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Opportunities for model-based precision dosing in the treatment of sickle cell anemia

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Abstract

Hydroxyurea is the primary pharmacotherapy to prevent complications of sickle cell anemia (SCA). Accumulated clinical experience across multiple age ranges has suggested that the use of an individualized maximum tolerated dose (MTD) will achieve optimal benefit of hydroxyurea treatment. However, the current empirical and trial-and-error approach for dose escalation often results in a lengthy titration process and is not strictly implemented in many clinics. Opportunities exist for pharmacokinetics model-based precision dosing of hydroxyurea to quickly achieve individual MTD. This review intends to introduce the use of a quantitative modeling approach including a Bayesian adaptive control strategy for the precision dosing of hydroxyurea. The rationale and practical considerations for the implementation of this approach are discussed. Future research directions with a focus on integrating specific safety and other clinical outcome endpoints into dose selection decision making are also discussed.

Keywords

hydroxyurea (HU); sickle cell anemia (SCA); pharmacometrics; D-optimal design; Bayesian individualized dosing

1. Introduction

For drugs like hydroxyurea that exhibit large inter-patient variability in pharmacokinetics, to attain maximum therapeutic outcome with an acceptable risk of side effects, individual dose titration to reach the maximum tolerated dose (MTD) is desired. Thus far, a trial-and-error approach for dose escalation is predominately used in clinical practice. As such, MTD for

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Conflict of Interest

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each patient is determined by gradually increasing the dose over several months based on tolerability and response parameters such as the absolute neutrophil count (ANC). This process is time-consuming, requires frequent clinic visits, and delays the full benefits of pharmacotherapy. It would be ideal if MTD could be predicted based on individual patient's demographics, genotype, and/or any other known biomarkers and measurable characteristics. It is often challenging, however, to explain the large observed variability in response by just a few factors, therefore making it difficult to establish an effective algorithm to predict MTD. This is particularly true for the pediatric population such as infants, where pharmacokinetic (PK) and pharmacodynamic (PD) variability often times is large and not well predicted or controlled by the chosen dosing strategy, whether weight- or age-based. An attractive option for MTD prediction is then a PK guided model-based precision dosing approach. This approach takes advantage of available prior PK information in the form of a model and updates the *a priori* information with individual patient data such as drug concentrations to draw inferences of the behavior of a drug in a particular patient over time.^{1, 2} In this way individual PK parameters can be estimated with maximum precision. A dosing regimen for drugs like hydroxyurea can then be personalized to achieve a pre-defined therapeutic target as quickly and precisely as possible.

Hydroxyurea is the primary and only disease-modifying therapy for sickle cell anemia (SCA) currently approved by the FDA. Previous studies have shown that patients who receive hydroxyurea at an MTD that is specific for them have greater clinical benefit than those who receive a standard lower dose, supporting the use of MTD to achieve the greatest benefit of hydroxyurea treatment.³ As mentioned above, the current empirical approach for dose escalation often results in a lengthy dose optimization process. In fact, the dose titration process is not strictly implemented across different institutions or not performed at all in many busy clinical practices, resulting in suboptimal dosing of hydroxyurea in many patients. We recently developed a model-based pharmacokinetically guided strategy using Bayesian adaptive control for individualized hydroxyurea treatment.⁴ This new precision dosing protocol uses a population pharmacokinetic model and individual concentration data to predict MTD for patients with SCA with the expectation to shorten the time of reaching MTD. This new regimen is currently being prospectively evaluated for potential clinical benefits in pediatric patient with SCA.

The aim of this paper is to review the methodology behind the model-based Bayesian adaptive approach and the rationale of using this approach for the precision dosing of hydroxyurea and other pharmacotherapeutic options for patients with SCA. Further, suggestions on how future research may assist in improving our understanding of hydroxyurea PK/PD as it relates to treatment and optimal dosing of hydroxyurea are discussed.

