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Short title: infliximab standardized doses in inflammatory bowel disease

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Abbreviations:

IFX: infliximab

UC: ulcerative colitis

IBD: Inflammatory bowel disease

DB: dose banding

WBD: weight-based doses

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Background

According to infliximab (IFX) license in Crohn's disease (CD), infusion doses are based on patient's body-weight. Dose banding providing standardized doses (SD) has been implemented in parenteral chemotherapy in order to optimize aseptic unit capacity and reduce drug expenditure, duration of hospital stay and costs without decreasing efficacy.

Material and method

The first part was a single-center retrospective analysis of consecutive CD patients receiving IFX maintenance therapy to determine standardized doses covering more than 50% of infusions. The second part was a prospective cohort study assessing the impact of SD compared to body-weight doses (BWD) on admission duration and costs.

Results

Six IFX SD covering more than 90% of infusion doses were implemented for dose banding. According to the Monte-Carlo simulation, there was no significant difference between IFX SD and BWD maintenance regimens. When assessed prospectively in 116 patients (75 patients treated with SD and 41 with BWD) corresponding to 128 infusions, hospitalization duration was shortened by 70 minutes per patient ($p<0.001$).

Conclusion

According to a pharmacokinetic model, IFX SD has a pharmacokinetic profile close to BWD and is associated with reduced length of hospitalization in a cohort of patients with CD. IFX SD implementation could optimize infusion units functioning and, save time and costs without decreasing efficacy.

Introduction

Infliximab (IFX) is a chimeric monoclonal antibody targeting tumor necrosis factor alpha (TNFα). Its efficacy has been demonstrated in inflammatory bowel disease (IBD), namely Crohn's disease (CD) and ulcerative colitis (UC), for induction and maintenance of clinical remission and mucosal healing, perianal fistulas closing as well as the need for surgery and hospitalization [1,2]. According to drug license, IFX is started with an induction regimen of 5mg/kg infusions administered at weeks 0, 2, and 6, followed by 5 mg/kg infusions every 8 weeks[3]. In case of insufficient clinical benefit or loss of response, IFX treatment can be optimized by increasing the dose and/or shortening the intervals between two infusions[4,5].

In daily practice, individualized doses of IFX are often prepared in a pharmacy unit according to the exact dose in mg/kg after clinical evaluation by the physician. A quantitative and qualitative control is performed before drug transportation to the infusion unit to ensure quality. Centralized handling and dispensing of IFX infusions to outpatient units is challenging for the pharmacy unit in order to decrease patient's waiting time[6]. Reducing the duration of patient's stay in the unit is relevant to improve patient satisfaction[7].

In recent years, hospitals have implemented dose banding for cytotoxic preparations. This system was defined by Plumridge et al. as "a system whereby trough agreement between prescribers and pharmacists, doses of drug calculated on an individualized basis are grouped into defined ranges or bands. Doses are rounded up or down to predetermined standard doses"[8]. In the beginning, standardized doses were applied to cytotoxic chemotherapy with no significant increase in inter-individual plasma exposure[9]. The main advantage of dose banding is anticipating infusion preparation using standardized doses before patient's arrival. This could help not only to decrease duration of patient's stay, but also to improve the

capacity planning of both pharmacy and outpatient unit. Moreover, standardized doses of cytotoxic chemotherapy were associated with reduction of drug wastage[10].

Regarding pharmacokinetics, standard IFX maintenance dosing of 5 mg/kg every 8 weeks results in a wide variation of drug exposure in patients and does not consistently achieve trough concentrations above 3-5 µg/mL, which is usually considered as the adequate therapeutic target for clinical remission[11]. Previous published pharmacokinetic models have shown that body weight is only one among many variables influencing IFX trough levels: gender, age, albuminemia, concomitant immunosuppressants or presence of antibodies to infliximab also influence drug concentrations[12]. Relationship between IFX clearance and body weight is not linear: clearance per kilogram decreases when the body weight increases[12,13].

