SciMedCentral

Journal of Drug Design and Research

Research Article

Oral Administration of Stereoisomeric Prednisolone Prodrugs in Rats

Ye Sheng, Xiaoyan Yang, Dhananjay Pal and Ashim K. Mitra*

Division of Pharmaceutical Sciences, University of Missouri-Kansas City, USA

***Corresponding author**

Ashim K. Mitra, University of Missouri Curators' Professor of Pharmacy Chair, Division of Pharmaceutical Sciences Vice-Provost for Interdisciplinary Research, University of Missouri - Kansas City, USA, Tel: 816-235-1615; Fax: 816-235-5779 ; Email : ye.sheng@mail.umkc.edu

Submitted: 15 May 2015

Accepted: 06 June 2015

Published: 10 June 2015

Keywords

- Prednisolone
- Stereoisomer
- Prodrug
- Oral
- AUC
- Bioavailability

Abstract

Prednisolone is commonly indicated for the treatment of ocular allergy, inflammation and uveitis. Topical administration of prednisolone suffers several limitations, which include poor aqueous solubility, rapid tear turnover rate, high cellular efflux and drainage to systemic circulation. Moreover, prednisolone permeation to posterior tissues such as retina following topical administration is highly restricted by aqueous humor outflow. The primary objective of the present study is to determine oral absorption of Stereoisomeric prodrugs of prednisolone. *In vitro* permeability of LLP, LDP, DLP, DDP across $Caco_2$ cells was found to be 1.8, 2.3, 2.1, 1.2 fold higher than prednislone. The Km of LLP, LDP, DLP towards rat liver microsome was 3.1, 3.1, 4.9 fold higher than prednisolone, which demonstrates lower affinity. To substantiate *in vitro* results, oral absorption study of prodrugs was conducted in rats. Results obtained from these studies indicate that Stereoisomeric prodrugs may be a viable strategy to improve ocular drug absorption following oral administration.

INTRODUCTION

Prednisolone, a powerful synthetic corticosteroid, is currently indicated for ocular inflammation, allergic reaction and uveitis [1-5]. Topical administration is a convenient method for drug delivery to anterior ocular tissues. However, this method of administration suffers from several limitations including tear turnover rate, rapid elimination to systemic circulation and poor permeation across corneal epithelium [6]. Moreover, prednisolone is poorly soluble in aqueous medium causing problem in the development of ophthalmic solutions. Importantly, aqueous humor outflow present a major challenge to prednisolone delivery to posterior ocular tissues such as retina following topical administration. Drug delivery through systemic circulation (oral or intravenous) may be an alternative strategy to treat ocular disorders. However for oral delivery, prednisolone is required to permeate intestinal epithelium and subsequently blood-ocular barriers to reach posterior ocular tissues. Blood-aqueous and blood-retinal barriers significantly limit transport of therapeutic agents from systemic circulation into ocular tissues [7]. Blood-retinal barrier poses a formidable barrier to drug delivery to retina and vitreous humor from systemic circulation [8-10]. Moreover, a major drug efflux pump i.e., P-glycoprotein (P-gp) is highly expressed at blood-retinal barrier (inner and outer) which limits drug transport to retina and vitreous humor [9,11,12]. Prednisolone has been reported to possess high affinity for P-gp [6,13-17].

Recently peptide transporters targeted prodrugs have been designed to improve drug transport across cell membranes. The influx transporters are widely employed due to high capacity and broad specificity. Previously, these transporters have been targeted to improve intestinal and ocular permeability of a wide range of compounds [18-24]. Peptide transporters are highly expressed on intestinal epithelia and blood-ocular barriers [25-28]. Such localization renders peptide transporter as an attractive target to improve intestinal and ocular absorption of prodrugs simultaneously. However, to improve ocular absorption from systemic circulation, prodrugs are needed to be stable in plasma. Several prodrugs previously developed in our laboratory have undergone rapid degradation to regenerate parent drug following oral administration [24,29]. Hence, to minimize such hydrolytic rate Stereoisomeric prodrugs have been designed and developed in the present study. These prodrugs demonstrated significant improvement in oral as well as corneal absorptions of acyclovir following oral administration [19].