2. Rationale for Hydroxyurea Dose Individualization

Hydroxyurea therapy offers significant clinical and laboratory benefits for children and adults with SCA.^{3, 5, 6} Main benefits include a reduction in the incidence of pain crises and acute chest syndrome.⁷ The main mechanism of action of hydroxyurea involves increasing the expression of fetal hemoglobin (HbF),^{8, 9} which helps decrease incidence of vaso-

occlusion and reduce hemolysis by preventing intracellular sickling.¹⁰ Accumulated experience from multiple studies across a broad range of patient ages has demonstrated that the clinical and laboratory benefits are greatest when hydroxyurea treatment is escalated to MTD as compared to a fixed standard dose.^{3, 10} As shown in Figure 1, higher doses of hydroxyurea are associated with overall better hematological responses, including higher Hb concentrations, higher percentages of HbF and higher mean corpuscular volumes (MCV).¹⁰ Based on this evidence, a recommendation was issued by a panel of experts in 2014 to use an established and practical protocol to ensure safe dose escalation of hydroxyurea to MTD for patients with SCA.⁷

The individual hydroxyurea MTD is highly variable in patients with SCA and ranges from 14.2 to 35.5 mg/kg/day in children (Figure 2; Data source: clinical trial entitled “Long Term Effects of Hydroxyurea Therapy in Children With Sickle Cell Disease”; i.e. HUSTLE trial; clinicaltrials.gov registry number NCT00305175)¹¹. This broad range of MTDs is hypothesized to be at least partially due to a substantial inter-patient variability in hydroxyurea pharmacokinetics and prevents the use of one standard dose to be effective in all patients with SCA. In adult patients, hydroxyurea exposure as measured by the area under the concentration time curve (AUC) varies approximately five-fold for a given dosing regimen, whereas in pediatric patients differences in exposure can vary 2–3 fold at the same mg/kg dose.^{11, 12} The traditional dosing strategy for hydroxyurea involves a titration process with all patients starting at the same empirical dose of 15–20 mg/kg/day, followed by fixed incremental increases every 4–8 weeks (in steps of ~2.5–5 mg/kg/day) until mild myelosuppression (as defined by complete blood count and reticulocyte count) is achieved, indicating that MTD has been reached.³ Once the MTD is reached, patients will continue with long-term maintenance treatment at this dose, with adjustments as needed for weight gain or based on changes in laboratory values. This dose escalation process, however, requires frequent outpatient visits and laboratory tests and usually takes 6–12 months to complete (Figure 3). Given the large between patient variability in dosing requirements it is attractive to develop a model-based precision dosing protocol of hydroxyurea for patients with SCA.

3. Model-Based Precision Dosing: The Concept

Drug disposition (pharmacokinetics) is a complicated process, involving absorption, distribution, metabolism and elimination (ADME) and can be influenced by many factors such as drug physiochemical properties, patient factors (age and weight), (patho) physiology and disease progression. To characterize drug disposition, “traditional” PK studies are performed using serial and rich sampling e.g. 6–8 samples within a single dosing interval from each subjects to obtain individual parameters. This approach however is not practical in the clinical setting and in patient populations where obtaining multiple samples is not feasible. The recent developments in population PK/PD model based study design and modeling enables the use of sparse sampling to generate accurate and precise estimates of drug exposure.^{1, 13}

The concept of Bayesian dosing is based on Bayes' Theorem, a statistical theorem which is also broadly used in other areas including engineering^{14, 15} and sports.^{16, 17} In the context of

dose optimization, pharmacokinetic-pharmacodynamic (PK/PD) model based Bayesian estimation was first described in the late 70's by pioneers such as Sheiner and Jelliffe,^{18, 19} and has been applied to drugs such as antibiotics with confirmed overall cost-effectiveness²⁰. In recent years, it has gained renewed momentum due to a great push for precision dosing under the Precision Medicine Initiative launched by the US government²¹ and rapid advances in computational power.²²

