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# Bespoke pharmacy:

TAILORING MEDICINES TO THE NEEDS OF PATIENTS

## — the role of therapeutic drug monitoring

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This part of the special feature on tailoring medicines to the needs of patients looks at the role of the therapeutic drug monitoring pharmacist

**P**harmacists who specialise in therapeutic drug monitoring (TDM) span a range of clinical areas and are therefore different from other types of pharmacy specialist who generally focus on one particular group of patients. Although often regarded as a specialist area that focuses on the measurement of drug concentrations, the ultimate aim of TDM is to determine doses of drugs that suit the characteristics of individual patients by applying knowledge of clinical pharmacokinetic principles. It could therefore be argued, with justification, that this “specialty” underpins the basic functions of all pharmacists<sup>1</sup> and gives them the opportunity to offer patients something that is unique<sup>2</sup> since few other health care professionals have expertise in this area.

The range of TDM specialist activities encompasses simple adherence to guidelines for dosage adjustment given in the British National Formulary, education of pharmacists and other health professionals on the theory behind drug dosage adjustment and collaboration with other health care professionals in research studies designed to develop dosage guidelines for specific patient groups.

### TDM SERVICES

**G**iving advice on drug therapy and ensuring that patients receive the optimal dose of a drug is the remit of every clinical pharmacist. In practice, this is done routinely by reference to published dosage guidelines. However, when patients exhibit unusual drug handling or response, the application of pharmacokinetic or pharmacodynamic theory, or both, may help

solve the problem.

In current practice, hospital pharmacists often advise on initial drug dosage regimens, drug concentration analysis and interpretation, and maintenance dosage regimens. These contributions to patient care require a basic understanding of pharmacokinetic principles. However, the availability of TDM specialists who are trained to deal with complex cases is valuable because simple approaches and standard guidelines are not always appropriate. For example, the safe and effective use of gentamicin has been rationalised by means of extended interval dosing in many clinical settings, and data can easily be misinterpreted if not analysed appropriately. For instance, if samples are not taken within the time frame required by the protocol (usually at between six and 14 hours after a dose), the pharmacist would usually have to wait until the next dose is taken and request a further sample at the appropriate time. However, simple application of pharmacokinetic principles would allow the initial sample to be interpreted and the appropriate dosage regimen to be determined without the need for further sampling. Similar problems can exist with conventional dosing if samples do not represent steady state peak and trough concentrations, either due to unequal dosage intervals or to non-optimal sampling times. Failure to account for these factors can lead to inappropriate dosage adjustments. Another illustration of the importance of careful interpretation lies in dealing with patients who are clinically unstable (eg, in the intensive therapy unit [ITU]), or where estimation of renal function is difficult (eg, a newborn infant or a cancer patient with a low muscle mass). In such cases, pharmacokinetic analysis of drug concentrations can be a better indicator of renal function and, in turn, a more sensitive index of the need to adjust the doses of other drugs.<sup>3</sup>

Complex patients generally demand higher

levels of expertise and in Glasgow, where there is a long tradition of pharmacy involvement in TDM,<sup>4,5</sup> a Bayesian pharmacokinetic package, “OPT”<sup>6</sup> (for optimisation) is used routinely to help interpret drug concentration measurements, identify patients who are clinically unstable and determine dosage adjustments. This program uses basic clinical information such as age, weight and creatinine concentration to calculate initial (“population”) estimates of drug clearance and volume of distribution. These initial estimates are then combined with details of the dosage history and the related concentration measurements and, via a Bayesian non-linear regression analysis, estimates of clearance and volume of distribution are determined for the individual. In simple terms, the program alters the set of initial estimates until the best fit of measured and predicted concentrations is obtained.<sup>6</sup> The application of a Bayesian function in the fitting procedure takes account of expected variability and reduces the likelihood of obtaining non-physiological clearance and volume of distribution estimates.

### ILLUSTRATIVE CASE

**A** patient was prescribed an initial dose of 120mg gentamicin followed by a dosage regimen of 80mg twice daily. In this case, the medical staff believed that the low dose was warranted in light of a degree of renal impairment, but this was not appropriate and the dose should have been higher.

Two samples for gentamicin analysis were taken with the morning bloods on days two and three. The first was taken nine hours after the first 80mg dose, the second 21 hours after the next 80mg dose. Although the prescribed dose would not have achieved the target peak of >8mg/L (target range 8–12mg/L), the data were difficult to interpret because of varying doses and dosage intervals.

