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Predictive modeling for improved anemia management in dialysis patients

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Abstract

Purpose of review—This review will explore the basic assumptions needed to perform predictive modeling of hemoglobin response to erythropoiesis stimulating agents (ESAs) and summarize the current literature in the area so that the practitioner can incorporate these tools as part of an improved anemia management process.

Recent findings—During the last year, several publications have demonstrated some advances in the field that may improve anemia management. The first of these was the publication of a randomized, controlled clinical trial of model predictive control in the dosing of erythropoietin. This work showed that hemoglobin variability can be decreased using predictive models of hemoglobin response. The second publication is potentially more interesting in the long run, as new markers of erythropoietin response were identified in a well-defined population of patients.

Summary—Predictive models of hemoglobin response improve anemia management by decreasing hemoglobin variability. This will result in more patients within the target range. Coupling these tools with new biomarkers of hemoglobin response has the potential to dramatically improve anemia management.

Keywords

control; dosing; erythropoietin

Introduction

Pharmacologic management of chronic disease has traditionally been performed in a trial-and-error fashion primarily guided by product labeling and implemented using unsophisticated rule-based protocols. Because drug dosing is inherently a closed-loop process, it will likely benefit from advancements in the field of automatic control. Automatic control methodology uses mathematical models to design algorithms, which can drive physical processes to operate in specific conditions with minimal human intervention. Indeed, control algorithms have been repeatedly demonstrated to facilitate drug dosing [1,2]. This review will explore the basic assumptions needed to perform predictive modeling of hemoglobin response and summarize the current literature in the area. As part of this review, we will discuss the different metrics that could be applied that would identify ‘improved’

anemia management, identify factors that might be included as part of the prediction, and present an overview of published techniques.

Definition of improved anemia management

The National Kidney Foundation's Dialysis Outcome Quality Initiative (DOQI) Clinical Practice Guidelines were published in 1997 [3]. The history of these recommendations shows how the definition of 'appropriate' anemia management has shifted from minimizing the number or percentage of patients receiving an erythropoiesis stimulating agent (ESA) with a hemoglobin (Hb) less than 11.0 g/dl to maximizing the percentage of patients between 10.0 and 12.0 g/dl. The target range for 'appropriate' anemia management has moved from 11.0 to 12.0 g/dl (years 1997–2006), to greater than or equal to 11 g/dl, with no evidence to maintain Hb greater than 13.0 g/dl (2006). Most recently the target range was 10.0–12.0 g/dl [4,5]. On 24 June 2011, the Food and Drug Administration (FDA) released new recommendations for ESAs, which were followed by a proposed policy change by Centers for Medicare and Medicaid (CMS) on 1 July 2011. Optimum anemia management has been a moving target since 1997 and a robust computer-based tool would be useful.

Computer control of anemia management

The first attempts to improve anemia management were the development of expert systems in the form of anemia management protocols. The first of these was outlined in the package insert and specified a starting dose and how to adjust the dose when above or below the target hemoglobin. As the hemoglobin target has changed over time, dialysis facilities and organizations have developed their own protocols based on the package insert.

To eliminate the variability in Hb response induced by human control, several investigators developed computer-based decision support systems for anemia management, essentially implementing the existing expert-based rules for initiation and dose adjustment. Perhaps the one that has been used the longest is the AMIE Renal programme (Media Innovations, University of Leeds). This tool provides for the dosing of both an ESA and iron. The programme did not demonstrate any improvement in the metrics measured in the study population but may be useful in bringing more poorly performing facilities up to the level of the demonstration facility [6].

Another application of computerized decision support for ESA dosing was performed by a dialysis provider (Dialysis Clinic Inc.) in 2005–2006 and published in 2009 [7]. In this publication, the authors report on the conversion of a paper anemia management protocol to a computerized decision support system with the understanding that the time needed to perform anemia management would decrease, but how Hb control would be impacted was unknown. The authors showed a 50% reduction in time spent by dialysis unit staff on anemia management, but no change in the likelihood of a monthly Hb of 11–12 g/dl or 10–12 g/dl when compared with manual dosing.

We have concluded from these data that the conversion of current expert systems for the management of anemia from paper to digital format may save staff time and standardize care across dialysis facilities but has not been demonstrated to improve any of the metrics used to define improved anemia management. More sophisticated means are likely needed to improve anemia management over what is obtainable using an expert system.

