detected-both were excreted unchanged or as glucuronide conjugates.

Evidence from clinical studies

Evidence for dexamethasone as a CYP3A4 substrate has been demonstrated in drug interaction studies with two CYP3A4 substrates (aprepitant, fosprepitant) [7,8] and one inhibitor (itraconazole) [9]. In a randomized, double- blind, placebo-controlled, 4-period crossover study in eight healthy subjects, Varis, et al. [9] examined effects of coadministration of itraconazole 200mg or placebo orally once daily for 4 days with an oral dose of 4.5mg dexamethasone or an intravenous dose of 5.0mg dexamethasone sodium phosphate. Itraconazole significantly increased the area under the curve ($AUC_{0-\infty}$) and the peak plasma concentration of oral dexamethasone by 3.7- fold and 1.7-fold respectively. An increase of 3.3-fold was seen in $AUC_{0-\infty}$ after intravenous administration of dexamethasone. This increase in dexamethasone systematic exposure was consequently associated with increase in the adrenal-suppressing effects of dexamethasone [9], suggesting that CYP3A4 was involved in dexamethasone metabolism.

In another open-label, randomized, incomplete-block, 3-period crossover study with 20 subjects, McCrea, et al. examined the effects of oral aprepitant (125mg aprepitant on day 1, 80mg aprepitant on days 2-5) on the standard oral dexamethasone regimen for chemotherapy-induced nausea and vomiting (20mg dexamethasone on day 1, 8mg dexamethasone on days 2-5). Coadministration of aprepitant with dexamethasone resulted in two-fold increase of plasma concentrations (AUC_{0-24}) of dexamethasone. The authors recommended a reduction in dexamethasone dose by 25-50% when administered with aprepitant. This effect was likely explained by competitive inhibition between substrates, with aprepitant showing greater affinity for CYP3A4 compared to dexamethasone [7]. Similarly, Marbury, et al. [10] conducted a study to test interactions between fosprepitant and dexamethasone. The results from this study led to the recommendation that dexamethasone dosing be reduced by up to 50% when given with intravenous fosprepitant (150mg). These studies provide conclusive evidence that CYP3A4 is involved in dexamethasone metabolism, and dexamethasone as a CYP3A4 substrate is sensitive to competitive inhibition by other strong CYP3A4 substrates [9,11].

Dexamethasone as an inducer of CYP3As

Suggested mechanisms of CYP3A induction

Enzyme induction is marked by an increase in mRNA expression of the gene encoding a specific enzyme [12]. The molecular mechanism through which dexamethasone can induce *CYP3A4* gene expression has been studied extensively. Classically, dexamethasone activates glucocorticoid receptors (GR), which can modulate gene expression by binding to promoter regions of target genes. However, *CYP3A* genes lack consensus regions for a GR response element, making GR binding to promoter regions implausible [13,14]. Additionally, there is no significant difference in constitutive hepatic expression of CYP3A in GR knockdown mice, compared to their wild-type counterparts, suggesting that activation of GR may not be directly responsible for *CYP3A* induction [13]. However, indirect involvement of GR activation cannot be ruled out. Pascussi, et al. showed that a sub-micromolar concentration of dexamethasone can increase the levels of the nuclear receptors pregnane X receptor (PXR), constitutive androstane receptor (CAR), and retinoid X receptor (RXR) in primary human hepatocytes, possibly through GR-stimulated induction of gene expression [15]; it was also reported that dexamethasone-activated GR upregulates CAR [16]. PXR and CAR have been linked to dexamethasone induced. *CYP3A4* induction. In vitro studies have reported that PXR and CAR can bind to and transactivate DNA nuclear response elements located in the promoter of the *CYP3A4* gene [17]. Thus, current evidence suggests that though the exact mechanism of *CYP3A4* gene induction may not be directly mediated by GR activation, GR activation may indirectly help modulate *CYP3A4* gene expression. Additionally, direct activation of PXR and CAR by dexamethasone to induce *CYP3A4* expression is a promising possibility, requiring further study.

Evidence for CYP3A4 induction in primary cultures of human hepatocytes

For several years, dexamethasone has been recognized as an inducer of CYP450 expressed in animal liver microsome. Pichard,

et al. [8] first reported dexamethasone 50-100μM as a CYP3A4 inducer using primary cultures of human hepatocytes. In this study, dexamethasone significantly increased cyclosporine-A (CsA) (specifically oxidized by CYP3A4) oxidase activity, when the two were given together [8]. The effect of dexamethasone on the de novo synthesis of CYP3A4 was determined using a radioimmunoassay and CYP3A4 mRNA accumulation. In this study, primary nonproliferating cultures of adult rat hepatocytes were incubated for 5 days with different steroids at varying concentrations. Dexamethasone (10μM) proved to be the most efficacious inducer increasing the rate of synthesis of CYP3A4 from 0.05% of total cellular protein synthesis in incubated control cultures to almost 9.5% in dexamethasone treated cultures [12].

