

Personalized Dosage Regimen of Ceftazidime-Tazobactam (Cef-Taz) 复方抗生素他他®的个性化给药方案

洪楠方¹
陈子嘉¹

¹Honz Research Institute of Pharmacometrics and Industrial Engineering
(honzresearch.github.io)

Zhengzhou, November 27, 2020



Motivation

Conflict of Interest

This research was sponsored by Honz Pharma Group.



Figure 1: 康芝药业的他他®是头孢他啶（Ceftazidime）、他唑巴坦钠（Tazobactam Sodium）按质量比3:1制成的注射用复方制剂



目录

1 Summary

2 Method

3 Q&A



目录

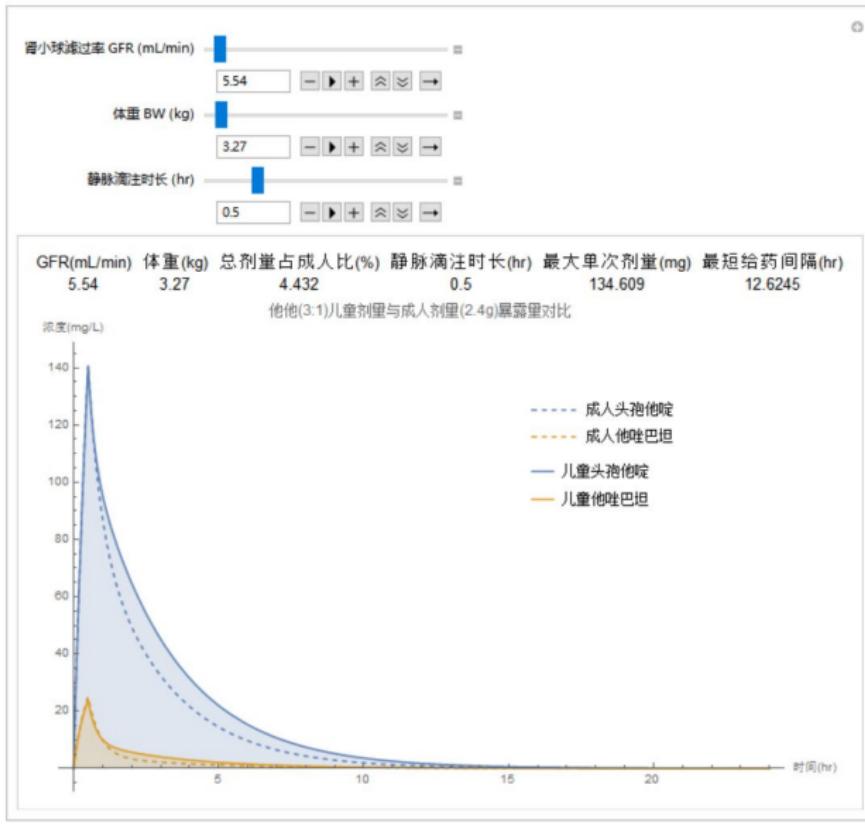
1 Summary

2 Method

3 Q&A



Dosing App



Result

We derived **maximal single dose** and **minimal dosing interval** of Cef-Taz for different patients with various **intended infusion duration time**. Scan QR code to try our **WebApp** with ease!

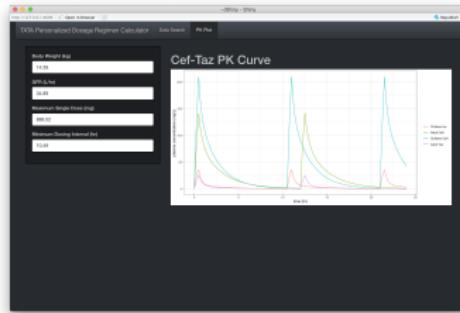


Figure 2: Cef-Taz Dosing App



目录

1 Summary

2 Method

3 Q&A



Method

参数	单位	单Cef	复Cef	单Taz	复Taz
V1	L	9.45		14.8	
V2	L	4.79		24.7	
Q	L/hr	7.07		13.1	
CL	L/hr	6.73	6.44	20.8	19.3

