Radioassay Profiles: A Laboratory Response to Cost Containment

Karen L. Blondeau, Susan M. Burpo, and Richard A. Holmes

University of Missouri-Columbia Hospital and Clinics, and Harry S. Truman Memorial Veterans Hospital, Columbia, Missouri

A clinical laboratory profile is a cadre of tests that addresses a medical problem in a more cost-effective manner than the performance of each test individually and sporadically. Nonisotopic profiles as well as radioassay profiles have been offered by reference laboratories for several years. Most hospital-based laboratories have been directed away from instituting disease-oriented profiles because certain profile tests are only rarely requested, which makes them economically impractical to perform. There is also a tendency in teaching hospitals to individualize each requested test because of the belief that it enhances physician analytical skills. Recent experience in our laboratory has shown that by carefully developing an aminoglycoside profile in close collaboration with the hospital pharmacy pharmacokinetic service the cost for the drug assays and the expense to the assaying laboratory can be reduced while significantly improving patient care. We can provide a gentamicin or tobramycin profile, consisting of three or more blood samples and run as batch assay, at a cost that is less than the price of two individual assays. This has been done without creating a significant revenue loss to our laboratory.

Our central radioassay laboratory provides service to our two hospitals with a battery of 25 in-house radioassays; an additional 30–40 radioassays are provided from different reference laboratories. Approximately 2,200 patient samples are received each month from the two hospitals. Our laboratory is equipped with two programmable multiwell scintillation counters, two refrigerated centrifuges, two fume hoods, several storage refrigerators, a variety of pipetting equipment, and two computers programmed to report the results.

The hospitals interact through a cooperative sharing agreement that has eliminated duplicate services. For example, the exclusiveness of our laboratory is demonstrated by a reimbursement policy in which the parent hospital is paid for each completed radioassay without considering collection from the patient. Although patient collection rates have consistently been low (~ 65%), the charges remain price-competitive because of our high sample volume, efficient use of personnel and equipment, and the use of profiles or series for responsible cost containment.

For reprints contact: Karen L. Blondeau, Nuclear Medicine Service, Harry S. Truman Veterans Hospital, 800 Hospital Dr., Columbia, MO 65201.

MATERIALS AND METHODS

The aminoglycosides, gentamicin and tobramycin, are among the in-house radioassays performed in our central radioassay laboratory. Both antibiotics are used therapeutically against several gram-negative bacteria and are rarely given prophylactically. Both gentamicin and tobramycin are excreted in the kidneys primarily by glomerular filtration (*1*). Since dose-related nephrotoxicity and ototoxicity have been reported when their narrow therapeutic ranges are exceeded over time, it is generally recommended that their optimum therapeutic doses be calculated (*1–4*). The concept of individualized aminoglycoside dosing was first introduced in 1976 (*5*). However, only a few institutions have adopted this strategy to date.

A clinical pharmacy consultation service was started in January 1982 at the University of Missouri-Columbia Hospital and Clinics. Initially, this pharmacy service was limited to only those patients admitted to the five intensive care units of the hospital. It was not until satellite pharmacies were established throughout the hospital that the service was expanded to include all hospitalized patients (*5*). For a short time, the Harry S. Truman Memorial Veterans Hospital provided a similar service, but it was discontinued when finances declined.

A consultation request from the physician to the clinical pharmacy initiates the aminoglycoside pharmacokinetic protocol. To calculate the optimum dose of aminoglycoside, the clinical pharmacist uses pharmacokinetic measurements that reflect the specific action and biodistribution of these drugs (*2,5*).

Determining the Volume of Drug Distribution

The aminoglycosides are administered intravenously in an initial dose of 1.7 mg/kg as the sulfate salt. They are infused over a 15–30 min period. Certain clinical factors such as ex-

tremity edema or general dehydration can adversely influence the rate of drug absorption and distribution. It is important that the patient's current body weight be measured and incorporated into the calculations since this information will be used to correct for changes in the extra-cellular space (*2,5*).

Rate and Amount of Tissue Absorption

Regardless of the prescribed dose, the actual amount of drug elimination is related directly to renal function. Diminished renal function is frequently observed in the elderly and/or critically ill patient and may increase body concentration of the drug and maintain a high serum level (*1,3,4*).