We hypothesized that IFX standardized doses provide a similar pharmacokinetic profile compared to body-weight doses in CD patients receiving maintenance therapy. The aims of the present study were to define several IFX standardized doses and then after implementation, to compare them to body-weight doses on both hospital stay duration and costs.

Material and methods

Determination of IFX doses bands

The first step of the present study consisted in a retrospective analysis of all consecutive CD patients who received IFX as maintenance therapy from January to December 2016 in the gastroenterology unit of Centre Hospitalier Universitaire de Bordeaux (France), to evaluate the number of infusions prescribed according to patients' body weight and their distribution in mg. The objective was to determine a maximum of six standardized pre-established IFX doses covering at least 60% of infusions administered during the study period, with a maximal variation of 15% as compared to body-weight doses as published in logarithmic dosing scale[14].

Monte-Carlo Simulation

The Monte-Carlo simulation was conducted using the last model reported in CD to compare the predicted pharmacokinetic profile after administration of IFX standardized doses or body-weight doses[13]. Monte-Carlo simulation is as a computer-based mathematical construction able to 'expand' the sample size of a study to provide predictions of the likely result on different therapeutic approaches. Monte-Carlo simulation provides information on pharmacokinetic variability across the population. The model was previously developed from the 580 CD patients randomized in the ACCENT-1 trial[1]. The simulation was conducted for 2 000 simulated naïve patients receiving IFX during the first year of treatment, corresponding to eight infusions administered at weeks 0, 2, 6, 14, 22, 30, 38 and 46. One thousand naïve subjects were included in each group using the following baseline characteristics: age, sex, weight, albumin level, and concomitant use of immunomodulation therapy. Anti-Infliximab antibodies (ATI) were considered negative for all naïve patients. Variables were assumed to

follow either normal or lognormal distributions. Median, range and standard deviation were equal to those reported in the ACCENT-1 trial[1].

The final model consisted of two-compartment model defined in terms of central and peripheral distribution volumes (Vc and Vp, respectively), as well as distributional and plasma clearances (Q and CL, respectively). For the IBD model, clearance was influenced by body weight, serum albumin level and ATI status, while central and peripheral distributions were only influenced by weight. The equations of the population parameters published in this model are[1]:

- $\mathrm{Cl\ (ml/kg/day)} = 5.42 \cdot \left(\frac{\mathrm{WGT}}{65}\right)^{-0,313} \cdot \left(\frac{\mathrm{ALB}}{4.1}\right)^{-0,855} \cdot 1.292^{\mathrm{ATI}} \cdot 0.863^{\mathrm{IMM}}$
- $\mathrm{V_1\ (ml)} = 52.4 \cdot \left(\frac{\mathrm{WGT}}{65}\right)^{-0,233}$
- $\mathrm{V_2\ (ml)} = 19.6 \cdot \left(\frac{\mathrm{WGT}}{65}\right)^{-0,588}$
- $\mathrm{Q\ (ml/day)} = 2.26$

(WGT: patient weight (kg); ALB: serum albumin level (g/dl); IMM: 1 in patient receiving concomitant immunomodulation therapy and 0 in patient not receiving concomitant immunomodulation therapy; anti-infliximab antibody (ATI): 1 in patients with detectable anti-IFX antibodies and 0 in those without detectable antibodies).

Results of the simulation of both dosing strategies were compared for the induction (the first three infusions) and the maintenance period (the five remaining). Outcomes for both periods were presented as follows:

i) concentration-time profile (c-t) distribution : 95th (2.5-97.5th) percentile intervals of the c-t profile;

ii) distribution of the area under the curve (AUC) of serum concentrations calculated by integration of the concentration-time curve by the trapezoidal method;

iii) serum concentration:

- maximum concentration (Cmax), defined as the peak concentration of infliximab, after the third infusion (end of the IFX induction at week 6) and the 8th infusion (end of the first year of treatment, week 46),
- IFX residual concentration, defined as a concentration minimum (Cmin) = 3 µg/mL, and percent of patients who had had a IFX trough levels > 3 µg/ml, before the fourth infusion (end of the induction period) and before the 9th infusion (end of the first year of treatment). IFX trough level > 3 µg/mL was associated with decrease of treatment failure[15].