The primary objective of this study is to investigate the potential of Stereoisomeric prodrugs of prednisolone to generate higher plasma levels following oral administration. Previously, Stereoisomeric prodrugs of prednisolone displayed significantly higher chemical and enzymatic stability [30] for oral absorption. Moreover, Stereoisomeric prodrugs demonstrated higher transport across P-gp over expressing cell line (MDCK-MDR1). Importantly, these prodrugs were recognized by

peptide transporters. It has been anticipated that Stereoisomeric prodrugs will generate higher oral absorption and display significant stability in plasma. From plasma, prodrugs may permeate blood-ocular barriers by targeting peptide transporters highly expressed at these cell membranes. Nevertheless, the present study aims to evaluate the oral pharmacokinetics of Stereoisomeric prodrugs of prednisolone.

MATERIALS AND METHODS

Materials

Prednisolone was purchased from Sigma-Aldrich (St. Louis, MO). Colon carcinoma cell line ($Caco_2$) was purchased from American Type Culture Collection (Manassas, VA, USA). The growth medium Dulbecco's modified Eagle's Medium (DMEM), TrypLE Express stable trypsin replacement and non-essential amino acids were purchased from In vitrogen (Grand Island, NY). Fetal bovine serum (FBS) was purchased from Atlanta biological. Penicillin, triton X-100, HEPES, D-glucose, streptomycin and other buffer components were purchased from Sigma Chemical Co. (St. Louis, MO) (Figure 1). Culture flasks (75 and 25 cm^2), 12-well plates (3.8 cm^2 growth area/well) and Transwell® inserts (0.4µm pore size, 12mm insert) with transparent polyester membranes were obtained from Costar (Bedford, MA, USA). Sprague Dawley rat plasma was procured from Valley Biomedical Inc. (Winchester, VA). Rat liver microsomes were purchased from XenoTech LLC (Lenexa, KS, USA). BD syringes and 27½ needles were obtained from Becton Dickinson and Company (NJ, USA). Sodium pentobarbital (Fetal Plus) was purchased from Henry Schein Animal Health (Columbus, OH).Jugular vein cannulated rats (n=12) were purchased from Harlan Laboratories, Inc. (Indianapolis, IN, USA).Rats were used in accordance with the protocol approved by University of Missouri-Kansas City (UMKC) Institutional Animal Care and Use Committee (IACUC). Animals were housed in Laboratory Animal Research Core (LARC) facilities at UMKC. Prodrugs such as L-Val-L-Val-prednisolone (LLP), L-Val-D-Val-prednisolone (LDP), D-Val-L-Val-prednisolone (DLP) and D-Val-D-Val-prednisolone (DDP) were synthesized according to a method described in our previous publication from our laboratory [30, 31].

METHODS

Cell culture

Caco2 cells (passages 21–30) were seeded in75 cm2 tissue culture flask in DMEM medium containing 10% FBS (heat inactivated), penicillin (100 units/mL) and streptomycin (100 µg/mL), pH 7.4. Cells were maintained at 37 °C in an atmosphere of 5% CO2 and 90% relative humidity. Medium was changed on every alternate day until cells were90% confluence and then every day before experiment (~21 days).

Transport studies

Transwell® inserts were coated with rat tail collagen (1mg/ml). Cells were seeded in 12-well Transwell® plate at a density of 300,000 per well and maintained at 37°C in an atmosphere of 5% CO2 and 90% relative humidity until use (~21 days). Before initiation of a transport study, cell monolayers were rinsed with DBPS (pH 7.4) at 37 °C, three times, 10 min each. To determine

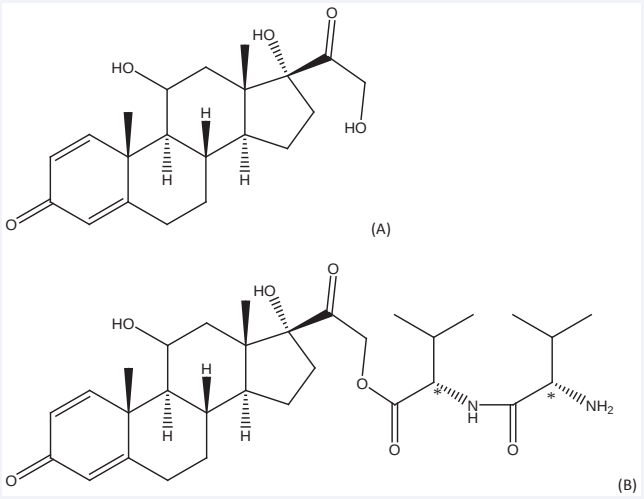

Figure 1 Structure of prednisolone.
(A) and val-val-prednisolone (LLP, LDP, DLP, DDP)
(B) * represents chirality center

A-B permeability, 0.5 mL of test solution was added to the apical donor chamber and 1.5ml of DPBS at basolateral receiving chamber. Similarly, to determine B-A permeability, 1.5 mL of test solution was added to the basolateral donor chamber and 0.5ml DPBS at apical receiving chamber. Approximately, 200 µL samples was collected from the receiving chamber and replaced with fresh DPBS (pH 7.4) to maintain sink conditions. Transport study was conducted for a period of 3 h. Samples were stored at −20 °C until further analysis by LC/MS/MS technique.

