Therapeutic drug monitoring or therapeutic drug management

Therapeutic drug monitoring (TDM) refers to the quantitative measurement of therapeutic drugs in serum, plasma or other biological fluids. The purpose of TDM assessment is to provide health care professionals with information to assist in adjusting a patient’s drug regimen to reach an optimal drug concentration that will ensure the patient achieves the desired therapeutic response without adverse drug reactions or toxicity. TDM assumes that there is a relation between serum drug concentration and its pharmacological effect. Indications for therapeutic drug monitoring include: lack of therapeutic effect or occurrence of adverse events, narrow therapeutic window, lack of possibility of optimizing drug dose based on clinical observation or laboratory results, substantial interindividual differences in pharmacokinetics, i.e., drug absorption, distribution, metabolism and excretion according to age, genotype, etc., comorbidities like renal and hepatic failure influencing drug excretion and metabolism, gastrointestinal disorders influencing drug absorption, non-linear pharmacokinetics, drug-drug interactions, difficulty in interpreting signs and symptoms of toxicity or therapeutic failure, potential patient compliance problems. Drugs that are commonly analyzed by therapeutic drug monitoring comprise: aminoglycoside antibiotics (gentamicin), vancomycin, antiepileptics (such as carbamazepine, phenytoin and valproic acid), digoxin, antiarrhythmics (such as procainamide and lidocaine), psychoactive drugs (lithium, tricyclic antidepressants), theophylline, immunosuppressants (cyclosporine, tacrolimus), methotrexate (1). For these drugs clinical experience or clinical trials should have shown that TDM improved outcome in the general or special populations as it is stated in the definition by the International Association for Therapeutic Drug Monitoring and Clinical Toxicology (ATDMCT) (2).

Economic considerations in therapeutic drug monitoring/management

It needs to be stressed out that TDM is not a simple analysis of a single drug concentration in the blood but it also encompasses interpretation of the value measured with the use of pharmacokinetic modelling, drawing appropriate conclusions about the result and advising the clinician who ordered the test how to modify drug dose or dosing interval. Therapeutic drug monitoring service can be provided by adequately trained health care professionals, either by clinical pharmacists or clinical pharmacol-
ogists. The Therapeutic Drug Management and Toxicology Division of the American Association for Clinical Chemistry advocates to replace the word “monitoring” with “management” in all references to TDM in order to emphasize the purpose of the actual monitoring of drug concentrations in biological fluids. “Management” implies that the laboratory measurement is an essential part of the treatment of the patient, whereas “monitoring” is focused on the analytical process, without reference to the clinical implications (3).

In times of increasing financial pressure for hospitals and their budgetary constraints, cost-effectiveness analyses for TDM are required, just in order to justify the staffing of a clinical pharmacokinetic service (4). In 1966, Donabedian proposed the structure-process-outcome method for the assessment of quality of health care (5). Schumacher and Barr translated this method to TDM. The evaluation of the structure component applied to TDM includes adequacy of the TDM testing equipment and facilities, qualifications of clinical and laboratory staff, presence of a TDM service, supervision, and administrative organization. The process component for TDM involves procedures such as appropriate indications for ordering a serum drug level, timing of the sample collection, communication of results to clinicians and intervention based on the results. The outcome component comprises the effect of an intervention on the outcome of the patient and its impact on the health care system, what applied to TDM includes speed of recovery, number of adverse effects, morbidity, mortality and cost savings associated with a TDM service. In 247 outcome and economic studies pertaining to the use of TDM all the evaluated variables were classified as process vs. outcome measures and system-related vs. patient-centered measures. The examples illustrate important differences in terminology:

- Process measures – What percentage of TDM blood samples was correctly drawn?
- Outcome measures – What percentage of patients had serum drug levels within the predefined drugs’ target concentration ranges?
- Patient-centered outcome measures – What percentage of patients on TDM are treated effectively and without adverse effects?

