Optimizing circadian drug infusion schedules towards personalized cancer chronotherapy:

Optimizing circadian drug infusion.

Roger J. W. Hill[1,*], Pasquale F. Innominato[2], Francis Lévi[3,+], and AnnabelleBallestaBallesta[4,+]

[1]*EPSRC & MRC Centre for Doctoral Training in Mathematics for Real-World Systems, University of Warwick, Coventry, UK*

[2]*North Wales Cancer Centre, Ysbyty Gwynedd, Betsi Cadwaladr University Health Board, Bangor, UK. & Cancer Chronotherapy Team, Cancer Research Centre, Division of Biomedical Sciences, Warwick Medical School, Coventry, UK*

[3]*Division of Biomedical Sciences, Warwick Medical School, University of Warwick, UK. & INSERM and Paris Sud university, UMRS 935, Team "Cancer Chronotherapy and Postoperative Liver Functions", Campus CNRS, Villejuif, F-94807, France.*

[4]*INSERM and Paris Sud university, UMRS 935, Team "Cancer Chronotherapy and Postoperative Liver Functions", Campus CNRS, Villejuif, F-94807, France. & Honorary position, University of Warwick,UK*

[*]*Corresponding author e-mail:r.hill.3@warwick.ac.uk*

[+]

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- **What is already known**:- Inter- and intra-patient variability in cancer chemotherapy response advocate for precise and personalized drug scheduling.
- **What this study adds**:- A mathematical framework to optimize drug infusion pump and quantify inter-patient variability in drug pharmacokinetics.

Abstract

Aims

Precision medicine requires accurate technologies for drug administration and proper systems pharmacology approaches for data analysis. Here, plasma pharmacokinetics (PK) data of the OPTILIV trial in which cancer patients received oxaliplatin, 5-fluorouracil and irinotecan via chronomodulated schedule delivered by an infusion pump into the hepatic artery were mathematically investigated.

Methods

A pump-to-patient model was designed in order to accurately represent the drug solution dynamics from the pump to the patient blood. It was connected to semi-mechanistic PK models to analyse inter-patient variability in PK parameters.

Results

Unexpected time delays of up to 1h41 between the actual pump start and the time of drug detection in patient blood was predicted by the model and confirmed by data. Sudden delivery spike in the patient artery due to glucose rinse after drug administration accounted for up to 10.7% of the total drug dose. New model-guided delivery profiles were designed to precisely lead to the drug exposure intended by

clinicians. Next, the complete mathematical framework achieved a very good fit to individual time-concentration PK profiles and concluded that inter-subject differences in PK parameters was the lowest for irinotecan, intermediate for oxaliplatin and the largest for 5-fluorouracil. Clustering patients according to their PK parameter values revealed two patient subgroups for each drug in which Inter-patient variability was largely decreased compared to that in the total population.

Conclusions

This study provided a complete mathematical framework to optimize chronomodulated drug infusion pumps and inform on inter-patient PK variability, a step towards precise and personalized cancer chronotherapy.

1 Introduction

Cancer management is challenged by large inter- and intra-patient variabilities in both disease progression and response to treatments. Thus, the quest for personalized cancer therapies has fostered the development of new technologies enabling multi-type measurements in individual patients and complex drug scheduling. To translate patient-specific datasets into individualized therapies and further ensure their precise administration, new mathematical approaches are required. Indeed, systems medicine, that involves the implementation of theoretical approaches in medical concepts, research and practice, is critically needed as emphasized in the roadmaps of the Coordinated Action for Systems Medicine (CaSyM) from the European Union (https://www.casym.eu, [1]) and of the Avicenna action (http://avicenna-isct.org/), and in other international consortia [2–5]. The final aim is a measurable improvement of patient health through systems-based practice which will enable predictive, personalised, participatory and preventive (P4) medicine [6].