Metabolism studies

Metabolic stability was carried out with rat liver microsomes (protein concentration 0.3 mg/mL). Microsomal solution consisted of 0.3 mg/mL rat liver microsomes, 5 mM glucose 6-phosphate, 1 U/mL glucose 6-phosphate dehydrogenase, 1 mM b-NADP1, and 5 mM magnesium chloride in 100 mM phosphate buffer (pH 7.4). Microsomal solution was maintained at 37ºC for 30 min prior to the addition of prednisolone or prodrugs. To this activated microsomal solution, prednisolone or prodrugs (25 µM) was added. Metabolic reaction was initiated with NADPH generating system. For time dependent metabolic stability study, samples (100 µL) were collected at different time points for a period of 2 h. For concentration dependent metabolism studies, various concentrations of prednisolone or prodrug (1-20 µM) were added to microsomal solution and incubated for 5min. An equal volume of ice-cold acetonitrile was added to withdrawn samples to arrest further metabolic reaction. Samples were stored in −80 °C until further analysis by LCMS/MS.

Oral Absorption Studies

Jugular vein cannulated rats (200-300 g) were employed to study oral absorption of prednisolone and prodrugs. Prior to the oral dosing, rats were fasted for a period of 2-3 h with free access to water. The animals were divided into three groups of four each and administered with prednisolone or prodrugs at a dose of about 69µmol/kg by oral gavage (~0.8 mL). Prednisolone or prodrug solution was prepared with 40% v/v of PEG-400 and

60% v/v. About, 200 µL of blood samples were withdrawn from jugular vein. Oral absorption study was conducted for a period of 7 h. About 200 µL of heparinized saline (10 IU/mL) was injected through the same vein to maintain the fluid volume and avoid clogging of cannula. Blood samples were centrifuged at 10,000 rpm for 7 min to obtain plasma. About 100 µL of plasma was collected and stored at –80°C until further analysis with LCMS/MS. At the end of an experiment, rats were euthanized with an overdose of sodium pentobarbital (100 mg/kg) according to the protocol approved by IACUC.

In vitro protein binding studies

The extent of prednisolone and prodrug binding to plasma proteins was determined using ultra filtration technique, according to a previously published protocol [32]. Briefly, rat plasma was diluted by 10% with isotonic phosphate-buffered saline (IPBS, pH 7.4). Prednisolone or prodrug was added at a concentration of 5 µM to rat plasma (500 µL) and maintained at 37 °C for 30 min with gentle agitation every 10 min. Samples were carefully transferred to Amicon ultra-0.5mL centrifugal filters (10 k NMWL, Millipore Corporation, Bedford, MA) and centrifuged at 10,000 g for 30 min. Filtrate (150 µL) was collected from the basal chamber to determine unbound concentrations of test compound. About150 µL of unfiltered samples was taken to determine bound concentrations. Concentrations of test compounds were determined with LCMS/MS. Ratio of concentration of test compound in the filtered samples to the sum of filtered and unfiltered samples was used to determine unbound fraction (*f*u).

DATA ANALYSIS

LCMS/MS analysis

Prednisolone and prodrug concentrations were determined with a rapid and sensitive LC/MS/MS technique. The instrumentation, multiple-reaction monitoring (MRM), ion source parameters, sample preparation and method development have been previously described in our recent publication [31].

Permeability Analysis

Apparent permeability Coefficient (P_{app}; cm/s) of prednisolone or prodrug was determined by linear regression analysis on the time course plot of amount of drugs transported across Caco-2 cell monolayer, according to the Eq.1. dM/dt represents the flux rate of prednisolone or prodrugs obtained from the slope of transport profile. A is the surface area of cell monolayer. C_d is initial concentration of drug or prodrug in the donor chamber.

$$P_{app} = \frac{dM / dt}{C_d \text{xA}} \quad (1)$$

Metabolism studies

Binding affinity constant (Km) with metabolizing enzymes was calculated by Michaelis-Menten kinetic model as shown in Eq.2.

$$\text{V} = \frac{V_{\max} \max \times [S]}{K_{m+[S]}} \quad (2)$$

Km represents the affinity constant, Vmax is binding capacity and[S]is the concentration of test compound. The intrinsic clearance of prednisolone and prodrugs was determined from the ratio of Vmax/Km. Data was processed using Kaleida Graph Software (Synergy Software, Reading, Pennsylvania).