About 75% of the studies reported system-related or process measures for assessing the value of TDM. It was shown that TDM as an intervention reduced the rate of undesirable system-related variables by 50% and increased the rate of desirable system-related variables by 100%. Likewise, TDM as an intervention reduces the rate of patient-centered outcome variables by 15% to 50% for such variables as adverse reactions, mortality rates and length of hospital stay. Patient-centered outcome measures are to be preferred. In process-oriented studies surrogate endpoints are used because of the lack of well-defined and measurable clinical parameters (6).

According to Ensom et al. there is a need to incorporate the patient-centered and outcome-oriented measures into clinical pharmacokinetic monitoring as many studies showed that it did not have a significant impact on specific patient outcomes and a few even found a negative impact. There is good evidence in only a few specific patient groups to support the benefit of TDM and defining those groups will help to minimize the time and money spent on TDM that provides no value (7).

Aim

The aim of this review was to summarize outcome and economic studies relevant to the use of therapeutic drug monitoring.

Aminoglycosides

Aminoglycoside antibiotics are important in the treatment of Gram-negative infections and as synergistic agents for the treatment of staphylococcal and streptococcal infections. They are still widely used despite the introduction of newer classes of antimicrobial agents. However, these agents have a narrow therapeutic index. Data suggest that a pharmacokinetic/pharmacodynamic relationship exists for some aspects of efficacy and toxicity of aminoglycosides. Peak serum drug concentrations and the ratio of peak serum drug concentration to minimum inhibitory concentration appear to correlate with their clinical efficacy. Tissue drug accumulation, as indicated by increasing trough concentrations, has been associated with ototoxicity and renal impairment. These relationships, and the wide inter- and intrapatient variability of pharmacokinetic parameters are the basis of therapeutic drug monitoring of aminoglycosides that aims to optimise therapy and avoid toxicity (8-10).

In 1979, Bootman et al. demonstrated in a retrospective analysis of severely burn patients with Gram-negative sepsis that patients in whom gentamicin was dosed individually based on TDM were characterized by longer hospital stay, but on the other hand, by significantly lower mortality rate compared to those in whom gentamycin levels were not monitored. The extra costs of the TDM service were outweighed by the overall savings made as a result of reduced mortality (11).
TDM services have been shown to reduce aminoglycoside nephrotoxicity. In the study of Slaughter and Cappelletty, the costs of providing TDM averaged SUS 301.87 (1997 values) per patient and the cost of management of single nephrotoxicity was estimated at SUS 4583 (1997 values). In order for the costs of providing a TDM service to 100 patients (SUS 30,187) to be offset by cost savings due to decreasing nephrotoxicity, the service would need to be able to reduce nephrotoxicity by 6.6%, resulting in a saving of SUS 30,248. Therefore, TDM service may be cost justified only in populations where nephrotoxicity rate is high (e.g., > 15%) (12).

In the study of van Lent-Evers et al., active therapeutic drug monitoring service (ATM), assuming that the hospital pharmacist is involved in deciding the initial dose and dosing interval of an aminoglycoside for an individual patient, was compared with standard nonguided TDM. ATM group comprised 105 patients and nonguided TDM comprised 127 patients, including 48 and 68 persons, respectively, with an infection on admission. In ATM patients peak gentamicin concentrations were significantly higher compared to nonguided TDM patients (10.6 ± 2.9 mg/L, 7.6 ± 2.2 mg/L; p < 0.01). High trough gentamicin concentrations (more than 2 mg/L) were observed in 23% of nonguided TDM patients and in only 3% of ATM patients (p < 0.01). There was a trend toward higher mortality in nonguided TDM patients. Subgroup analysis of patients with an infection at admission showed significantly less mortality in the ATM group measured at day 28 after admission (p = 0.023). ATM reduced the length of hospital stay for all patients in the study (20.0 ± 1.4 days, 26.3 ± 2.9 days; p = 0.045) and for patients admitted with an infection (12.6 ± 0.8 days, 18.0 ± 1.4; p < 0.001) compared to the nonguided TDM group. There was significantly less nephrotoxicity in ATM patients compared with the nonguided TDM group (2.9%, 13.4%; p < 0.01). ATM was shown to save costs in comparison with the usual care with nonguided TDM. Total costs calculated as the sum of costs related to the number of days in the ward, intensive care unit costs, intervention and TDM costs and expressed in Dutch guilders (DFL), were lower for all patients (13,125 ± 9,267, 16,862 ± 17,721; p < 0.05) and for patients admitted with an infection (8,883 ± 3,778, 11,743 ± 7,437; p < 0.01). The ATM strategy provided better control of therapy because the a priori consultation facilitated consideration of physiologic and pathologic parameters with the intention of treating the patient and not the levels. Tailoring the dose and the interval to the patient’s need and adjusting the duration of the aminoglycoside course based on the patient’s response became feasible. This resulted in a decrease in mortality, length of hospital stay and reduction in the incidence of nephrotoxicity proving the cost-effectiveness of ATM. Subgroup analysis showed that it was even more beneficial for patients admitted to the hospital with a suspected or proven infection (13).