Optimizing chemotherapeutics index is complex at multiple levels. First, large

inter-patient variabilities are demonstrated in drug pharmacokinetics, tolerability and antitumor efficacy [1, 7–9]. Next, important intra-patient variabilities arise from the fact that tumour and healthy tissues, rather than being static over time, display time-dependent variations, in particular over the 24h span, which are called circadian rhythms [10]. The circadian timing system (CTS) controls each mammalian cell via their molecular clock composed of approximately 15 genes. The CTS-driven control of most physiological functions of the organism has great implications for pharmacotherapies as drug Absorption, Distribution, Metabolism and Elimination (ADME) display 24h-rhythms with differences of up to several folds between minimum and maximum activities [11, 12].

In the field of Cancer Research, circadian rhythms appear as a major domain of host-tumour differences since normal cells usually display well synchronized variations over the 24h span, whereas circadian rhythms are often disrupted in malignant tumours [13]. Chronotherapy -that is administering drugs according to the patient's biological rhythms over 24 h- is a growing field in medicine and especially in oncology. Indeed, several randomized phase III clinical trials in metastatic colorectal cancer patients showed that cancer chronotherapy achieved an up-to-5-fold decrease in treatment side effects and nearly doubled antitumor efficacy compared to conventional administration of the same drug doses. However, the administration of the same chronomodulated schedule to patients with metastatic colorectal cancer significantly increased the survival in men while reducing that in women as compared to conventional administration [12]. Furthermore, circadian biomarker monitoring in individual patients recently revealed up to 12 h inter-patient differences regarding the timing of midsleep, the circadian maximum in skin surface temperature or that in physical activity [14]. These investigations have highlighted the need for the individualization of drug combinations and chrono-infusion schemes to further improve treatment outcome, taking into account the patients sex, chronotype and genetic background.

Clinical findings about cancer chronotherapy have motivated the development of innovative technologies for chronomodulated drug delivery including the Mélodie® infusion pump (Axoncable, Montmirail, France, [15]). This portable electronic pump allows for the administration of up to 4 compounds according to pre-programmed schedules over the 24 h span. It was used in several clinical trials for the chronomodulated delivery of irinotecan (CPT11), oxaliplatin (L-OHP) and 5-fluorouracil (5-FU) into the central vein of metastatic colorectal cancer patients [12]. The Mélodie® pump was recently used to infuse those three anticancer drugs directly into the hepatic artery of metastatic cancer patients in the translational European OPTILIV Study [16]. In this study, the plasma pharmacokinetics of oxaliplatin revealed inconsistencies between programmed delivery schedules and observed drug concentration within the patient blood. Such inconsistencies between targeted drug exposure patterns and plasma drug levels motivated the design of a mathematical model of fluid dynamics within the pump system. This pump-to-patient model was then connected to semi-physiological PK models to investigate the inter-patient variability in drug PK after hepatic artery administration. Thus, this systems pharmacology study aimed to develop predictive mathematical models allowing for the quantitative and general understanding of i) the pump dynamics, irrespective of the drug delivery device, and ii) patient-specific whole-body PK of irinotecan, oxaliplatin and 5-fluorouracil after drug administration using an infusion pump. Such mathematical techniques would then allow for precise and personalized drug timing.

2 Methods

2.1 OPTILIV Clinical Datasets

The OPTILIV trial included 11 colorectal cancer patients with liver metastases (7 men and 4 women with median age of 60). The combination of irinotecan, oxaliplatin and

5-fluorouracil was delivered to patients by Hepatic Artery Infusion (HAI) using the Mélodie® pump [16]. The patients received an intravenous administration of cetuximab 500 mg/m^2 over 2 h 30 min on the morning of day 1 which was not modelled. From day 2, chronomodulated HAI of irinotecan (180 mg/m^2), oxaliplatin (85 mg/m^2) and 5-fluorouracil (2800 mg/m^2) were given (Figure 1). Irinotecan was delivered as a 6-h sinusoidal infusion starting at 02:00, with a peak at 05:00 on day 2. Oxaliplatin was administered as an 11h 30min sinusoidal infusion beginning at 10:15 with a peak at 16:00 on days 2, 3 and 4. Five-fluorouracil was also delivered as an 11h 30min sinusoidal infusion beginning at 22:15 with peak delivery at 04:00 at night, on days 3, 4 and 5. Between each drug infusion, there was a glucose serum flush which cleared the tubing. This was a 30-min sinusoidal infusion beginning at 09:45, and then again at 21:45 i.e. at the end of each infusion (Figure 1).