Pharmacokinetic analysis

Non-compartmental analysis of observed plasma concentration against time profiles was applied to generate oral pharmacokinetic parameters. Pharmacokinetic software, Phoenix Win Nonlin, version 6.3 (Pharsight, Mountain View, CA) was employed to execute non-compartmental analysis. Cmax (maximum plasma concentration) and T_{max} (time to reach C_{max}) were obtained from the concentration-time profile. Area under plasma concentration time curves (AUC_{∞}) was determined. Elimination rate constant (ke) was determined from the slope of the terminal phase of the plasma concentration-time curve. Elimination half-life (t1/2=0.693/ke)was also generated from the elimination rate constant. Mean residence time (MRT) was determined from the ratio of AUMC/AUC.

Statistical analysis

All experiments were performed at least in quadruplicates (n-=4). *In vitro* results are expressed as mean ± S.D. Student t-test was applied for statistical comparison of mean values. A value of $p < 0.05$ was considered to be as statistically significant. Oral pharmacokinetic parameters are expressed as mean ± SEM (n=4).

RESULTS AND DISCUSSION

Transport studies

Transepithelial transport from absorptive to secretive (A-B) and secretive to absorptive (B-A) direction was conducted across $Caco_2$ cells. Results obtained from this study are displayed in Table 1. Since $Caco_2$ cells express P-gp on the apical surface, a typical P-gp substrate would demonstrate significantly higher B-A transport relative to A-B transport. In our study, A-B and B-A permeabilities of prednisolone across Caco2 cells were 4.5 x 10^{-6} and 12.3 x 10^{-6}cm/s, respectively. Efflux ratio (B-permeability/A-B permeability) was observed to be 2.7. This result indicates that prednisolone possess substrate affinity for P-gp.

Most of the prodrugs displayed excellent transport in the absorptive direction relative to prednisolone. LLP displayed A-B and B-A permeability values of 8.3 x 10^{-6} and 9.6 x10^{-6}cm/s. A-B permeability rate of LLP was about 1.8-fold higher relative to prednisolone. Importantly, the efflux ratio obtained was 1.2 indicating significant evasion of P-gp mediated efflux.

Table 1: Permeability rates of prednisolone and prodrugs across $Caco_2$ cells.

Drug/ Prodrug	A-B Papp x 10^{-6} cm/sec	B-A Papp x 10^{-6} cm/sec	Efflux ratio	A-B transport (Fold Difference)
Prednisolone	4.50	12.3	2.7	-
LLP	8.3	9.6	1.2	1.8
LDP	10.2	11.5	1.1	2.3
DLP	9.3	9.4	1.0	2.1
DDP	5.3	7.7	1.5	1.2

Similarly, LDP and DLP prodrugs also displayed much higher A-B permeability relative to prednisolone. LDP and DLP prodrug displayed approximately 2.3 and 2.1-fold higher transport compared to prednisolone. Moreover, the efflux ratio of LDP and DLP observed was 1.1 and 1.0 respectively indicating none or negligible P-gp affinity. Relatively, DDP did not exhibit significant A-B permeability rate compared to prednisolone. Based on these results, it is clear that prodrugs of prednisolone may display minimal affinity towards major drug efflux pumps compared to the parent drug.

Previously, the transepithelial permeability of prodrugs was observed to be significantly higher compared to prednisolone in P-gp over expressing cells (MDCK-MDR1 cells). Results obtained from the present study confirm evasion of P-gp at apical surface of intestinal epithelial cells ($Caco_2$) by prodrugs. Hence, following oral administration, prodrugs are expected to generate significantly higher systemic levels relative to prednisolone. Such higher oral absorption may further enhance transport across blood-ocular barriers following oral administration relative to prednisolone (Table 2).

Oral pharmacokinetics

Oral pharmacokinetics of prednisolone and prodrugs (LDP and DLP) was determined in rats. LDP and DLP prodrugs were selected due to their higher transport across $Caco_2$ cells relative to other prodrugs. Moreover, these prodrugs were observed to be chemically, metabolically and enzymatically more stable compared to LLP [30]. Pharmacokinetic parameters obtained for prednisolone and prodrugs following oral dosing at equimolar concentrations are depicted in Table 3. Plasma concentration-time profiles are displayed in Figure 2.