Direct drug costs

The cost of each IFX infusion administered in 2016 for each individual patient was compared to the theoretical price of the corresponding standardized dose during the same period, using the French reference price of IFX at this time. In March 2016, the cost of one 100 mg IFX vial was 382.275 €. For each infusion, we assumed that vial sharing was realized.

Impact of IFX SD implementation

A prospective, case-control study was conducted in our unit from February 1st to March 31st 2017 after implementation of IFX standardized doses in daily practice, including all CD patients admitted for an IFX infusion as maintenance therapy. Patients receiving an IFX dose between 250 and 1000 mg were included into the standardized doses group while those having doses lower than 250mg or higher than 1000mg received body-weight doses (control group).

In the standardized doses group, drug preparation was anticipated by the pharmacy unit (treatment validation and preparation at the pharmacy, delivery to the gastroenterology unit before patient admission) and was administered immediately after clinical validation. In the body-weight doses group, the treatment was prepared after clinical validation including weight assessment and sent to the clinical unit. Patients were analysed only if exact hospital stay duration could be measured in minutes.

Statistical analysis

Statistical analysis was performed with R software. The comparison between both dosing strategies was performed using paired Student's t-tests. A p-value < 0.05 was considered as a significant difference. Monte-Carlo simulation was conducted using the SIMULX® software developed by INRIA and marketed by the LIXOFT® company.

The study protocol follows ethical guidelines and was approved by the local ethic committee of Bordeaux University Hospital (number: CE-GP 2019 -28).

Results

Determination of the IFX standardized doses

From January to December 2016, 262 CD patients have been treated by IFX maintenance therapy, corresponding to 1290 infusions (figure 1): 946 (73.3%) infusions corresponded to 5 mg/kg IFX with doses ranging from 215 to 628 mg including 851 (90%) doses between 250 and 500 mg. For the 344 (26.7%) infusions administered at 10 mg/kg, doses ranged from 410 to 1050 mg including 313 (91%) varied from 500 to 1000 mg.

Considering these findings, standardized doses were determined for patient's body weight between 50 kg – corresponding to 250 mg for 5mg/kg or 500 mg for 10 mg/kg – and 100 kg – corresponding to 500 mg for 5mg/kg or 1000 mg for 10 mg/kg. Using a log band scale and assuming a maximum deviation of 15%, three doses were retained in each protocol (table 1). If the dose was increased to 10 mg/kg, two bags could be administrated using the available doses in the 5 mg/kg protocol. The deviation in each band between the individual dose and the standardized doses varied from -12.5% to +12.0% and did not decrease with weight.

Monte-Carlo simulation

The comparison of the 95% concentration-time profile distribution during one year showed no difference between both dosing strategies. The ratio of concentration between both strategies throughout the period (mean distribution and extremum of the 95^{th} interval c-t profile distribution) ranged from 96% to 109%. None of the strategy tended to a better variability of c-t drug profile (figure 2).

There was no difference between the two groups concerning the AUC after infusion of standardized or bodyweight doses of IFX (p=0.96) during either induction or maintenance

periods. The median value of AUC during induction period was 158.7 [min;max = 64.8 ; 325.5] mg.h/l in the body weight doses group versus 158.9 mg.h/l [66.5 ; 350.4] in the standardized doses group. The variability (CV%) was similar in both groups (respectively 32.4% and 33.8%).

When compared to body weight doses, standardized doses did not provide any difference on peak and trough concentrations on both induction and maintenance regimens (table 2). At the end of the induction period, 29.9% of patients in the body weight doses group had a residual concentration upper than 3 µg/ml versus 30.7% in the standardized doses group. After one year of treatment, this was achieved in 22.3% of patients of the body-weight doses group versus 24.1% in the standardized doses group.