Glomerular Filtration Clearance

Since aminoglycosides are excreted by glomerular filtration, it has been recommended that renal function be assessed before beginning drug therapy (*3,7*). Appel and Neu (*3*) reported a 2-hr blood half-life of gentamicin in patients with normal renal function (120 ml/min); whereas in patients with GFRs of < 10 ml/min, the half-lives were as long as 55 hr. Hemodialysis and peritoneal dialysis also alter aminoglycoside clearance. Hemodialysis has been shown to remove 50–70% of gentamicin in 6–12 hr (*3*). The serum creatinine level is commonly used to evaluate renal function and has been employed to determine the aminoglycoside dose interval (*7*). A serum creatinine level of 1.5 mg/dl requires a dosing interval of every 8 hr while a serum creatinine > 3 mg/dl may require dosing every 24 hr (*5*).

In patients with normal renal function, a preinfusion blood sample is taken prior to the administration of the test dose. Two postinfusion samples are taken at one hour following the infusion and a second after a period equal to 1 or 2 estimated half lives of the drug. The drug half-life is calculated by multiplying the patient's most recent serum creatinine concentration by 3 (*5*). A third postinfusion sample may be collected after a period equal to 3 half lives of the drug. If the most recent creatinine is > 3 mg/dl, three postinfusion serum aminoglycoside determinations should be collected over the next 12–24 hr (*5*).

Dialysis patients are routinely scheduled for four sample collections. The first, one hour after the dose is administered, the second, immediately pre-dialysis, the third, 1 hr post-dialysis, and the fourth, a preinfusion sample drawn prior to the next administered dose (trough level) (*5*).

Once the patient's clinical condition has stabilized, only two samples (preinfusion and 1-hr postinfusion) are required. If the patient begins to show clinical signs of renal or fluid imbalance, an additional sample is then required and three samples become routine (*5*).

At our institution, the serum peak and trough levels of gentamicin and tobramycin are usually 5–8 mcg/ml and 1 mcg/ml, respectively, depending on the patient's condition. A trough level of 2 mcg/ml may be acceptable in patients with renal insufficiency to prevent prolonged periods of subtherapeutic drug concentration (*5*). A special gentamicin dosing protocol is followed in our institution for neonatal patients, and a special tobramycin protocol is followed for children with cystic fibrosis.

The number of daily patient samples received for aminoglycoside assay is a reflection of the hospital's case mix and the type and severity of the patient's infection. The University of Missouri–Columbia Hospital and Clinics is a tertiary care hospital and these types of infections constitute 5–8% of the total hospital admissions.

Therapeutic Window

Figure 1 illustrates the dosing plan we use for aminoglycoside treatment within the narrow therapeutic window. An acceptable peak level is < 10 mcg/ml but > 4 mcg/ml, with the trough level 1–2 mcg/ml. Serum concentrations > 10 mcg/ml are in the toxic range. Although the peak level will usually indicate therapeutic success, prolonged subtoxic peak levels or repeated overdosing can result in renal and inner ear toxicity. Subtherapeutic levels of either gentamicin or tobramycin will usually result in clinical failure (*8,9*). The dilemma facing both the clinician and clinical pharmacist is to select the optimum dose of aminoglycoside sufficient to treat the disease and yet avoid the severe side-effects.

Aminoglycoside Serum Concentration

The sensitivity of the radioassay method for aminoglycoside monitoring is well established, and its measurements correlate well with other testing methods (*10,11,13*). However, Rotschafer et al. (*12*) found that although radioimmunoassay (RIA) and fluorescent polarization immunoassay (FPI) are comparable, certain calculated pharmacokinetic conditions resulted in significant differences in dose recommendations and suggested that this could also occur between other testing methods. They also concluded that careful monitoring of trough and peak levels is necessary regardless of the method used (*12*).

The values from our laboratory are accurate for determining the dose curve. Following administration, the aminoglycoside serum concentrations can be fit to a one or two-compartment pharmacokinetic model (*5*). One hour after administration and the rapid initial intravascular mixing (distribution half-life = 5 – 15 min), the University of Missouri–Columbia Hospital and Clinics pharmacist fits the time and serum concentration to the one-compartment open model

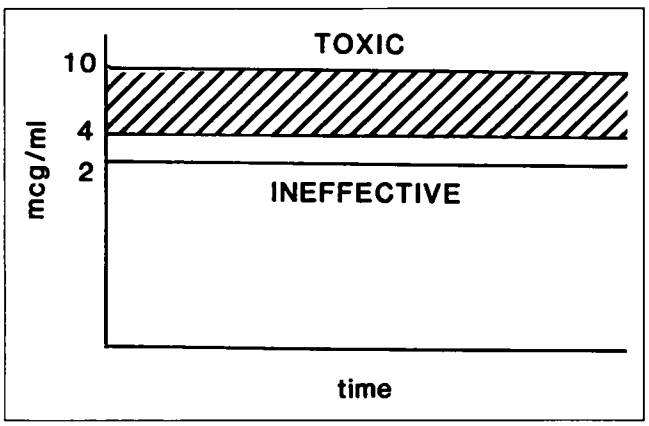

FIG. 1. Shaded area indicates narrow therapeutic window of > 4 mcg/ml – < 10 mcg/ml.