Plasma pharmacokinetics (PK) data was gathered after the first dose of irinotecan, oxaliplatin and 5-fluorouracil. Plasma concentrations of irinotecan and SN38 were determined in mg/ml at the start of infusion, then at 2, 3, 4, 6, 8 h 15 min and 31 h 45 min post HAI onset, for a total of seven time points, including baseline. Oxaliplatin concentrations were determined by measuring both platinum plasma levels, unbound and total. Oxaliplatin binds to proteins in the blood and the free Pt fraction is the biologically active one. Thus, oxaliplatin concentrations were determined at the start time of infusion, then at 3, 6, 9 h, 11 h 30 min and 17 h 15 min post HAI onset, for a total of six time points, including baseline. Plasma concentrations of 5-fluorouracil were determined at the start of infusion, then at approximately 3 h, 5 h 45 min, 9 h and 11 h 30 min post HAI, for a total of five time points, including baseline.

2.2 Pump description

The Mélodie® pump system weighs 500 g when empty (excluding drug reservoirs and batteries) and measures 160 x 98 x 34 mm. The pump consists of four channels which

correspond to the four reservoirs that are connected to the pump. Each reservoir can have a maximum volume of 2 L. The four channels are controlled by four independent mechanisms which control the delivery to the infusion tube (Figure 1). For the OPTILIV study, the infusion tube comprised of two sections, the first was 135mm long with a diameter of 2.5mm, and the second section was 1500mm long with a diameter of 1mm. The two sections had a total volume of 1.84ml. The four pump reservoirs were loaded with irinotecan, oxaliplatin, 5-fluorouracil and 5% glucose solution respectively, with the latter one being used for washes in between drug infusions [17].

2.3 Mathematical modelling

A pump-to-patient mathematical model was designed as follows, irrespective of the drug delivery device. The drug solutions dynamics from the pump to the patient's blood was modelled using a Partial Differential Equation (PDE). This method was chosen as PDEs can take into account both time and space which was key for modelling systems in 2 dimensions such as pump delivery. The PDE was solved using a backward finite difference method programmed within Python 3.5.2 (https://www.python.org/). The drug PK models were based on Ordinary Differential Equations (ODEs) programmed using Python 3.5.2 and solved using the odeint function from the scipy library [18].

PK model parameter estimation involved a weighted least square approach. The minimization of the least square cost function was performed by the Covariance Matrix adaptation Evolution Strategy (CMAES) within Python which has been shown to be successful at handling complex cost function landscapes [19]. Model goodness of fit was assessed using the χ^2 test.

To ensure PK model parameter numerical identifiability given the available data, parameter sensitivity regarding the least-square cost function was computed via a global Sobol sensitivity analysis [20]. This method assesses the relative contributions of each parameter to the variance in the cost function obtained when parameter values are var-

ied, and thus allows for the identification of parameters which have no effect on the cost function and are therefore not identifiable from the available dataset. PK models were fit to single-patient plasma PK datasets independently to obtain patient-specific parameter values.