In a 1-year retrospective historically controlled study before and after the implementation of guidelines, Fonzo-Christe et al. evaluated their impact on dosing and TDM practice, blood sampling, and therapeutic concentrations of gentamicin in newborns. Guidelines recommending once-daily dosing (ODD) or extended-interval dosing (EID) and trough concentration measurement were developed and implemented as clinical decision support in the computerized prescriber order entry system in Geneva University Hospitals. After implementation of the guidelines, an ODD/EID regimen was almost exclusively used (97.7% versus 61.6%, p < 0.001), the percentage of peak concentrations (0.9% versus 17.2%, p < 0.001) and the number of blood samples per patient (87.1% having 0 or 1 concentration measured versus 48.0, p < 0.001) relevantly decreased. More than two-thirds of newborns had trough concentrations under 1 mg/L what was significantly higher percentage in comparison with about one-third before implementation (p < 0.001). Although cost-effectiveness analysis was not performed, better outcome and lower cost of TDM favor such proceedings (14).

**Vancomycin**

Like for aminoglycosides, there seems to be a relationship between vancomycin serum concentrations and both its efficacy and toxicity. A prospective cohort study was conducted to document differences in the outcome of vancomycin therapy in patients managed through a therapeutic drug monitoring (TDM) service (n = 61) and patients managed empirically (n = 55). Outcome measures were as follows: duration of therapy, total vancomycin dosage, infection site, concomitant antibiotics, body temperature, white blood cell counts, length of hospital stay and nephrotoxicity. On average, patients receiving TDM had less nephrotoxicity (7% vs. 24%), needed lower cumulative vancomycin dosages (of 5 g less) and had shorter hospital stays (38 vs. 44.5 days) in comparison with those who did not receive TDM (15).

In the study of Fernandez de Gatta et al., 70 immunocompromised febrile patients with hematologic malignancies were randomly assigned to
either a vancomycin therapeutic drug monitoring group (n = 37) or to a control group (n = 33). The rates of minor nephrotoxicity were 33.3% and 13.5% in the control and TDM group, and the rates of moderate nephrotoxicity were 9.1% and 0%, respectively. A decreased incidence of nephrotoxicity proves a real clinical benefit from the vancomycin monitoring program in this patient population. An incremental cost of $435 per case of nephrotoxicity prevented was calculated for the TDM for vancomycin therapy what makes it a cost-effective procedure again in this high-risk population (16).

Based on the data of the above mentioned studies Darko et al. performed a decision analysis to model the cost-effectiveness of pharmacokinetic dosage adjustment of vancomycin to prevent nephrotoxicity. It was assumed that at least two - one peak and one trough - vancomycin serum concentrations would be obtained during therapy. The frequency of trough concentrations less than or equal to 10 mg/L and greater than 10 mg/L was calculated. The probabilities of nephrotoxicity associated with vancomycin trough concentrations data were derived from recent clinical trials. The mean cost of treating nephrotoxicity was SUS 11,233. The cost of preventing one vancomycin-associated nephrotoxic episode with TDM was calculated as SUS 25,166. The subgroup analysis revealed a cost of 8,363 dollars /nephrotoxic episode prevented in ICU patients, SUS 5,000 in oncology patients and SUS 5,564 in those receiving concomitant nephrotoxic drugs. Thus the TDM for vancomycin therapy may be not cost-effective for all patients, although it can be cost-effective for patients having the greatest risk of developing nephrotoxicity (17).