using a programmable calculator equipped with a printer.* Results are plotted semilogarithmically to determine pharmacologic regression (clearance). The relationship of time and the log of serum concentration is linear and allows one to visually confirm that the recommended peak level matches the extrapolated peak value. It can also identify possible errors in the serum concentration.

Cost-Effective Fee Determinations

Charges for the profiles are cost effective for the following reasons: 1) the consultation service provided by pharmacy; 2) the low price of aminoglycoside radioassays; and 3) the economy of performing batch serum assays by the laboratory. The pharmacy service charges $40.00 for each completed pharmacokinetic consultation and $20.00 for partially completed consultations that are cancelled by the primary care clinician before they are completed. Cost to the patient for a dose of gentamicin (as of March 1985) is $0.27 per 80 mg, while a dose of tobramycin costs $4.78 per 80 mg. This is nearly a 17:1 difference in price and indicates an economic preference for gentamicin.

To reduce the cost to the patient of multiple individual aminoglycoside samples, we designed a cost-effective single multiple-sample batch radioassay. Our laboratory charge to the UMCHC patient for a single aminoglycoside sample is $29.00. The charge includes an estimated 1 hr turn-around time for processing the sample, receiving it in the laboratory, performing the assay, and reporting the results. Our laboratory not only provides a written report for each assay, but all therapeutic drug results are also called to the patient's floor and to the satellite pharmacy immediately after they are completed.

The charge for an aminoglycoside profile is $45.00 per batch of three or more samples that have all been assayed in the same run. Currently, the cost of a commercial aminoglycoside kit is approximately $60.00/100 tubes or $0.60 per tube. Each assay is run in duplicate including the controls. The profile charge results in a significant savings to the patient of between $32 and $60 when three or five samples are requested for each consultation. The profile charge assumes that three or more samples on a single patient will be received in a composite batch or individually throughout the day until a specific cutoff time of 1:00 p.m. Since all samples are run in a single batch this eliminates the need for more than one set of standards and controls.

Pharmacy Service coordinates all protocol patients so that the majority of the samples arrive in time for the daily run. On occasion, however, an additional run may be added in the morning if requested by the clinical pharmacist to complete a patient dosage determination.

Clinical Use of the Aminoglycoside Profile

Figure 2 demonstrates the increased use of the gentamicin profile during the initial period. During the same period, the tobramycin profile did not increase concomitantly and the overall use of tobramycin appears to have decreased. This may be attributed to the fact that in early March 1985, the house staff was first informed of the significant price differential of the two drugs and were encouraged to use gentamicin instead of tobramycin.

The three months of accumulated data (February–April, 1985) indicate a slight reduction in aminoglycoside revenues that appear to result from a decrease in the overall number of individual assays ordered rather than a marked increase in the number of profiles requested. We project that the economics of the aminoglycoside profiles will probably increase their use, which should aid in the maintenance of our present financial advantage.

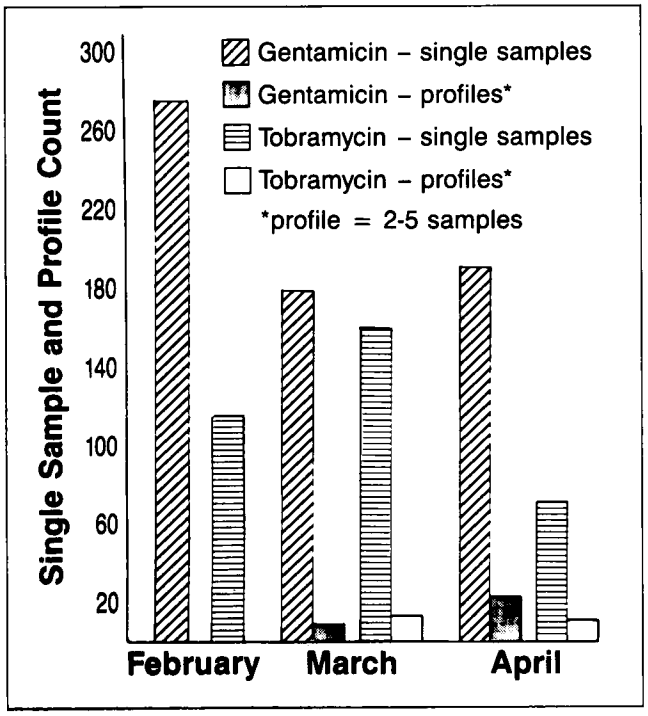

FIG. 2. Bars indicate trend in aminoglycoside usage since introduction of the profile.

