The Aminoglycosides Antibiotics (AG)

Introduction

- Aminoglycosides have bactericidal activity against most gram-negative bacteria including Citrobacter, Enterobacter, E. Coli, Klebsiella, Proteus, Pseudomanas, Salmonella, Serratia and Shigella.
- Aminoglycosides are active against most strains of Staphylococcus aureus and S. epidermidis. Most strains of enterococcus are resistant to aminoglycosides alone, however when used in combination with penicillins they are often effective in enterococcal endocarditis due to synergistic antimicrobial mechanisms.
- The Aminoglycosides are the mainstay in the treatment of serious gram-negative systemic infections. A disadvantage of the Aminoglycosides is their association with nephrotoxicity and Ototoxicity, both of which are associated with elevated trough levels and sustained elevated peak levels.

Dosing

A-Conventional dosing:

The total daily dose usually given in three equal daily doses for gentamicin , tobramycin or netilmicin or 2-3 equal daily doses for Amikacin.

B-Once daily AG (Extended interval dosing)

The total daily dose of AG may be given once daily. Although of the extremely high peak concentrations obtained during extended-interval dosing of aminoglycosides, it can be difficult to understand why increased toxicity is not seen in patients. The hypothesized reason is that both nephrotoxicity and ototoxicity are due to accumulation of aminoglycoside in the relevant tissue. Because the dosage interval is prolonged in extended-interval administration, aminoglycoside concentrations are low for a long period of time and may allow for diffusion of drug out of tissue and into the blood which avoids drug accumulation in the ear and kidney.

➢ Basic Clinical Pharmacokinetic parameters

All the AG have similar pharmacokinetics. The average Vd of AG for patients without disease states and conditions that alter the ph.k parameters of AG is 0.26 L/kg (range: 0.2 - 0.3 L/kg) and the average T1/2 is 2 hours (range of 1.5 – 3 hours)**…**

➢ Therapeutic Drug Monitoring Of Aminoglycosides

A-Sampling Time

****In patient with normal renal function, AG serum conc. should be measured <u>after 3-4 doses.</u>

**If AG are given as 1- hour infusion ----------distribution has an opportunity to occur during infusion time ----------peak conc. can be obtained immediately at the end of infusion.

**If AG are given as 1/2 hour- infusion ----------distribution has not complete at the end of infusion ----------wait additional 1/2 hour before peak conc. is measured.

While the trough conc. is obtained just or within 30 min. before the next dose **.

B-Selection of steady state concentration

Aminoglycosides steady state conc. is selected based on site and severity of infection as well as the infecting organism.

A-severe infection such as G-ve pneumonia or septicemia or infection with organism like *P. aeroginosa* generally require peak steady state conc. of 8-10 mcg /ml for gentamicin , tobramycin or netilmicin or 25 – 30 mcg/ml for Amikacin .

B-Moderate infection at site that are easily penetrated by AG such intra-abdominal infections usually require peak steady state conc. of 5-7 mcg /ml for gentamicin , tobramycin or netilmicin or 15-25 mcg/ml for Amikacin .

C- Treating UTI due susceptible organism or Using AG synergistically with penicillins or other Antibiotics for the treatment of G+ve infections such as infective endocarditis generally require peak steady state conc. of 3-5 mcg /ml for gentamicin , tobramycin or netilmicin or 12-15 mcg/ml for Amikacin .

D-Desirable trough steady state conc. are chosen based on avoidance of potential toxicity so the steady state trough conc. should be maintained < 2 mcg /ml for gentamicin , tobramycin or netilmicin or < 5-7 mcg/ml for Amikacin .

C-Toxicity:

Exceeding peak steady state conc. of 12- 14 mcg /ml for gentamicin, tobramycin or netilmicin or 35-40 mcg/ml for Amikacin ----------lead to an increased risk of Ototoxicity.

Ototoxicity can be permanent if appropriate changes in AG dosing are not made. Exceeding trough steady state conc. of 2-3 mcg /ml for gentamicin, tobramycin or netilmicin or 10 mcg/ml for Amikacin ----------lead to an increased risk of nephrotoxicity.

Unlike Ototoxicity, AG-induced –nephrotoxicity is usually reversible if the AG is withdrawn sooner after renal function tests change.

Keeping the peak and trough con. Within the suggested range does not prevent nephrotoxicity or Ototoxicity in patients but it hoped to decrease likelihood of these serious adverse effects.

