The therapeutic monitoring of antimicrobial agents

Evan J. Begg, Murray L. Barclay & Carl M. J. Kirkpatrick

Department of Clinical Pharmacology, Christchurch Hospital, Christchurch, New Zealand

Aims To review the basis and optimal use of therapeutic drug monitoring of antimicrobial agents.

Methods Antimicrobial agents for which a reasonable case exists for therapeutic drug monitoring are reviewed under the following headings: pharmacokinetics, why monitor, therapeutic range, individualization of therapy, sampling times, methods of analysis, interpretative problems and cost-effectiveness of monitoring.

Results There is a strong historical case for monitoring aminoglycosides. The recent move to once-daily dosing means that criteria for therapeutic drug monitoring need to be redefined. Vancomycin has been monitored routinely but many questions remain about the most appropriate approach to this. A case can be made for monitoring teicoplanin, flucytosine and itraconazole in certain circumstances.

Conclusions The approach to monitoring aminoglycosides is being redefined in the light of once daily dosing. It may be that less stringent monitoring is required in some circumstances but toxicity, especially ototoxicity, remains a problem with these drugs. Monitoring to avoid high AUCs (areas under the concentration-time curve) is recommended. The ideal method for monitoring vancomycin remains to be defined although a reasonable case exists for measuring trough concentrations, mainly to ensure efficacy. Teicoplanin is sometimes monitored to ensure efficacy while flucytosine may be monitored to avoid high concentrations associated with toxicity. Itraconazole has various pharmacokinetic problems and monitoring has been suggested to ensure that adequate concentrations are achieved.

Keywords: antimicrobial agents, therapeutic drug monitoring

Introduction

Most antibiotics, such as the β-lactams, macrolides and quinolones have a wide therapeutic index and therefore do not require therapeutic drug monitoring. Some, such as the aminoglycosides and vancomycin, have a narrow therapeutic index, and toxicity may be severe and irreversible. Therapeutic drug monitoring may be appropriate for these drugs. Other drugs such as teicoplanin, flucloxacillin and the antifungal agents itraconazole, flucytosine and fluconazole are monitored in certain circumstances.

The aminoglycosides

There is a strong case for monitoring aminoglycoside concentrations [1]. However, the recent move to once-daily dosing has resulted in the need to re-evaluate monitoring strategies.

Correspondence: Associate Professor Evan Begg, Department of Clinical Pharmacology, Christchurch School of Medicine, PO Box 4345, Christchurch, New Zealand. E-mail: evan.begg@chmeds.ac.nz

Pharmacokinetics

The pharmacokinetics of the aminoglycosides are relatively simple. These drugs are hydrophilic with low protein binding, and are eliminated renally. They have no stereoisomerism and are not subject to genetic polymorphism. The volume of distribution (V) approximates that of the extracellular fluid volume, and the clearance (CL) that of the glomerular filtration rate [2]. The λ_z-phase $t_{1/2}$ is approximately 2.5 h in patients with normal renal function, although there is a slow terminal elimination phase of 100–150 h, related to distribution into a 'deep compartment'.

Aminoglycoside pharmacokinetics vary markedly according to the state of the disease that is being treated. Infections are associated with altered hydration and permeability of biological barriers. The V and CL may therefore change dramatically during therapy. Severe

infection, or burns, can be associated with an increased V, which may require higher doses to achieve desired peak concentrations [3, 4]. Pre-renal failure may follow dehydration resulting in impaired aminoglycoside clearance, which may subsequently improve during fluid replacement and resolution of the infection.

Why monitor aminoglycosides?

The aminoglycosides have a low therapeutic index. Bactericidal efficacy is directly related to peak concentrations (concentration-dependent killing) while toxicity is related to total drug exposure [1]. Nephrotoxicity (usually reversible) and ototoxicity (often irreversible) are the major forms of toxicity [5].

The desired plasma concentration-time profile for aminoglycosides differs from that of most other drugs involved in therapeutic drug monitoring. For most drugs the aim is to have minimal fluctuations (i.e. a flat profile) within the dosing interval to keep the concentrations within a 'therapeutic range'. A single plasma concentration measurement, representative of accumulation, is usually all that is required for monitoring.

For the aminoglycosides, the desired concentration-time profile includes a high peak concentration (for efficacy) followed by a low trough concentration (to prevent accumulation). The dose interval is substantially longer than the half-life. For therapeutic drug monitoring of the aminoglycosides, it has been traditional to monitor both a peak and a trough concentration. With the recent move to once daily dosing, this approach needs to be reconsidered.

Therapeutic ranges

For many years, peak concentrations of 6–10 mg l^{-1} and trough concentrations of ≤ 2 mg l^{-1} were advocated for gentamicin, tobramycin and netilmicin, with double these values for amikacin. SI units are not used because gentamicin is not a single entity but a mixture of substances with differing side groups. It therefore does not have a molecular weight and so measurement is in mass rather than molar units. Although this does not pertain to tobramycin or netilmicin, the same units are used for convenience. The therapeutic ranges have been based largely on studies that have demonstrated poor outcome associated with suboptimal peak concentrations [6–8].