Other studies have also used dexamethasone as a classical CYP3A4 inducer, like rifampicin [2,18]. Marre, et al. evaluated hepatic CYP isozymes involved in docetaxel biotransformation using HLMs and hepatocytes. They found that docetaxel metabolism was increased by 44% with rifampicin (50μM) treatment and 41% by dexamethasone (50μM) [18]. While the above-mentioned effect was shown at supratherapeutic concentrations (10-100μM), [19]. studied the effects of a more pharmacologically relevant dose of 1μM dexamethasone on testosterone hydroxylation in human hepatocytes. They observed a 1.5- 3fold induction of testosterone hydroxylation in 4 of 7 samples treated with dexamethasone. However, the effects were not statistically significant.

To evaluate the concentration-dependent effects observed in the human hepatocyte cell culture model, McCune, et al. studied the effects of dexamethasone on CYP3A4 activity determined in nine preparations of primary cultures of human hepatocytes. To establish the maximal level of CYP3A4 induction, hepatocytes were preincubated with dexamethasone (2μM-250μM) or rifampicin 10μM (positive control) for 24-36 hours before treatment. Average increases in CYP3A4 activity of 1.7-, 1.9-, 3.9-, 6.9-, and 6.6-fold were observed after exposure to dexamethasone at 2, 10, 50, 100, or 250μM concentrations, respectively [2]. The concentration at which 50% of the maximum effect is achieved and maximum effect for the composite data were 51.22 μmol/L and 6.60-fold induction over control, respectively. The maximum level of CYP3A4 activity observed at dexamethasone concentrations ≥100μmol/L was like the maximum increase in CYP3A4 activity achieved with rifampicin. Results showed a variable concentration-dependent increase in CYP3A4 activity among the nine different hepatocyte preparations. At lower concentrations of 2μM and 10μM dexamethasone, CYP3A4 activity differed by 12- and 16-fold between the nine hepatocyte preparations, respectively. While at concentrations of 50μM up to 250μM dexamethasone, CYP3A4 activity varied by only 2-5-fold, suggesting that all hepatocyte cultures achieved similar ceiling levels of CYP3A4 activity. These results suggest that the variability in the extent of CYP3A4 induction by dexamethasone may be a result of varying baseline activity, rather than a differential ceiling capacity.

Evidence for CYP3A induction from pre-clinical studies

Several limitations for using the preclinical in vivo systems makes primary human hepatocyte cultures the gold-standard system for CYP450 induction studies. One of the limitations is the species differences both in the level and spectrum of enzymes induction, specifically, the difference in the interaction with the nuclear receptors, e.g. GR, PXR, and CAR. Therefore, studies using rodents might not precisely mirror human physiology [20]. However, the development of humanized and knockout animal models provides more reliable predictors for evaluating drug metabolism and drug safety profile in humans [20]. Using these strategies, Scheer, et al. evaluated the responses of the human and murine PXR to dexamethasone using either deleted PXR gene locus or mice humanized at the PXR gene locus, in addition to mice with seven deleted functional *CYP3A* genes [20]. Interestingly, they found that dexamethasone was a more powerful inducer of CYP3A proteins in wild-type mice than in mice humanized for PXR. For instance, a 3mg/kg dose proved a significant induction of CPY3A11 in wild-type mice but not in the PXR humanized mice. Nevertheless, a comparable induction level occurred at a 30mg/kg [20]. This high dose of 30mg/kg was also associated with increased risk of hepatotoxicity in comparison with the untreated controls in all the mouse lines. The increased risk of hepatotoxicity raised safety concerns about the concomitant use of dexamethasone with other CYP3A4 substrates [21].

More recent evidence by Li, et al. [22] showed that the repeated administration of 8mg/kg dexamethasone dose in human breast cancer xenograft mice resulted in auto-induction of CYP3A activity and time-dependent dexamethasone pharmacokinetics (pharmacokinetics with time-dependent clearance). In another study, Doi, et al. showed that compared to control rats, acute renal failure (ARF) rat models showed a reduced metabolic rate of midazolam (a sensitive CYP3A4 substrate). This effect was further studied with the concomitant administration of midazolam with dexamethasone. Results showed that the metabolic rate of midazolam was increased only 1.4 times in control rats compared to almost 19.6 times in ARF rats, suggesting the higher induction of hepatic protein expressions of CYP3A enzymes in ARF rats than in control rats [21]. These results could be explained in part by what was already know about the reduced hepatic drug metabolism, as reflected by reduced midazolam metabolism in ARF rats compared to control as a result of impaired renal function [21], therefore, the extent of CYP3A4 induction might be predicted from the level of basal CYP3A4 activity before exposure to an inducer of CYP3A4 [2]. Thus, pre-clinical data suggests induction of CYP3A4 activity by dexamethasone. Whether this effect is clinically significant is discussed in the next section.