Table 1: 他他®群体PK分析结果



Method

$$\text{CL} = \text{CL}_R = (\text{GFR} \cdot f_{u,p} + \overbrace{\text{CL}_{\text{Active Secretion}}}^0)(1 - F_R) \quad (1)$$

$$= \text{GFR} \cdot \overbrace{f_{u,p} \cdot (1 - F_R)}^{\text{constant}} \quad (2)$$

$$\propto \text{GFR} \quad (3)$$

Personalized PK Parameters

- $V \propto BW$
- $Q \propto BW^{0.75}$
- $CL \propto GFR$



Method

$$\text{总剂量} = \text{AUC} \cdot \text{CL} \quad (4)$$

$$\propto \overbrace{\text{AUC}}^{\text{constant}} \cdot \text{GFR} \quad (5)$$

$$\propto \text{GFR} \quad (6)$$



Personalized Dosage Regimen

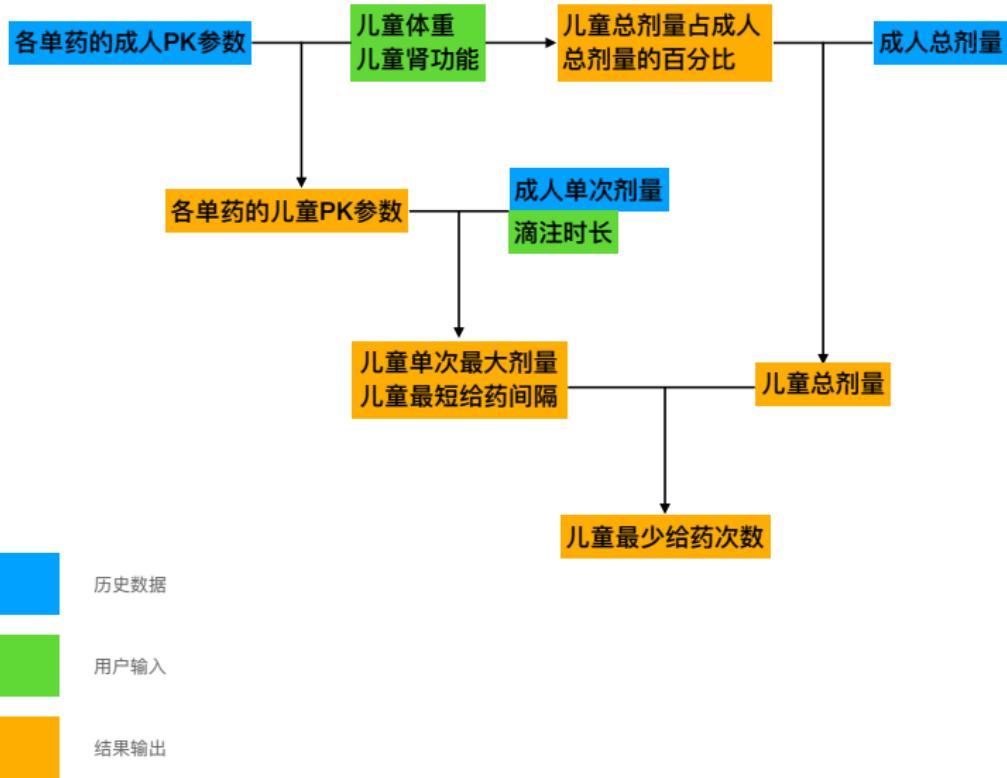
给定静脉滴注时长，计算最大单次剂量和最短给药间隔，使得各组分同时满足

$$1\% \leq \frac{C_p}{C_{p,\max}} \leq 100\% \quad (7)$$

并求得最少给药次数：

$$\left\lceil \frac{\text{总剂量}}{\text{最大单次剂量}} \right\rceil \quad (8)$$

Workflow Summary



Acknowledgment

感谢刘东阳师兄
感谢陈子嘉同事



Figure 3: 陈子嘉在Bechstein D-282上弹奏Rachmaninov、Liszt、Chopin

目录

1 Summary

2 Method

3 Q&A



Hypothesis

- Cef和Taz在药用剂量范围内PK均呈线性[Auclair and Ducharme (1999); Sy et al. (2019)]
- Cef完全从肾以原形排泄[Welage et al. (1984)]。Taz有80%从肾以原形排泄[Carpenter et al. (2017)]，另有20%被代谢为无药物活性的水解代谢物M1[Derendorf and Dalla (1996)]。在肾排泄过程中，OAT1转运体被Cef与Taz所共用[Jariyawat et al. (1999); Wen et al. (2018)]，因此Cef与Taz的复方清除率可能会因为竞争作用低于单方清除率。
- 我们采集了12名中国受试者（平均体重61.58kg，平均年龄22.42岁，平均身高172.5厘米）单方Cef 1800mg、单方Taz 600mg、复方Cef 1800mg + Taz 600mg的PK数据。为了探究Cef和Taz的药物相互作用，二房室模型的 V_1 、 V_2 、 Q 由单、复方PK数据同时拟合，而 CL 由单、复方PK数据各自拟合。



Hypothesis