Drug costs

The actual direct cost of the 1290 IFX bodyweight doses was compared to their theoretical cost if standardized doses had been applied: the average cost of one bodyweight infusion was 1 882 € and would have been 1 888€ using standardized doses. Among the whole cohort, annual cumulative IFX cost difference between both strategies in 2016 would have been 5 188 € in favour of body-weight doses, corresponding to less than 0.3% of the annual IFX expenditure (p=0.59) (Table 3).

Impact of IFX standardized dose implementation

From February 1st to March 31st 2017, among the 262 CD patients treated by IFX in our unit, 116 (51M/65F; median age: 41 years) were included into the case-control study (75 in the standardized dose group and 41 in the body-weight dose group), corresponding to 128 infusions (84 in standardized dose group and 44 in body-weight dose group). Mean duration of stay in the unit (± standard deviation) was 238 ± 21 minutes in the standardized dose group compared to 308 ± 32 min in the body-weight dose group (p<0.001). The reduction of

admission stay in the standardized dose group was mainly related to the decrease waiting time between clinical assessment and the onset of infusion: 16 min versus 84 min with body-weight doses ($p<0.001$).

Discussion

Few data are available so far on dose banding with biologics in IBD, especially with IFX. In the present study, the modelization of two IFX regimens in simulated naïve CD patients, one based on body weight and the other on six banding doses, did not show any difference. The model demonstrated that, as compared to a WBD strategy, the prescription of IFX with six banding doses did not significantly change the concentration-time profile distribution, the AUC and the serum concentration. Pharmacokinetic models are powerful tools that can help to understand variations in exposure in a patient population[16,17]. Clearance of monoclonal antibodies is influenced by multiple other factors than weight including concomitant immunosuppressive agents use, gender, serum albumin concentration and inflammatory burden[18,19]. In patients admitted with severe colitis treated with IFX, a faecal loss of the drug has also been reported[20]. Moreover, it has been suggested that the binding of anti-TNF to the membrane-bound TNF in IBD is one of the main predictor of clinical response[21]. Given the complexity of predicting the clinical and pharmacokinetic response to anti-TNF therapy, mainly with IFX, our study further confirms that body weight is not a major parameter to determine serum concentration.

Among anti-TNF agents used in IBD, IFX is the only one administered according to body weight. Adalimumab is given at a fixed dose every two weeks, and golimumab has only two maintenance regimens according the EMA license (50 mg every 4 weeks in patients with body weight below 80 kg, and 100 mg every for weeks above 80 kg). More recently available biologic agents with other mode of action, such as vedolizumab, are also delivered with a fixed dose. Recently, phase I/III trials conducted both in rheumatology and gastroenterology have focused on a new CT-P13 (infliximab biosimilar) formulation delivered subcutaneously [22,23]. Importantly, only three infliximab doses have been evaluated: 90, 120 and 180 mg in rheumatoid arthritis and 120, 180 and 240 mg in Crohn's disease. In both indications, efficacy

and safety results at one year were not different between patients who received subcutaneous and intravenous CT-P13. Moreover, the mean serum concentrations in all subcutaneous cohorts consistently exceeded the threshold of target therapeutic concentration.

Using IFX dose banding is also probably associated with more simple and faster procedures in the pharmacy unit leading to shortened patient's stay duration in infusion unit. The time savings theoretically induced by DB should be taken into account for the hospital's organization and patient's quality of life.

Costs have become a key issue in IBD and biologics represent now a major part of the overall costs of the disease [24]. The development of IFX biosimilars has dramatically change the economic model and the relationship between institutions and health care systems. Controlled studies conducted in IBD have confirmed those performed in rheumatology showing that IFX biosimilars have similar efficacy, safety and immunologic profiles than the princeps[25].

In conclusion, according to a modelization model, a similar pharmacokinetic profile is obtained with IFX dose banding compared to weight-based dosing of the drug. Dose banding provides a cost-effective approach with several advantages over weight-based dosing, including a simplified process of infusion preparation, an optimized hospital organisation, and a shortened time spent in the infusion unit.