There are no clearly established therapeutic ranges for once-daily dosing. Some groups have arbitrarily suggested that trough concentrations should be less than 2, 1 or 0.5 mg l^{-1} [9–11]. However, there is no rationality for this approach because concentrations at 24 h will be unrecordable, using conventional assay technology, in patients with normal renal function [12]. Concentrations of 0.5–2 mg l^{-1} at 24 h would indicate an overdose in these patients. Clearly the concept of a trough concentration is not relevant to once-daily dosing.

There is little need for monitoring peak concentrations during once daily dosing. Peak concentrations will always be well in excess of those seen during multiple daily dosing and therefore within the useful range of bactericidal effect for most bacteria (usually 5–10 times the MIC). Peak concentration measurement is therefore unnecessary except for pharmacokinetic dose individualization [12].

Individualization of therapy

Various methods of dose prediction have been used successfully. A summary of these can be found in Begg *et al.* [1] and Morike *et al.* [13]. Nomograms relating dosing to estimates of renal function were the first attempts to individualize dosing, utilizing the pharmacokinetic relationship between aminoglycoside clearance and renal function.

The next dosing method to gain favour was the dose individualization of Sawchuk & Zaske [14], based on a one-compartment pharmacokinetic model. The advantage of this method was that after the first dose, future doses could be based upon an assessment of the patient's own pharmacokinetics (i.e. V *and* CL) for the relevant aminoglycoside. This method was shown to have advantages over nomograms and methods based on physician intuition, in terms of achieving desired peak and trough concentrations [15, 16]. Bayesian methods have also been used in the dose prediction of aminoglycosides [17]. These have the advantage of obtaining useful information from a smaller number of samples than with the Sawchuk & Zaske approach [14], but in practice performance is similar for the two approaches.

With the advent of once daily dosing, the scene has virtually returned to the formative years of aminoglycoside dosing. Most proponents of once-daily dosing have simply employed an arbitrary initial dose, usually 3–7 mg kg^{-1} day^{-1}, based on the total amount that would have been prescribed over 24 h during multiple-daily dosing. This approach to choice of dose seems reasonable, at least for the starting dose. It remains unclear how drug concentrations measured for monitoring should be interpreted, and indeed at what time points drug concentrations should be measured.

Some groups [12, 18, 19] have advocated sampling at a time or times earlier than 24 h after the dose, when the concentration is still measurable. The exact timing of these samples can vary in relation to renal function. MacGowan & Reeves [18] proposed the measurement of a single sample at 8 h. However, it was unclear how dosing should proceed as a result of this estimate, although this method would lend itself to Bayesian forecasting. Nicolau *et al.*

[19] proposed a dose of 7 mg kg^{-1} followed by the measurement of a single serum concentration between 6 and 14 h after the first dose. This concentration is compared with a nomogram (the Hartford nomogram) which indicates whether the dose interval should be 24, 36 or 48 h. Although dose intervals longer than 24 h make good theoretical sense, there is little clinical evidence to support this. A recent report noted an 18% incidence of ototoxicity (5/28) in patients with haematological malignancies treated using this approach [20]. This is of some concern and suggests that some patients may be receiving excessive doses. The concern is strengthened by a study of the use of the Hartford nomogram in trauma surgery patients, which resulted in AUC estimates that exceeded 100 mg l^{-1} h in over 50% patients [21].

Begg *et al*. [12] suggested a target area under the curve (AUC) approach, based on the notion that the same total dose should be given over 24 h as would be given using dose-individualization with multiple-daily dosing. In order to assess the AUC in a given patient, they advocated measuring a concentration at or around 1 h postinfusion and a second concentration somewhere between 6 and 22 h after the first dose, the time of the second sample adjusted in relation to renal function [12]. From these two concentrations and assuming a one-compartment model, the AUC is calculated. Subsequent doses can be adjusted to achieve any desired AUC. The desired target AUC values related to doses of 5, 6 and 7 mg kg^{-1} day^{-1} in a patient with a population mean value for V of 0.25 l kg^{-1} and CL of 4 l h^{-1} are 72, 86 and 101 mg l^{-1} h. Bayesian approaches can be used with the AUC method [22] and have the advantage that useful information can be obtained from a single measured concentration.

Dosing in renal impairment and the elderly

The pharmacokinetics of the aminoglycosides are altered predictably when glomerular filtration is impaired. Patients with renal dysfunction, elderly patients and neonates will often have impaired clearance and dosing should allow for this. It should be noted that although there is a close relationship between aminoglycoside clearance and clinical estimates of renal function such as calculated creatinine clearance, this relationship is by no means exact. Extrarenal losses, such as through sequestration into third spaces and removal of fluid from third spaces, can also occur [23].

Once daily dosing during increasing renal impairment is complicated since the concentration-time profile approaches that of a continuous infusion. Therefore, the advantage of once daily dosing (high peak concentrations followed by a decline to unrecordable concentrations) is progressively lost with greater renal dysfunction.

The elderly may be particularly susceptible to nephrotoxicity and ototoxicity. This suggests a need for an even more vigilant approach to dosing, enhancing the case for therapeutic drug monitoring.

Sampling times

With multiple daily dosing, peak concentrations should be measured at least 0.5 h after the end of the infusion or a bolus dose, to allow for distribution to be complete. The exact time of sampling is not important but it should be recorded accurately. The ideal time to measure the trough concentration is at the end of the dosage interval. Any time within 0.5 h before the next dose is close enough in practice. The exact time should be recorded to allow pharmacokinetic interpretation. For once daily dosing, the timing of sampling is less clear and is dependent on the method of dose individualization that is followed.