Of the same concern may be the potential for treatment failure because of underdosing to avoid the risk of toxicity. Thirty one episodes of Gram-positive peritonitis in peritoneal dialysis patients were reviewed in the study by Mulhern et al. in an attempt to identify the risk factors for peritonitis relapse. All patients were treated with 4 weekly doses of intravenous vancomycin. Nine peritonitis episodes complicated by a relapse were identified. Peritonitis episodes preceding a relapse were then compared to relapse-free episodes and there was drawn a conclusion that a suboptimal trough serum vancomycin level (cumulative 4-week trough serum vancomycin level < 12 mg/L or an initial 7-day trough serum level < 9 mg/L) was the only clinical parameter that identified peritonitis episodes at risk for relapse (18).

**Antiepileptic drugs**

Rane et al. have demonstrated that therapeutic drug monitoring consisting of a minimum of two drug estimations per year offers significant benefit in terms of better seizure control, fewer adverse events and greater chances of remission in adult patients with generalized tonic-clonic epilepsy. A retrospective, post hoc pharmacoeconomic analysis of a cohort of 25 patients who had undergone TDM and 25 controls matched for age, disease, duration of drug therapy and duration of epilepsy clinic attendance was carried out. At interview one year after treatment, in the study group 11/25 patients had achieved complete seizure control, 10/25 patients had 50% reduction in seizure frequency, while 4/25 patients still had uncontrolled epilepsy whereas in control group 2/25 patients had reached complete control, 11/25 patients had 50% reduction in seizure frequency, while 12/25 patients still had uncontrolled epilepsy. There was a significant difference in seizure control between groups. The incidence of adverse events was also significantly lower in the TDM group (2/25 vs. 10/25; p < 0.05). TDM patients also had a better social status: at the time of interview 19 vs. 12 patients were earning, 15 vs. 7 patients were married and had children. The cost per sample analyzed to the hospital was 147 Indian rupees. The cost to the hospital per seizure prevented was estimated 22.35 rupees while the cost to the patient prevented was 22.35 rupees while the cost to the patient per seizure prevented was 4.50 Indian rupees (19).

**Digoxin**

A post-hoc analysis of the Digitalis Investigation Group trial was performed in order to assess variations in serum digoxin concentration and their association with mortality and hospitalization in patients with heart failure. The analysis was restricted to men with a left ventricular ejection fraction of 45% or less (n = 3782). Patients randomly assigned to receive digoxin were divided into 3 groups based on serum digoxin concentration at 1 month (0.5-0.8 ng/mL, n = 572; 0.9-1.1 ng/mL, n = 322; and ≥ 1.2 ng/mL, n = 277) and compared with patients assigned to receive placebo (n = 2611). The primary end point of the Digitalis Investigation Group trial was all-cause mortality within 37 months of randomization. There was no difference in all-cause mortality among patients randomly assigned to placebo and patients assigned to digoxin who had serum digoxin concentrations assessed. However, patients with serum digoxin concentrations of 0.5 to 0.8 ng/mL had a 6.3% (95% CI, 2.1-
10.5% lower mortality rate compared with patients receiving placebo, digoxin was not associated with a reduction in mortality among patients with serum digoxin concentrations of 0.9 to 1.1 ng/mL, whereas patients with serum digoxin concentrations of 1.2 ng/mL and higher had an 11.8% (95% CI, 5.7-18.0%) higher mortality rate than patients receiving placebo. Similarly, patients with higher serum digoxin concentrations had higher crude rates of all-cause hospitalization and patients with lower serum digoxin concentrations had lower crude rates of all-cause hospitalization than patients randomly assigned to placebo. This study strongly suggests that digoxin offers a survival advantage in a narrow therapeutic window and therefore TDM of digoxin may be warranted in men with heart failure and left ventricular dysfunction (20).