- 假设Cef和Taz的表观分布容积并不因为单复方而有差异，其单复方的PK差异仅仅是因为共用排泄转运体所致，则我们群体PK结果显示，Cef与Taz的复方清除率确实略微低于单方清除率。我们可以进一步假设Cef和Taz全部由肾小球滤过排泄[Shi et al. (2018)]
- 由于Cef和Taz没有参与肾主动分泌过程（见FDA批准的Ceptaz[®]说明书），因此 $CL_{Active\ Secretion} = 0$
- 而Cef和Taz的血浆蛋白结合率都不高（分别为5-23%和20-23%），因此虽然新生儿和婴幼儿的血浆总蛋白较成年人为低，但该因素对本品的PK影响不大，可以假设 $f_{u,p}$ 不变
- Cef的重吸收在药用剂量范围内可以忽略[Verhagen et al. (1994)]，Taz未见报道有重吸收，可以假设 $(1 - F_R)$ 不变



Hypothesis

- Zong and Li (2013)整理了中国儿童（0-18岁）各性别、各年龄的体重分布。假定18岁以后体重为恒定值，由于12例受试皆为男性，因此取18岁男性体重中位数61.4kg为参照点

$$V_{\text{儿童}} = V \cdot \frac{BW}{61.4} \quad Q_{\text{儿童}} = Q \cdot \left(\frac{BW}{61.4} \right)^{0.75} \quad (9)$$

- Pottel et al. (2010)拟合了比利时儿童（中国儿童的数据未见报道）的各年龄GFR中位数（0-14岁），得出：

$$GFR_{\text{儿童}} = \begin{cases} 1.45 \cdot \text{Month} + 5.54 & (0-11 \text{ months}) \\ 5.33 \cdot \text{Age} + 18.9 & (1-14 \text{ years}) \end{cases} \quad (10)$$

我们假定上式也适用于中国儿童（0-20岁），假定上式可以外推至20岁时的125 mL/min，且20岁以后恒定不变，且GFR全年龄段男女之间的差异可忽略不计(Fenton et al. (2018))



GFR for Kidney Damage I

Liao et al. (2011)提到针对中国人MDRD公式，可根据血清肌酐浓度Scr (mg/dL)、年龄Age (yrs)，计算肾小球滤过率GFR (mL/min)：

$$GFR = \begin{cases} 175 \cdot Scr^{-1.234} \cdot Age^{-0.179} \cdot 0.79 & \text{if male} \\ 206 \cdot Scr^{-1.234} \cdot Age^{-0.227} \cdot 0.803 & \text{if female} \end{cases} \quad (11)$$

Cockcroft and Gault (1976)提出通过血清肌酐浓度Scr (mg/dL)、年龄Age (yrs)、体重BW (kg)，计算肌酐清除率Ccr (mL/min)的公式：

$$Ccr = \begin{cases} \frac{(140 - Age) \cdot BW}{72 \cdot Scr} & \text{if male} \\ \frac{(140 - Age) \cdot BW}{72 \cdot Scr} \cdot 0.85 & \text{if female} \end{cases} \quad (12)$$