Following pharmacokinetic analysis, the

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patient's "Bayesian" (individual) clearance was found to be similar to the "population" clearance estimate and there was good agreement between the measured and predicted concentrations. Figure 1 shows the report from "OPT", with details of the dosage history, concentration measurements, pharmacokinetic parameters and the dosage recommendation of 240mg every 48 hours. A simplified version of this report would have been given to the clinician. The modified dose was prescribed and a follow-up concentration measurement confirmed that it was appropriate. (Figure 2, p163) shows that the target peak of >8mg/L (but <12mg/L) was reached once the dose had been increased.)

pharmacist with specific expertise in clinical pharmacokinetics and TDM. These pharmacists generally cover units or wards in which patients have unusual or changing drug dosage requirements, such as ITUs, special care paediatric units, cardiothoracic surgery units and oncology wards. They monitor and optimise therapy for individual patients and offer advice to medical staff on dosage adjustment and drug analysis. In some cases, the pharmacist also takes responsibility for prescribing and monitoring drugs such as aminoglycosides, glycopeptide antibiotics and warfarin. This unique area of expertise is an obvious target for the extension of pharmacist prescribing in the future.

Rapid access to drug assay results is an important component of an efficient service and this is achieved through close collaboration with scientists and clinicians within the microbiology and clinical chemistry labora-

tories. However, models of service vary from hospital to hospital. At Stobhill Hospital, the TDM pharmacist is based within the biochemistry department and responsibility for the interpretation of drug assay results is held jointly by the pharmacist and a senior biochemist. They interpret results for inpatients, monitor the advice given by other clinical pharmacists and provide support to outpatient clinics and general practitioners. In other hospitals, the problem of achieving timely access to results has been solved electronically through direct computer access to laboratory data or through regular laboratory visits. This collaborative approach encourages discussion with other professionals and allows patients' therapy to be modified according to clinical, microbiological and pharmacokinetic targets. Efficient transfer of data is essential to ensure that clinical pharmacists can make recommendations that directly influence patient care.

Overall support for TDM services is provided by the area pharmacy specialist who visits the hospitals in Glasgow and offers advice on service provision and monitoring. In west Glasgow hospitals, clinical pharmacokinetic input from pharmacists on wards is continually reviewed, coded and used to assess the clinical areas that require the highest level of expertise, to evaluate pharmacists' contributions to patient care and to determine training needs.

## TDM SERVICE MODELS

Each hospital in Glasgow and the surrounding area has at least one

Patient	Joe Bloggs	Clinical Pharmacokinetics Unit			
Patient ID no.	1234	Western Infirmery			
Department	ITU	Glasgow 0141 211 2022			
Date	28/2/2003				
Drug	Gentamicin				
Data file	C:\OPT6DATA\GENTAMIC\1234.OPT				
Age (years)	67				
<b>SUMMARY OF PRESENT TREATMENT</b>					
Date	Time of Admin	Dose	Route	Admin over (mins)	Preparation
28/1/2003	14:00	120.00	IV	10	gentamicin
28/1/2003	22:00	80.00	IV	10	gentamicin
29/1/2003	14:00	80.00	IV	10	gentamicin
<b>CONCENTRATION MEASUREMENTS (mg/L)</b>					
Date	Time of sample	Predicted conc.	Measured conc.	SD	Diff
29/1/2003	7:00	3.58	3.62	0.69	0.04
30/1/2003	7:00	1.60	1.60	0.24	0.00
<b>PARAMETER ESTIMATES</b>					
	BAYESIAN	POPULATION			
	Mean	67% Range	Mean		
Conc. at start of monitoring	0.00	0.00-0.00	0.00mg/L		
Clearance	1.54	1.42-1.68	1.79L/h		
Vol. of distribution	23.5	20.0-27.7	23.3L		
Elimination rate constant	0.066/h				
Elimination half-life	10.6h				
<b>REPORT</b>					
Peaks are too low and troughs are too high on the present dose. Recommend changing to 240mg every 48 hours with re-analysis of a trough in two days to confirm dose requirements.					
<b>STEADY STATE DOSE RECOMMENDATION</b>					
Preparation	Gentamicin				
Dose	240mg intravenously				
Administered over	15 minutes				
Dosage interval	48 hours				
and on this dosage regimen the predicted steady state concentrations should be:					
Minimum concentration	0.5mg/L				
Average concentration	3.2mg/L				
Maximum concentration	10.6mg/L				
Predicted concentration	9.9mg/L, 60 minutes post dose				

