Journal of Process Control 45 (2016) 76–83

Contents lists available at ScienceDirect

Journal of Process Control

journal homepage: www.elsevier.com/locate/jprocont

Platelet count control in immune thrombocytopenic purpura patient: Optimum romiplostim dose profile

Chia-Hung Tsai [a], James B. Bussel [b], Allison A. Imahiyerobo [b], Stanley I. Sandler [a], Babatunde A. Ogunnaike [a,*]

[a] Department of Chemical and Biomolecular Engineering, University of Delaware, Newark, DE, 19716, USA
[b] Pediatrics, Weill Cornell Medical College, New York, NY, 10065, USA

ARTICLE INFO

Article history:
Received 19 April 2016
Received in revised form 25 July 2016
Accepted 26 July 2016
Available online 1 August 2016

Keywords:
Immune thrombocytopenic purpura
Biological system modeling
Model-based control
Nonlinear systems
Optimization

ABSTRACT

Patients with immune thrombocytopenic purpura (ITP), a disease featuring abnormally low platelet count, are susceptible to excessive bleeding. One of the more effective treatment regimens is to increase platelet production with romiplostim. However, current romiplostim treatment strategies tend to produce undesirable responses where platelet count oscillates between dangerously low and extremely high values, as a consequence of the complex nonlinear dynamics associated with platelet production. This study aims to determine the optimum romiplostim dose profile required to maintain a stable platelet count for a specific ITP patient. Using the specific patient's platelet count data obtained in response to a series of romiplostim doses, a pharmacokinetics/pharmacodynamics model was developed, validated, and analyzed to obtain insight into the patient's physiological characteristics. The model was subsequently used to investigate the performance of three control strategies for weekly and bi-weekly treatment regimens. A stable platelet count is more likely to be achieved in the specific patient with weekly treatments. Bi-weekly treatments are less effective because fundamental characteristics of romiplostim make oscillations in platelet count unavoidable at this treatment frequency. Model-based decisions determined using patient-specific mathematical models are potentially useful for designing better treatment regimens for ITP patients. The strategies developed in this work provide potential solutions to the highly variable responses observed among ITP patients undergoing romiplostim treatment. The approach can also be applied to other diseases with complex system dynamics.

1. Introduction

Our objective is to develop an effective and implementable control strategy for maintaining a specific platelet count—PLT ($\times 10^9$/L), at 70—in a patient with Immune Thrombocytopenic Purpura (ITP). The normal range of PLT in healthy individuals is between 150 and 400. While ITP is generally defined as PLT < 150, symptoms vary significantly with different values of PLT (Table 1). Mild cases of ITP, where 30 < PLT < 150, are frequently untreated because symptoms are often unobservable [1,2]. However, treatment is usually required when PLT < 30 [3], since sustained periods of extremely low PLT (e.g., PLT < 10) can lead to serious and sometimes fatal complications [4].

1.1. Mechanism of platelet production regulation

Platelet production is regulated according to the following mechanism: The hormone thrombopoietin (TPO) stimulates the proliferation, maturation, and differentiation of platelet precursor cells (megakaryocytes) by binding to c-Mpl, the TPO receptor on the plasma membrane of these platelet precursor cells. Binding of TPO to megakaryocytes activates two pathways: the JAK/STAT5 pathway, which results in cell proliferation, and the MAPK pathway, which promotes megakaryocyte differentiation [5,6], leading to the production of platelets.

TPO is primarily synthesized by hepatocytes at a constant rate in the liver [7] and then secreted into the blood stream. Since c-Mpl is present on the plasma membrane of platelets, TPO can also bind to platelets. This results in an inverse relationship between the circulating concentration of TPO and the platelet count [7,8]. When platelet count is high, more TPO will bind to platelets, thereby lowering TPO concentration and consequently reducing the availability of TPO for stimulating megakaryocytes. This ulti-

* Corresponding author.
E-mail address: ogunnaike@udel.edu (B.A. Ogunnaike).

http://dx.doi.org/10.1016/j.jprocont.2016.07.008
0959-1524/

Table 1
Physiological implications of platelet count.

Platelet count, PLT ($\times 10^9$/L)	Description	Symptoms	Treatment suggestion
150 < PLT < 400	normal	None	none
30 < PLT < 150	mild ITP	might be asymptomatic or symptoms including: excessive bruising, spontaneous nose bleeds, spontaneous bleeding from gums, and prolonged bleeding from cuts	no treatment required
PLT < 30	high risk of bleeding	subarachnoid bleeding, gastrointestinal bleeding, and intracranial hemorrhage	treatment usually required; evaluations should be made for the decision of treatment
PLT < 10	severe ITP		treatment required

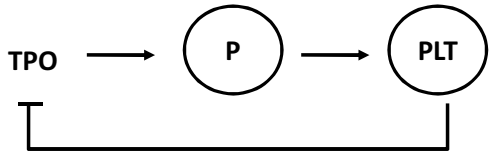

Fig. 1. Schematic of platelet production regulation. TPO: thrombopoietin; P: precursor (megakaryocyte); PLT: platelet.

mately lowers the stimulatory effect of TPO on platelet production. Therefore, as more platelets are produced, the effective production rate is reduced automatically by this natural feedback regulatory mechanism whereby the stimulatory TPO is sequestered from megakaryocytes by the produced platelets (Fig. 1). Conversely, when platelet count is low, more TPO will be available and the increased TPO concentration will thus exert an enhanced stimulatory effect on megakaryocytes, ultimately leading to increased platelet production.