How often to sample is also an important question. Aminoglycoside therapy is not usually for longer than 7 days except for bacterial endocarditis, or for cystic fibrosis by inhalation. With multiple-daily dosing, the frequency of monitoring should reflect this clinical situation, i.e. more often if patient is unstable, less often if stable. With once daily dosing it is logical to follow the same rules until new information allows these rules to be re-formulated.

For longer term therapy, such as for bacterial endocarditis, repeat monitoring may be performed at increasing intervals if the measured concentrations are relatively stable. Since the target concentrations for the treatment of endocarditis are often lower than conventional target concentrations, the need for stringent monitoring may be less. The aminoglycosides are used in this context more for a greater than additive effect, with the β-lactam antibiotic given concurrently, than for primary bactericidal efficacy.

Methods of analysis

The aminoglycosides are usually analysed using immunoassays such as EMIT (Enzyme Multiplied Immunoassay Technique; Syva and Behring diagnostic products, CA, USA) or FPIA (Fluorescence Polarization Immunoassay; Abbott, Abbott Park, IL, USA). Some aminoglycosides, such as tobramycin, netilmicin and amikacin, can be analysed using h.p.l.c., but this is not feasible for gentamicin because it is not a single substance. The EMIT and FPIA assays are relatively cheap, labour non-intensive, and have good reproducibility. They are not particularly sensitive, however. The limits of quantification are around 0.29 mg l^{-1} for the FPIA assay and 0.25 mg l^{-1} for the EMIT assay, which may be low enough for monitoring of trough concentrations using older dosing regimens but not low enough for assessing

trough concentrations during once-daily aminoglycoside dosing.

There are various quality assurance programmes (QAP) available worldwide. In Australasia the main QAP is that of the Royal College of Pathologists of Australia. In the United Kingdom, the equivalent is UKNEQAS Scheme organized by the Antimicrobial Reference Laboratory, Southmead Hospital, Bristol.

Interpretative problems

A minor laboratory problem relates to inactivation of gentamicin *in vitro* in the presence of ticarcillin and some other β-lactam antibiotics [24]. The effect is to lower the measured concentration of the aminoglycoside. The longer the time interval between collection and measurement, the greater the effect. The interaction between aminoglycosides and ticarcillin is due to drug complexing and can occur if the two drugs are mixed in a syringe or giving set. Such mixing should be avoided.

Cost effectiveness/benefits of monitoring

Monitoring of aminoglycoside concentrations, particularly with effective dose prediction, has been shown to be cost-effective [25–27]. Once daily aminoglycoside dosing is cheaper than multiple daily dosing in terms of nursing time and infusion equipment and may require less monitoring, although the exact strategy for monitoring has yet to be established [28]. It is possible that total daily doses of aminoglycoside lower than those used traditionally may prove to be effective. If so, toxicity will inevitably be less likely, and there will be less need for monitoring. Some studies appear to support the notion that therapeutic drug monitoring may not be necessary in patients with uncomplicated infections and normal renal function [29, 30]. However such studies have used crude measures of nephrotoxicity and ototoxicity and many patients appear to be underdosed. We believe that evidence must be robust before less stringent monitoring is adopted. It may be that, in certain specific circumstances, no monitoring is necessary, but the conclusion that monitoring is unnecessary is premature and potentially dangerous.

Vancomycin

Therapeutic drug monitoring is frequently employed during vancomycin therapy. Many have questioned the need for this, especially in uncomplicated patients with normal renal function [31–33]. However, most authors agree that monitoring is often useful.

Pharmacokinetics

The pharmacokinetics of vancomycin are relatively simple, with low protein binding, renal elimination with no metabolism, and no pharmacogenetic problems. V is around $0.4\ l\ kg^{-1}$, the CL approximates that of glomerular filtration rate and the $t_{½}$ is approximately 6 h in patients with normal renal function [2]. A complicating feature is that the pharmacokinetic profile is best described by a 2- or 3-compartment model which makes calculations difficult with a handheld calculator.

Why monitor vancomycin?

Vancomycin has a low therapeutic index, with nephrotoxicity and ototoxicity complicating therapy [34]. It has been traditional to monitor peak and trough concentrations, much as for the aminoglycosides. However, because the bactericidal action of vancomycin is quite different from that of the aminoglycosides, many have questioned the need to measure peak concentrations [35]. Vancomycin, like β-lactam antibiotics, works best if the concentration at the site of activity is maintained above the minimum inhibitory concentration (MIC) throughout the dose interval (so called time-dependent killing). This argues against the need for peak concentration measurement, and suggests that a continuous infusion may be the ideal. In practice, a continuous infusion is rarely administered, and spaced dosing at 6 or 12 h intervals is more common [35]. Efficacy can usually be assumed if the trough concentration is above the MIC of the infecting organism.

It is likely, although unproven, that toxicity is related to total vancomycin exposure. It would seem logical to monitor some index of vancomycin accumulation, such as a trough concentration. Variability of vancomycin concentrations in renal failure, renal support therapies, obesity, liver failure, neutropenia, malignancy and sepsis strengthens the case for monitoring in these conditions [36]. Similarly in the intensive care situation where drugs with important haemodynamic effects are coadministrated, therapeutic drug monitoring is strongly recommended [37].