Regarding the PK study, the sampling points at 21:45 for oxaliplatin, 9:45 for irinotecan and 9:45 for 5-fluorouracil occurred very close to the 30 min glucose flush which could largely influence plasma drug concentrations. However, the exact time of patient blood collection for PK studies was not always reported at minute resolution. Keeping the theoretical sampling time led to inconsistent model fit to data which led us to make the following assumptions for the actual blood sampling time. The collection time of the data points at theoretically 21:45 for oxaliplatin, 9:45 for irinotecan and 9:45 for 5-fluorouracil were unchanged if the drug concentration at the preceding data point was greater than the current one. If not, the collection time was modified and set equal to the glucose peak time, such value leading to the best model fit. Overall, the collection time was changed compared to the theoretical one for patients 1, 2, 3 and 7 for oxaliplatin, for patient 5 for 5-fluorouracil, and for no patients for irinotecan.

2.4 Inter-patient variability and patient clustering based on PK parameters

Given the relatively small number of patients, the inter-patient variability in parameter values was assessed using a nearly unbiased estimator of coefficient of variation (CV),

$$\left(1+\frac{1}{4n}\right)\times\frac{\sigma}{\mu}\times 100,$$

where μ is the parameter mean, σ the parameter standard deviation and n is the number of patients.

Next, fuzzy c-means clustering was used to define patient clusters based on indi-

vidual PK parameters, for each drug separately. The fuzzy c-means clustering was done using a python library sckit-fuzzy (http://pythonhosted.org/scikit-fuzzy/). The number of clusters was chosen to maximise the fuzzy partition coefficient while having a number of patients within a single cluster being higher than 3. Fuzzy partition coefficient is a measure of how well the fuzzy clusters and hard clusters agree. Hard cluster are when patient is assigned a cluster definitively, whereas fuzzy clusters assign a probability of being in each cluster to each patient. Plotting the clustering results was done using a multidimensional scaling algorithm implemented in Python using the library sklearn.manifold [21]. This method projects multidimensional data onto a 2D plane while trying to keep distance metric scaled relative to original data. To access the quality of the MDS projections Shepard diagrams were plotted and the correlation coefficients were calculated. The correlation coefficient was high for all models ($>$ 0.98) which showed that the MDS projections are accurate.

3 Results

The overall objective of this study was to investigate the inter-patient variability in the plasma PK of the three anticancer drugs administered during the OPTILIV trial. A first strategy consisted in using compartmental PK modelling taking the delivery profiles programmed into the infusion pump as inputs for the plasma compartments. However, such methodology revealed inconsistencies between the best-fit model and the data, including delays of several hours. We then concluded that the fluid dynamics from the pump to the patient had to be quantitatively modelled. Hence, we designed the complete model in two sequential mathematical studies. First, we studied the drug solution dynamics from the pump to the patient blood for which the model was based on partial differential equations. This novel model of the pump delivery system took into account the specificities of the equipment used in order to accurately predict drug delivery in the patients' blood, although it could be easily adapted to any drug delivery

devices. Second, we connected this model to compartmental PK models based on ordinary differential equations. This complete framework allowed the investigation of inter-patient variability in drug PK after hepatic artery administration.

3.1 Pump-to-patient drug solution dynamics

3.1.1 Model design

The pump-to-patient model is a transport equation representing the dynamics of the drug solution along the administration tube, with respect to time (t) and one-dimensional space (x) (1). x is the distance along the tube from the pump (x=0) to the patient (x=L). The drug solution was assumed to be incompressible so that the fluid velocity was considered as constant along the whole tube. Thus, the concentration in the tube $U(x,t)$ changes with respect to the following equation:

$$\frac{\partial U}{\partial t} = -V(t)\frac{\partial U}{\partial x} + D\frac{\partial^2 U}{\partial x^2} + \partial(x)S(t) \qquad t \in [0,T], \quad x \in [0,L] \tag{1}$$