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Tables

Table 1. Infliximab dose banding table based on the retrospective analysis of 262 CD patients corresponding to 1290 infusions administered from January to December 2016

Infliximab dose regimen	Weight [Range] (kg)	Prescribed dose [Range] (mg)	Given dose (mg)	Variance [below; above] (%)
5 mg/kg	[50 ; 62]	[250 ; 314]	275	[-12.4 ; 10.0%]
	[62.2 ; 79]	[315 ; 399]	350	[-12.3% ; 11.1%]
	[79.2 ; 100]	[400 ; 500]	450	[-12.5% ; 10.0%]
10 mg/kg	[50 ; 62]	[501 ; 620]	550	[-11.2 ; 9.8%]
	[62.2 ; 79]	[621 ; 790]	700	[-11.4% ; 12.7%]
	[79.2; 100]	[791 ; 1000]	900	[-10.0% ; 13.8%]

Table 2. Comparison of serum concentration of IFX using the both dosing strategy according to the Monte-Carlo simulation model.

		Induction period			**Maintenance period**		
		WBD	SD	t-test (p)	WBD	SD	t-test (p)
Peak	**mean**	**104.63**	**104.28**	**0.64**	**86.91**	**86.61**	**0.67**
concentration	+/- sd	10.88	12.42		5.72	7.51	
(µg/ml)	median	103.40	103.46		86.39	86.17	
	CV (%)	10.40 %	11.91 %		6.58 %	8.7 %	
Trough	**mean**	**2.88**	**2.94**	**0.76**	**2.22**	**2.28**	**0.77**
concentration	+/- sd	3.17	3.24		2.40	2.44	
(µg/ml)	median	1.73	1.68		1.42	1.39	
	CV (%)	110 %	110.2%		108.1 %	107.01%	

Table 3. Comparison of infliximab direct costs for estimated standardized doses and bodyweight-based doses (WBD) infusions in the whole cohort .

Weight-based dose			Standardized dose		
Prescribed dose (mg)	Infusion (n)	Direct drug cost (€)	Given dose (mg)	Infusion (n)	Direct drug cost (€)
[250 ; 310]	224	*243 374 €*	275	224	*236 395 €*
[311 ; 395]	306	*408 321 €*	350	306	*410 270 €*
[396 ; 500]	314	*533 027 €*	450	314	*541 417 €*
[501 ; 620]	143	*306 488 €*	550	143	*300 657 €*
[621; 799]	110	*297 054 €*	700	110	*293 768 €*
[801 ; 1000]	93	*308 401 €*	900	93	*318 646 €*
Total	**1190**	**2 239 672 €**	**Total**	**1190**	**2 244 860 €**

Figure legends:

Figure 1. Distribution of the 1290 prescribed doses of infliximab (5 mg/kg) produced during one year.

Figure 2. Comparison of the 95th percentile concentration time profile between weight-based dosing (c-t profile WBD) and dose banding (c-t profile DB).