To estimate the most likely pharmacokinetic parameters and the dose required to achieve the therapeutic target in real-time for a specific patient (and the uncertainty around these estimates), three elements are needed 1) the knowledge of the probability density function of the population PK/PD parameters, i.e. the Bayesian prior. These data are obtained from previously studied patients which could be from a different population (e.g. adult vs. pediatric population) but ideally come from a similar population. Previously developed population PK or PK/PD models including both typical values of model parameters and inter-patient variabilities normally are used as the prior information; 2) individual data such as one or more plasma concentration measurements and patient specific parameters such as body weight and renal function; 3) a pre-defined target of drug exposure or biomarker measurements for dose estimation. Both Bayesian prior and individual data are then included in a mathematical optimization equation where the objective function value is minimized when a set of individual parameter values (solution) best fit the observed data set (maximum a posteriori probability (MAP) Bayesian estimation).^{1, 19, 22} These individual PK/PD values can then be used to derive a future dosing regimen to best achieve a given target drug exposure or biomarker effect in that particular patient.

Although an informed decision for dose selection requires a detailed understanding of both PK (the expected time course of drug exposure at the effect sites), and PD (the likelihood of effectiveness and the potential for adverse effects), objective and sensitive biomarkers for PD response are often lacking. A first and more practical step is then to characterize drug exposure, i.e. by using PK optimization. As observed in the case of hydroxyurea, large inter-patient variability in drug exposure (i.e. AUC of plasma concentration vs. time) exists resulting in variable treatment effect. Clinically, the rationale for measuring drug concentrations is that while imperfect, there is almost always a better relationship between the action of a given drug and its concentration in the blood or at its effect site(s) than between the dose of the drug given and the effect.

While traditional richly sampled concentration-time data may be sufficient to estimate individual pharmacokinetic parameters without "prior information", a Bayesian approach has great advantages in situations where only sparsely collected concentration data are available. In addition, this is particularly attractive in special populations such as neonates and infants from whom only very few samples can normally be taken. As Bayesian estimation may only require few concentration measurements, it is critical to identify the sampling time-windows that are most informative for estimation of the PK parameter of interests such as AUC. To maximize the information, the variance of pharmacokinetic parameters (the information of the population pharmacokinetic model) are to be minimized using algorithms such as D-optimality criteria.²³ A range of sampling windows that are not

strictly fixed can be identified which in addition offers significant flexibility for implementation in clinical protocols.

To apply Bayesian dose estimation, special clinical software is needed, although other general statistical programs like R and SAS could also be utilized for this purpose according to a user's specification. About a dozen clinical software packages are currently available for Bayesian estimation,^{24, 25} such as the commonly used programs MwPharm²⁶ and BestDose.^{27, 28} MwPharm was originally developed at the University of Groningen in the Netherlands for educational purposes and is now commercially available (www.mediware.cz). BestDose provides dose optimization using a nonparametric approach for Bayesian adaptive control and was developed by Drs. Jelliffe and Neely's research group at the University of Southern California.²⁹ Unfortunately despite the availability of these software platforms, these modern day tools are not part of the training curricula of medical or pharmacy schools which poses a significant barrier for implementation in clinical practice.³⁰

4. Application of Bayesian Approach in Hydroxyurea Dosing Individualization

We recently developed a PK - guided dosing algorithm for children, based on hydroxyurea exposure as measured by the AUC after a single dose, with the goal to significantly shortening the time to reach MTD.⁴ As a first step, a population PK model was constructed using pediatric pharmacokinetic data collected as part of the HUSTLE trial (96 patients aged 1.2 to 16.6 years old).¹¹ The robustness of the developed PK model was confirmed by advanced model evaluation and validation techniques.⁴ This pharmacokinetic model was then employed to inform the optimal time windows for sample collection under the D-optimal design criteria. The following clinically feasible and informative sampling times identified were: pre-dose (baseline), 15–20 minutes, 50–60 minutes, and 3 hours after an oral dose. With recently developed and novel approaches in sample collection and measurement, plasma volumes as low as 10 μ L can be sufficient for determination of hydroxyurea concentration.³¹ One of the challenges faced in the development of this Bayesian dosing strategy was the lack of consensus on a hydroxyurea exposure target associated with the likelihood of achieving desired clinical outcomes. As a practical compromise, the average value of the AUC obtained from 69 patients at their MTD in the HUSTLE trial was adopted as the initial exposure target.¹¹ Accordingly, the mean AUC target for initial dose titration was 115 mg·h/L.⁴ Figure 4 demonstrates an example of the Bayesian estimation steps. In this case, the hydroxyurea population PK model⁴ serves as the “Bayesian prior” and predicts a population average pharmacokinetic profile (green dashed line). Three individual plasma concentrations were collected at optimal time points (red circles) with reported results of 10.42 mg/L at 17 minutes, 17.60 mg/L at 50 minutes and 15.99 mg/L at 2.92 hours after oral administration of a standard 20 mg/kg initial dose. A pre-dose sample (i.e. baseline concentration) was not collected in this patient as this was the first dose. After taking into account both population prior information and the individual data, the Bayesian algorithm generated an area under the curve (AUC) prediction of 90 mg·h/L (blue line). Based on the exposure target of 115 mg·h/L, a new dosage of 25.5

