Chapter 7

Pharmacokinetics and Metabolism of Hematopoietic Proteins

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1. INTRODUCTION

Hematopoietic growth factors or colony-stimulating factors (CSFs) are a group of glycoproteins regulating the survival, proliferation, and differentiation of hematopoietic progenitor cells as well as the function and activation of the mature cells. These factors include macrophage-CSF (M-CSF, also known as CSF-1), granulocyte-CSF (G-CSF), granulocyte macrophage-CSF (GM-CSF), multipotential CSF or interleukin-3 (IL-3), and erythropoietin (Epo) (Metcalf, 1985, 1986; Clark and Kamen, 1987; Sieff, 1987). The term CSF was derived from in vitro studies showing that these factors stimulated the growth of colonies of bone marrow progenitor cells in a semisolid agar medium. The factors were named according to the progenitor population that they stimulated. A schema of the actions of the CSFs is shown in Fig. 1. The CSFs are produced by a variety of cells and range in molecular mass from 14 to 90 kDa (Table I). These factors have been purified, cloned, and produced through recombinant DNA techniques. The recombinant factors have been shown to have biologic properties and actions that are similar to the naturally occurring factors. The availability of quantities of the recombinant factors has resulted in their introduction into clinical trials and into the market.
Figure 1. Interactions of the CSFs with hematopoietic cells. Progenitor cells identified in *in vitro* culture systems are CFU-GEMM (colony-forming unit, granulocyte-erythrocyte-macrophage-monocyte-megakaryocyte), CFU-MEG (CFU-megakaryocyte), CFU-Eo (CFU-eosinophil), CFU-GM (CFU-granulocyte-monocyte), CFU-E (CFU-erythroid), and BFU-E (burst-forming unit-erythroid); n, neutrophil; e, eosinophil; b, basophil; m, monocyte/macrophage; E, erythrocyte; and M, megakaryocyte.

The pharmacokinetics of these factors have been evaluated in animals and in man. Early studies, however, utilized impure or poorly characterized fractions and the interpretation of these results is difficult. With the availability of recombinant proteins, these limitations were overcome and definitive studies have been completed. In general, the biologic effects of these factors can be quantitated by measuring the effects on the target hematopoietic cell population. This has provided a basis for relating the pharmacokinetic profile of the factor to the pharmacodynamic response. As clinical trials and the therapeutic applications of these factors are expanded, the knowledge and understanding of the pharmacokinetics of the drug will be critical to guide the clinician in the choice of dosing routes and schedule.

The majority of the literature on CSFs deals with descriptions of the cloning, purification, and identification of the factors and the *in vitro* and *in vivo* biologic effects. There have been, however, relatively few references to the pharmacokinetics of these factors. When pharmacokinetic parameters are reported, these reports are often limited to a brief indication of a calcu-