Also even if the serum conc. is controlled within the suggested range, duration of therapy exceeding 14 days or therapy with other nephrotoxic drug such as vancomycin can predispose the patient to the side effects.

D-Estimation of AG volume of Distribution

A- If the patient is non obese
Use the Actual body weight to estimate Vd.

B- For those patients whose weight is more than 30 % above their IBW
use the following formula to estimate Vd :

$$V = 0.26\,[IBW + 0.4\,(TBW - IBW)]$$

Where IBW: ideal body weight TBW : total body weight .

C –For patient who is overhydrated…… use the following formula to estimate Vd

$$V = (0.26 \cdot DBW) + (TBW - DBW)$$

E-Estimation of AG elimination rate constant

AG are almost totally eliminated unchanged in the urine, there is a good relationship between CrCl and AG elimination rate constant:

$$Ke=0.00293(CrCl) + 0.014$$

where Ke is the AG elimination rate constant in h^{-1} and CrCl is the creatinine clearance in mL/min.

G-Effect of disease states and conditions on AG pharmacokinetics and dosing

AG pharmacokinetics parameters are affected (increased or decreased) by many conditions like:

1-obesity 2-Renal dysfunction 3-Burn 4- Cystic fibrosis 5-Ascitis (increase Vd)

6-Premature infant (Increase Vd) 7-Dialysis (remove the drug--------decrease the T 1/2)

INITIAL DOSAGE DETERMINATION METHODS

Several methods to initiate aminoglycoside therapy are available.

- The pharmacokinetic dosing method is the most flexible of the techniques.

- The Hull and Sarubbi nomogram uses the dosing concepts in the pharmacokinetic dosing method.

- The Hartford nomogram is designed for use when extendedinterval dosing is desired.

- Literature-based recommended dosing is a commonly used method to prescribe initial doses of aminoglycosides to pediatric patients.

Pharmacokinetic Dosing Method

The goal of initial dosing of aminoglycosides is to compute the best dose possible for the patient given their set of disease states and conditions that influence aminoglycoside pharmacokinetics and the site and severity of the infection. In order to do this, pharmacokinetic parameters for the patient will be estimated using average parameters measured in other patients with similar disease state and condition profiles.

Steps

1- ELIMINATION RATE CONSTANT ESTIMATE

2-VOLUME OF DISTRIBUTION ESTIMATE

3-SELECTION OF APPROPRIATE PHARMACOKINETIC MODEL AND EQUATIONS

4-STEADY-STATE CONCENTRATION SELECTION

5-DOSAGE COMPUTATION

Example 1 JM is a 50-year-old, 70-kg (5 ft 10 in) male with gram-negative pneumonia. His current serum creatinine is 0.9 mg/dL, and it has been stable over the last 5 days since admission. Compute a gentamicin dose for this patient using conventional dosing.

1. *Estimate creatinine clearance.*

This patient has a stable serum creatinine and is not obese. The Cockcroft-Gault equation can be used to estimate creatinine clearance:

$$CrCl_{est} = [(140 - age)BW] / (72 \cdot SCr) = [(140 - 50\ y)70\ kg] / (72 \cdot 0.9\ mg/dL)$$

$$CrCl_{est} = 97\ mL/min$$

2. Estimate elimination rate constant (ke) and half-life (t1/2).

The elimination rate constant versus creatinine clearance relationship is used to estimate the gentamicin elimination rate for this patient:

$$k_e = 0.00293(CrCl) + 0.014 = 0.00293(97\ mL/min) + 0.014 = 0.298\ h^{-1}$$

$$t_{1/2} = 0.693/k_e = 0.693/0.298\ h^{-1} = 2.3\ h$$

3. ***Estimate volume of distribution (V).***

The patient has no disease states or conditions that would alter the volume of distribution from the normal value of 0.26 L/kg:

$V = 0.26\ L/kg\ (70\ kg) = 18.2\ L$

4. ***Choose desired steady-state serum concentrations.***

Gram-negative pneumonia patients treated with aminoglycoside antibiotics require steady-state peak concentrations (Cssmax) equal to 8–10 μg/mL;
steady-state trough (Cssmin) concentrations should be <2 μg/mL to avoid toxicity.
Set Cssmax = 9 μg/mL and Cssmin = 1 μg/mL.