Immunosuppressants

Cyclosporine was the first immunosuppressive agent to receive serious attention regarding pharmacokinetics, pharmacodynamics and TDM. Most centers use two target ranges, one for initial therapy and the second for maintenance therapy thereafter. Because of the considerable variability in the bioavailability, metabolism, and excretion of cyclosporine in transplant recipients and because of the drug’s narrow therapeutic index, dosage individualization based on blood cyclosporine concentration is required to reduce the risk for either underdosage or toxicity. Nevertheless, there are no studies published that have formally looked at the cost-effectiveness of TDM for cyclosporine and other immunosuppressants. Because it has been clearly established that TDM increases the chance of one-year survival of transplanted kidney from 60% to 95%, a randomized study that investigates the cost-effectiveness of TDM vs. no monitoring in transplant patients would be ethically unacceptable (21).

However, prospective concentration-controlled studies performed with validated analytical methodology for cyclosporine and other immunosuppressants, examining the risk/benefit ratio for specific concentrations of these drugs in specific patient groups would be highly recommended. The vast majority of centers use a predose trough blood sample for cyclosporine analysis. It has been recently demonstrated that trough concentrations correlate poorly with the AUC (area under the curve), and thereby do not adequately reflect cyclosporine exposure, whereas improved correlation with clinical effects of the drug is achieved by evaluating its total exposure, i.e., AUC (22). A practical limitation of this approach is the necessity to collect several blood samples at defined time points. Adequate cyclosporine exposure during the first 4 hours after intake (AUC0-4) has been proven to correlate with freedom from rejection and toxicity and C2 (a 2-hour postdose cyclosporine level) has been determined to be the best single-timepoint predictor of the AUC0-4 (23).

The study of Shenoy et al. purposed to compare the safety, efficacy, and pharmacoeconomics of cyclosporine monitored by C2 levels and tacrolimus monitored by trough levels in de novo liver transplant recipients. After informed consent, 60 de novo liver transplant recipients were randomized in a 1:1 fashion to receive either tacrolimus (trough, 6-10 ng/mL) or cyclosporine (C2, 600-1200 ng/mL) and corticosteroids. The primary endpoint was the rate of acute rejection at 12 months. Incidence of infection, adverse events, and drug costs were secondary endpoints. Early acute rejection occurred in 27% of tacrolimus-treated patients and 23% of cyclosporine-treated patients (NS). Recurrent HCV occurred in 21% of tacrolimus-treated patients and 61% of cyclosporine-treated patients (p = 0.04). The incidence of new onset diabetes mellitus, requirement for antihypertensives and for cholesterol medications were similar between the groups. Annual calcineurin inhibitor costs were lower for cyclosporine (US$ 5432 ± 2091 vs. US$ 8291 ± 3948, p = 0.001), although total 1-year posttransplant drug costs were similar (US$ 17,214 ± 16,600 vs. US$ 15,151 ± 11,699, NS) (24).

CONCLUSIONS

Therapeutic drug monitoring service providing appropriate pharmacokinetic interpretation and recommendations to clinicians has already been proven either to be cost-effective or to improve outcome. The question of at least the same importance is how to increase the effectiveness of TDM, i.e., determining specific patient groups, developing reliable and easy to use assays, etc. In conclusion, it can be recapitulated that TDM of aminoglycosides is cost-effective, leads to a reduction of mortality, nephrotoxicity and length of hospital stay. TDM of vancomycin results in reduced nephrotoxicity and is cost-effective in selective patients populations, such as ICU patients, oncology patients and patients treated with other nephrotoxic drugs. TDM of classic antiepileptic drugs can offer significant benefit in terms of better seizure control and fewer side effects. TDM of digoxin may be useful in cardiac failure. Because of a shortage of donor organs, considerable interindividual variability and risk for
drug-drug interactions therapy with immunosuppressants must be guided by TDM.

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