where $V(t)$ is the fluid velocity inside the tube in mm/h, D is the drug diffusion coefficient in mm^2/h. The source term $S(t)$ represents the infusion profile programmed into the pump in mg/h and $\partial(t)$ is an indicator function which is equal to 1 at $x = 0$ and 0 otherwise to represent drug infusion at the start of the tube. Initial conditions along the tube are u(0,x)=0. The velocity and source terms are programmed into the pump via the fluid delivery rate to enter the tube per time (ml/h). The total tube volume was set to 1.84 mL as in the equipment used in the OPTILIV study. Since both the source term and velocity are then defined by the fluid delivery rate they are converted using the radius of the tube and the concentration of each drug, this means radius and length of the tube does not effect the solution dynamics of the drug computed by our 1-D spatial model as long as the total volume is kept constant and the velocity and source terms

are calculated with respect to these measurements. Thus, for the sake of simplicity, the original infusion tube which was constituted of two sections of different diameters was simplified in numerical simulations to a tube of radius 1mm and total length 2340mm that had the same total volume as the original set-up. An example of the PDE model simulations in time and space for oxaliplatin delivery is shown in Figure 2a.

3.1.2 Differences between programmed infusion profiles and actual drug delivery in the patient's blood

The pump infusion schemes used in the OPTILIV trial were simulated for the three drugs: irinotecan, oxaliplatin and 5-fluorouracil. Whereas the drug profiles programmed into the pump followed a smooth sinusoidal function, the actual drug delivery in the patient artery differed from the programmed profiles by two main features. First, the model predicted a significant time delay between the actual start of the drug delivery by the pump and the time the drug first reached the patient blood (Figure 2b,d,f). This delay was equal to 1 h 41 min for oxaliplatin, 1 h 20 min for 5-fluorouracil and 30 min for irinotecan. It was explained by the model as the time taken to fill the infusion tube with the solution containing the drug. The delay was drug-specific as it depended on the solution drug concentration and the velocity of the solution in the tube driven by the programmed input profiles. Next, at the end of the infusion profiles, the pump stopped and did not administer the amount of drug left inside the tube. This remaining drug was flushed out by the glucose rinse subsequent to drug administration which induced a sudden delivery spike in the patient artery (Figure 2c,e,g). The amount of drug in this spike was expressed in percentage of total drug delivered and was equal to 10.7% for oxaliplatin, 5.36% for 5-fluorouracil and 1.85% for irinotecan.

Our systems approach revealed important differences between the intended drug infusion profile and the actual administration into the patient artery. Hence, we developed optimized infusion profiles that strictly achieved the drug administration intended by

clinicians. The same equipment was considered to avoid cost of changing. Drug concentrations of the infusion solutions were kept unchanged in order to avoid possible problems of stability. In order to administer the drug in the patient's blood following a smooth sinusoidal function, a profile in three parts is required as follows (Figure 3). The first part of the profile is an initial bolus to fill the tube between the pump and the patient with the drug solution. Once the tube is filled, the original sinusoidal profile starts. Then, to solve the problem of the amount of drug left in the tube when the pump stops, the original sinusoidal profile needs to be interrupted when the total drug amount has left the drug bag. Then, a subsequent glucose rinse needs to be infused according to the final segment of the sinusoidal curve in order to deliver the drug remaining in the tube at the correct rate.

3.2 Inter-patient variabilities in irinotecan, 5-fluorouracil and oxaliplatin PK after chronomodulated administration

The pump-to-patient model provided accurate predictions of the drug infusion into the patients' blood, which was a prerequisite to study the inter-patient variability in the PK of irinotecan, oxaliplatin and 5-fluorouracil. A compartmental physiological model was designed for each drug.

3.2.1 Compartmental models of irinotecan, oxaliplatin and 5-fluorouracil pharmacokinetics

PK models represented the drug fate in: the Liver, to accurately represent hepatic delivery, the Blood, the location of data, and the rest of the body known throughout this paper as *Organs*. Each model assumed that the drug was delivered directly into the liver compartment to represent the Hepatic Artery Infusion (HAI, Figure 4,5,6). All transports in between compartments were considered as passive and represented by linear kinetics. Drug clearance was considered for each compartment and represented renal

elimination for the Blood compartment, intestinal elimination for the Organs compartment and biliary excretion for the Liver compartment. Any chemical species bound either to plasma proteins or to DNA was assumed to be unable to move between compartments or to be cleared from the system. Parameter identifiability analysis revealed poor sensitivity of the clearance rate constant in the Organs compartment and transport rate constants to and from the Blood and the Organs compartments. Hence, Organs clearance was assumed to be equal to that of the Liver compartment, and Organs uptake and efflux rate constants were assumed to be equal, for all three drugs.