Models of erythropoietin pharmacodynamics

Early in the development of recombinant erythropoietin (EPO), the basis for prediction of response was investigated. The pharmacodynamics of EPO were determined assuming that

Hb production increases linearly with EPO dose levels. The equations used contained two patient-specific parameters: erythropoietic sensitivity and erythrocyte lifespan [8]. An important message from this work was that Hb levels would not stabilize for approximately 14 ± 4 weeks, the estimated erythrocyte lifespan determined by the mathematical model. Similar work was performed by Brockmöller *et al.* [9] using a more advanced model based on the one proposed by Garred and Pretlac [8]. Of interest from this work was the finding that the efficacy of EPO was correlated with EPO clearance. A population pharmacodynamic approach with dose adjustment scheme was published by Uehlinger *et al.* [10]. These authors also use a measure of erythrocyte production rate and erythrocyte lifespan. It is likely that these analyses performed on data collected in the late 1980s do not adequately capture today's patient characteristics, due to changes in iron management, inflammation, and other temporal differences.

Alternatives to traditional methods of dosing were proposed at about the same time by researchers in Italy [11,12]. However, other than a theoretical application of the principles of process control, no successful clinical applications have been reported. Because of the time delay between the dosing of an ESA and the observable Hb response, as well as the nonlinear nature of that relationship, supporting ESA dosing with automatic control methods may be desirable.

Application of predictive modeling for erythropoiesis stimulating agent therapy

Historically, the Hb target in ESA therapy is one of the narrowest of therapeutic ranges for all the drugs that are monitored and has further been confused by recent FDA and CMS policy changes. Most therapeutic drug monitoring (TDM) agents have well defined pharmacokinetic or pharmacodynamic models by which dose adjustments are made (e.g., aminoglycoside antibiotics, theophylline, etc.) and dosing has become somewhat routine. Other drugs that exhibit nonlinear pharmacokinetics, like phenytoin, are also somewhat routine due to the development of proper therapeutic drug monitoring routines. Up until 2007, ESA dosing was simple, as our metric at the time that related to good anemia management was the percentage of patients with a Hb above 11 g/dl and sophisticated tools were not needed. This has changed for ESAs, and automatic control tools that aid in performing more precise ESA dosing may prove beneficial in managing the anemia of chronic kidney disease. For automatic control methods to improve anemia management over standard techniques, two main components are needed: a model of Hb response to ESA dose and a controller that chooses the proper dose of ESA to maintain stable Hb.

Many models of the dose–response relationship between Hb and ESA have been presented in the literature and some of the early ones have already been presented in this review. One concern with these models is the ever-changing dialysis environment and population, and a better understanding of erythropoiesis in dialysis patients may invalidate some of their assumptions.

As an alternative to those models, we proposed a model of ESA pharmacodynamics based on the concept of Artificial Neural Networks (ANN) [13]. ANNs are flexible nonlinear regression tools with a distributed architecture mimicking the structure of the human brain. Under certain conditions, ANNs are capable of discovering relationships encoded in data sets and extrapolating them onto new data. In application to ESA response prediction, we have compared an ANN's with a standard linear regression approach and demonstrated its advantage in terms of precision of Hb level prediction [13]. In another study, we have also applied the ANN approach to determine which of the physiologic factors measured as part of the standard clinical practice influence the ESA response [14]. Independently of our

efforts, other researchers have also explored the ANN approach to ESA response prediction, achieving promising results as well [15].

On the basis of this work we have developed and published the results of using a model predictive control (MPC) algorithm for anemia management [16,17•]. The MPC approach applied to ESA dosing is based on a model ESA response, which is used to predict Hb over multiple time steps into the future. On the basis of this prediction, a new ESA dose is solved for, in order to achieve a stable Hb response near a user-specified target level over an extended period of time. In these studies, we used an ANN-based pharmacodynamic ESA response model estimated from data retrospectively collected in a dialysis population to which the algorithm was subsequently applied prospectively. On the basis of the results of these studies, we lay out the philosophy of how we think anemia management can be improved using sound engineering. Figure 1 shows a simplified schematic of how MPC works. Although in our studies we used FDA/Kidney Disease Outcomes Quality Initiative specified Hb targets across the whole study population, MPC is not constrained to one Hb target or range, unlike current expert system-based anemia management protocols. MPC can ultimately have a different Hb target for every patient. This Hb target, as well as other user-specified information, such as limits on Hb rate of rise or ESA dose increment/decrement, is supplied to the dose optimiser, which uses the Hb predicted by the model to solve for the optimal ESA dose at a given point in time as shown in Fig. 2. Using advanced optimization techniques and machine learning algorithms, an MPC-based anemia management algorithm can be empowered not only to achieve stable patient-specific Hb, but also to minimize the ESA and iron use or to meet other objectives specified by the user.