Significantly higher plasma concentration of prodrugs was observed relative to prednisolone. AUC generated by prednisolone was approximately 720 ± 159 min*umol/L. AUC of LDP and DLP prodrugs was 1166 ± 175 and 1532 ± 348 min*umol/L, respectively. AUC produced by LDP and DLP was about 1.6 and 2.1-fold higher relative to prednisolone. This result indicates that prodrugs generate higher systemic concentrations following oral administration. Such higher systemic levels may be due to higher intestinal permeability, circumvention of P-gp, recognition by peptide transporters and reduced intrinsic clearance. Interestingly, Cmax generated by LDP (8 µM) and DLP (8 µM) was also higher relative to prednisolone (5 µM). Tmax was very similar for both prednisolone and prodrugs and ranged between 35-40 min. Elimination rate constant (ke) of prednisolone and prodrugs have been also determined. Interestingly, elimination of prednisolone was observed to be faster relative to prodrugs. The key values generated by prednisolone, LDP and DLP are approximately 0.007, 0.003 and 0.005 min^{-1}, respectively. Elimination half-life observed was significantly lower for prodrugs relative to prednisolone. Importantly, the mean residence time (MRT) was significantly higher for LDP and DLP relative to prednisolone. MRT displayed by prednisolone, LDP and DLP was about 160, 232 and 196 min, respectively. This study indicates that the residence time of prodrugs in systemic circulation is significantly higher relative to prednisolone. Such higher residence time may result in higher prodrug concentrations in systemic circulation. Previously, we have demonstrated that prodrugs not only interacted with peptide transporters but also significantly circumvent efflux pump such as P-gp [30]. With recognition by peptide transporters and lower efflux by P-gp, it is anticipated that prodrugs might generate higher intraocular levels relative to prednisolone from systemic circulation. In future studies, we will determine intraocular concentrations of prednisolone and prodrugs following oral and/or intravenous administration in rats according to the protocol previously published from our laboratory [19]. Such studies will delineate the efficacy of prodrugs to generate higher concentrations in various ocular tissues following oral and or intravenous administration relative to prednisolone. Interestingly, amino acid prodrugs were not observed as intermediate, which indicates the degradation occurs predominantly at the ester bond between the parent drug and dipeptide.

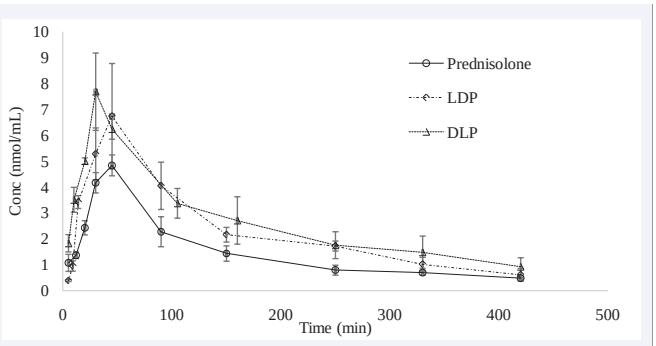

Figure 2 Plasma profiles of prednisolone and prodrugs were obtained in Male Sprague Dawley rats. Dose, 69 µmol/kg of Prednisolone or prodrugs was administered with the aid of oral gavage. Results are expressed as mean ±SEM (n=4).

Table 2: Oral pharmacokinetic parameters of prednisolone and prodrugs in rats.

PK parameters	Prednisolone	LDP	DLP
AUC (umol*min/L)	720 ± 159	1166 ± 175	1532 ± 348
Cmax (umol/L)	5.1 ± 0.2	8 ± 3	8 ± 2
Tmax (min)	40 ± 9	40 ± 9	35 ± 9
ke (1/min)	0.007 ± 0.001	0.003 ± 0.001	0.005 ± 0.001
$t_{1/2}$ (min)	100 ± 17	244 ± 87	164 ± 42
MRT (min)	160 ± 20	232 ± 42	196 ± 34

Table 3: Metabolic stability of prednisolone and prodrugs in liver microsomes.

Compounds	Km (µM)	Vmax (µM/min/mg protein)	CLint (mL/min/mg protein)
Prednisolone	0.47	0.19	0.40
LLP	1.43	0.15	0.10
LDP	1.43	0.14	0.10
DLP	2.28	0.20	0.09
DDP	1.98	0.11	0.06

Liver microsomal stability studies

CYP3A4-mediated metabolism results in low oral bioavailability of a wide range of therapeutic agents. Prednisolone has been reported to be metabolized by CYP3A4 enzyme [33-36]. Higher metabolic rate may significantly reduce systemic concentrations of prednisolone, which may further diminish concentrations available for absorption across blood-ocular barriers. Hence, the efficacy of prodrugs to circumvent CYP3A4-mediated metabolism has been studied. Previously, several prodrugs developed in our laboratory have displayed high efficacy in evading CYP3A4-mediated metabolism [18, 37-39]. Results of metabolic stability of prednisolone and prodrugs obtained from this study are presented in Table 3.

