Probing a Potential *In Vivo* Drug–Excipient Interaction: Temporal Effects of a Modified β-Cyclodextrin on the Intravenous Pharmacokinetics of a Model High-Affinity Drug Ligand

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ABSTRACT: The investigational synthetic ozonide, OZ209, has previously been shown to have high binding affinity for sulfobutylether$_7$–β-cyclodextrin [(SBE)$_7$–β-CD] resulting in altered pharmacokinetics when administered intravenously to rats in a (SBE)$_7$–β-CD aqueous formulation. In the present study, OZ209 and (SBE)$_7$–β-CD have been used to probe whether a modified β-CD excipient, on systemic administration, can bind to and alter the pharmacokinetics of a coadministered drug. When (SBE)$_7$–β-CD was administered 60 min after OZ209, a spike in the concentration of OZ209 in blood and plasma was detected within 2 min of the (SBE)$_7$–β-CD infusion, and this was accompanied by a temporary decrease in the whole blood-to-plasma partitioning ratio of OZ209, the duration of which was dependent upon the dose of (SBE)$_7$–β-CD. Administration of (SBE)$_7$–β-CD also resulted in increased urinary excretion of OZ209. By contrast, administration of (SBE)$_7$–β-CD 4 h prior to OZ209 had no pronounced effect on the blood or plasma pharmacokinetics of OZ209, consistent with the (SBE)$_7$–β-CD having been largely eliminated prior to the administration of OZ209. This study is the first to demonstrate an *in vivo* drug–excipient interaction between a modified β-CD and a coadministered drug, and also demonstrates that such an interaction can be avoided through appropriate consideration of CD pharmacokinetics. © 2012 Wiley Periodicals, Inc. and the American Pharmacists Association J Pharm Sci 101:3381–3389, 2012

Keywords: cyclodextrins; ozonide; clearance; distribution; disposition; interactions; excipient; renal excretion; pharmacokinetics; LC–MS

INTRODUCTION

Modified cyclodextrins (CDs) have a well-established role as pharmaceutical excipients in intravenous (i.v.) drug formulations because of their ability to substantially improve the apparent aqueous solubility of many poorly soluble drugs.[1–5] For example, sulfobutylether$_7$–β-cyclodextrin [(SBE)$_7$–β-CD] is currently included in five US Food and Drug Administration-approved parenteral products (Nexterone® (Baxter Healthcare Corp., Deerfield, IL) and Vfend® (Pfizer, New York, NY) given i.v., Abilify-IM® (BMS/Otsuka Pharmaceutical Company, Tokyo, Japan), Geodon® (Pfizer,

Abbreviations used: AUC, area under the blood or plasma concentration–time curve; B–P, blood-to-plasma concentration ratio; CD, cyclodextrin; CL, clearance; LLOQ, lower limit of quantitation; (SBE)$_7$-β-CD, sulfobutylether$_7$-β-cyclodextrin; OZ209, *cis*-adamantane-2-spiro-3′-8′-(aminomethyl)-1′,2′,4′-trioxaspiro [4.5] decane mesylate; $t_{1/2}$, terminal elimination half-life.

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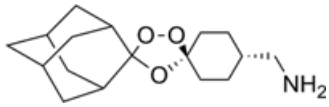

Figure 1. Chemical structure of OZ209 (free base form).

New York, NY) given intramuscularly, and Cerenia® (Pfizer, New York, NY) given subcutaneously)[4] and numerous other products are at various stages of clinical development.[6]