We can contrast the MPC-based and a traditional anemia management approach using Fig. 2. Both techniques use the prior Hb (T, T-1) measurement(s) and ESA dose, and possibly a time-ordered series of Hb and ESA, to estimate where the patient is in relation to the therapeutic range and the rate of change in Hb. Using only prior Hb value, the standard techniques might call for a 25% dose increase, which in 1 month actually achieves the desired response (predicted response 2), but if the rate of rise is ignored or the patient responds vigorously to the treatment an excursion above 12 g/dl will occur in 2 months. On the basis of the model predictions, the MPC algorithm will be aware of the excursion and recommend a lower dose (predicted response 3). It is possible, then, that anemia management in this way will be more efficient in terms of decreasing Hb variability, which we have already demonstrated in a randomized controlled trial. We have also shown that the MPC approach can better maintain the population (in this case a dialysis facility) at a predefined Hb value. Another great advantage of the MPC approach is that no design modifications are necessary to change the target Hb or provide individual Hb targets for every patient. On the other hand, a standard AMP does not have this flexibility.

Coupling the results seen with MPC and the development of new biomarkers of erythropoietin response may lead to further improvement in anemia management. We have recently identified 16 biomarkers that are predictive of both good and poor response [18••]. Specifically, oncostatin M receptor β and cysteine/histidine-rich 1 were associated with poor and good response, respectively. Adding additional predictors of response will likely further improve upon the gains we have demonstrated.

Conclusion

Anemia management since the introduction of recombinant erythropoietin has been primarily driven by economic factors. This appears to be the case given bundled payment for the administration of routine drugs. Tools are available that can maximize the hemoglobin response in a majority of patients and at the same time be responsive to the economic

concerns. Work is continuing in this area and needs to be expanded to a much larger population to determine the overall utility.

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References and recommended reading

Papers of particular interest, published within the annual period of review, have been highlighted as:

- of special interest
- of outstanding interest

Additional references related to this topic can also be found in the Current World Literature section in this issue (p. 676).

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This study is the only randomized controlled clinical trial of a predictive algorithm for anemia management. The authors show that model predictive control can decrease hemoglobin variability compared with a traditional approach. The limitations of the study are a small sample size ($n = 60$) and no concurrent control for iron.
- 18••. Merchant ML, Gaweda AE, Dailey AJ, et al. Oncostatin M receptor β and cysteine/histidine-rich 1 are biomarkers of the response to erythropoietin in hemodialysis patients. *Kidney Int.* 2011; 79:546–554. [PubMed: 21150872] In this recent study, the authors report the finding of 16 peptide fragments that sort with erythropoietin response. Erythropoietin resistance was defined over a 6-month observation period, which avoided transient resistance. Fragments of oncostatin M receptor β were associated with poor response, with receiver operator characteristic (ROC) curves of 0.95–0.99. Fragments of cysteine/histidine rich 1 were associated with good response, with a ROC curve of 0.91. Other peptide fragments associated with poor response were fibrinogen α and β , complement C3, and Factor XIII.

Key points

- Improved anemia management can be accomplished using predictive models or hemoglobin response to guide dose selection.
- New biomarkers of hemoglobin response to erythropoietin may identify those patients who are most resistant.
- More work needs to be done in a larger population of patients that includes both an erythropoiesis stimulating agent (ESA) and iron dosing to show the full effect of these techniques.

Figure 1. Schematic diagram of model predictive control applied to erythropoietin administration

The dose optimizer is responsible for picking the correct dose of EPO^* to administer to the patient following interrogation of the patient model with all possible EPO doses. The patient model is responsible for returning the predicted hemoglobin (Hb_{pred}) for each proposed administered EPO. Hb is the hemoglobin observed in the patient given EPO^* .

Figure 2. Schematic diagram of the method used by model predictive control to determine best dose

The dose optimizer will present multiple potential doses to the model, depicted as predicted response 1, predicted response 2, and predicted response 3. T is the currently observed time. T+1, T+2, T+3 are the forward predictions at 1, 2, and 3 months in the future. The dose optimizer will select the dose associated with predicted response 1 as it meets the selection parameters attaining the desired response at time T+3.