TDM improves the efficacy of cyclosporine A in aplastic anemia patients

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Scope of the lecture:
In this lecture, we will first introduce the development and current situation of TDM center in China-Japan Friendship Hospital (CJFH), and then display how clinical pharmacists cooperate with TDM staffs, recommend TDM detection and explain the results to doctors. At last, we will take cyclosporine as an example, to show the improvement effect of TDM on drug efficacy.

Learning objectives:
1. The history and current situation of TDM center of CJFH.
2. The way of communication among TDM staffs, pharmacists and doctors on TDM detection and results interpretation.
3. The necessity of TDM for cyclosporine and the improvement of TDM on efficacy of cyclosporine in anima aplastic anemia patients.

Extended abstract:
Part 1: the development and current situation of TDM center in CJFH
The TDM center in CJFH was established at the same time as the CJFH being found in the mid-1980s. Doctors and pharmacist began to pay attention to the impact of blood concentration on the drug efficacy at that time, and published some research papers.

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茶碱缓释片药代动力学及临床疗效观察
Pharmacokinetic of Theophylline Substained-Release Tablets and Its Clinical Curative Effect Observation

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内容提要 本文对支气管哮喘、喘息型支气管炎患者共43例口服茶碱缓释片后，用紫外分光光度计测定血药浓容积为28.线表现峰型对应用茶碱

Analysis of 63 cases of cyclosporine therapeutic drug monitoring data
环孢素 A血药浓度监测 63例分析

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摘要 对63例肾移植患者(男47例，女16例)术后环孢素 A全血浓度常规监测进行了统计分析，其中有26例术后发生排异反应，以第 2年为最多，其次是 4~ 12 个月。198份血样测定结果统计分析表明，术后排异反应组与无排异反应组之间给药剂量及环孢素 A血浓度存在显著性差异($P < 0.05$)，男女患者排异反应发生率有较大区别。在合并用药中，发现酮康唑能显著升高环孢素 A血浓度，与已有报道一致。

关键词 环孢素 A,血药浓度监测,排异反应,合并用药

环孢素 A(Cyclosporine A, CsA)作为一种强效免疫抑制剂，被广泛地应用在器官移植术中。CsA的血药浓度和免疫抑制作用的强度呈量效依赖关系，也和肝脏和肾脏的损害及其它一些毒性相关[1]。又因 CsA有很大的药动学个体差异，应及时监测血药浓度，以保证其治疗效果，防止发生排异反应或毒性反应。本文就我院近年来 63例肾移植患者使用 CsA监测情况做了分析，对术后排异反应及血药浓度的影响因素进行了考察。*

1 监测对象

1989年 4月至 1995年 5月在中日友好医院接受肾移植术后使用 CsA的患者 63例，男47例，女 16例，年龄 13~ 59岁，平均 34岁，原发病均为慢性肾功能不全或慢性肾炎、尿毒症。其中术后发生排异反应的 26例，每例患者常规治疗，对治疗药物没有特殊限制。

2 监测方案

2.1 监测方法 每例患者在服药前取血 2ml，放入含有抗凝剂枸橼酸钠的试管内，取 50μl全血，加 50μl细胞破碎剂，充分振摇，再加 300μl沉淀剂，摇匀后高速(10000r/min)离心 5min。

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Fig. 1 Research papers of TDM center in CJFH in the early years

Now, our TDM center has developed into one of the biggest TDM laboratories in

China，and is the supporting institute of Chinese TDM association. Our TDM team is composed of 10 staffs, and most of them have PhD or MD degree.

Fig. 2 the TDM team in CJFH

The TDM center can detect blood concentration for 26 kinds of drugs, including immunosuppressants, antiepileptic drugs, and so on. We also work on pharmacogenomic testing, and investigate effect ofgenetic polymorphism on blood concentration, efficacy, and adverse effect of drugs.

Table 1 List of major drugs detected in TDM center of CJFH

Category	**Name**				
Antibiotics	Imipenem	Meropenem	Linezolid	Teicoplanin	Vancomycin
Antiepileptic drug	Carbamazepine	Phenobarbital	Phenytoin	Valproic acid	
Antifungal drugs	Itraconazole	Voriconazole	Fluconazole		
Immunosup-pressants	Cyclosporine	Tacrolimus	Sirolimus	Mycophenolic acid	

