Venous Irritation, Pharmacokinetics, and Tissue Distribution of Tirilazad in Rats Following Intravenous Administration of a Novel Supersaturated Submicron Lipid Emulsion

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Purpose. To compare the venous irritation, pharmacokinetics, and tissue distribution of tirilazad in rats after intravenous administration of a submicron lipid emulsion with that of an aqueous solution.

Methods. Venous irritation was determined by microscopic evaluation of injury to the lateral tail veins of rats. Pharmacokinetic parameters were determined by following plasma concentrations of drug. Tissue distribution of [14C]-tirilazad was determined by quantitative whole body autoradiography.

Results. Single dose injections of tirilazad as an emulsion at doses ranging from 1.52 mg to 13.5 mg were non-irritating whereas the solution was irritating at a dose of 1.3 mg. The pharmacokinetic parameters were not statistically different between the emulsion and the solution (p > 0.2) at doses of 6 mg/kg/day and 20 mg/kg/day. However, at 65 mg/kg/day dose, a higher AUC(0,6) (4-fold) and lower Vss (18-fold) and CL/5-fold) were observed for the lipid emulsion as compared to the solution (p < 0.05). Tissue distribution showed higher initial concentrations (two fold or more) in most tissues for the solution. These values, however, equilibrated by 4 h and AUC(0,4) differences were less than two fold in most tissues.

Conclusions. Formulating tirilazad in the lipid emulsion significantly reduces the venous irritation without changing the pharmacokinetics and tissue distribution at low doses.

KEY WORDS: submicron lipid emulsion; supersaturation; tirilazad; venous irritation; pharmacokinetics; tissue distribution.

INTRODUCTION

Tirilazad (structure shown in Fig. 1a) is an i.v. administered free radical scavenger that has been investigated for therapeutic intervention in aneurysmal subarachnoid hemorrhage, ischemic stroke, and spinal cord injury (1,2), and currently is investigated for renal cytoprotection. This lipophilic compound has an extremely low aqueous solubility at physiological pH. The current formulation of tirilazad (FREEDOX® IV Solution) employs the mesylate salt of the drug at a concentration of 1.5 mg/mL in a pH 3.0 citrate buffer. This formulation has been associated with pain at the injection site, venous irritation, and occasionally thrombophlebitis (3,4). These side effects may be due to the acidity of the vehicle, the irritant nature of the drug, and possible precipitation of the drug after intravenous administration. To alleviate the local pain and venous irritation, FREEDOX® IV Solution is often diluted four fold before use, resulting in a larger and less convenient injection volume. Hence, there is considerable interest in the development of a more concentrated yet less painful i.v. formulation of tirilazad.

Parenteral lipid emulsions that are formulated using a biocompatible emulsifying agent to disperse an oil in an aqueous phase are used for drug delivery, as well as for parenteral nutrition, oxygen transport, and diagnostic imaging (5). These oil-in-water (o/w) systems based largely on vegetable oils are stabilized by phosphatides and they resemble chylomicrons, the natural fat particles present in the circulation that carry endogenous and exogenous lipophiles. The oil phase of lipid emulsions acts as a solubilizer of lipophiles. Thus, solubility of lipophilic drugs can be significantly enhanced in a lipid emulsion, leading to smaller administration volumes compared to an aqueous solution. Additionally, since lipophilic drugs are incorporated within the innermost oil phase, they are sequestered from direct contact with body fluids and tissues. Thus lipid emulsions can minimize the pain associated with intravenously administered drugs by exposing the tissue to lower concentrations of the drug or avoiding a tissue-irritating vehicle. This has been demonstrated with diazepam (6), methohexitol (7), clarithromycin (8) and etomidate (9). Lastly, due to their resemblance to chylomicrons, lipid emulsions are well tolerated and present a lower incidence of side effects as compared to other systems based on organic solvents, pH adjustments, and surface active agents (for example, Cremophor), since there is less chance of drug precipitation upon administration (10). Thus, a lipid emulsion appears to be a viable alternative for the intravenous administration of tirilazad.

In a previous paper (11), we reported the development of a supersaturated submicron lipid emulsion of tirilazad and demonstrated its excellent stability. The purpose of this article is to evaluate the effects of supersaturated tirilazad emulsions on venous irritation, pharmacokinetics, and tissue distribution of tirilazad. The emulsion data are compared to the aqueous solution of tirilazad mesylate (FREEDOX®IV Solution).

MATERIALS AND METHODS

Materials

Tirilazad free base, [14C]-tirilazad free base (specific activity 33.0 μCi/mg), [14C]-tirilazad mesylate (specific activity 33.07 μCi/mg), glycerin (USP grade) and FREEDOX® IV Solution (hereafter the solution) were provided by Pharmacia & Upjohn (Kalamazoo, MI). Miglyol 810 was supplied by Hus America, Inc. (Piscataway, NJ). Fractionated soybean lecithin and butylated hydroxytoluene (BHT) were purchased from Sigma Chemicals (St. Louis, MO). Organic solvents, all of
HPLC grade, were obtained from Burdick and Jackson (Muskegon, MI).

Drug Formulation

Tirilazad emulsions were formulated with Miglyol 810 (MCT) at levels ranging from 10% to 30%, butylated hydroxy toluene (BHT) was used in amounts relative to MCT at a ratio of 0.1:10, fractionated soybean lecithin and glycerin were used at 1.2% and 2.4% in deionized water, respectively. Preparation steps have already been described in detail (11). The physical and chemical stability of the emulsions were assessed using methods already described (11). The mean particle diameter ranged from about 200 to 300 nm and was independent of drug load (11).

Venous Irritation

Groups of eight male Sprague-Dawley rats (Crl:CD[BR], Charles River Laboratories, Portage, MI) received infusions of 2 mL of 0.75 mg/mL the solution or 1 mL of 1.5 mg/mL the solution (positive control), and 10% MCT emulsions containing 0.76 mg/mL, 1.65 mg/mL, and 3.34 mg/mL tirilazad and a 20% MCT emulsion containing 6.75 mg/mL tirilazad. Also given were 4 mL each of 0.9% sodium chloride for injection USP (negative control), 20% MCT emulsion vehicle, 3.34 mg/mL of 10% MCT emulsion. Rats were infused while in a Broome-type rodent restrainer. Leakage was detected by watching for blebs during the infusion. Rats were killed 24 h after infusion and sections of the tail at 1, 2, 3, and 5 cm proximal to the most cranial injection site were preserved in 10% neutral buffered...