The irinotecan model had nine compartments as each of the three Liver, Blood and Organs, had three sub-compartments: the parent drug irinotecan, and its active metabolite SN38, either free or bound, either to proteins or to DNA (Figure. 4). Initial irinotecan administered in the liver was assumed to be only in the form of the parent drug. Irinotecan was activated into SN38 via MichaelisMenten kinetics with the parameter estimates K_{M} taken from [22]. In each organ, SN38 could bind and unbind to proteins, to represent both the formation and dissociation of complexes with topoisomerase 1 which is the main drug target, and the interactions with other proteins such as albumin [23]. Since the parent drug irinotecan shows significantly lower affinity to DNA and protein binding, only SN38 binding was considered for the sake of simplicity [24]. SN38 clearance terms accounted for SN38 elimination including its deactivation into SN38G though UDP-glycosyltransferases (UGTs).

The oxaliplatin PK model had six compartments corresponding to bound and free platinum (Pt) molecules in the liver, blood and other organs. Oxaliplatin is rapidly metabolised into platinum complex forms [25], which were not distinguished with in the current data so as all metabolites of oxaliplatin were assumed to have the same PK properties in the model. Initial oxaliplatin administered in the liver was assumed to be free. Free Pt could bind to proteins and unbinding from proteins was also included in all compartments (Figure 5).

The model for 5-fluorouracil had three compartments. The drug clearance accounted for both drug elimination and drug metabolism in each compartment (Figure 6). Protein binding of 5-fluorouracil was neglected in the model because of the low protein affinity of this drug [26].

3.2.2 Inter-patient variability in irinotecan, oxaliplatin and 5-fluorouracil PK parameters.

Overall, each of the three drug models showed a very good fit to data (χ^2 test, $p < 0.1$ for all models, Figure. 7,8,9).

The irinotecan model had an almost perfect fit and showed a rapid accumulation of both irinotecan and SN38 in the plasma of patients (Figure 7). The subsequent elimination was faster for CPT11 as compared to SN38 as a result of protein and DNA binding. No obvious impact on irinotecan and SN38 plasma concentrations was observed regarding the time needed to fill the infusion tube or the 30-min glucose delivery spike, as predicted by the pump-to-patient model.

The fit for the oxaliplatin PK model captured all general trends (Figure 8). The model did predict a delay in plasma Pt concentrations at the start of the infusion due to the pump-to-patient drug transport and a spike during the glucose flush for all patients. This drug spike had an effect on the time of maximum concentration t_{max} of the free Pt by shifting the time by up to 6 h. While the model fit was excellent for total Pt concentrations, that for ultrafiltrate Pt was less accurate which may be explained by the lower order of magnitude of the concentrations associated with higher experimental errors. In particular, the model underestimated the free platinum peak concentrations after the glucose flush for the patients with the most significant rise in concentration, that are patients 2, 3 and 7.

The 5-fluorouracil model showed a very good fit to data and predicted the glucose flush to induce a late spike in plasma drug concentration which could not be seen in

the data, probably because blood sampling frequency was not high enough (Figure 9). This model-predicted spike in 5-fluorouracil concentration would not change the t_{max}. The predicted spike AUC was equal to approximately 5% of the total AUC which was in agreement with the pump-to-patient model prediction. This was only calculable for 5-fluorouracil since its elimination was fast enough for its concentration to be close to zero by the time the glucose flush began.