Therapeutic ranges

Many putative 'therapeutic ranges' are illusionary. This is the case with vancomycin, at least for peak concentrations. Ranges for peak concentrations of 20–40 $mg\ l^{-1}$ have been widely quoted, but with little supportive evidence. The original report of Geraci *et al.* [38] suggested that peaks greater than 50 $mg\ l^{-1}$ should be avoided, based on two cases of ototoxicity at concentrations greater than 80 $mg\ l^{-1}$. Repetitive citation of this paper in the

literature has resulted in the 'establishment' of the peak concentration strategy. One of the problems with peak concentration measurement is that the range is meaningless unless the timing of sampling is also stated. A peak concentration of 40 mg l^{-1} has an entirely different meaning if the sample was taken just after the end of the infusion than if taken 1 or 2 h later. A survey of Australasian hospitals indicated that peaks were sampled from immediately postinfusion to 3 h later and yet were all considered with reference to the same therapeutic range of 20–40 mg l^{-1} [35]. The folly of this is obvious. In summary, there is little justification for peak concentration measurement except for use in pharmacokinetic modelling.

A stronger but incomplete case can be made for trough concentration monitoring. The given range of 5–10 mg l^{-1} has reasonable literature support and reflects the need for the concentration of antibiotics to be above the MIC of the organism for the duration of the dose interval. Concentrations below the MIC have been associated with therapeutic failure. The MIC of vancomycin is approximately 1.5 mg l^{-1} for many susceptible organisms. The protein binding of vancomycin is approximately 50% which would argue that the minimum total concentration should be at least 3 mg l^{-1}. Trough concentrations above 10 mg l^{-1} have been associated with an increased risk of nephrotoxicity [34, 39, 40]. It should be noted that nephrotoxicity with vancomycin alone is not common, usually around 5%, and is usually reversible [39]. A range of 5–10 mg l^{-1} for trough concentrations appears to have some validity.

Individualization of therapy

Approaches to dosing of vancomycin have included empirical, nomogram, individualized, and Bayesian methods [41]. It is generally accepted that vancomycin should be administered by slow infusion (for at least 1 h) to avoid the 'red man syndrome' [42].

Empirical dosing methods usually involve administration of a total daily dose in adults of 2 g daily in 2–4 divided doses. The relationship between vancomycin clearance and renal function has enabled dosing guidelines to take renal function into account [43]. This process has been refined into nomograms such as those of Matzke *et al.* [44] and Moellering *et al.* [45]. These nomograms recommend dosing on a mg kg^{-1} basis. It appears that total body weight is more appropriate than ideal body weight [46].

Individualized dosing methods based on the approach of Sawchuk & Zaske [14] for aminoglycosides have been used with varying success. The approach is based on a one-compartment model, and may lead to underestimation of the AUC [47]. At steady state this is unlikely to create significant error. Bayesian predictive models have also been used [48, 49]. They require a minimal number of samples, and can accommodate 1- or 2-compartment models. Pryka *et al.* [50] found that the 2-compartment model had less bias and more precision in non-steady-state situations, but once steady-state had been achieved the performance for the two models was similar. From a practical point of view, the individualized and Bayesian methods are probably equally useful at achieving target concentrations and subtle differences are unimportant [41]. There is far greater uncertainty about what the target concentrations of vancomycin should be.

Sampling times

The lack of support for peak concentration measurement suggests that only trough concentrations should be monitored. Trough concentrations should be measured just prior to the next dose, within half an hour of the end of the dosage interval. If pharmacokinetic modelling is contemplated, the measurement of another concentration is required early in the dose interval. A trough concentration is all that is necessary for Bayesian forecasting. This approach has proved both accurate and precise in most patients with normal renal function [51]. The exact timing of the sampling is unimportant but needs to be known for interpretation.

The question of how often to sample is also important. As with aminoglycosides, the clinical state may be changing during the early part of therapy. The timing of repeat sampling depends on the clinical circumstances. If very high doses are being used, or if the clinical condition is changing rapidly, sampling should be more frequent.

Methods of analysis

Vancomycin is generally analysed using immunoassays such as EMIT or FPIA. For research purposes vancomycin is also analysed by h.p.l.c [52]. The limit of quantification for the EMIT assay is 5 mg l^{-1} and 2.0 mg l^{-1} for FPIA. Quality control programs are the same as for the aminoglycosides.

Interpretative problems

Vancomycin degrades spontaneously at 37°C [53]. A metabolic product (CDP-1) accumulates in some circumstances (e.g. marked renal failure and patients on dialysis) and is detected by nonspecific assays such as FPIA [54]. FPIA may overestimate vancomycin concentrations by over 50% in patients with renal failure [55].

Cost-effectiveness/benefits of monitoring

Information about the true cost-effectiveness of monitoring of vancomycin is lacking. One study demonstrated a decrease in nephrotoxicity associated with a therapeutic drug monitoring service [56] and another has demonstrated cost savings [57]. A nomogram approach based on actual body weight, estimated CL_{Cr} and a targeted trough concentration of 5–20 mg l^{-1} in 120 patients with $CL_{Cr} > 30$ ml min^{-1} proved cheaper and as effective as a traditional pharmacokinetic approach [58].