RESULTS AND DISCUSSION

We feel that our present and projected success in using the aminoglycoside profiles results from the following three factors:

1. Excellent Communication and Coordination. With the Pharmacy Service serving as the key coordinator, consultation is conducted in an extremely efficient manner. Ordered blood samples are drawn properly by an i.v. team nurse and are processed and delivered expeditiously to the central radioassay laboratory. At check-in, those requests indicating the aminoglycoside profile are isolated and refrigerated until all specimens are received before the cutoff time and the batch radioassays are run.
2. Single Test. Aminoglycoside levels lend themselves well to the profile design. Multiple samples of a single drug on the same patient keep logistics simple.
3. Efficiency of the Central Radioassay Laboratory. In our hospital and laboratory, radioimmunoassay of the aminoglycosides has been the preferred method of serum

measurement since 1976. We have had essentially no problems adjusting to the hospital's call for cost containment because of the government's change in prospective Medicare payment. Nor has the need to add an occasional radioassay run to the daily schedule proven to be a problem from either the aspect of manpower or cost. We project that the profiles will increase our radioassay volume, resulting in an improvement in our income and allowing us to expand the clinical activities of our laboratory. We are currently preparing profiles for hyperthyroidism (serum T_4, serum T_3, free T_4), hypothyroidism (serum T_4, TSH, T_3RU), and amenorrhea (FSH, LH, prolactin) which we hope to offer in the near future.

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FOOTNOTE

*Texas Instrument-59 Model, Dallas, TX.

REFERENCES

1. Whelton A, Solez K. Aminoglycoside nephrotoxicity—A tale of two transports. *J Lab Clin Med* 1982;99:148-55.

2. Schottelius DD. Therapeutic drug monitoring: Fundamental pharmacologic concepts. *J Clin Immunol* 1984;7:247-53.

3. Appel GB, Neu HC. The nephrotoxicity of antimicrobial agents (second of three parts). *New Eng J Med* 1977;296:722-28.

4. Schentag JJ, Cerra FB, Plaut ME. Clinical and pharmacokinetic characteristics of aminoglycoside nephrotoxicity in 201 critically ill patients. *Antimicrob Agents Chemother* 1982;21:721-26.

5. Moore RA, Tonnies FE. Aminoglycoside dosing service provided by baccalaureate-level pharmacists. *Am J Hosp Pharm* 1984;41:98-105.

6. Noone P, Parsons TMC, Pattison JR, et al. Experience in monitoring gentamicin therapy during treatment of serious gram-negative sepsis. *Br Med J* 1974;1:477-81.

7. Cockcroft DW, Gault MH. Prediction of creatinine clearance from serum creatinine. *Nephron* 1976;16:31-41.

8. Flynn TW, Pevonka MP, Yost RL, et al. Use of serum gentamicin levels in hospitalized patients. *Am J Hosp Pharm* 1978;35:806-08.

9. Jackson GG, Riff LJ. Pseudomonas bacteremia: Pharmacologic and other bases for failure of treatment with gentamicin [Suppl]. *J Inf Dis* 1971;124: S185-91.

10. Pippenger CE, Schottelius DD. Techniques utilized in therapeutic drug monitoring. *J Clin Immunol* 1984;7:254-61.

11. Fukuchi H, Yoshida M, Tsukiai S, et al. Comparison of enzyme immunoassay, radioimmunoassay, and microbiologic assay for amikacin in plasma. *J Clin Immunol* 1984;7:690-93.

12. Rotschafer JC, Berg HC, Nelson RB, et al. Observed differences in gentamicin pharmacokinetic parameters and dosage recommendations determined by fluorescent polarization, immunoassay, and radioimmunoassay methods. *J Clin Immunol* 1984;7:443-47.

13. Castro A, Steele B. A fluorescent immunoassay for theophylline: Description and comparison to enzyme immunoassay, liquid chromatography, and radioimmunoassay. *J Clin Immunol* 1984;7:281-84.