Title

Appropriateness of repetitive therapeutic drug monitoring and laboratory turn around time

Running title: Appropriateness of repetitive drug monitoring

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Abbreviations

CE-IVD, conformité européenne-in vitro diagnostic

HPLC, high performance liquid chromatography

ICU, intensive care units

IQR, interquartile range

LC-MS, liquid chromatography-mass spectrometry

TAT, turn around time

TDM, therapeutic drug monitoring

Dear Editor,

Appropriateness is a pivot player for laboratory medicine, by improving the "*efficiency and efficacy in total health care*" and reducing the "*underuse, overuse, and misuse*" of the tests [1]. However, a non-negligible percentage of tests are inappropriate [2] as witnessed by several studies [3,4,5]. In particular, a time interval between two consecutive prescriptions of therapeutic drug monitoring (TDM) lesser than 5 drug half-lives (the time to achieve the steady state) can lessen TDM appropriateness. On the contrary, a careful planning of daily and weekly laboratory activities may result in a reduced turn-around-time (TAT) from sample withdrawal up to final report, even in the case of repetitive TDM prescriptions. The workplan could be based on several criteria, as well as disease severity, the need for urgent therapies (i.e., daptomycin and voriconazole for severe infections), standard treatment (amiodarone for arrythmias) or prophylactic use (levetiracetam), a narrow therapeutic interval and/or a low therapeutic index.

Therefore, we investigated whether the repetitive TDM prescription for amiodarone, daptomycin, voriconazole, and levetiracetam was appropriate in a third-level university hospital. The four drugs were chosen because they are characterized a) by a long-term prescription due to the chronic disease (i.e., amiodarone and levetiracetam) or b) by a short course due to severe infections that require a prompt and effective pharmacological intervention (daptomycin and voriconazole). Moreover, TAT of these four drugs was evaluated as a measure of efficiency of the planned laboratory activities. TDM requests for amiodarone, daptomycin, voriconazole, or levetiracetam between April 2012 and December 2016 included those for inpatients and outpatient. All TDM prescriptions and corresponding reports for amiodarone, daptomycin, levetiracetam and voriconazole were obtained from the electronic database of the Pisa University Hospital in an anonymized form, and this allowed the inclusion of all consecutive patients. Every record was a single TDM request for an individual patient regarding

one drug but it did not contain any information that could disclose patient's identity. Indeed, the query adopted for data extraction did limit the information to the drug, time of prescription and report, requesting clinical unit.

For the purposes of the present study, we adopted two definition of appropriateness. First, the repetition of TDM requests for a drug in the same patient was considered appropriate when the time interval between two consecutive requests was at least 5 half-lives of the drug. This definition may be applied to every drug regardless the nature of each possible factor affecting its pharmacokinetics. Therefore, the minimum time interval between two consecutive TDM prescriptions was set at 2 days for all drugs, with the exception of amiodarone for which the time interval was set at 5 days. Second, laboratory activities are appropriate when TDM results may promptly guide changes in drug dosage if needed. We decided that TAT was appropriate when the final report was ready within 3 days from prescription for amiodarone, daptomycin and voriconazole or 7 days for levetiracetam. Finally, the present analysis did not take into consideration delays in sample analyses and reporting due to late dispatch to our laboratory and laboratory closures for Sundays (7.3-9.6% of weekly samples were dispatched to the laboratory on Saturday), National holydays and other vacations.

Results showed that a variable percentage (range, 0.4-46.0%) of repetitive TDM prescriptions were inappropriate (Table 1), especially for amiodarone, whereas levetiracetam has the lowest inappropriateness rate. Interestingly, for each drug the highest rates of inappropriate prescriptions were recorded for inpatients, and especially for those admitted to ICUs, emergency wards, infectious disease, cardiovascular and geriatrics units. The importance of these findings relies on the mandatory role of repeated TDM to control and treat severe diseases [6]. Indeed, those differences were likely depending on factors such as disease severity, rapid changes in drug pharmacokinetics [7,8,9] and concerns about clinical outcomes (i.e., arrhythmias, endocarditis, infections in bone-marrow transplant recipients) in sharp contrast

with drugs usually prescribed for long-term treatment and prophylaxis, admission to an ICU instead of an ambulatory, or different access to TDM facilities (inpatients *vs*. outpatients). Noteworthy, the inclusion of specific rules (based on the adequate time interval between two consecutive TDM prescriptions) within the electronic prescribing system may help in increasing the appropriateness of TDM requests, as already implemented at our hospital for other laboratory tests.