Teicoplanin

Teicoplanin, like vancomycin, is a glycopeptide antibiotic that acts in a time-dependent manner. Its pharmacokinetics include a V of around 1 l kg^{-1}, protein binding of 90% and a prolonged terminal $t_{1/2}$ of 150–180 h which is important during long-term therapy [59]. Teicoplanin is cleared unchanged renally, and doses should be reduced appropriately in patients with renal dysfunction. Dose-related nephrotoxicity and ototoxicity appear to be much less of a problem than with vancomycin [60].

Many methods have been used to quantify teicoplanin concentrations but none is entirely satisfactory for routine clinical monitoring [59]. FPIA is the most convenient method, but it may not be accurate at low concentrations [61]. Therapeutic drug monitoring of teicoplanin is performed occasionally to ensure efficacy. Trough concentrations of > 10 mg l^{-1} have been recommended for most infections and > 20 mg l^{-1} for endocarditis [62]. Post-dose concentrations of > 40 mg l^{-1} may improve outcome [36]. Monitoring has been advocated particularly in patients who have high clearance, such as children, intravenous drug abusers, burns patients and patients with neutropenia [36, 63]. 'Red man syndrome' appears to be much less of a problem with teicoplanin than with vancomycin [64].

Antifungal agents

Individualization of antifungal therapy has been proposed and reviewed [62, 65]. No specific recommendations have been developed, although under certain circumstances drug monitoring may assist therapy. The case for monitoring is perhaps strongest for flucytosine and itraconazole. There may be a case for occasional monitoring of other azoles, such as ketaconazole and fluconazole, to ensure that adequate concentrations are achieved. As is the case with all therapeutic drug monitoring, if it provides an answer to a clearcut question, then it is worthwhile.

Flucytosine

Flucytosine is a synthetic antifungal agent that is selectively converted by fungal cells to fluorouracil which replaces uracil thereby disturbing protein synthesis. Flucytosine is well absorbed, with a V similar to that of body water and it is eliminated unchanged through the kidneys [66]. Doses should be appropriately adjusted for renal dysfunction [67]. Monitoring with flucytosine is not so much to ensure adequate concentrations for efficacy but to avoid toxicity. At high concentrations, bone marrow toxicity and hepatotoxicity (both usually reversible) have been reported [68]. The predominant bone marrow toxicity is thrombocytopenia, which along with hepatotoxicity seems to occur with greater frequency at peak concentrations > 100 mg l^{-1} [69].

Stamm *et al*. [70] recommended avoiding peak concentrations of > 100 mg l^{-1} (2 h after an oral dose, or 30 min after an i.v. dose) to prevent bone marrow toxicity. They advocated more frequent monitoring in patients with renal dysfunction or existing bone marrow depression. Toxicity appears to be a particular problem when concentrations rise as a result of renal insufficiency induced by amphotericin B which is often used concurrently [67]. While a lower end of the 'therapeutic range' has not been established for flucytosine, concentrations < 25 mg l^{-1} should be avoided to prevent emergence of resistance [71]. If administration is by continuous infusion a serum concentration of 50 mg l^{-1} is recommended [66].

Itraconazole

Itraconazole is a relatively new synthetic triazole broad spectrum antifungal agent. It is used increasingly in leukaemia and AIDS patients and during transplantation, especially for the treatment and prophylaxis of aspergillus infections.

Itraconazole is highly lipophilic, highly protein bound ($> 99\%$), extensively metabolized, has nonlinear pharmacokinetics and is subject to enzyme inhibition [67, 72, 73]. Absorption is variable, and particularly poor in the unfed state (high gastric pH) and in patients with AIDS or bone marrow transplants [74]. These are all good reasons for therapeutic drug monitoring, especially to ensure that concentrations are adequate. Trough concentrations of itraconazole above 250 μg l^{-1} have been suggested as satisfactory for most fungal infections [75]. A combined total concentration of > 1000 μg l^{-1} for the parent plus the active metabolite hydroxyitraconazole, has also been recommended [76]. Adverse effects related to itraconazole are largely gastrointestinal and appear to be dose-related. Itraconazole, which is metabolized by CYP3A4, is subject to enzyme induction by drugs such as rifampicin,

phenytoin and carbamazepine and is itself a strong inhibitor of CYP3A4 [73].

A problem during therapeutic drug monitoring of itraconazole is that concentrations are assay-dependent, with the metabolite being recorded as parent in non-specific microbiological assays. The preferred method of analysis is h.p.l.c., with both parent and metabolite assessed [77].

Further work is necessary before the place of therapeutic drug monitoring for itraconazole is firmly established, although monitoring is recommended in life-threatening fungal infections. Steady state may take some time to be reached (1–2 weeks) because of the nonlinear pharmacokinetics.

Conclusion

Aminoglycosides should continue to be monitored even with 'once daily' dosing until it is clear that there are circumstances where monitoring is unnecessary. Justification for vancomycin monitoring is less clear, and there may be circumstances, such as short courses and short dose intervals in relatively uncomplicated patients, in which monitoring may not be necessary. For the other drugs it is likely that monitoring is only feasible in larger teaching hospitals where expertise is available for useful interpretation.

References

1 Begg EJ, Barclay ML. Aminoglycosides—50 years on. *Br J Clin Pharmacol* 1995; 39: 597–603.

2 Benet LZ, Williams RL. Design and optimisation of dosage regimens. In *The Pharmacological Basis of Therapeutics*, eds. Gilman AG, Rall TW, Nies AS, Taylor P. Eighth Edition. New York, Pergamon Press, 1990: 1650–1735.