The model fit to each individual patient PK data allowed to investigate the inter-patient variability in resulting PK parameters (Figure 10a,b,c). The CV of each PK parameter was calculated among the patient population. Then, the mean CVs for the entire parameter set of each drug model were calculated. Irinotecan had the smallest mean CV with a value of 96.11%, and a large range from 1.39 to 213.34%. Mainly four parameters showed inter-patient variability that were irinotecan uptake from Blood to Liver or Organs, irinotecan bioactivation into SN38, SN38 unbinding from proteins and SN38 clearance in Liver and Organs. Oxaliplatin had the second smallest mean CV at 103.61%, with the smallest range from 58.93 to 150.19%. All seven parameters displayed inter-patient variability with uptake into the Liver and clearance from Liver or Organs having the largest CVs. 5-fluorouracil had the largest value of mean CV, 140.06%, with a range from 74.80 to 287.38%. Among the 5 model parameters, 3 of them showed inter-patient variations and corresponded to the drug uptake from the Blood to the Liver, and drug clearance parameters.

For each drug model, individual patient parameter sets were then utilized to determine patient clusters. Two patient clusters were found regarding PK parameters of irinotecan, oxaliplatin or 5-fluorouracil, with fpc values of 0.785, 0.831 and 0.963 respectively (Figure 10d,e,f). For irinotecan, clusters were composed of 7 and 4 patients, for oxaliplatin, 6 and 4 patients, and for 5-fluorouracil, of 6 and 3 patients. Only patients 4 and 9 were in the same cluster for all three drugs. Parameter CVs were then reassessed for each cluster and were largely decreased as compared to those obtained

for the entire patient population. Indeed, the mean CVs were for irinotecan and were equal to 58.72% and 78.50% for each of the patient clusters. For oxaliplatin, mean CVs within the clusters were equal to 73.71% and 47.93% and for 5-fluorouracil, they were equal to 64.04% and 28.76%.

4 Discussion

Precision and personalized medicine requires accurate technologies for drug administration and proper systems pharmacology approaches for individual patient multidimensional data analysis. Here, plasma PK data of the OPTILIV trial in which patients received irinotecan, oxaliplatin and 5-fluorouracil through a chronomodulated schedule delivered by an infusion pump into the hepatic artery were mathematically analysed. To allow for an accurate analysis of PK patient data, a model of the pump drug delivery was successfully designed and connected to semi-mechanistic PK models. The overall framework achieved a very good fit to individual time-concentration profiles, thus giving insights into inter-patient variability and paving the path to treatment optimization.

The simulations for the pump-to-patient model showed a delay between the actual start of the pump and the time when the drug appeared in the patient blood which was due to the delay needed for the drug solution to fill up the infusion tube and eventually reach the patient. The length of this delay depends on both the drug solution concentration and the volume of the infusion tube, so that its importance was high for oxaliplatin, intermediate for 5-fluorouracil and minor for irinotecan. However, temporal accuracy is key for precision medicine especially in the context of chronomodulated drug delivery and all administration profiles should be corrected for these delays in order to properly administer the treatment schedules initially intended by the oncologists.

In addition to such "pump-to-body" delay, the increase in free Pt concentration near 22:00 shown in the PK data was explained by a spike in oxaliplatin delivery resulting from the glucose rinse flushing out the residual oxaliplatin left within the infusion tube. This phenomenon was well captured and quantified by oxaliplatin PK model which predicted that the quantity of drug delivered in the final spike was equal to 10.7% of the total dose. The model also showed that the t_{max} of oxaliplatin plasma concentration was shifted by several hours due to this delivery profile spike. In silico simulations also predicted that the glucose flush would alter the PK of 5-fluorouracil, however the

sampling scheme did not cover the time when this would theoretically happen so that this prediction could not be verified experimentally. The spike only accounted for a small amount of the total drug dose of 5.36% and may not have caused any significant detrimental effect. The delivery spike due to the glucose rinse did not seem to have influenced the plasma concentration profile of irinotecan because the drug concentration in the solution was much lower and the flow rate programmed into the pump was much higher as compared to oxaliplatin and 5-fluorouracil administration. Indeed, the spike only accounted for less than 2% of the total dose of irinotecan.