Prednisolone displayed km and V_{max} values of about 0.47 μM and 0.19 μM/min/mg protein. Intrinsic clearance was approximately 0.4 mL/min/mg protein. Interestingly, prodrugs displayed lower affinity and intrinsic clearance relative to prednisolone. The km and V_{max} value of LLP were 1.43 μM and 0.15 μM/min/mg protein respectively. LLP affinity towards metabolizing enzymes was about 70% lower compared to prednisolone. Moreover, the intrinsic clearance is about 0.10 mL/min/mg protein which is 4-fold lower relative to prednisolone. LDP and DLP prodrug demonstrated km values of 1.43 and 2.28 μM, respectively. Intrinsic clearances produced by LDP and DLP are approximately 0.10 and 0.09 mL/min/mg protein respectively. About 4-fold lower intrinsic clearance is observed for LDP and DLP compared to prednisolone. Enzyme affinity of LDP and DLP is approximately 3 and 5-fold lower relative to prednisolone. DDP displayed km and intrinsic clearance values of 1.98 μM and 0.06 mL/min/mg protein, respectively. Affinity of DDP is approximately 4-fold lower compared to prednisolone. Intrinsic clearance appears to be about 7-fold lower relative to prednisolone. Based on these results, it can be concluded that prodrugs are more stable towards CYP3A4 metabolism relative to prednisolone. This evasion of metabolizing enzymes might significantly elevate prodrug concentration in systemic circulation. Such higher concentration in systemic circulation might further result in higher transport across blood-ocular barriers (Figure 3).

Protein binding studies

Affinity of prednisolone and prodrugs towards plasma proteins was also determined. Disposition of compounds from systemic circulation is significantly governed by plasma protein binding. Lower binding of prodrugs to plasma proteins will result in higher unbound concentrations in systemic circulation for transport across blood-ocular interfaces. Unbound concentration of prednisolone obtained was approximately 0.360±0.005 μM, which is approximately 7% of prednisolone available in unbound form in plasma. Unbound fraction of LDP and DLP are about 0.47±0.06, and 0.43±0.09 μM, respectively corresponding to 9.4 and 8.6% of LDP and DP available in unbound form in plasma. This study clearly indicates that free prodrugs are abundant at higher concentrations in plasma relative to prednisolone, which may further result in higher transport across blood-ocular barriers.

CONCLUSION

Stereoisomeric prodrugs demonstrated higher potential for intestinal absorption relative to prednisolone. Importantly, affinity towards efflux transporter, metabolizing enzymes and intrinsic clearance of prodrugs was significantly lower compared to prednisolone. Oral absorption studies demonstrated that prodrugs can generate significantly higher systemic concentrations relative to prednisolone. Moreover, prodrugs produce slightly higher unbound concentrations in systemic circulation. Due to higher affinity towards peptide transporters, higher metabolic stability and ability to circumvent P-gp, it can be suggested that prodrugs may produce higher concentrations in intraocular tissues from systemic circulation. From the results of oral dosage studies of rats, it is determined that all prodrugs follow mechanism of ester bond decomposition. In future studies, efficacy of prodrugs to generate higher intraocular concentrations following oral and/or intravenous administration will be examined.

ACKNOWLEDGEMENTS

Supported by NIH grants RO1 EY09171 and R01 EY70659.