5. ***Use intermittent intravenous infusion equations to compute dose .***

Calculate required dosage interval (τ) using a 1-hour infusion:

$\tau = [(\ln Cssmax - \ln Cssmin) / ke] + t'$

$= [(\ln 9\ \mu g/mL - \ln 1\ \mu g/mL) / 0.298\ h^{-1}] + 1\ h = 8.4\ h$

$k_0 = Css_{max}\ k_e V[(1 - e^{-k_e \tau}) / (1 - e^{-k_e t'})]$

$k_0 = (9\ mg/L \cdot 0.298\ h^{-1} \cdot 18.2\ L)\{[1 - e^{-(0.298\ h^{-1})(8\ h)}] / [1 - e^{-(0.298\ h^{-1})(1\ h)}]\} = 172\ mg$

6. ***Compute loading dose (LD), if needed.***

Loading doses should be considered for patients with creatinine clearance values below 60 mL/min.

The administration of a loading dose in these patients will allow achievement of therapeutic peak concentrations quicker than if maintenance doses alone are given.

However, since the pharmacokinetic parameters used to compute these initial doses are only *estimated* values and not *actual* values, the patient's own parameters may be much different than the estimated constants and steady state will not be achieved until 3–5 half-lives have passed.

$LD = k0/(1 - e^{-ke\tau}) = 170 \text{ mg} / [1 - e^{-(0.298\ h^{-1})(8\ h)}] = 187 \text{ mg}$

As noted, this loading dose is only about 10% greater than the maintenance dose and wouldn't be given to the patient. Since the expected half-life is 2.3 hours, the patient should be at steady state after the second dose is given.

Example 2 Same patient profile as in example 1, but serum creatinine is 3.5 mg/dL indicating renal impairment.

1. Estimate creatinine clearance.

This patient has a stable serum creatinine and is not obese. The Cockcroft-Gault equation can be used to estimate creatinine clearance:

$CrClest = [(140 - age)BW] / (72 \cdot SCr) = [(140 - 50\ y)70\ kg] / (72 \cdot 3.5\ mg/dL)$

$CrClest = 25\ mL/min$

2. Estimate elimination rate constant (ke) and half-life (t1/2).

The elimination rate constant versus creatinine clearance relationship is used to estimate
the gentamicin elimination rate for this patient:

$ke = 0.00293(CrCl) + 0.014 = 0.00293(25\ mL/min) + 0.014 = 0.087\ h^{-1}$

$t1/2 = 0.693/ke = 0.693/0.087\ h^{-1} = 8\ h$

3. *Estimate volume of distribution (V).*

The patient has no disease states or conditions that would alter the volume of distribution from the normal value of 0.26 L/kg:
V = 0.26 L/kg (70 kg) = 18.2 L

4. *Choose desired steady-state serum concentrations.*

Gram-negative pneumonia patients treated with aminoglycoside antibiotics require steady-state peak concentrations (Cssmax) equal to 8–10 μg/mL; steady-state trough (Cssmin) concentrations should be <2 μg/mL to avoid toxicity.
Set Cssmax = 9 μg/mL and Cssmin = 1 μg/mL.

5. Use intravenous bolus equations to compute dose .

Calculate required dosage interval (τ):
$\tau = [(\ln Cssmax - \ln Cssmin) / ke] = (\ln 9\ \mu g/mL - \ln 1\ \mu g/mL) / 0.087\ h^{-1} = 25\ h$

$D = Css_{max}\ V(1 - e^{-ke\tau})$

$D = 9\ mg/L \cdot 18.2\ L(1 - e^{-(0.087\ h^{-1})(24\ h)}) = 143\ mg$

6. Compute loading dose (LD), if needed.

Loading doses should be considered for patients with creatinine clearance values below 60 mL/min. The administration of a loading dose in these patients will allow achievement of therapeutic peak concentrations quicker than if maintenance doses alone are given. However, since the pharmacokinetic parameters used to compute these initial doses are only *estimated* values and not *actual* values, the patient's own parameters may be much different from the estimated constants and steady state will not be achieved until 3–5 half-lives have passed.

$$LD = Css_{max} V = 9 \text{ mg/L} * 18.2 \text{ L} = 164 \text{ mg}$$

Round loading dose to 165 mg. It would be given as the first dose. The next dose would be a maintenance dose given a dosage interval away from the loading dose, in this case 24 hours later.

Hull and Sarubbi Nomogram Method

- The Hull and Sarubbi aminoglycoside dosing nomogram is a quick and efficient way to apply pharmacokinetic dosing concepts without using complicated pharmacokinetic equations. With a simple modification, it can also be used for obese patients.
- If the patient is ≥30% above ideal body weight, an adjusted body weight (ABW) can be calculated and used as the weight factor

ABW (in kg) = IBW + 0.4(TBW − IBW),

where IBW is ideal body weight in kilograms and TBW is actual total body weight in kilograms . Also, the Salazar and Corcoran method of estimating creatinine clearance in obese patients should be used to compute renal function in these individuals.