Upon i.v. administration of a formulation containing a drug–CD complex, extensive dilution, competitive displacement by endogenous compounds, and competitive binding of the drug ligand to plasma proteins and blood/tissue components ensures rapid and essentially complete dissociation of the drug–CD complex with minimal impact on the pharmacokinetic profile as compared with CD-free formulations.[7,8] However, in instances wherein a drug has an unusually high binding affinity for the CD (e.g., binding constants $>1 \times 10^5$ M^{-1}),[9] incomplete and/or delayed dissociation can occur, resulting in an altered pharmacokinetic and/or pharmacodynamic profile of the drug. One such example is that of the investigational synthetic ozonide, OZ209 (*cis*-adamantane-2-spiro-3′-8′-(aminomethyl)-1′,2′,4′-trioxaspiro [4.5] decane mesylate; Fig. 1), which has a high binding affinity for $(SBE)_7$–β-CD (approximately 2×10^6 M^{-1}),[10] and as a result, exhibited altered i.v. pharmacokinetics when administered to rats in a formulation containing $(SBE)_7$–β-CD compared with a CD-free aqueous formulation.[11] Specifically, there was a decrease in the steady-state volume of distribution (V_{ss}) and plasma clearance (CL) of approximately 42- and 7-fold, respectively, a time-dependent change in the blood–plasma (B-P) partitioning, and a greater than 200-fold increase in the renal excretion of OZ209 when administered in the $(SBE)_7$–β-CD-containing formulation compared with an aqueous control formulation. Given that, binding constants between drug-like molecules and modified β-CDs are typically in the range of 10^2–10^4 M^{-1},[7] the interaction between OZ209 and $(SBE)_7$–β-CD is clearly an exceptional case that should not be taken out of context and generalized across all drugs. This interaction does, however, provide a useful exemplar to probe whether a modified β-CD used to parenterally deliver a specific agent could bind to and alter the pharmacodynamics and pharmacokinetics of a second coadministered drug. The theoretical potential for such a drug–excipient interaction has been acknowledged previously[9]; however, to the best of our knowledge, it has not been observed either experimentally or in clinical practice.

In the study described herein, $(SBE)_7$–β-CD has been dosed i.v. to rats either prior to or after i.v. administration of OZ209 in a CD-free aqueous solution. Plasma and blood concentration–time profiles and urinary excretion data for OZ209 have been compared with those in control animals (dosed with OZ209 but not $(SBE)_7$–β-CD) to assess the magnitude and duration of the effect of the CD on the pharmacokinetics and renal elimination of the ozonide.

MATERIALS AND METHODS

Chemicals

cis-Adamantane-2-spiro-3′-8′-(aminomethyl)-1′,2′,4′-trioxaspiro [4.5] decane mesylate was kindly provided by Dr. J. L. Vennerstrom, University of Nebraska Medical Center (Omaha, Nebraska). $(SBE)_7$–β-CD (Captisol®, Ligand Pharmaceuticals, La Jolla, CA; β-CD sulfobutylether, seven sodium salt, lot #CY-03A-01040-NC, molecular weight 2162 g/mol) was generously donated by Cydex Pharmaceuticals, Inc. (Overland Park, Lenexa, KS). Water used in the study was purified using a Milli-Q system (Merck Millipore, Billerica, MA), and all other reagents were of analytical grade.

Dosing Formulations

cis-Adamantane-2-spiro-3′-8′-(aminomethyl)-1′,2′,4′-trioxaspiro [4.5] decane mesylate was administered to rats at a dose of 19.0 mg/kg as free base (64.9 μmol/kg). OZ209 formulations were prepared as 3.75 mg/mL solutions of OZ209 mesylate salt (equivalent to 2.82 mg/mL of the free base) in an aqueous vehicle containing 25 mM citrate buffer (pH 3.0) and 5% (w/v) glucose. OZ209 formulations were prepared immediately prior to the dosing to minimize the potential degradation of the ozonide in aqueous solution.[12] A volume of 2.0 mL was administered to each rat.

$(SBE)_7$–β-CD OZ209 was administered to rats at doses of 720 and 72 mg/kg (330 and 33 μmol/kg, respectively). Formulations of $(SBE)_7$–β-CD were prepared as 0.1 or 0.01 M solutions in normal saline. A volume of 1.0 mL was administered to each rat.

All solutions were filtered through a 0.22 μm sterile filter (Millex®-GV; Millipore) prior to the dosing.

Animals

Male Sprague–Dawley rats weighing 275–315 g were supplied by Monash Animal Services (Clayton, Victoria, Australia). All procedures were conducted in accordance with the Australian Code of Practice for the Care and Use of Animals for Scientific Purposes, and the study protocols were reviewed and approved by the Animals Ethics Committee at Monash University (Monash University Ethics approval number VCPA/2008/02).

Rats were housed in microisolator cages in a temperature- and humidity-controlled environment