REFERENCES

1. Hedayatfar A, Hashemi H, Asgari S, Chee SP. Comparison of efficacy and ocular surface toxicity of topical preservative-free methylprednisolone and preserved prednisolone in the treatment of acute anterior uveitis. Cornea. 2014; 33: 366-372.
2. Lane SS, Holland EJ. Loteprednol etabonate 0.5% versus prednisolone acetate 1.0% for the treatment of inflammation after cataract surgery. J Cataract Refract Surg. 2013; 39: 168-173.
3. Hossain MM, Mohiuddin AA, Hossain MA, Aziz MA. Diclofenac sodium and prednisolone acetate ophthalmic solution in controlling inflammation after cataract surgery. Mymensingh Med J. 2010; 19: 343-347.
4. Arellanes-Garcia L, Padilla-Aguilar G, Navarro-Lopez P, Espinoza-Martinez C. Efficacy of prednisolone and rimexolone in HLA-B27 positive patients with acute anterior uveitis. Gac Med Mex. 2005; 141: 363-366.
5. Biswas J, Ganeshbabu TM, Raghavendran SR, Raizada S, Mondkar SV, Madhavan HN. Efficacy and safety of 1% rimexolone versus 1% prednisolone acetate in the treatment of anterior uveitis--a randomized triple masked study. Int Ophthalmol. 2004; 25: 147-153.
6. Hariharan S, Gunda S, Mishra GP, Pal D, Mitra AK. Enhanced corneal absorption of erythromycin by modulating P-glycoprotein and MRP mediated efflux with corticosteroids. Pharm Res. 2009; 26: 1270-1282.
7. Cunha-Vaz J. The blood-ocular barriers. Surv Ophthalmol. 1979; 23: 279-296.
8. Cunha-Vaz J, Bernardes R, Lobo C. Blood-retinal barrier. Eur J Ophthalmol. 2011; 21 Suppl 6: S3-9.
9. Steuer H, Jaworski A, Elger B, Kaussmann M, Keldenich J, Schneider H, et al. Functional characterization and comparison of the outer blood-retina barrier and the blood-brain barrier. Invest Ophthalmol Vis Sci. 2005; 46:1047-1053.
10. Cunha-Vaz JG. The blood-retinal barriers. Doc Ophthalmol. 1976; 41: 287-327.
11. Constable PA, Lawrenson JG, Dolman DE, Arden GB, Abbott NJ.

P-Glycoprotein expression in human retinal pigment epithelium cell lines. Exp Eye Res. 2006; 83: 24-30.

12. Kennedy BG, Mangini NJ. P-glycoprotein expression in human retinal pigment epithelium. Mol Vis. 2002; 8: 422-430.

13. Van der Heyden S, Croubels S, Gadeyne C, Ducatelle R, Daminet S, Murua Escobar H, Sterenczak K, Polis I, Schauvliege S, Hesta M, Chiers K. Influence of P-glycoprotein modulation on plasma concentrations and pharmacokinetics of orally administered prednisolone in dogs. Am J Vet Res. 2012; 73: 900-907.

14. Troutman MD, Thakker DR. Efflux ratio cannot assess P-glycoprotein-mediated attenuation of absorptive transport: asymmetric effect of P-glycoprotein on absorptive and secretory transport across Caco-2 cell monolayers. Pharm Res. 2003; 20: 1200-1209.

15. Karssen AM, Meijer OC, Van der Sandt IC, De Boer AG, De Lange EC, De Kloet ER. The role of the efflux transporter P-glycoprotein in brain penetration of prednisolone. J Endocrinol. 2002; 175: 251-260.

16. Oka A, Oda M, Saitoh H, Nakayama A, Takada M, Aungst BJ. Secretory transport of methylprednisolone possibly mediated by P-glycoprotein in Caco-2 cells. Biol Pharm Bull. 2002; 25: 393-396.

17. Nakayama A, Eguchi O, Hatakeyama M, Saitoh H, Takada M. Different absorption behaviors among steroid hormones due to possible interaction with P-glycoprotein in the rat small intestine. Biol Pharm Bull. 1999; 22: 535-538.

18. Wang Z, Pal D, Mitra AK. Stereoselective evasion of P-glycoprotein, cytochrome P450 3A, and hydrolases by peptide prodrug modification of saquinavir. J Pharm Sci. 2012; 101: 3199-3213.

19. Talluri RS, Gaudana R, Hariharan S, Mitra AK. Pharmacokinetics of Stereoisomeric Dipeptide Prodrugs of Acyclovir Following Intravenous and Oral Administrations in Rats: A Study Involving In vivo Corneal Uptake of Acyclovir Following Oral Dosing. Ophthalmol Eye Dis. 2009; 1: 21-31.

20. Talluri RS, Samanta SK, Gaudana R, Mitra AK. Synthesis, metabolism and cellular permeability of enzymatically stable dipeptide prodrugs of acyclovir. Int J Pharm. 2008; 361:118-124.

21. Gunda S, Hariharan S, Mitra AK. Corneal absorption and anterior chamber pharmacokinetics of dipeptide monoester prodrugs of ganciclovir (GCV): in vivo comparative evaluation of these prodrugs with Val-GCV and GCV in rabbits. J Ocul Pharmacol Ther. 2006; 22: 465-476.