The pump-to-patient model further showed that these inconsistencies between the actual and intended drug administration could be overcome with a simple and easily constructed adaptation of the infusion profiles, given the specific dimensions of the infusion tube. The new profile showed a much better match with the original intended administration profile.

Inter-patient differences in maximum plasma drug concentrations and in the time at which it occurred led us to further investigate variability in between subjects. Irinotecan showed the lowest mean variability although four parameters out of 10 had high CVs. Clustering analysis indicated that patients could be classified into two clusters with respect to irinotecan PK parameters but with the lowest fpc which meant there was less of a clear distinction between clusters. However, inter-subject variability within each cluster was decreased compared to that in the total patient population as mean CVs was 96.11% for all patients as compared to 58.72% and 78.50% within each cluster. Regarding oxaliplatin, there was a high variability between patients for most of the PK model parameters. Clustering according to oxaliplatin PK parameters split patients into two clusters, which were more distinct than for irinotecan, as demonstrated by a higher fpc value. Clustering allowed to largely decrease inter-subject variability as mean CV in the entire patient population was equal to 103.61% as compared to 47.93% and 73.71% in each cluster. The largest inter-patient variability was found for 5-FU which

mainly resulted from differences in 3 parameters out of 5. Clustering also concluded to two clusters, however with a fpc value which was much higher than that of the other drugs meaning that the clusters were more distinct. Repeating CV analysis on the patients within each cluster allowed for an important drop in inter-subject variability as mean parameter CVs were equal to 140.06% in the total population and to 64.04% and 28.76% in each cluster.

The measure of inter-patient variability could be interpreted as indicators of the need for personalisation as high differences between subjects implies high potential benefit of drug administration personalisation. Here, we demonstrated that the PK of all three considered drugs displayed important inter-subject variability. Even in this small cohort of patients, a posteriori patient clustering according to their PK parameters allowed for a dramatic decrease in inter-subject variability within each subgroup, especially for 5-fluorouracil. The remaining clinical challenge lays in determining clinical biomarkers for stratifying patients before drug administration, in order to reach the intended plasma PK levels. In order to do so, we performed semi-physiological analyses and identified 4 critical PK parameters for irinotecan and 3 parameters for 5-fluorouracil, while the study for oxaliplatin did not provide clear conclusions. For irinotecan, SN38 clearance parameter which accounted for SN38 deactivation into SN38G though UGT enzymes displayed large inter-patient variability. This is in agreement with several pharmacogenetics studies demonstrating the existence of several polymorphisms in the gene UGT1A1 which were associated with decreased SN38 plasma levels [27].

5 Conclusion

In conclusion, a mathematical framework was designed to allow for accurate analysis of patient PK data. A model of the dynamics of the drug solution from the pump to the patient's blood was designed, irrespective of the drug delivery device. It was

used to represent the chronomodulated drug administration though the Mélodie® infusion pump into the patient hepatic artery of irinotecan, oxaliplatin and 5-fluorouracil. The model revealed significant inconsistencies between the drug profiles programmed into the pump which corresponded to the drug exposure intended by clinicians and the actual plasma PK levels. Importantly, it allowed for the design of innovative drug infusion profiles to be programmed into the pump to precisely achieve the desired drug delivery into the patient's blood. Next, the pump-to-patient model was connected to semi-physiological models of the PK of irinotecan, oxaliplatin and 5-fluorouracil. The overall framework achieved a very good fit to data and gave insights into inter-patient variability in the PK of each drug. Potential clinical biomarkers for treatment personalisation were suggested although further investigations in larger cohorts of patients are required. Overall, this complete framework informs on drug delivery dynamics and patient-specific PK of irinotecan, oxaliplatin and 5-fluorouracil towards precise and personalized administration of these drugs.

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