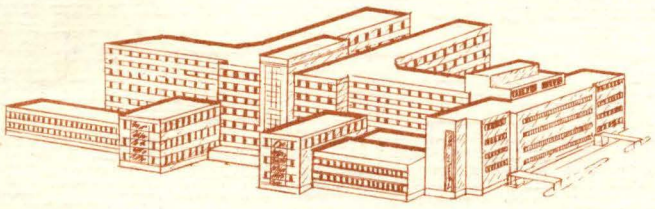

THE MOSES H. CONE MEMORIAL HOSPITAL

GREENSBORO, NORTH CAROLINA

PHARMACY COMMITTEE NOTES

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AMINOGLYCOSIDE SERUM LEVELS

Since gentamicin was introduced in 1969, the aminoglycosides have grown to provide a major therapeutic modality for treatment of gram-negative infections. During the last ten years research has continued to define their usefulness in terms of clinical effectiveness and toxicity. Accurate predictions of peak and trough aminoglycoside serum levels, based on increasing pharmacokinetic knowledge, have enabled clinicians to exploit the relationship of serum levels to the underlying conditions and toxicity. It is the purpose of this paper to assess the current status of this relationship.

Pharmacology

The aminoglycosides are a group of parenteral antibiotics which include kanamycin, amikacin, tobramycin, gentamicin, sisomicin and netilmicin. The latter two are still investigational. While the primary indication for aminoglycosides remains aerobic gram-negative bacilli, they are often combined with β-lactam antibiotics for a synergistic effect against certain streptococci, staphylococci, klebsiella and pseudomonas.[1,2] As a group, the aminoglycosides share similar pharmacologic characteristics. They are (1) rapidly absorbed from injection sites, (2) have a volume of distribution which approximates the extracellular fluid space, (3) are not metabolized in the human body, (4) have no significant protein binding and (5) are eliminated primarily through glomerular filtration. The half-life in patients with normal renal function averages 2.3 hours; in anephric patients approximately 70 hours.[1] There is a direct correlation between increasing serum half-life and decreasing renal function.[3]

Aminoglycoside Serum Levels

Aminoglycoside serum levels are monitored for two reasons: to ensure adequate therapeutic levels are reached and to check for drug accumulation. To interpret these levels correctly, several important factors must be

kept in mind: (1) the time the sample is drawn, (2) the type of assay procedure used, and (3) the clinical condition being treated.

Timing Serum Samples

The terms peak (Cp^{max}) and trough (Cp^{min}) are frequently used in reference to aminoglycoside serum levels. Peak levels should be drawn 1.5 hours following an intramuscular dose or 0.5 hours after an intravenous dose.[2] Intravenous doses should be administered over an 0.5 hour infusion time. Trough levels should be obtained just before the next dose. While peak levels are dependent upon the aminoglycoside dose, the route of administration and the infusion time, if given intravenously, accurate timing of serum levels is essential for useful clinical interpretation.

The first set of peak and trough levels is obtained after "steady state" is reached. This is usually five drug half-lives or after forty-eight hours. If the initial peak level is within the desired range and the patient has stable renal function, additional levels may not be needed. Frequent determinations are helpful in patients exhibiting changes in renal function or when the dosage regimen is altered.

Assay Procedures

At present, there are three methods available for the assay of unlabeled aminoglycosides.[3] These are: microbiological (bioassay); biochemical (radioenzymatic and radioimmune) and physical-chemical (gas-liquid and high pressure liquid chromatography).

Of these, the more economical and widely used is the agar-diffusion bioassay. The most commonly encountered interference with the bioassay is the presence of other antibiotics in the sample.[4] Usual approaches to circumvent this problem include the use of β-lactamases (added to the specimen or the agar) to destroy penicillins and cephalosporins or the use of multiple antibiotic resistant test organism or a combination of both. It is good practice for the clinician to list the antibiotics the patient is receiving when an antibiotic serum level is requested. Good laboratory practice and quality control are essential to the bioassay because results in one study were found "highly misleading" 25% of the time.[5]

The enzymatic and radioimmunoassays are specific and highly accurate (5 to 10% error). They can also provide data in as little as one to two hours.[2] However, they are expensive and require access to radioactivity counting instrumentation.

The recently developed physical-chemical assays using chromatography are promising, but are generally available only at research centers.

Clinical Applications

It is important to realize that aminoglycoside concentration in inflammatory lesions of the pleural, peritoneal, pericardial and synovial spaces approximates one-half the peak serum level.[2] The concentration in pulmonar secretions may be even lower (25 to 40% of peak serum level) while that of the renal cortical tissue may accumulate in concentrations which are 10 to 50 times that in serum.[1] Studies in the literature correlating peak serum

levels and therapeutic outcome generally point to a minimum peak serum level of 4 mcg/ml, except in certain conditions. Below are recommended peak serum levels based on certain clinical infections.[2]

CLINICAL CONDITION	PEAK SERUM CONCENTRATION	
	GEN & TOB	AMK
Uncomplicated Lower UTI	2-4 mcg/ml	15 mcg/ml
Enterococcal Endocarditis (for synergy with penicillin)	2-4 mcg/ml	15 mcg/ml
Gram Negative Septicemia	6-8 mcg/ml	20-30 mcg/ml
Serious Gram-Negative Pneumonia	8 mcg/ml	20-30 mcg/ml