The analysis of TAT for the 4 drugs clearly showed 3 different reporting rates. Amiodarone had the highest rates, with 95.1% of reports signed within the next day of blood withdrawal (Figure 1). This feature is mainly due to the availability of a HPLC instrument dedicated to amiodarone TDM from Monday to Saturday. The two antimicrobial drugs had superimposable rates of reporting, especially on the same day (43-44.7%) and within 72 h (92-93.9%) from blood collection. At difference with amiodarone, the analysis of daptomycin and voriconazole plasma levels are performed thrice a week (Monday, Wednesday and Friday), but this plan allows the final reporting of more than 90% of requests within 72 h. Finally, levetiracetam TDM request should be finalized within 7 days from blood withdrawal because the drug is prescribed to prevent seizures, and the reporting rate is the lowest among those analysed (Figure 1). However, the current workplan seems to be adequate to report those TDM requests (14.9% of the total) coming from ICUs. Indeed, 83.2% of final reports were available within 3 days.

The discussion of the present results brings to consider the knowledge of drug pharmacokinetics and the analysis of TAT as important bases to rationalize TDM prescriptions and to improve laboratory activities. In particular, TAT values can refine daily and weekly workload, as the present data may suggest. Indeed, our weekly agenda seems to be appropriate because two resident technicians working 6 days a week (8 AM-3 PM) are capable to analyse approximately 80% of the samples within the next 48 h from TDM prescription regardless the drug. It is likely that 4 daily sessions per week (whatever the drug could be) could probably ensure a 24-h

reporting rate of about 80% or more in most cases. Moreover, this kind of analyses could help in the choice of instrumental platforms (i.e., immunometric or chromatographic instruments) depending on the units of personnel within the laboratory, the need for time-consuming preanalytical processing of samples, the number of samples and, hence, the need of a high process automation (i.e., robotic handling systems).

In conclusion, the percentage of inappropriate repetitive prescriptions is variable and may depend on several factors, such as disease severity and patient's health status. In order to increase the appropriateness of TDM requests, the Clinical Pharmacology Unit is now involved in hospital staff meetings, and future analyses will inform us about the efficacy of these educational meetings [10]. Together with a better definition of which drug needs a more frequent repetitive TDM protocol, the present findings may help in a better planning of daily activities in order to offer an efficient service to patients and caregivers.

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Table 1. Patients, total and repetitive prescriptions of therapeutic monitoring (TDM) for the four listed drugs are presented, together with median and interquartile range (IQR) values of time elapsed (in days) between two consecutive prescriptions. The percentage of inappropriate repetitive testing is also ahown for each drug

Drug		Total	Repetitive TDM	
			Inpatients	Outpatients
Amiodarone	Patients (n)	468	64	13
	Prescriptions (n)	611	102	108
	Median (days)		4	131
	IQR (days)		2 – 77	36 – 214
	Inappropriate tests		46.1%	5.3%
Daptomycin	Patients (n)	217	74	14
	Prescriptions (n)	739	172	28
	Median (days)		5	7
	IQR (days)		3 – 7	3 – 9
	Inappropriate tests		8.7%	3.6%
Voriconazole	Patients (n)	105	33	26
	Prescriptions (n)	349	85	66
	Median (days)		4	14
	IQR (days)		2 – 7	7 – 26
	Inappropriate tests		16.0%	7-5%
Levetiracetam	Patients (n)	820	103	267
	Prescriptions (n)	1864	293	750
	Median (days)		11	139
	IQR (days)		4 – 42	69 – 261
	Inappropriate tests		8.2%	0.4%