Evidence for CYP3A induction from clinical studies

While several *in vitro* and preclinical *in vivo* studies suggest that dexamethasone induces human CPY3A4 activity, the clinical significance of this induction is still contradictory. For instance,

Watkins, et al. [23] studied the CYP3A4 induction effect of dexamethasone using the erythromycin breath test (biomarker for hepatic CYP3A4 activity) by measuring the increase in the rate of production of $^{14}CO_2$ in breath of five patients after the administration of 16-24mg/day dexamethasone dose for 2-9 days. A 55% increase in the mean hepatic CYP3A4 catalytic activity was reported. McCune, et al. [2] studied the effect of 8mg twice daily dexamethasone for 5 days on CYP3A4 activity; this dose is commonly used for the supportive care of cancer patients. They tested12-healthy volunteers using the erythromycin breath test immediately before the first dose and on the fifth day of dexamethasone administration. The results of the study indicated that dexamethasone, increased the mean hepatic CYP3A4 activity by an average of 25.7%, which could be related to either the stabilization of protein turnover or an increased production of CYP3A4 protein [2]. It is noteworthy that CYP3A4 induction was inversely correlated with the baseline erythromycin breath test result as a measure of the baseline CYP3A4 activity. The authors suggest that the 25.7% mean increase in hepatic CYP3A4 activity may not be clinically significant. Villikka, et al. [24] studied the effect of a lower dexamethasone dose of 1.5mg/kg for 4 days in 10 healthy volunteers on the pharmacokinetics of the triazolam, a sensitive CYP3A4 substrate. In contrast to the previous study, dexamethasone failed to show a statistically significant effect on triazolam pharmacokinetic parameters. Hellmann, et al. [25] studied the effects of the co-administration of rifampicin (a potent CYP3A4 inducer) and dexamethasone (weak CYP3A4 inducer) on the pharmacokinetic, pharmacodynamic, and safety profiles of bortezomib. Bortezomib is primarily metabolized by CYP3A4 and CYP2C19.

Results from 61 patients with relapsed or refractory multiple myeloma or non-Hodgkin's lymphoma enrolled and randomized to receive 3 cycles of bortezomib, showed that co-administration of rifampicin reduced the mean bortezomib maximum plasma concentration (C_{max}) by approximately 23% and the mean area under plasma concentration-time curve from 0-72 hours (AUC_{0-72}) by approximately 45%. In contrast, co-administration of 40mg dexamethasone dose daily on day 1-4 and 9-12 during bortezomib cycle 3 only had no effect on mean AUC_{0-72}. Though the mean bortezomib C_{max} was reduced by 20% after co-administration of dexamethasone, this difference in C_{max} was equivalent to the observed variability in C_{max} during cycle 2. A recent nested case–control study based on data from 120 patients [3] documented a clinically important interaction between lapatinib, predominantly metabolized by CYP3A4, and dexamethasone 8 mg daily dose for 2-28 days. Co-administration of the drugs was associated with an increased incidence of hepatotoxicity (~five-fold increase compared to controls), possibly through induction of CYP3A4 metabolism. Although, clinical evidence indicates that lapatinib-induced hepatotoxicity is idiosyncratic, it was recently shown that metabolism of lapatinib generates a reactive quinoneimine metabolite species which has been implicated in other examples of idiosyncratic hepatotoxicity [3].

In summary, evidence from clinical studies thus suggests that dexamethasone induction of CYP3A4 varies depending on the dosage regimen used and the substrate tested. Though, adequate reports suggest that administering dexamethasone chronically may induce CYP3A4, the mean level of induction was considered as non-clinically relevant (<25%) based on the FDA criteria. Moreover, the induction appears to be dose-related and could be observed in subjects with low baseline activity of CYP3A.

Conclusion

The CYP3A subfamily enzymes metabolize ~30% of clinically used drugs from almost all therapeutic categories [26]. Current evidence suggests that dexamethasone is a substrate for CYP3A4. Though dexamethasone seems to induce CYP3A4 activity in some studies, the clinical significance of the extent of induction is still uncertain. It would be wise to monitor concentrations of other CYP3A substrates if administered in conjunction with dexamethasone, however a definite drug interaction based on enzyme induction cannot be established at this point.

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Conflict of Interest

No conflict of interest.

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