Because they are insoluble in lipids, the aminoglycosides are essentially excluded from most body cells including adipose tissue, and from organs such as the central nervous system and eye. Penetration of the blood-ocular barrier is so meager that effective therapy of bacterial endophthalmitis requires periocular injections.[2] Intrathecal or intraventricular administration is necessary to ensure adequate concentrations in the cerebrospinal fluid.[2]

Dosing

Although the pharmacologic properties of the aminoglycosides are relatively uncomplicated, the dose-serum level profile curve has been found to be unpredictable, both in terms of peak serum levels and elimination half-life from the plasma.[4] A number of nomograms, dosing schedules, etc., have been proposed for each of the various aminoglycoside antibiotics.[8] Although most acknowledge the importance of renal function, several fail to account for such important factors as the loading dose, lean body weight, patient age and sex. The Pharmacy Department at Moses Cone Hospital has developed a computer assisted program for dosing the aminoglycosides based on the above criteria. This program provides estimated peak and trough levels based on the current pharmacokinetic data. These calculated levels are not intended to replace laboratory determined drug serum levels but to supplement them in the clinical management of the patient.

Toxicity

Aminoglycosides accumulate and persist in the human renal cortex in concentrations markedly higher than those in the serum.[9] It is not surprising therefore that the kidneys are a major target of aminoglycoside toxicity. Studies suggest a correlation between nephrotoxicity and elevated trough levels. Dahlgren et al 1975 found a correlation between increasing trough levels of gentamicin and nephrotoxicity.[10] Goodman et al prospectively compared the rates of gentamicin toxicity in a small number of patients treated by variable dose or variable frequency regimens. Deterioration of renal function occurred with similar frequency in both groups. The only significant predictor of nephrotoxocity was a trough level of gentamicin greater than 4 mcg/ml.[11]

In both these studies, however, the occurrence of high trough levels could be interpreted as an early sign of renal damage rather than the cause of it. Known contributing factors to nephrotoxicity include: hypotension, dehydration, age, prior administration of aminoglycosides and concomittant

administration of potent loop diuretics.[1] The relationship of combinations of aminoglycosides with cephalosporins to nephrotoxicity is controversial.

The most prominent risk factor for ototoxicity in the use of aminoglycosides appears to be preexisting renal impairment.[3] In one extensive review, this was present in 64% of patients who experienced gentamicin related ototoxicity.[4] Although the aminoglycosides have not been shown to have a particular affinity for the vestibular or cochlear apparatus, they diffuse much more readily into the perilymph of the inner ear than into the CSF or vitreous humor of the eye. There is a linear relationship between dose and perilymph concentration of gentamicin which suggests that the peak serum level might be a crucial determinant of ototoxicity.[4]

In man, as in animal models, damage to the vestibular system predominates over cochlear impairment. In a major review of gentamicin ototoxicity, two-thirds of the patients showing toxicity had evidence of vestibular damage alone.[3] Damage to both vestibular and auditory apparatus is usually bilateral. With early cessation of therapy, damage may be reversible; but with continued administration of drugs, damage is often permanent.[3]

Conclusion

To interpret aminoglycoside serum levels correctly, it is important to note the timing of serum samples, the type of laboratory assay used and the underlying clinical condition being treated. The correlation between serum levels and toxicity is not as clearly defined as that between serum level and clinical condition. While most studies suggest a trough of 4 mcg/ml as predictive of nephrotoxicity, it is difficult to prove an exact causative effect. Excessive peak levels have been associated with ototoxicity. The Pharmacy Department has constructed a computer assisted aminoglycoside dosing program designed to calculate peak and trough levels. These calculated levels are not intended to replace laboratoy determined drug serum levels but to supplement them in the clinical management of the patient.

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Chip Day, R.Ph.

AMINOGLYCOSIDE KINETIC DATA

The Pharmacy Department has estimated serum _____ levels for this patient using the following formulas:

1. Creatinine Clearance (Ccr) = $\frac{(140 - \text{Age})\ (\text{wt in Kg})}{(\text{Serum Creatinine})\ (72)}$ (Ccr females = .85 Ccr male)

2. Peak Plasma Concentration (Cp^{max}) = Dose ÷ ((Volume of Distribution) $(1-e^{-Ket})$)

3. Minimum Plasma Concentration (Cp^{min}) = (Cp^{max}) (e^{-Ket})

4. Elimination Rate Constant Gentamycin (Ke^{Gent}) = Ccr x .00285 + .015

5. Elimination Rate Constant Tobramycin (Ke^{Tobra}) = Ccr x .0031 + .01

6. Elimination Rate Constant Amikacin (Ke^{Amik}) = Ccr x .0027 + .01

The following patient data was used:

Age: _____ Drug: _____

Lean Body Weight: _____ Dose: _____

Sex: _____ Interval: _____

Scr: _____ Date Drawn: _____

The calculated levels are:

Cp^{max}: _____ mcg/ml

Cp^{min}: _____ mcg/ml

Creatinine Clearance: _____ ml/min

Comments:

Pharmacist: _____ Date: _____

Note: The above are estimates of serum levels based on kinetic data for this drug. Any change in renal status will alter these calculations. It is hoped that this information will be of interest and value to you in this patient's clinical management. If you have any questions, please contact the pharmacy.

NOT A PERMANENT PART OF PATIENT'S RECORD

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