Population Pharmacokinetic–Pharmacodynamic Modeling of Filgrastim (r-metHuG-CSF) in Healthy Volunteers

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The pharmacokinetic–pharmacodynamic (PK–PD) relationship of the granulopoietic effects of Filgrastim in healthy volunteers was characterized via a population approach. Healthy male volunteers were enrolled into a four-way crossover clinical trial. Subjects received four single doses of Filgrastim (375 and 750 µg iv and sc) with an intervening washout period of 7 days. Serum concentrations of Filgrastim were determined using an enzyme-linked immunosorbent assay. Absolute neutrophil count (ANC) was determined. Data analysis was performed using mixed-effects modeling as implemented in the NONMEM software package. The final PKPD model incorporates a two-compartment PK model with bisegmental absorption from the sc site, first-order and saturable elimination pathways, and an indirect PD model. A sigmoidal Eₘₐₓ model for the stimulation of ANC input rate (kᵢ) was superior to the conventional Eₘₐₓ model (3 ± SE: Eₘₐₓ = 12.7 ± 1.7; EC₅₀ = 4.72 ± 0.72 ng/ml; Hill = 1.34 ± 0.19). In addition, a time-variant scaling factor for ANC observations was introduced to account for the early transient depression of ANC after Filgrastim administration. The absolute bioavailability of subcutaneously administered Filgrastim was estimated to be 0.619 ± 0.058 and 0.717 ± 0.028 for 375 µg and 750 µg sc doses, respectively. The time profiles of concentration and ANC, as well as the concentration–ANC relationship of Filgrastim in healthy volunteers were well described by the developed population PK–PD model.

KEY WORDS: Filgrastim; G-CSF; pharmacokinetic–pharmacodynamic modeling; population approach; neutrophil; NONMEM; bisegmental input.

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INTRODUCTION

Filgrastim (granulocyte colony-stimulating factor, r-metHuG-CSF, Neupogen®) is a hematopoietic growth factor that selectively stimulates neutrophil production (1). It is a valuable therapeutic agent used for the treatment of neutropenia associated with chemotherapy (1), aplastic anemia (2) and for the mobilization of peripheral blood progenitor cells for transplantation (3). Filgrastim has been shown to reduce the frequency and severity of febrile neutropenic episodes in patients receiving chemotherapy (4).

Binding of Filgrastim to a specific cell-surface receptor results in the proliferation, differentiation, and accelerated maturation of neutrophilic precursor cells, as well as enhancement of mature cell function. Usual routes of administration of Filgrastim are intravenous (iv) and subcutaneous (sc) injections. Neutrophil counts increase following both routes of administration. The pharmacokinetics of the drug appears to be complex. Clinical studies reveal that clearance and half-life of the drug are dose-dependent (5). In this study, the absolute bioavailability of subcutaneously (sc) administered Filgrastim in healthy volunteers was determined using a population approach. In addition, a mixed-effect model was developed to characterize the pharmacokinetic–pharmacodynamic (PK–PD) relationship of the granulopoietic effects of Filgrastim in healthy volunteers.

METHOD

Volunteers and Study Design

Healthy volunteers were chosen in this study to reduce potential variability in response due to marrow status. Sixteen healthy male volunteers (18–45 years old) were enrolled into a single-blind randomized four-way crossover clinical trial. This sample size is within the range commonly used and recommended for bioavailability studies (6). It was estimated that a power of 80% could be achieved based on previous work (7) and the method proposed by Liu and Chow (8). The protocol of this study was approved by the Ethics Review Committee (Freiburger Ethik-Kommission International).

Subjects received single doses of Filgrastim (375 and 750 µg iv and sc) with an intervening washout period of 7 days. For iv administration the infusion rate was fixed at 1 ml/min (25 min) for both doses. For sc administration either 1.25 ml or 2.5 ml of 300 µg/ml Filgrastim solution were given subcutaneously under the abdominal skin. During the iv infusion and sc injection, the subjects were in a supine position. Thereafter subjects were free to move about. One subject dropped out after receiving one sc dose. A