- Steady-state peak concentrations are selected as discussed in the pharmacokinetic dosing method section and used to determine a loading dose from the nomogram.

TABLE:- Aminoglycoside Dosage Chart

1. Compute patient's creatinine clearance (CrCl) using Cockcroft-Gault method: CrCl = [(140 − age)BW] / (SCr × 72). Multiply by 0.85 for females. Use Salazar-Cocoran method if weight >30% above IBW.

2. Use patient's weight if within 30% of IBW, otherwise use adjusted dosing weight = IBW + [0.40(TBW − IBW)]

3. Select loading dose in mg/kg to provide peak serum concentrations in range listed below for the desired aminoglycoside antibiotic:

AMINOGLYCOSIDE	USUAL LOADING DOSES	EXPECTED PEAK SERUM CONCENTRATIONS
Tobramycin Gentamicin Netilmicin	1.5–2.0 mg/kg	4–10 μg/mL
Amikacin Kanamycin	5.0–7.5 mg/kg	15–30 μg/mL

4. Select maintenance dose (as percentage of loading dose) to continue peak serum concentrations indicated above according to desired dosage interval and the patient's creatinine clearance. To maintain usual peak/trough ratio, use dosage intervals in clear areas.

Percentage of Loading Dose Required for Dosage Interval Selected

CrCl (mL/min)	EST. HALF-LIFE (HOURS)	8 HOURS (%)	12 HOURS (%)	24 HOURS (%)
>90	2–3	90	–	–
90	3.1	84	–	–
80	3.4	80	91	–
70	3.9	76	88	–
60	4.5	71	84	–
50	5.3	65	79	–
40	6.5	57	72	92
30	8.4	48	63	86
25	9.9	43	57	81
20	11.9	37	50	75
17	13.6	33	46	70
15	15.1	31	42	67
12	17.9	27	37	61
10*	20.4	24	34	56
7*	25.9	19	28	47
5*	31.5	16	23	41
2*	46.8	11	16	30
0*	69.3	8	11	21

*Dosing for patients with CrCl ≤10 mL/min should be assisted by measuring serum concentrations.

Example 1 JM is a 50-year-old, 70-kg (5 ft 10 in) male with gram-negative pneumonia. His current serum creatinine is 0.9 mg/dL, and it has been stable over the last 5 days since admission. Compute a gentamicin dose for this patient using conventional dosing.

1. *Estimate creatinine clearance.*

This patient has a stable serum creatinine and is not obese. The Cockcroft-Gault equation can be used to estimate creatinine clearance:

$$\text{CrCl}_{\text{est}} = [(140 - \text{age})\text{BW}] / (72 \cdot \text{SCr}) = [(140 - 50\ \text{y})70\ \text{kg}] / (72 \cdot 0.9\ \text{mg/dL})$$

$$\text{CrCl}_{\text{est}} = 97\ \text{mL/min}$$

2. *Choose desired steady-state serum concentrations.*

Gram-negative pneumonia patients treated with aminoglycoside antibiotics require steady-state peak concentrations (C_{ssmax}) equal to 8–10 μg/mL.

3. *Select loading dose.*

A loading dose (LD) of 2 mg/kg will provide a peak concentration of 8–10 μg/mL.

LD = 2 mg/kg(70 kg) = 140 mg

4. *Determine estimated half-life, maintenance dose, and dosage interval.*

From the nomogram the estimated half-life is 2–3 hours, the maintenance dose

(MD) is 90% of the loading dose [MD = 0.90(140 mg) = 126 mg], and the dosage interval is 8 hours.

Example 3 ZW is a 35-year-old, 150-kg (5 ft 5 in) female with an intraabdominal infection. Her current serum creatinine is 1.1 mg/dL and is stable. Compute a tobramycin dose for this patient using conventional dosing.

1. *Estimate creatinine clearance.*
This patient has a stable serum creatinine and is obese [IBWfemales (in kg) = 45 + 2.3(Ht − 60 in) = 45 + 2.3(65 − 60) = 57 kg]. The Salazar and Corcoran equation can be used to estimate creatinine clearance:

$$\mathbf{CrClest(male)} = \frac{(\mathbf{137 - Age})[(\mathbf{0.285 * Wt}) + (\mathbf{12.1 * Ht2})]}{\mathbf{51 * Scr}}$$

$$= 117 \text{ mL/min}$$

2. *Choose desired steady-state serum concentrations.*
Intraabdominal infection patients treated with aminoglycoside antibiotics require steady-state peak concentrations (Cssmax) equal to 5–7 μg/mL.