Figure 1: Report from the pharmacokinetic package, OPT

## APPLICATION OF TDM

Although the routine workload revolves around a long established group of drugs, particularly the aminoglycoside antibiotics, vancomycin, digoxin and phenytoin, the application of clinical pharmacokinetic principles can be useful in other areas. For example, the cause of one patient's poor response to antitubercular therapy when changed from an intravenous to an oral regimen was found to be poor compliance, even though he was an inpatient. Initial concerns that low concentration measurements indicated erratic absorption of rifampicin were not supported when pharmacokinetic analysis revealed that the concentration-time profile achieved after a supervised dose was normal. Pharmacokinetic consultations also extend to drugs that are less commonly monitored, for example, the interpretation of teicoplanin data collected from patients receiving the drug at an outpatient IV antibiotic clinic<sup>7</sup> or determining flucytosine dosage requirements for a patient receiving haemofiltration.<sup>8</sup>

## EDUCATIONAL ASPECTS

Education and training of undergraduate pharmacy students and postgraduate pharmacists (and other health care professionals) is the second main role of the TDM

specialist. Pharmacy students at the University of Strathclyde are introduced to basic pharmacokinetics and dosage individualisation in their third year and additional lecture and workshop sessions on exemplary cases involving gentamicin and digoxin are held in their fourth year. Preregistration training study days in Greater Glasgow include a half-day on TDM. A further two days of basic pharmacokinetics and TDM are provided within the clinical pharmacy training course offered to pharmacists who are at Stage II of the Scottish Hospital Pharmacists Vocational Training Scheme.<sup>9</sup> However, clinical pharmacokinetic practice is mainly taught at postgraduate level through the MSc in clinical pharmacy (University of Strathclyde) or the MSc in clinical pharmacology (University of Glasgow). Many clinical pharmacists with expertise in TDM contribute to these undergraduate and postgraduate courses and the area specialist co-ordinates the clinical pharmacokinetics modules of the MSc courses. In addition, there are opportunities to provide lectures, workshops and training sessions for other health professionals such as junior medical staff, clinical scientists and nurses. Specialist training in the Bayesian package, "OPT"<sup>6</sup> is available to pharmacists who use the program within their clinical practice, although this program is no longer being developed and an alternative package that is compatible

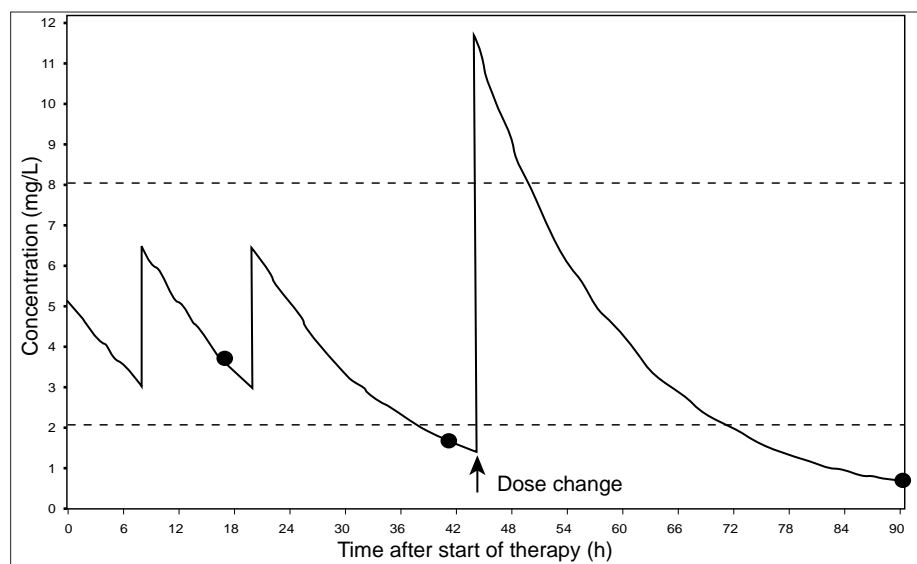


Figure 2: Measured concentrations (●) and predicted concentration-time profile (—) following Bayesian analysis of three concentration measurements

with newer operating systems will be required in the future.

