Report

Pharmacokinetics of the Aldose Reductase Inhibitor Imirestat Following Topical Ocular Administration

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Received March 10, 1989; accepted September 6, 1989

The pharmacokinetics of imirestat following topical ocular administration were evaluated in a series of studies in rabbits and dogs. Following single topical doses to both albino and pigmented rabbits, imirestat was subject to rapid uptake into the cornea followed by an initial rapid decline and then very slow elimination, with a t1/2 of approximately 130 hr. Drug was rapidly absorbed into aqueous humor, with concentrations declining to nondetectable levels by 12 hr. Imirestat was retained in the lens following topical dosing similar to that in cornea, with an apparent elimination t1/2 of 140 hr. Vitreous humor concentrations of drug were detectable for up to 72 hr after dosing. There was no apparent difference in the disposition of the drug between albino and pigmented rabbits. Bioavailability following topical dosing increased with dose, although not in a linear fashion. Formulation pH did not have an appreciable effect on ocular bioavailability. There was detectable systemic absorption following topical dosing, with plasma concentrations in rabbit being 50 to 75% of that observed following an equivalent intravenous dose. However, drug levels in the dosed eyes were significantly higher than in contralateral undosed eyes. Multiple dosing of imirestat for 6 weeks resulted in accumulation of drug in rabbit lens. Concentrations were higher in lens cortex than lens nucleus, with the time course for accumulation being different for the two. Our data suggest that imirestat penetrates into ocular tissue following topical dosing and is retained in lens and cornea, potential sites of action for the drug.

KEY WORDS: aldose reductase inhibitor; imirestat; ALO1576; HOE843; ocular pharmacokinetics.

INTRODUCTION

Imirestat [2,7-difluoro-spiro(9H-fluorene-9,4’-imidazolidine)-2’,5’dione; ALO1576; HOE843; Fig. 1] is a highly potent aldose reductase inhibitor (ARI) that is currently being evaluated clinically as a potential systemic therapy for some of the pathological conditions associated with diabetes mellitus, such as neuropathy, retinopathy, and cataract (1). In addition to its ability to prevent cataract formation in experimental models of diabetes (2), imirestat has also been shown to delay or prevent lens changes in nondiabetic oxidative cataract models following topical ocular administration (3). The drug is therefore being evaluated clinically as a potential anticytaract therapy via the topical ocular route of administration.

Imirestat is a weak acid with a low aqueous solubility and a pKₐ of 7.35. The drug is approximately 85% bound to plasma proteins, with the protein binding being highly pH dependent at physiological pH (4). Pharmacokinetic studies in rats have shown that systemically administered imirestat is distributed extensively into body tissues and has a low systemic clearance and a long biologic half-life (5). A similar pharmacokinetic pattern has been observed in preliminary studies in rabbits. It has also been shown that the drug is retained by certain tissues of the rat (i.e., eye, testes, kidney) which contain significant amounts of aldose reductase, suggesting that high affinity binding of imirestat to the enzyme may be responsible for the persistence of drug in these tissues (5).

It has also been demonstrated that intact imirestat is the only component in rat plasma following iv or oral administration of 14C-imirestat (5), suggesting that the disposition of 14C-imirestat may be representative of the disposition of the intact drug. This, along with in vitro metabolism data which demonstrate very slow metabolism of imirestat, suggests that measurements of radioactivity following topical dosing of 14C-imirestat may be representative of the disposition of the parent drug.

In order to understand better the disposition of imirestat following topical ocular administration, five separate pharmacokinetic studies were conducted: (1) single-dose ocular pharmacokinetics in rabbits; (2) effect of dose and pH on ocular bioavailability in rabbits; (3) systemic absorption following topical dosing to rabbits; (4) systemic absorption following topical dosing to dogs; and (5) multiple-dose ocular pharmacokinetics in rabbits.

MATERIALS AND METHODS

Materials

Radiolabeled 14C-imirestat was synthesized by Pathfinder Laboratories (St. Louis, MO). The material was found

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to have >98% radiochemical purity, with a specific activity of 42.3 mCi/mmol. Various suspension formulations were prepared by dispersing nonradiolabeled imirestat and 14C-imirestat in a standard phosphate-buffered formulation vehicle, adjusting the pH to obtain the desired value and ball milling overnight. Each formulation studied contained 0.01% benzalkonium chloride and 0.01% EDTA.

Animal Treatment and Sample Collection

Study 1. Single-Dose Ocular Pharmacokinetics of 14C-Imirestat. Sixty (60) New Zealand albino rabbits weighing between 2 and 4 kg and 60 Dutch Belted pigmented rabbits weighing between 1.5 and 2.5 kg were administered a single 30-μl topical ocular dose of 0.05% 14C-imirestat suspension (pH 6.5) to each eye. Four rabbits of each species were sacrificed at each of the following times after dosing: 0.33, 0.67, 1, 2, 4, 6, 8, 12, 24, 48, 72, 96, 120, 144, and 168 hr. Aqueous humor, cornea, lens, and vitreous humor were collected separately from each eye. Aqueous humor and vitreous humor were directly analyzed for total radioactivity by liquid scintillation spectrometry. The other tissue samples were solubilized with Soluene for 2 days, followed by decolorization with 30% hydrogen peroxide prior to measurement of total radioactivity.

Study 2. Effect of Dose and pH on Ocular Bioavailability of 14C-Imirestat. Forty (40) New Zealand albino rabbits weighing between 2 and 4 kg were divided into five treatment groups of eight animals each. Each group received a single 30-μl topical ocular dose to both eyes of one of the following five formulations: (1) 0.1% 14C-imirestat, pH 7.5; (2) 0.1% 14C-imirestat, pH 6.5; (3) 0.1% 14C-imirestat, pH 6.5; (4) 0.05% 14C-imirestat, pH 6.5; and (5) 0.01% 14C-imirestat, pH 6.5. Four rabbits from each group were sacrificed at 20 and 60 min following dosing. Aqueous humor, cornea, lens, and vitreous humor were collected from both eyes and were analyzed as described in Study 1.

Study 3. Systemic Absorption of 14C-Imirestat Following Topical Dosing to Rabbits. Sixteen (16) New Zealand albino rabbits weighing between 2 and 4 kg were divided into two treatment groups of eight animals each. One group received a single 50-μl topical ocular dose of 0.1% 14C-imirestat suspension (pH 6.5) in one eye only. The other groups received an intravenous injection of 50 μg of 14C-imirestat dissolved in propylene glycol:ethanol:water (5:1:4) into the marginal ear vein. The iv dose delivered an equivalent dose to the systemic circulation as was contained in the 50-μl dose of the 0.1% imirestat suspension. Four rabbits from each group were sacrificed at 4 and 12 hr after dosing. Aqueous humor, cornea, lens, and vitreous humor were collected from both eyes and were treated as described in Study 1. In addition, plasma samples were collected at 0, 1, 4, 8, and 12 hr from the groups sacrificed at 12 hr.

Study 4. Systemic Absorption of 14C-Imirestat Following Topical Dosing to Dogs. Twelve (12) beagle dogs were

![Fig. 2. Mean (N = 8) 14C-imirestat concentrations in cornea, aqueous humor, lens, and vitreous humor following a single topical ocular dose of 0.05% 14C-imirestat suspension in rabbits. Open circles represent data from New Zealand albino rabbits and filled circles are data from Dutch Belted pigmented rabbits.](image-url)