3 Zaske DE, Cipolle RJ, Solem LD, Strate RG. Rapid individualization of gentamicin dosage regimens in 66 burn patients. *Burns* 1981; **7**: 215–220.

4 Hoey LL, Tschida SJ, Rotschafer JC, Guay DRP, Vance-Bryan K. Wide variation in single daily dose aminoglycoside pharmacokinetics in patients with burn injuries. *J Burn Care Rehabil* 1997; **18**: 116–124.

5 Barclay ML, Begg EJ. Aminoglycoside toxicity and relation to dose regimen. *Adverse Drug React Toxicol Rev* 1994; **13**: 207–234.

6 Noone P, Parsons TMC, Pattison JR, Slack RCB, Garfield-Davies D, Hughes K. Experience in monitoring gentamicin therapy during treatment of serious gram-negative sepsis. *Br Med J* 1974; **1**: 477–481.

7 Moore RD, Smith CR, Lietman PS. The association of aminoglycoside plasma levels with mortality in patients with gram-negative bacteremia. *J Infect Dis* 1984; **149**: 443–448.

8 Moore RD, Smith CR, Lietman PS. Association of aminoglycoside plasma levels with therapeutic outcome in gram-negative pneumonia. *Am J Med* 1984; **77**: 657–662.

9 Prins JM, Buller HR, Kuijper EJ, Tange RA, Speelman P. Once versus thrice daily gentamicin in patients with serious infections. *Lancet* 1993; **341**: 335–339.

10 Konrad F, Wagner R, Neumeister B, Rommel H, Georgieff M. Studies on drug monitoring in thrice and once daily treatment with aminoglycosides. *Intensive Care Med* 1993; **19**: 215–220.

11 Ter Braak EW, De Vries PJ, Bouter KP, *et al*. Once-daily dosing regimen for aminoglycoside plus β-lactam combination therapy of serious bacterial infections: Comparative trial with netilmicin plus cefriaxone. *Am J Med* 1990; **89**: 58–66.

12 Begg EJ, Barclay ML, Duffull SB. A suggested approach to once-daily aminoglycoside dosing. *Br J Clin Pharmacol* 1995; **39**: 605–609.

13 Morike K, Schwab M, Klotz U. Use of aminoglycosides in elderly patients—pharmacokinetic and clinical considerations. *Drugs Aging* 1997; **10**: 259–277.

14 Sawchuk RJ, Zaske DE, Cipolle RJ, Wargin WA, Strate RG. Kinetic model for gentamicin dosing with the use of individual patient parameters. *Clin Pharmacol Ther* 1977; **21**: 362–369.

15 Begg EJ, Atkinson HC, Jeffery GM, Taylor NW. Individualised aminoglycoside dosage based on pharmacokinetic analysis is superior to dosage based on physician intuition at achieving target plasma drug concentrations. *Br J Clin Pharmacol* 1989; **28**: 137–141.

16 Hickling K, Begg E, Moore ML. A prospective randomised trial comparing individualised pharmacokinetic dosage prediction for aminoglycosides with prediction based on estimated creatinine clearance in critically ill patients. *Intensive Care Med* 1989; **15**: 233–237.

17 Burton ME, Brater DC, Chen PS, Day RB, Huber PJ, Vasko MRI. A Bayesian feedback method of aminoglycoside dosing. *Clin Pharmacol Ther* 1985; **37**: 349–355.

18 MacGowan A, Reeves D. Serum aminoglycoside concentrations: the case for routine monitoring. *J Antimicrob Agents* 1994; **34**: 829–837.

19 Nicolau DP, Freeman CD, Belliveau PP, Nightingale CH, Ross JW, Qintiliani R. Experience with a once-daily aminoglycoside program administered to 2184 adult patients. *Antimicrob Agents Chemother* 1995; **39**: 650–655.

20 El Bakri F, Pallett A, Smith AG, Duncombe AS. Ototoxicity induced by once-daily gentamicin. *Lancet* 1998; **351**: 1407–1408.

21 Finnell DL, Davis GA, Cropp CD, Ensom MH. Validation of the Hartford nomogram in trauma surgery patients. *Ann Pharmacother* 1998; **32**: 417–421.

22 Duffull SB, Kirkpatrick CMJ, Begg EJ. Comparison of two Bayesian approaches to dose-individualisation for once daily dosing regimens. *Br J Clin Pharmacol* 1997; **43**: 125–135.

23 Hickling KG, Begg EJ, Perry RE, Atkinson HC, Sharman JR. Serum aminoglycoside clearance is predicted as poorly by renal aminoglycoside clearance as by creatinine clearance in critically ill patients. *Crit Care Med* 1991; **19**: 1041–1047.

24 Trissel LA. (ed). Handbook on injectable drugs, sixth edition. *Bethesda, USA: Am Soc Hospital Pharmacists* 1990; 358–361.

25 Destache CJ, Meyer SK, Rowley KM. Does accepting pharmacokinetic recommendations impact hospitalization? A cost-benefit analysis. *Ther Drug Monit* 1990; **12**: 427–433.

26 Crist KD, Nahata MC, Ety J. Postive impact of a therapeutic drug-monitoring program on total aminoglycoside dose and cost of hospitalization. *Ther Drug Monit* 1987; **9**: 306–310.