mg/kg is then estimated for this patient to precisely achieve this target. In this case, MwPharm was used as the software platform for Bayesian estimation of the individual AUC, and a suggested dosing regimen was calculated in order to reach to the initial exposure target of 115 mg·h/L.

This new dosing strategy is now being prospectively evaluated in a clinical trial entitled “Therapeutic Response Evaluation and Adherence Trial” (TREAT; [ClinicalTrials.gov](https://clinicaltrials.gov/ct2/show/study/NCT02286154) registry number NCT02286154). One of the primary objectives of this study is to develop and prospectively evaluate a population pharmacokinetic/pharmacodynamics model of hydroxyurea to predict the maximum tolerated dose (MTD) in children with SCA. The dose of hydroxyurea is individually determined using the developed PK-guided dosing algorithm and the primary outcome measure is the “Time to Reach Maximum Tolerated Dose”. In addition, this trial is expected to provide a thorough evaluation of other potential clinical benefits of this individualized dosing approach for hydroxyurea treatment.

5. Conclusions and Future Directions

In conclusion, the described Bayesian adaptive control dosing strategy holds great promise to change the paradigm of how hydroxyurea is dosed. Given that only three blood samples are needed to estimate hydroxyurea exposure, this new strategy has been shown to be clinically attractive and feasible. It may also be particularly valuable in regions with a high incidence of SCA but with limited resources for health care delivery (e.g. Sub-Saharan Africa). One of the practical issues for Bayesian estimation implementation is the measurement of hydroxyurea in real time. Traditional assays may require large volumes of blood which would be difficult to collect, store and ship. With the recent advances in technology for hydroxyurea concentration measurement³¹, as little as 10 microliter of blood collected using dry blood spot cards or micro-sampling devices would be sufficient for hydroxyurea concentration determination. This type of technology offers great convenience for sample collection, storage and shipment, and therefore is promising for use in areas where SCA is most prevalent but where resources are limited.

This model-based dosing approach may also benefit patients with SCA undergoing treatment with other drugs such as deferasirox and busulfan where significant inter-patient variability in drug exposure has been reported.^{32–34} Busulfan is an alkylating agent commonly used as part of conditioning regimens for patients with severe SCA undergoing blood and marrow transplantation.³⁵ The therapeutic window for busulfan treatment is narrow and personalized dosing has been implemented in order to achieve optimal clinical outcome.^{36, 37} The traditional approach for dosage titration requires 4–9 blood samples drawn over 6 hours after busulfan administration.^{36, 38} With model based precision dosing, as few as two concentrations at optimal sampling times over four hours accurately predict busulfan PK parameters for individualized dose adjustment, as described by Neely et al.²⁷ A recent published guideline from the American Society for Blood and Marrow Transplantation (ASBMT) Practice Guidelines Committee recognizes the use of population PK approaches to shorten the time period for busulfan PK sampling.³⁷ Several PK model-based Bayesian dosing strategies have been recently developed,^{27, 39} which hold great promise to reduce the burden and to improve the cost-effectiveness of busulfan treatment.