1.2. Pathology and treatment of ITP

Under normal conditions, the intrinsic biological feedback regulatory mechanism described above and illustrated in Fig. 1 maintains homeostatic production of platelets. In ITP patients, however, complications arise because of the simultaneous incidence of increased platelet destruction and decreased platelet production [9] as a result of any number of conditions including autoimmune responses, reduced TPO production rate due to pathological disorders in the liver, or pathological changes in the c-Mpl receptor or post-receptor signaling events in megakaryocytes [10]. While the root cause of ITP is unknown, an understanding of TPO regulation of platelet production indicates that platelet production can be increased to compensate for inappropriately low production by enhancing TPO levels. Therefore, a logical ITP treatment option is to employ "TPO mimetics", such as romiplostim, that act through the same mechanism as TPO.

Romiplostim, a fusion protein analog of TPO, contains two copies of the human immunoglobulin (IgG_1) Fc domain, each covalently linked at its C-terminus to a peptide chain containing two c-Mpl-binding peptides [11]. It has been approved in many countries as a treatment for adult patients with chronic ITP [12] and has been shown to increase platelet count (to PLT $\geq$ 50) in the majority of ITP patients [13–15].

However, peak platelet count in response to single romiplostim treatment is highly variable from patient to patient [16]. For example, a platelet count of 130×10^9/L achieved with 1 μg/kg/week in one patient requires 3 μg/kg/week in another [14], possibly due to differences among patients in the extent of decreased platelet production and increased platelet destruction [9].

Furthermore, the time required to reach peak platelet count after romiplostim administration, a delay that reflects the time required for megakaryocyte differentiation, varies significantly from patient to patient, with medians ranging from 10 to 16 days [16,17]. As a result of the mechanism of romiplostim action, the peak response for each individual patient is generally higher at lower initial platelet counts and attenuated with increasing values of platelet count—a defining characteristic of nonlinear systems. The effect of one romiplostim injection on any particular patient will therefore affect the efficacy of the next, adding another layer of complexity to the problems created by the nonlinear and time delay dynamics. Consequently, maintaining platelet count at a stable value with romiplostim is fundamentally challenging.

The manufacturer recommendation is weekly administration of romiplostim, with the dose depending on the current platelet count. However, as noted above, the time to reach the peak platelet count after romiplostim treatment is more than a week for many patients. Thus it is likely that treatment will be administered while platelet count is still rising, but more importantly, current platelet count measurement will not adequately reflect the full effect of the immediately preceding treatment. In this case, however, excess romiplostim will simply be sequestered by the platelets, so that its stimulatory effect on platelet production will be muted. The converse is more problematic. If a treatment is administered when platelet count is decreasing, and the dose is determined on the basis of current measurement, platelet count will almost surely continue to decrease and may decrease to an unacceptably low value because it takes a few days for administered romiplostim to take effect. By the time the treatment takes effect, the actual platelet count will not be near the value upon which the treatment dose was based so that the treatment is likely to have been seriously underestimated. To be effective, a treatment strategy must take the complex dynamic characteristics of romiplostim action into consideration.

By now, it has become well established that mathematical modeling is an efficient tool for understanding complex biological systems [18]. In the specific case in question here, pharmacokinetic/pharmacodynamic (PKPD) models of romiplostim have been used effectively to capture the characteristics and mechanisms of romiplostim metabolism in healthy humans [8] and ITP rats [12]. A relatively recent study developed a K-PD model (with the P in PK omitted to indicate the absence of data on drug concentration in the serum) for the effect of romiplostim on platelet production using data from ITP patients, approximating the pharmacokinetic part with a single compartment model [17]. The data reported in the study showed highly variable responses to romiplostim administration in ITP patients, leading the authors to divide the data into two subpopulations each characterized by significantly different parameter estimates. The K-PD model representing the population characteristics of romiplostim-induced platelet production in the patients was subsequently used to investigate two quantized dosing strategies with the objective of preventing PLT > 400, the conventional upper limit of platelet count in normal individuals. The simulation results showed that from 12 weeks to 42 weeks, PLT can be maintained between 20 and 400 with both dosing strategies in 75% of the subjects, while PLT was predicted to fall below 20 (high bleeding risk) in 20% of the subjects and rise above 400 (increased thrombotic risk) in the remaining 5% of the subjects over the same period.