3. *Select loading dose*

A loading dose (LD) of 1.7 mg/kg will provide a peak concentration of 5–7 μg/mL.

Because the patient is obese, adjusted body weight (ABW) will be used to compute the dose:

ABW = IBW + 0.4(TBW − IBW) = 57 kg + 0.4(150 kg − 57 kg) = 94 kg

LD = 1.7 mg/kg(94 kg) = 160 mg

4. *Determine estimated half-life, maintenance dose, and dosage interval.*

From the nomogram the estimated half-life is 2–3 hours, the maintenance dose (MD)

is 90% of the loading dose [MD = 0.90(160 mg) = 144 mg], and the dosage interval is

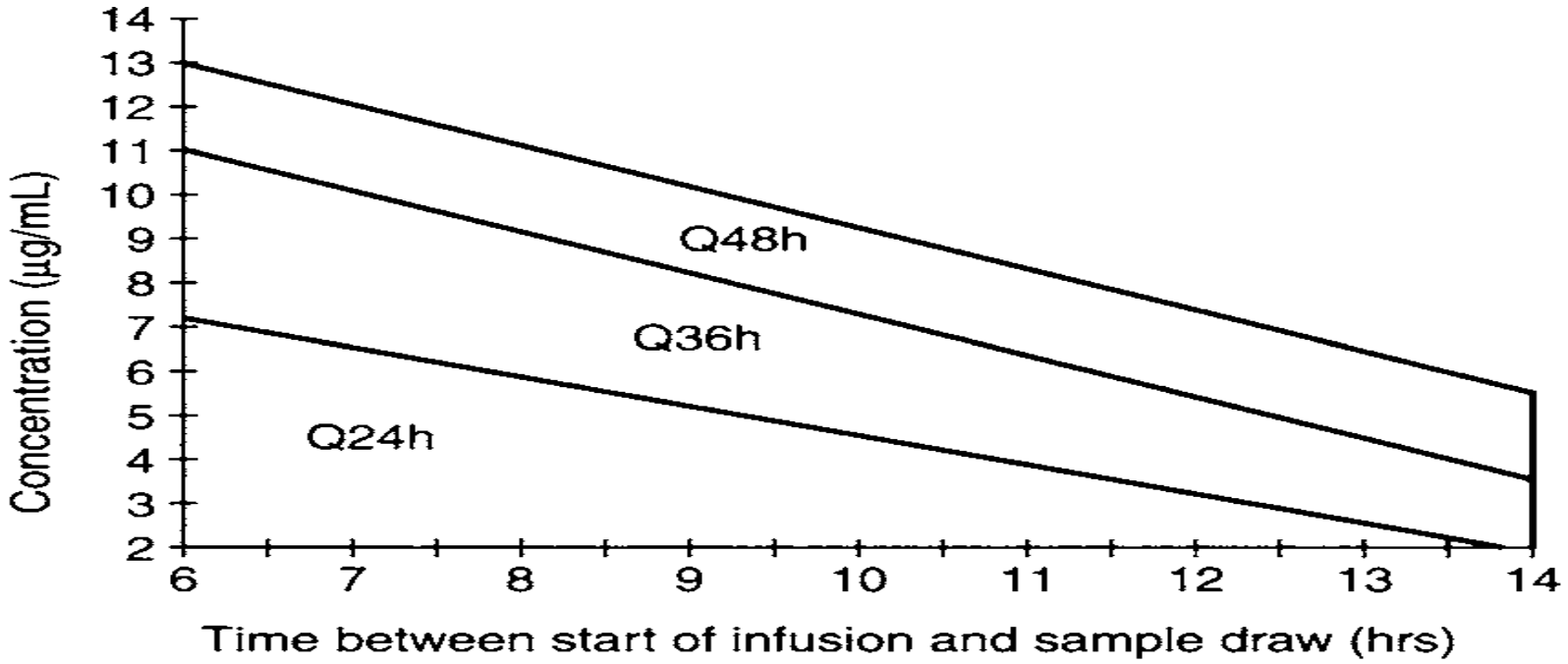
8 hours. Aminoglycoside doses should be rounded to the nearest 5–10 mg.