27 Van Lent-Evers NAEM, Mathot RAA, Geus WP, Van Hout BA, Vinks AATMM. Impact of goal-orientated and model-based clinical pharmacokinetic dosing of aminoglycosides on clinical outcome: a cost-effectiveness analysis. *Ther Drug Monit* 1999; **21**: 63–73.

28 Nicolau DP, Wu AHB, Finocchiaro S, *et al*. Once-daily aminoglycoside dosing: Impact on requests and costs of therapeutic drug monitoring. *Ther Drug Monit* 1996; **18**: 263–266.

29 Christensen S, Ladefoged K, Frimodt-Moller N. Experience with once daily dosing of gentamicin: considerations regarding dosing and monitoring. *Chemotherapy* 1997; **43**: 442–450.

30 Logsdon BA, Phelps SJ. Routine monitoring of gentamicin serum concentrations in pediatric patients with normal renal function is unnecessary. *Ann Pharmacother* 1997; **31**: 1539–1540.

31 Edwards DJ, Pancorbo S. Routine monitoring of serum vancomycin concentrations: waiting for proof of its value. *Clin Pharm* 1987; **6**: 652–654.

32 Freeman CD, Quintiliani R, Nightingale CH. Vancomycin therapeutic drug monitoring: is it necessary? *Ann Pharmacother* 1993; **27**: 594–598.

33 Saunders NJ. Why monitor peak vancomycin concentrations? *Lancet* 1994; **344**: 1748–1750.

34 Duffull SB, Begg EJ. Vancomycin toxicity. What is the evidence for dose dependency? *Adverse Drug React Toxicol Rev* 1994; **13**: 103–114.

35 Duffull SB, Chambers ST, Begg EJ. How vancomycin is used in clinical practice—a survey. *Aust NZ J Med* 1993; **23**: 662–666.

36 MacGowan AP. Pharmacodynamics, pharmacokinetics and therapeutic drug monitoring of glycopeptides. *Ther Drug Monit* 1998; **20**: 473–477.

37 Pea F, Porreca L, Baraldo M, Furlanut M. High vancomycin dosage regimens required by intensive care unit patients cotreated with drugs to improve haemodynamics following cardiac surgical procedures. *J Antimicrob Chemother* 2000; **45**: 329–335.

38 Geraci JE, Heilman FR, Nichols DR, Wellman WE. Antibiotic therapy of bacterial endocarditis. VII. Vancomycin for acute micrococcal endocarditis. *Staff Meetings Mayo Clinic* 1958; **33**: 172–181.

39 Rybak MJ, Albrecht LM, Boike SC, Chandresekar PH. Nephrotoxicity of vancomycin, alone and with an aminoglycoside. *J Antimicrob Chemother* 1990; **25**: 679–687.

40 Cimino MA, Rotstein C, Slaughter RL, Emrich LJ. Relationship of serum antibiotic concentrations to nephrotoxicity in cancer patients receiving concurrent aminoglycoside and vancomycin therapy. *Am J Med* 1987; **83**: 1091–1096.

41 Garrelts JC, Godley PJ, Horton MW, Karboski JA. Accuracy of Bayesian, Sawchuk-Zaske, and nomogram dosing methods for vancomycin. *Clin Pharm* 1987; **6**: 799.

42 Healy DP, Sahai JV, Fuller SH, Polk RE. Vancomycin-induced histamine release and 'red man syndrome': Comparison of 1 and 2 hour infusions. *Antimicrob Agents Chemother* 1990; **34**: 550–555.

43 Lake KD, Peterson CD. A simplified dosing method for initiating vancomycin therapy. *Pharmacotherapy* 1985; **5**: 340–344.

44 Matzke GR, McGory RW, Halstenson CE, Keane WF. Pharmacokinetics of vancomycin in patients with various degrees of renal function. *Antimicrob Agents Chemother* 1984; **25**: 433–437.

45 Moellering RC Jr. Pharmacokinetics of vancomycin. *J Antimicrob Chemother* 1984; **14**: 43–52.

46 Penzak SR, Gubbins PO, Rodvold KA, Hickerson SL. Therapeutic drug monitoring of vancomycin in a morbidly obese patient. *Ther Drug Monit* 1998; **20**: 261–265.

47 Ackerman BH, Olsen KM, Padilla CB. Errors in assuming a one-compartment model for vancomycin. *Ther Drug Monit* 1990; **12**: 304–305.

48 Burton ME, Gentle DL, Vasko MR. Evaluation of a Bayesian method for predicting vancomycin dosing. *DICP* 1989; **23**: 294–299.

49 Hurst AK, Yoshinaga MA, Mitani GH, Foo KA, Jelliffe RW, Harrison EC. Application of a Bayesian method to monitor and adjust vancomycin dosage regimens. *Antimicrob Agents Chemother* 1990; **34**: 1165–1171.

50 Pryka RD, Rodvold KA, Garrison M, Rotschafer JC. Individualizing vancomycin dosage regimens: one- versus two compartment Bayesian models. *Ther Drug Monit* 1989; **11**: 450–454.

51 Andres I, Lopez R, Pou L, Pinol F, Pascual C. Vancomycin monitoring: one or two serum levels? *Ther Drug Monit* 1997; **19**: 614–619.

52 Hu MW, Anne L, Forni T, Gottwald K. Measurement of vancomycin in renally impaired. *Analytical Abstracts* 1991; **53**: l321–l1322.