Another drug that could benefit from PK-guided dosing is deferasirox. Deferasirox is an oral iron chelator effective for reduction of body iron in iron-overloaded patients with transfusion-dependent anemias.^{40, 41} Despite its effectiveness and clinically manageable safety profile, appropriate dosing of deferasirox according to the severity of iron burden and iron intake, together with the careful monitoring of laboratory parameters and adverse events, is recommended.^{40, 42} Clinical PK data are available for deferasirox³² which provides opportunities to guide its optimal use by applying model-based approaches. As some patients do not respond adequately to traditional doses of iron chelators, further research is needed and a PK-biomarker model based approach could improve the current empirical dosing. In addition to abovementioned drugs, several new drugs such as rivipansel are in development for the treatment of SCA.^{43, 44} Population PK and PK/PD modeling studies have been conducted or are part of the development plans and provide opportunities to develop model based precision dosing strategies. A recent FDA guidance for drug labeling in the clinical pharmacology section urges to report primary PK parameters such as clearance and volume of distribution and intra-/inter-subject variability for those parameters.⁴⁵ Providing this information as part of the labeling will facilitate the development of clinical PK/PD dosing tools and software for clinical use of model based precision dosing.

However, this PK-guided dosing approach is not without limitations. Ultimately, determining the optimal dose not only requires a good understanding of PK (exposure) but also of PD (efficacy and safety) targets. Toxicity measures, including absolute neutrophil count (ANC) are the primary clinical parameters to define hydroxyurea MTD but are not integrated into the current model-based MTD prediction. Although in general a higher dose correlates with a larger increase in HbF, as indicated by several clinical trials,¹ a quantitative description of the relationship between hydroxyurea exposure (PK), the likelihood of myelosuppression (safety), and the increase of fetal hemoglobin (efficacy) is lacking. To tackle this, a full characterization of the exposure-response (E-R) relationship is needed to identify the therapeutic target that would give the desired efficacy, while staying within the safety range of reduced ANC. Using HbF% and mean corpuscular volume (MCV) as biomarkers for response, Paule et al. developed turnover models to describe exposure-efficacy of hydroxyurea treatment.¹² Based on the models, different dosing regimens were compared by simulation for better HbF% and MCV improvements. Future studies should also focus on using both efficacy and safety i.e. the myelosuppression of hydroxyurea treatment as PD endpoints.¹² Another important research direction would be the further development of mechanistic models, i.e. models based on physiology and systems pharmacology, that consider hydroxyurea concentrations at the target sites (leukocytes and erythrocytes), as described for several other drugs.⁴⁶ Such physiological or semi-physiological models could include knowledge gained from *in vitro* studies (such as the time course of leukocyte maturation after hydroxyurea treatment) and include molecular pathways of hemoglobin expression and regulation (e.g. HbF induction). Additionally, mechanistic models are well suited for covariate modeling which may identify significant predictors of dosing and response of hydroxyurea treatment. Should the exposure-response relationship of hydroxyurea be established in a mechanistic way, novel precision dosing strategies could be further proposed to improve clinical outcomes in patients with SCA.

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Abbreviations

SCA	sickle cell anemia
MTD	maximum tolerated dose
PK	pharmacokinetics
PD	pharmacodynamics
AUC	area under the concentration-time curve
Hb	hemoglobin
HbF	fetal hemoglobin

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Figure 2.

The distribution of dose change from a standard initial dose of 20 mg/kg/day at first treatment of hydroxyurea (Day 1) and after the patient reach to their MTD (MTD). Data source: a clinical trial entitled “Long Term Effects of Hydroxyurea Therapy in Children With Sickle Cell Disease” (i.e. HUSTLE trial; [clinicaltrials.gov](https://clinicaltrials.gov/ct2/show/study/NCT00305175) registry number NCT00305175; n = 64).

Figure 3.
Time duration to reach MTD in pediatric patients in the HUSTLE trial.

Figure 4.

An example of individualized dosing using Bayesian adaptive control. This example was taken from a patient who was 9 months old with a body weight of 11 kg. A standard 20 mg/kg initial dose of hydroxyurea was given and Bayesian-estimated dose to attain the target AUC was recommended based on three concentration measurements collected at the optimal sampling times.