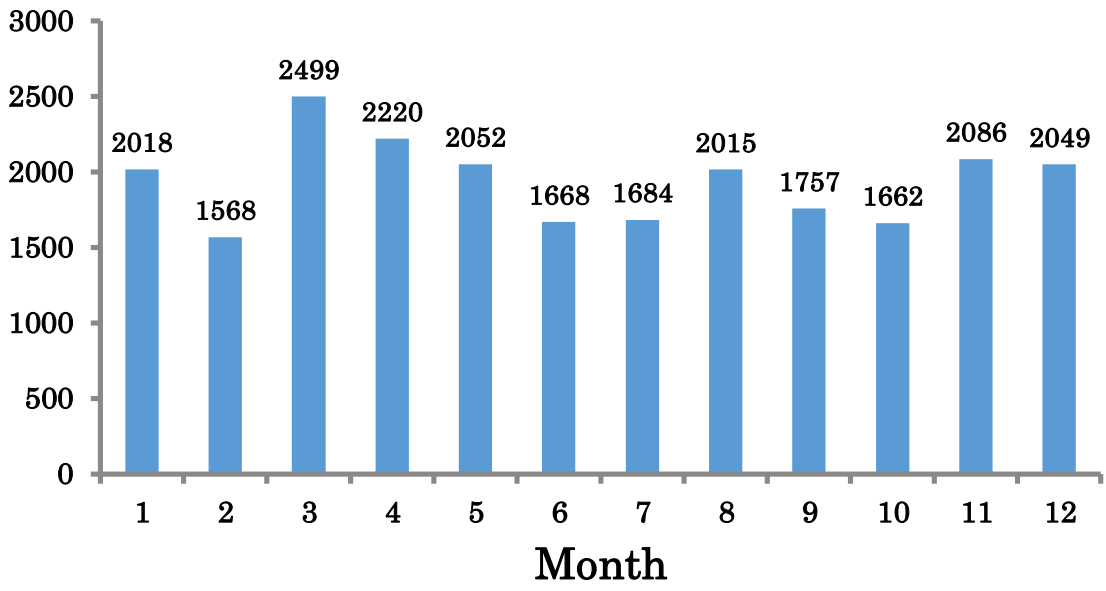

Fig. 3 Amount of TDM testing in CJHFin 2016

Part 2: Cooperation between TDM staffs and clinical pharmacists

TDM staffs in CJFH cooperate closely with clinical pharmacists to deal with problems in clinical practice. Usually, clinical pharmacists tell TDM staffs problems that clinicians encountered and then they will discuss together how to solve it. After reaching an agreement, TDM staffs will establish detection methods and blood samples from patients will be collected to detect drug concentration. Then, clinical pharmacists advise clinicians to adjust drug doses based on detection results and pharmacological parameters of drugs. The following is an example:

A lung transplant patient with poor kidney function was infected. He was treated with Piperacillin, Ganciclovir and Caspofungin, but didn't get better. The clinical pharmacist then advised the clinician to do TDM testing for the aforementioned drugs to determine whether the doses were appropriate. However, the TDM center had not yet established detection methods for these three drugs at that time. In order to acquire blood drug concentration as soon as possible, our TDM staffs established a method to detect these three drugs simultaneously within two days, and our clinical pharmacists designed dose adjustment proposals according to related guidelines and package inserts of these medications. Following dose adjustment based on TDM results, the infection symptoms disappeared and the patient was cured.

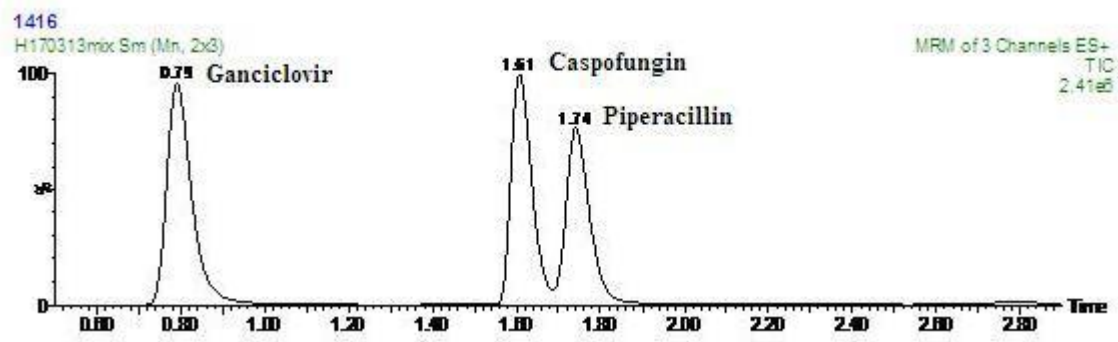

Fig. 4 Simultaneous detection of Piperacillin, Ganciclovir and Caspofungin

Part 3: TDM improves the efficacy of cyclosporine A in aplastic anemia patients

Cyclosporine A (CSA) is widely used for treating aplastic anemia (AA). An appropriate blood concentration of CSA is also required for AA patients, which is recommended to be 100–200 μg/L for trough blood levels by British Society for Haematology (Br J Haematol. 2016 Jan;172(2):187-207), and 150-250 μg/L by Chinese Society for Haematology (Chin J Hematol. 2010 Nov; 31(11):790-792).

Key recommendations for IST

- **The current standard first line IST is horse ATG (ATG-ATGAM) combined with ciclosporin (CSA). Grade 1A**
- **Immunosuppressive therapy is recommended first line therapy for non-severe AA patients requiring treatment (see indications in text), severe or very severe AA patients who lack a matched sibling donor (MSD), and severe or very severe AA patients aged >35-50 years. Grade 1A**

Fig. 5 CSA is recommended for treating AA (Br J Haematol. 2016 Jan;172(2):187-207)

Table 2 Amount of TDM cases of AA patients in CJFH among yeas

Year	No. of Patients	No. of Cases	Average cases for each patients
2011	28	98	3.50
2012	37	105	2.84
2013	36	132	3.67
2014	20	60	3.00

However, AA patients usually cannot achieve the target concentrations by using the dose of CSA recommended by package inserts. Doses adjustment based on results of TDM is required.

Table 3 Results of the first TDM testing of AA patients

Concentration (ng/mL)	No. of Cases	% of Cases	Average Concentration (ng/mL)
<150	32	46.37	79.03±43.15
150-250	23	33.33	199.43±26.04
>250	14	20.29	490.25±306.17

Our data indicated the efficacy of CSA is related with times of TDM testing in AA patients.

Table 4 Effect of times of CSA TDM testing on response rate in AA patients

Times of TDM testing	Response		None Response	% of Response
	Complete	Partial		
≤3	2	9	17	39.28
4-10	4	19	6	78.57
>10	1	7	4	66.67