Subject: Extended Interval (“Once-Daily”) Gentamicin and Tobramycin Dosing Protocol

Purpose: Recently a better understanding of the pharmacodynamics of the aminoglycoside antibiotics has led to investigations utilizing extended interval dosing (i.e. q 24h, q 36h, q 48h) as opposed to the traditional multiple daily doses. These extended interval regimens take advantage of the peak or concentration-dependent bacterial killing and the observed postantibiotic effect. Concentration-dependent killing refers to the fact that the higher the peak concentration of the aminoglycoside, the faster the rate of kill of the bacteria. Peak concentrations with the extended interval dosing are much greater than when the dose is divided into multiple daily doses (peaks of 15-25mg/L with extended interval compared to 5 – 8 mg/L with multiple daily doses). The post antibiotic effect refers to the observation that the aminoglycosides inhibit bacterial growth even when their concentration falls below the minimum inhibitory concentration. This phenomenon is likely due to sustained intercellular concentrations which continue to kill bacteria even when the serum level appears subtherapeutic. With extended interval dosing, the trough concentrations are low and frequently undetectable. However, the postantibiotic effect prevents regrowth of bacteria during periods of low antibiotic concentrations.

In addition, clinical studies in both animals and humans have demonstrated less toxicity (nephrotoxicity, ototoxicity) associated with the extended interval dosing. Uptake of aminoglycosides into the renal cortex and inner ear tissues is a saturable process. Single high doses of aminoglycosides result in less uptake than when given in multiple daily doses. Less tissue uptake has been suggested as the reason for the reduced nephrotoxicity observed with the extended interval regimens but has yet to be proven to result in reduced risk of ototoxicity. The effect of extended interval regimens on development of ototoxicity is currently unknown due to the lack of routine audiometric tests during aminoglycoside therapy.

Another advantage to the extended interval regimens is the potential cost savings. Since peak levels utilizing the extended interval regimens exceed the MIC by several fold (usually greater than 10 fold), peak levels are unnecessary. A single level drawn 6 to 14 hours after the first dose is all that is necessary to determine appropriateness of the interval and the risk for potential toxicity. Additional cost savings due to decreased nursing and pharmacy time with fewer doses being compounded and administered should also be considered.

Policy: 1.0 Creatinine Clearance/Initial Dose and Interval
1.1 greater than or equal to 60 ml/minute / 7 mg/kg every 24 hours
1.2 40 to 60 ml/minute / 7 mg/kg every 36 hours
1.3 20 to 40 ml/minute / 7 mg/kg every 48 hours
1.4 Less than 20 ml/minute / 7 mg/kg, then follow levels to determine time of next dose (level less than 1 mcg/ml)
2.0 Dosing should be based on patient’s actual body weight, unless the patient is significantly obese (i.e., 20% over ideal body weight [IBW]). In cases of significant obesity, an adjusted body weight (ABW) should be utilized.

2.1 Adjusted Body Weight
\[ ABW = IBW + 0.4 \times (\text{Actual wt} - \text{IBW}) \]

2.2 Ideal Body Weight
- IBW (male) = 50 kg + 2.3 kg/inch for each inch over 5.0 ft.
- IBW (female) = 45 kg + 2.3 kg/inch for each inch over 5.0 ft.

3.0 Monitoring:
3.1 A peak serum level one hour after the infusion starts and a serum level after the first dose between 6 – 14 hours after the start of the 30 minute infusion is recommended. Evaluate the result utilizing the Data Kinetics dosing software in “Extended-Interval” mode.

3.2 Serum creatinine concentrations for determination of renal function should be obtained every 2 to 3 days while on therapy.

3.3 Repeat serum gentamicin or tobramycin levels should be obtained with significant reductions in renal function or weekly when therapy extends beyond 5 days.

3.4 Interval adjustment will be calculated using Data Kinetics dosing software in “Extended-Interval” mode.

4.0 Patient Exclusions:
- Pediatrics
- Pregnancy
- Burns (greater than 20% BSA)
- Ascites
- Dialysis
- Endocarditis
- Immunocompromised patients
- Cystic fibrosis
- Meningitis
- Pulmonary infections in mechanically ventilated patients

References:

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