#### RESEARCH AND DEVELOPMENT

It is important to monitor how TDM services impact on drug use and patient care and a further role for the clinical pharmacokinetics pharmacist is in the area of audit, research and development. Because services

are provided in collaboration with a range of professionals (eg, microbiologists), the TDM pharmacist may need to approach developments (eg, developing new guidelines and protocols) with caution to avoid being regarded as a threat. For example, before introducing an antibiotic TDM interpretation service, an audit was conducted in collaboration with the microbiology department. This audit highlighted problems with

initial doses and paved the way for the introduction of guidelines and for an interpretation service supported by clinical pharmacists.<sup>10</sup> The success of this project was highlighted recently when staffing problems led to the temporary withdrawal of the clinical pharmacy service from a ward area. This resulted in a significant decline in the clinical usefulness of gentamicin insofar as the percentage of satisfactory gentamicin peak concentrations declined from over 90 per cent<sup>10</sup> to 24 per cent. The introduction of a support pharmacist achieved an increase to 56 per cent within six months and it is hoped that further improvements will occur following reintroduction of the full clinical pharmacy service.

Opportunities for collaborative research and development also occur through pharmacists working in other hospitals or specialties. Intensive therapy is an area where clinical pharmacokinetic expertise is especially important. Patients often have unstable renal function or develop acute renal failure that demands the use of renal replacement therapy. A knowledge and understanding of pharmacokinetics can help to determine appropriate dosage regimens for such patients, while offering the opportunity to participate in research studies.<sup>11</sup> Occasionally, difficult cases requiring pharmacokinetic interpretation arise through drug overdose.<sup>12</sup> Alternatively, unusual clinical situations can arise from a range of specialties such as oncology<sup>13</sup> or nephrology.<sup>14</sup> Of particular interest at present is paediatrics, where for many years drug doses were determined empirically, often with no clear scientific rationale. The application of population pharmacokinetic techniques and Bayesian methodology<sup>15</sup> to such data can help in the development and evaluation of paediatric dosage guidelines.<sup>16</sup> Knowledge of clinical pharmacokinetics therefore provides opportunities to collaborate with pharmacy specialists in a range of areas.

## FUTURE PROSPECTS

Looking to the future, immunosuppression is an established but expanding area for TDM. The introduction of new drugs and new methods for monitoring concentrations will increase the demand for interpretation. For example, "absorption profiling" (ie, measuring three to four samples over the first four hours to estimate the area under the curve) and "C<sub>2</sub>" monitoring (measurement of a two-hour post-dose "peak") have been shown to have clinical advantages over conventional trough analysis for ciclosporin.<sup>17</sup> Newer immunosuppressants, such as mycophenolate mofetil, tacrolimus and sirolimus all have narrow therapeutic ranges and monitoring of concentrations is required to ensure optimal therapy.<sup>18</sup>

In the field of oncology, there is an increasing interest in the use of population

techniques and limited sampling strategies to design dosage regimens and optimise therapy.<sup>19</sup> In some cases, phenotyping (or genotyping) of enzyme function has been used to identify patients with dihydropyrimidine dehydrogenase or thiopurine methyltransferase deficiency who are at risk of life-threatening toxicity.<sup>20</sup> More recently, genotyping a range of drug metabolising enzymes and transporters has become popular due to their roles in the metabolism of and response to a number of drug classes, including anti-cancer drugs, antidepressants, and antihypertensives.<sup>21</sup> If pharmacogenetics is the TDM of the future,<sup>22</sup> it is important that the mistakes of the past are not repeated. Results need to be interpreted appropriately to be clinically useful and since genotype does not always equate to phenotype, there will still be a role for drug individualisation based on serum level interpretation. As with traditional TDM, pharmacists are ideally placed to bridge the gap between the pure scientists and clinical staff.

## CONCLUSIONS

The role of the TDM pharmacist is challenging because it requires a scientific approach to problem solving. Although the specialty declined to some extent during the 1990s, recent developments in pharmacogenetics and population pharmacokinetic/pharmacodynamic modelling demand that pharmacists develop the skills to interpret the data and ensure that these techniques are used appropriately.

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