The prescribed maintenance dose would be 145 mg every 8 hours.

Hartford Nomogram Method for Extended-Interval Dosing

- The most widely used extended-interval aminoglycoside dosage nomogram for patients with renal dysfunction is the Hartford nomogram which uses a 7-mg/kg dose
- The Hartford nomogram includes a method to adjust doses based on gentamicin serum concentrations. This portion of the nomogram contains average serum concentration/time lines for gentamicin in patients with creatinine clearances of 60 mL/min, 40 mL/min, and 20 mL/min. A gentamicin serum concentration is measured 6–14 hours after the first dose is given, and this concentration/time point is plotted on the graph

TABLE:- Hartford Nomogram for Extended-Interval Aminoglycosides



nomogram for gentamicin and tobramycin at 7 mg/kg.

1.Administer 7-mg/kg gentamicin with initial dosage interval

2. Obtain timed serum concentration, 6–14 hours after dose (ideally first dose).

3. Alter dosage interval to that indicated by the nomogram zone (above q48 h zone, monitor serial concentrations, and administer next dose when (<1 g/mL).

Example 1 JM is a 50-year-old, 70-kg (5 ft 10 in) male with gram-negative pneumonia. His current serum creatinine is 0.9 mg/dL, and it has been stable over the last 5 days since admission. Compute a gentamicin dose for this patient using extended-interval dosing.

1. *Estimate creatinine clearance.*

This patient has a stable serum creatinine and is not obese. The Cockcroft-Gault equation can be used to estimate creatinine clearance:

$$\text{CrClest} = [(140 - \text{age})\text{BW}] / (72 \cdot \text{SCr}) = [(140 - 50\ \text{y})70\ \text{kg}] / (72 \cdot 0.9\ \text{mg/dL})$$

$$\text{CrClest} = 97\ \text{mL/min}$$

2. *Compute initial dose and dosage interval*

A dose (D) of 7 mg/kg will provide a peak concentration >20 μg/mL.

$$D = 7\ \text{mg/kg}(70\ \text{kg}) = 490$$

Dosage interval would be 24 hours using the nomogram. Extended-interval aminoglycoside doses should be rounded to the nearest 10–50 mg.

The prescribed maintenance dose would be 500 mg every 24 hours.

3. *Determine dosage interval using serum concentration monitoring.*

A gentamicin serum concentration measured 10 hours after the dose equals 3 μg/mL.

Based on the nomogram, a dosage interval of 24 hours is the correct value and does not need to be altered

Literature-Based Recommended Dosing

- Because of the large amount of variability in aminoglycoside pharmacokinetics, even when concurrent disease states and conditions are identified, many clinicians believe that the use of standard aminoglycoside doses for pediatric patients is warranted. The original computation of these doses was based on the pharmacokinetic dosing methods described
- for neonates that are below 10 mg are usually rounded to the nearest tenth of a milligram. If serum creatinine values are available, estimated creatinine clearance can be computed using equations that are specific for pediatric patients
- age 0–1 year, CrClest (in mL/min/ 1.73 m2) = (0.45 · Ht) / SCr;
- age 1–20 years, CrClest (in mL/min/1.73 m2) = (0.55 · Ht) / SCr,
- where Ht is in cm and SCr is in mg/dL .

Example 1 MM is a 3-day-old, 1015-g male with suspected neonatal sepsis. His

serum creatinine has not been measured, but it is assumed that it is typical for his age and weight. Compute an initial gentamicin dose for this patient.

1. *Compute initial dose and dosage interval.*

Often, serum creatinine measurements are not available for initial dosage computation

in neonates. The dosage recommendations for this population assume typical renal function, so it is important to verify that the assumption is valid. From the pediatrics dosage recommendations given in earlier in the chapter, a patient in this age and weight category should receive gentamicin 2.5 mg/kg every 18–24 hours.

Because the patient is in the lower end of the age range, it is likely he has lower renal

function due to poor organ maturation. Based on this information, the longer dosage

interval will be chosen. (Note: Grams will be converted to kilograms before the computation is made.)

Dose = 2.5 mg/kg(1.015 kg) = 2.5 mg

The prescribed dose would be 2.5 mg every 24 hours.

Quiz:-

a patient was given an intravenous loading dose of phenobarbital 600 mg over a period of about an hour. One day and four days after the dose was administered phenobarbital serum concentrations were 12.6 mg/L and 7.5mg/L, respectively. Calculate the ph.k parameters……..