22. Jain R, Duvvuri S, Kansara V, Mandava NK, Mitra AK. Intestinal absorption of novel-dipeptide prodrugs of saquinavir in rats. Int J Pharm. 2007; 336: 233-240.

23. Anand BS, Katragadda S, Gunda S, Mitra AK. In vivo ocular pharmacokinetics of acyclovir dipeptide ester prodrugs by microdialysis in rabbits. Mol Pharm. 2006; 3: 431-440.

24. Anand BS, Katragadda S, Mitra AK. Pharmacokinetics of novel dipeptide ester prodrugs of acyclovir after oral administration: intestinal absorption and liver metabolism. J Pharmacol Exp Ther. 2004; 311: 659-667.

25. Brandsch M. Drug transport via the intestinal peptide transporter PepT1. Curr Opin Pharmacol. 2013; 13: 881-887.

26. Rubio-Aliaga I, Daniel H. Peptide transporters and their roles in physiological processes and drug disposition. Xenobiotica. 2008; 38: 1022-1042.

27. Atluri H, Anand BS, Patel J, Mitra AK. Mechanism of a model dipeptide transport across blood-ocular barriers following systemic administration. Exp Eye Res. 2004; 78: 815-822.

28. Dias C, Nashed Y, Atluri H, Mitra A. Ocular penetration of acyclovir and its peptide prodrugs valacyclovir and val-valacyclovir following systemic administration in rabbits: An evaluation using ocular microdialysis and LC-MS. Curr Eye Res. 2002; 25: 243-252.

29. Katragadda S, Jain R, Kwatra D, Hariharan S, Mitra AK. Pharmacokinetics of amino acid ester prodrugs of acyclovir after oral administration: interaction with the transporters on Caco-2 cells. Int J Pharm. 2008; 362: 93-101.

30. Sheng Y, Wang Z, Pal D, Mitra AK. Stereoisomeric prodrugs to improve prednisolone absorption. Journal of Drug Design and Research. 2015; 2: 1012-1020.

31. Sheng Y, Yang X, Pal D, Mitra AK. Prodrug approach to improve absorption of prednisolone. Int J Pharm. 2015; 487: 242-249.

32. Boffito M, Hoggard PG, Reynolds HE, Bonora S, Meaden ER, Sinicco A, Di Perri G, Back DJ. The unbound percentage of saquinavir and indinavir remains constant throughout the dosing interval in HIV positive subjects. Br J Clin Pharmacol. 2002; 54: 262-268.

33. Li C, Kim M, Choi JS. Effects of prednisolone on the pharmacokinetics of loratadine after oral and intravenous administration of loratadine in rats. Arch Pharm Res. 2010; 33: 1395-1400.

34. Zhang ZY, Chen M, Chen J, Padval MV, Kansra VV. Biotransformation and in vitro assessment of metabolism-associated drug-drug interaction for CRx-102, a novel combination drug candidate. J Pharm Biomed Anal. 2009; 50: 200-209.

35. Kawashiro T, Yamashita K, Zhao XJ, Koyama E, Tani M, Chiba K, et al. A study on the metabolism of etoposide and possible interactions with antitumor or supporting agents by human liver microsomes. J Pharmacol Exp Ther. 1998; 286: 1294-1300.

36. Waxman DJ, Attisano C, Guengerich FP, Lapenson DP. Human liver microsomal steroid metabolism: identification of the major microsomal steroid hormone 6 beta-hydroxylase cytochrome P-450 enzyme. Arch Biochem Biophys.1988; 263: 424-436.

37. Patel M, Mandava N, Gokulgandhi M, Pal D, Mitra AK. Amino Acid Prodrugs: An Approach to Improve the Absorption of HIV-1 Protease Inhibitor, Lopinavir. Pharmaceuticals (Basel). 2014; 7: 433-452.

38. Luo S, Wang Z, Patel M, Khurana V, Zhu X, Pal D, et al. Targeting SVCT for enhanced drug absorption: synthesis and in vitro evaluation of a novel vitamin C conjugated prodrug of saquinavir. Int J Pharm. 2011; 414: 77-85.

39. Agarwal S, Boddu SH, Jain R, Samanta S, Pal D, Mitra AK. Peptide prodrugs: improved oral absorption of lopinavir, a HIV protease inhibitor. Int J Pharm. 2008; 359: 7-14.

Cite this article

Sheng Y, Yang X, Pal D, Mitra AK (2015) Oral Administration of Stereoisomeric Prednisolone Prodrugs in Rats. J Drug Des Res 2(2): 1015.