The Engineering of Anemia Management Protocols in Chronic Kidney Disease

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Objective
To design a new, patient-specific anemia management protocol using feedback control principles by explicitly considering the dynamic structure of the erythropoiesis, together with models of the biosystem’s uncertainties.

Background
• In chronic kidney disease (CKD), endogenously produced erythropoietin (EPO) is inappropriately low for the level of anemia. In addition there is EPO resistance so that EPO that is produced works less effectively. A shortened RBC life-span further contributes to the anemia of CKD.
• The discovery of recombinant human EPO has shifted the treatment of anemia for patients on dialysis away from blood transfusions.
• Erythropoiesis is a nonlinear, dynamic biosystem. However, its interaction with an anemia management protocol results in a new nonlinear system, whose behavior can be very different from that observed in pharmacokinetic/pharmacodynamic (PK/PD) studies.
• Current anemia management protocols fail to achieve desired response.
• Current protocols can be analyzed and new protocols can be designed through the principles of feedback control systems.

Methods
Pharmacokinetics Model
• A single pool of EPO in blood, intravenous (IV) dose as an impulsive input, and a Michaelis-Menten function capturing nonlinear clearance.

Pharmacodynamics Model
• Stimulatory effects of EPO on differentiation, maturation, and proliferation of hematopoietic stem cells into reticulocytes is described using a nonlinear, time-delayed function of EPO concentration.
• Reticulocyte and RBC dynamics are described using cellular lifespan distribution functions.

Clinical Data
• Retrospective data set consisting of 49 subjects having Hgb measured 3x-week, 3x-week IV EPO administration, over a period of 18 months.

PK/PD Parameter Estimation
• Simulink Design Optimization Tool (The MathWorks, Inc.) for estimating nominal PK/PD parameters.
• Quantify uncertainty in PK/PD parameters.

Model Simplification
• Pharmacokinetics and cell production represented as nonlinear function of EPO dose.

Design of New Anemia Management Protocol
• Apply feedback control principles (Quantitative Feedback Theory) to protocol design to maintain target Hgb level.
• Assess protocol performance with regard to Hgb variations in the face of uncertainty.

Results
New vs. Standard Protocol
• Hgb measurement noise (std=0.8)
• Bleeding (1.5 g/dL at day 600)

Discussion
• Model-based, feedback control principles offer an improved approach for designing anemia management protocols.
• Intercurrent events (e.g., iron status, infection) and uncertainty in endogenous EPO levels complicate the design of protocols.
• Real-time adaptation of such protocols to variations in EPO responsiveness would further improve results.
• Inclusion of iron administration in the protocol may be necessary; lack of iron PK/PD models is presently a hurdle.