GFR for Kidney Damage II

两式联立，可通过年龄Age (yrs)、体重BW (kg)、GFR (mL/min)，计算Ccr (mL/min)，取两位有效数字：

$$C_{cr} = \begin{cases} \frac{GFR^{0.81} \cdot (140 - Age) \cdot BW}{3909} \cdot Age^{0.145} & \text{if male} \\ \frac{GFR^{0.81} \cdot (140 - Age) \cdot BW}{3909} \cdot Age^{0.184} \cdot 0.735 & \text{if female} \end{cases} \quad (13)$$

当病患需要获得更精确的GFR值，尤其是对于肾功能受损人群时，可通过此公式转换。



References I

- Auclair, B. and Ducharme, M. P. (1999). Piperacillin and tazobactam exhibit linear pharmacokinetics after multiple standard clinical doses. *Antimicrobial agents and chemotherapy*, 43(6):1465–1468.
- Carpenter, J. W., Tully Jr, T. N., Gehring, R., and Guzman, D. S.-M. (2017). Single-dose pharmacokinetics of piperacillin/tazobactam in hispaniolan amazon parrots (*amazona ventralis*). *Journal of avian medicine and surgery*, 31(2):95–101.
- Cockcroft, D. W. and Gault, H. (1976). Prediction of creatinine clearance from serum creatinine. *Nephron*, 16(1):31–41.
- Derendorf, H. and Dalla, T. C. (1996). Pharmacokinetics of piperacillin, tazobactam and its metabolite in renal impairment. *International journal of clinical pharmacology and therapeutics*, 34(11):482–488.



References II

- Fenton, A., Montgomery, E., Nightingale, P., Peters, A. M., Sheerin, N., Wroe, A. C., and Lipkin, G. W. (2018). Glomerular filtration rate: new age-and gender-specific reference ranges and thresholds for living kidney donation. *BMC nephrology*, 19(1):1–8.
- Jariyawat, S., Sekine, T., Takeda, M., Apiwattanakul, N., Kanai, Y., Sophasan, S., and Endou, H. (1999). The interaction and transport of β -lactam antibiotics with the cloned rat renal organic anion transporter 1. *Journal of Pharmacology and Experimental Therapeutics*, 290(2):672–677.
- Liao, Y., Liao, W., Liu, J., Xu, G., and Zeng, R. (2011). Assessment of the ckd-epi equation to estimate glomerular filtration rate in adults from a chinese ckd population. *Journal of International Medical Research*, 39(6):2273–2280.



References III

- Pottel, H., Mottaghy, F. M., Zaman, Z., and Martens, F. (2010). On the relationship between glomerular filtration rate and serum creatinine in children. *Pediatric nephrology*, 25(5):927–934.
- Shi, Z.-R., Chen, X.-K., Tian, L.-Y., Wang, Y.-K., Zhang, G.-Y., Dong, L., Jirasomprasert, T., Jacqz-Aigrain, E., and Zhao, W. (2018). Population pharmacokinetics and dosing optimization of ceftazidime in infants. *Antimicrobial agents and chemotherapy*, 62(4).
- Sy, S. K., Zhuang, L., Sy, S., and Derendorf, H. (2019). Clinical pharmacokinetics and pharmacodynamics of ceftazidime–avibactam combination: a model-informed strategy for its clinical development. *Clinical pharmacokinetics*, 58(5):545–564.
- Verhagen, C., Mattie, H., and Van Strijen, E. (1994). The renal clearance of cefuroxime and ceftazidime and the effect of probenecid on their tubular excretion. *British journal of clinical pharmacology*, 37(2):193–197.



References IV

- Welage, L. S., Schultz, R. W., and Schentag, J. (1984). Pharmacokinetics of ceftazidime in patients with renal insufficiency. *Antimicrobial agents and chemotherapy*, 25(2):201–204.
- Wen, S., Wang, C., Duan, Y., Huo, X., Meng, Q., Liu, Z., Yang, S., Zhu, Y., Sun, H., Ma, X., et al. (2018). Oat1 and oat3 also mediate the drug-drug interaction between piperacillin and tazobactam. *International Journal of Pharmaceutics*, 537(1-2):172–182.
- Zong, X.-N. and Li, H. (2013). Construction of a new growth references for china based on urban chinese children: comparison with the who growth standards. *PloS one*, 8(3):e59569.