Figure 1

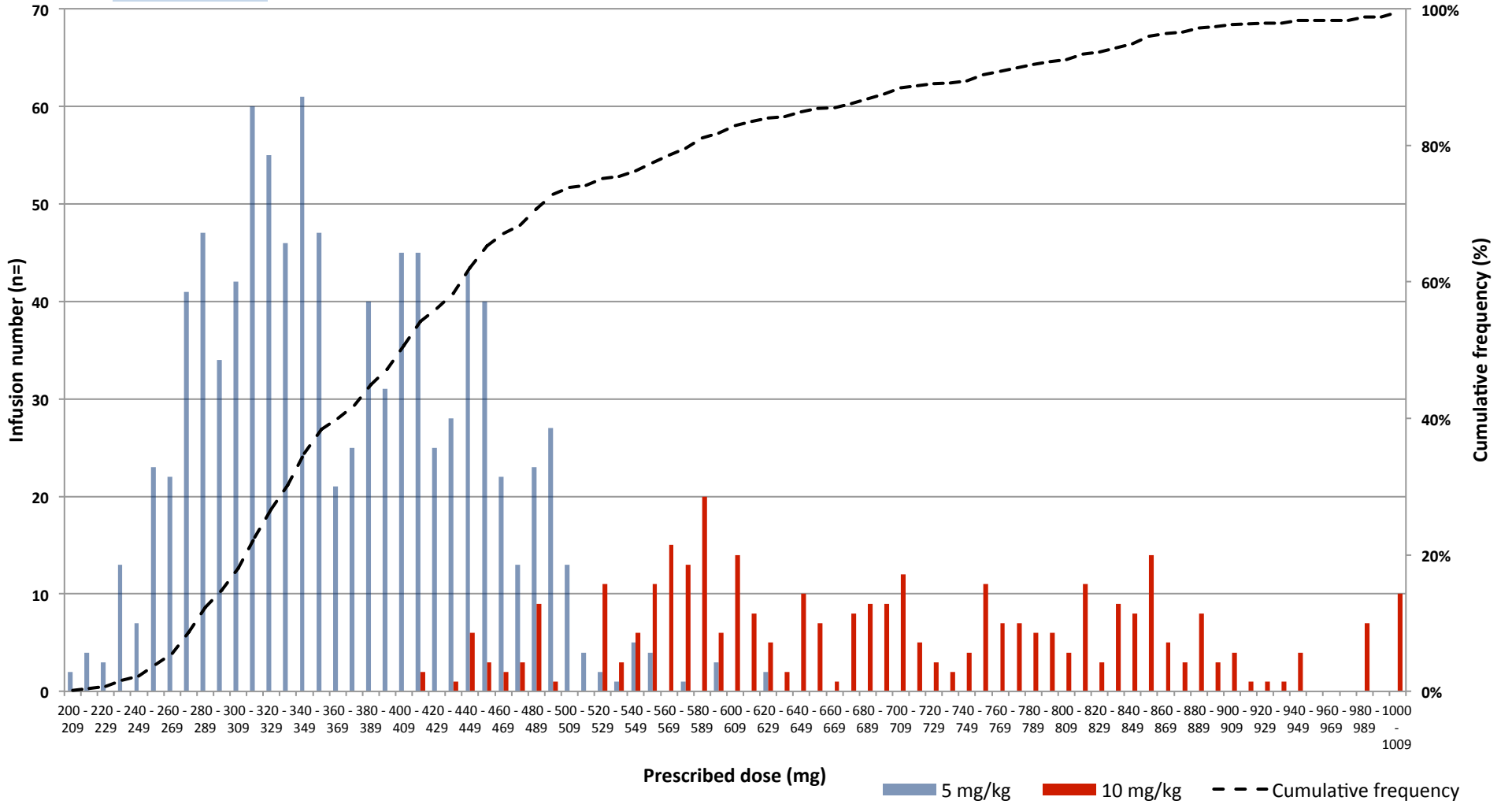
Infusion number (n=)
Cumulative frequency (%)
70
60
50
40
30
20
10
0
100%
80%
60%
40%
20%
0%
200 - 209
220 - 229
240 - 249
260 - 269
280 - 289
300 - 309
320 - 329
340 - 349
360 - 369
380 - 389
400 - 409
420 - 429
440 - 449
460 - 469
480 - 489
500 - 509
520 - 529
540 - 549
560 - 569
580 - 589
600 - 609
620 - 629
640 - 649
660 - 669
680 - 689
700 - 709
720 - 729
740 - 749
760 - 769
780 - 789
800 - 809
820 - 829
840 - 849
860 - 869
880 - 889
900 - 909
920 - 929
940 - 949
960 - 969
980 - 989
1000 - 1009
Prescribed dose (mg)
5 mg/kg
10 mg/kg
Cumulative frequency