Figure and figure legend

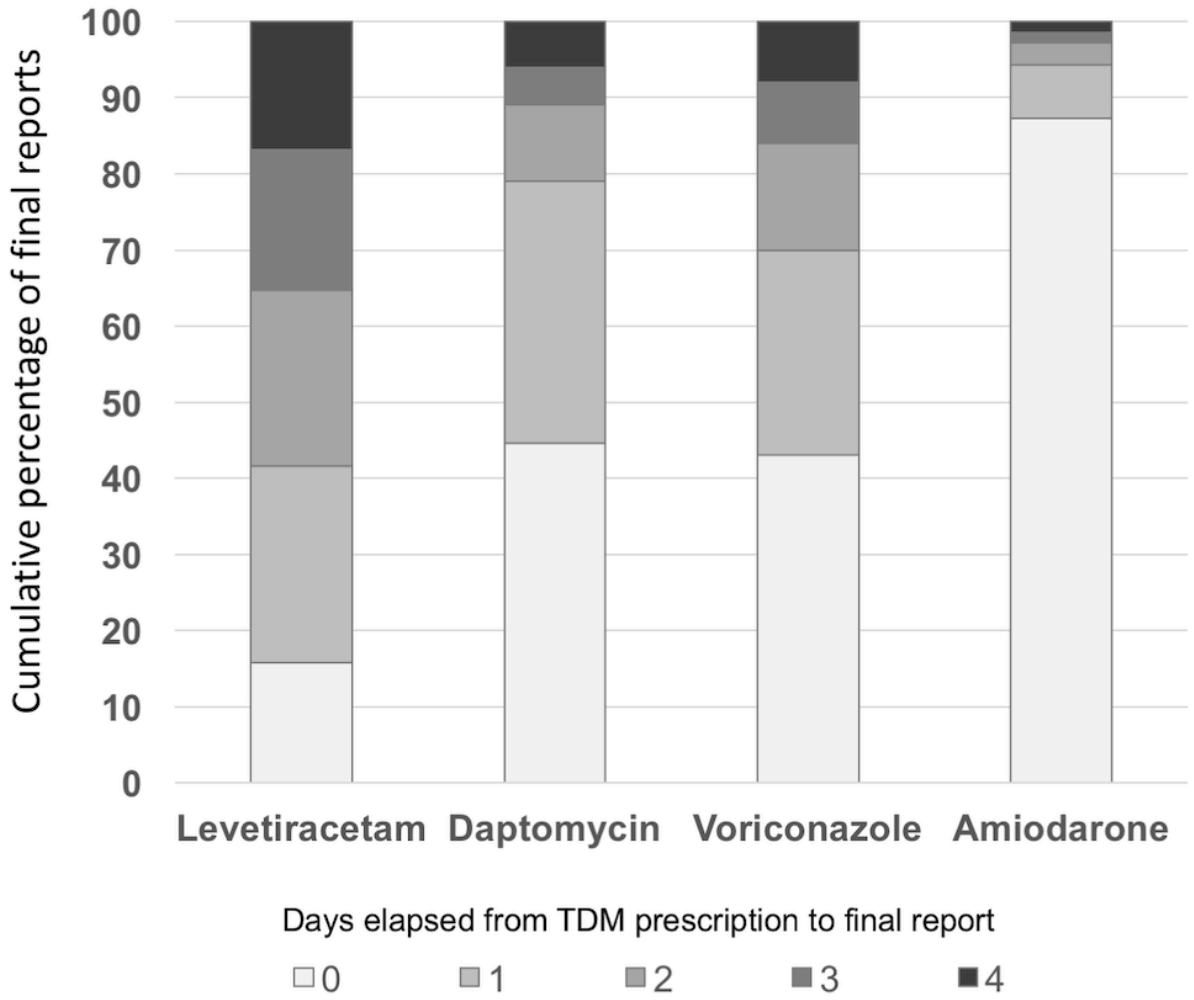

Figure 1. Cumulative percentage of final reports produced within a specified time interval from TDM prescription. The TAT is shortest for amiodarone and longest for levetiracetam.