53 White LO, Edwards R, Holt HA, Lovering AM, Finch RG, Reeves DS. The in-vitro degradation at 37° C of vancomycin in serum, CAPD fluid and phosphate-buffered saline. *J Antimicrob Chemother* 1988; **22**: 739–745.

54 Morse GD, Nairn KD, Bertino SJ, Walshe JJ. Overestimation of vancomycin concentrations utilising fluoescence polarising immunoassay in patients on peritoneal dialysis. *Ther Drug Monit* 1987; **9**: 212–215.

55 Somerville AL, Wright DH, Rotschafer JC. Implications of vancomycin degradation products on therapeutic drug monitoring in patients with end-stage renal disease. *Pharmacotherapy* 1999; **19**: 702–707.

56 Welty TE, Copa AK. Impact of vancomycin therapeutic drug monitoring on patient care. *Ann Pharmacother* 1994; **28**: 1399.

57 Lake KD, Peterson CD. Evaluation of a method for individualising vancomycin therapy: experience in 205 patients. *Pharmacotherapy* 1988; **8**: 284–286.

58 Karam CM, McKinnon PS, Neuhauser MM, Rybak MJ. Outcome assessment of minimizing vancomycin and dosing adjustments. *Pharmacotherapy* 1999; **19**: 257–266.

59 Brogden RN, Peters DH. Teicoplanin. A reappraisal of its antimicrobial activity, pharmacokinetic properties and therapeutic efficacy. *Drugs* 1994; **47**: 823–854.

60 Wood MJ. The comparative efficacy and safety of teicoplanin and vancomycin. *J Antimicrob Chemother* 1996; **37**: 209–222.

61 Bourget P, Lesne-Hulin A, Sertin A, Maillot A, Alaya M, Martin C. Fluorescence polarization immunoassay: Does it always represent a reliable method to monitor treatment with teicoplanin? Comparison with data obtained by high-performance liquid chromatography. *Int J Pharmaceut* 1997; **146**: 174.

62 Reeves DS, MacGowan AP, Holt HA, Lovering AM, Warnock DW, White LO. Therapeutic monitoring of antimicrobials. *J Antimicrob Chemother* 1995; **35**: 213–226.
63 Steer JA, Papini RP, Wilson AP, *et al*. Pharmacokinetics of a single dose of teicoplanin in burn patients. *J Antimicrob Chemother* 1996; **37**: 545–553.
64 Sahai J, Healy DP, Shelton MJ, Miller JS, Ruberg SJ, Polk R. Comparison of a vancomycin and teicoplanin-induced histamine release and 'red man syndrome'. *Antimicrob Agents Chemother* 1990; **34**: 765–769.
65 Summers KK, Hardin TC, Gore SJ, Graybill JR. Therapeutic drug monitoring of systemic antifungal therapy. *J Antimicrob Chemother* 1997; **40**: 753–764.
66 Vermes A, Guchelaar H-J, Dankert J. Flucytosine: a review of its pharmacology, clinical indications, pharmacokinetics, toxicity and drug interactions. *J Antimicrob Chemother* 2000; **46**: 171–179.
67 Lyman CA, Walsh TJ. Systemically administered antifungal agents. A review of their clinical pharmacology and therapeutical applications. *Drugs* 1992; **44**: 9–35.
68 Kauffman CA, Frame PT. Bone marrow toxicity associated with 5 fluorocytosine therapy. *Antimicrob Agents Chemother* 1977; **11**: 244–247.
69 Vermes A, Van der Sijs H, Guchelaar H-J. Flucytosine: correlation between toxicity and pharmacokinetic parameters. *Chemotherapy* 2000; **46**: 86–94.
70 Stamm AM, Diasio RB, Dismukes WE, Shadomy S, Cloud GA, Bowles CA. Toxicity of amphotericin B plus flucytosine in 194 patients with cryptococcal meningitis. *Am J Med* 1987; **83**: 236–242.
71 Viviani MA. Flucytosine—what is its future? *J Antimicrob Chemother* 1995; **35**: 241–244.
72 Tucker RM, Denning DW, Hanson LH, *et al*. Interaction of azoles with rifampin, phenytoin and carbamazepine: *in vitro* and clinical observations. *Clin Infect Dis* 1992; **14**: 165–174.
73 Poirier JM, Cheymol G. Optimisation of intraconazole therapy using target drug concentrations. *Clin Pharmacokin* 1998; **35**: 164–473.
74 Kintzel PE, Rollins CJ, Yee WJ, List AF. Low itraconazole serum concentrations following administration of itraconazole suspension to critically ill allogenic bone marrow transplant recipients. *Ann Pharmacother* 1995; **29**: 140–143.
75 Tricot G, Joosten G, Boogaerts MA, Van de Pitte J, Cauwenbergh G. Ketoconazole vs itraconazole for antifungal prophylaxis in patients with severe granulocytopenia: preliminary results of two randomised studies. *Rev Infect Dis* 1987; **9**(Suppl 1): 94–99.
76 Van Custen J. The *in vitro* antifungal spectrum of itraconazole. *Mycoses* 1989; **32**: 7–13.
77 Poirier JM, Lebot M, Descamps P, Levy M, Cheymol G. Determination of itraconazole and its active metabolite in plasma by column liquid chromatography. *Ther Drug Monit* 1994; **16**: 601.