Figure 2

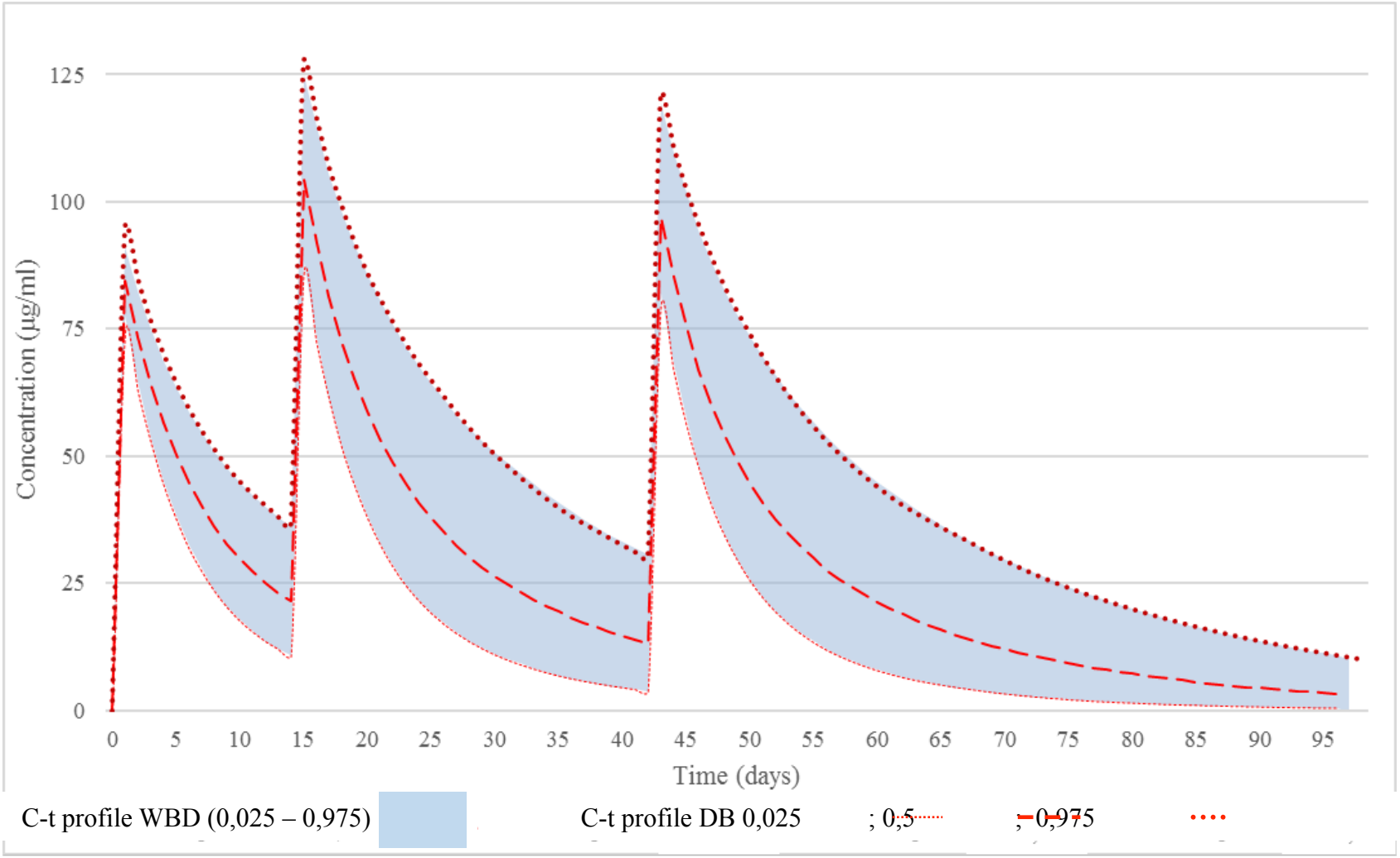

Figure 5. Comparison of the 95th percentile concentration time profile between dose base weight dosing (c-t profile WBD) versus dose banding dosing (c-t profile DB)