MODERN APPLIED MEDICAL RESEARCH
2(5): 01-08
ISSN: 2582-9181
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Clinical pharmacology of gentamicin

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RESEARCH ARTICLE

Received: **20-05-2022**
Accepted: **30-05-2022**
Published: **31-05-2022**

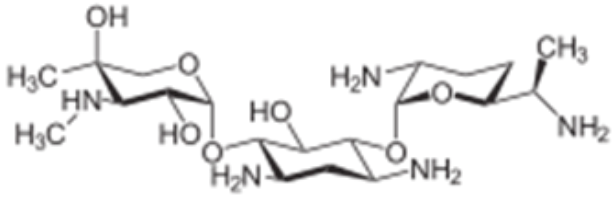
DOI:
10.36099/mamr.250122

Abstract: Gentamicin is an important agent for the treatment of many serious gram-negative bacillary infections. Gentamicin is the aminoglycoside of first-choice because of its activity against all but the most resistant gram-negative aerobes. Gentamicin preparations are available for parenteral, ophthalmic, and topical administration. The recommended intramuscular or intravenous dose of gentamicin sulfate is 5 to 7 mg/kg given over 30 to 60 min in adult patients with normal renal function. The efficacy and safety of gentamicin have been reported and gentamicin may induce nephrotoxicity or ototoxicity. Gentamicin penetrates into bone, skeletal muscle, wound tissue, ischemic foot ulcers, and in subcutaneous tissue in significant amounts. The pharmacokinetics of gentamicin have been studied in febrile neutropenic patients and in healthy subjects and gentamicin's mean elimination half-life is about 3 hours. The pharmacokinetics of gentamicin have been investigated in tetraplegic and in paraplegic patients and in healthy subjects and the mean elimination half-life of gentamicin is about 2 hours. The prophylaxis, treatment, and trials with gentamicin have been extensively studied. Gentamicin penetrates into the cerebrospinal fluid in significant amounts and gentamicin treats bacterial meningitis in infants. Gentamicin is poorly transferred across the human placenta and poorly migrates into the breast-milk. The aim of this study is to review gentamicin efficacy and safety, toxicity, diffusion into body-tissues, pharmacokinetics, prophylaxis, treatment, and trials, penetration of gentamicin into the cerebrospinal fluid, gentamicin treatment of bacterial meningitis, and gentamicin transfer across the human placenta and migration into the breast-milk.

Keywords: *breast-milk, cerebrospinal-fluid, efficacy-safety, gentamicin, meningitis, pharmacokinetics, prophylaxis, tissue-concentration, toxicity, treatment, trials.*

1. INTRODUCTION

Gentamicin is an important agent for the treatment of many serious gram-negative bacillary infections. It is the aminoglycoside of first-choice because of its lower cost and reliable activity against all but the most resistant gram-negative aerobes. Gentamicin preparations are available for parenteral, ophthalmic, and topical administration. The typical recommended intramuscular or intravenous dose of gentamicin sulfate when used for the treatment of known or suspected gram-negative organisms as a single agent or in combination therapy for adults with normal renal function is 5 to 7 mg/kg given over 30 to 60 min. For patients with renal dysfunction, the interval may be extended. For patients who are not candidates for extended-interval dosing, a loading dose of 2 mg/kg and then 3 to 5 mg/kg per day, given as divided doses every 8 to 12 hours, are recommended. Dosages at the upper end of this range may be required to achieve therapeutic concentrations for trauma or burn patients with septic shock, patients with cystic fibrosis, and others in whom drug clearance is more rapid or volume of distribution is larger than normal. Several dosage schedules have been suggested for newborns and infants: 3 mg/kg once-daily for preterm newborns less than 35 weeks of gestation; 4 mg/kg once-daily for newborns more than 35 weeks of gestation; 5 mg/kg daily in two divided doses for infants with severe infections; and 2 to 2.5 mg/kg thrice-daily for children up to 2 years of age. Peak plasma concentrations range from 4 to 10 mg/ml (dosing: 1.7 mg/kg thrice-daily) and 16 to 24 mg/ml (extended-interval dosing: 5 mg/kg once-daily). It should be emphasized that the recommended doses of gentamicin do not always yield desired concentrations. Periodic determination of the plasma concentration of gentamicin is recommended strongly. Gentamicin is absorbed slowly when it is applied topically in an ointment and somewhat more rapidly when it is applied as a cream. When the gentamicin is applied to large areas of denuded body surface, as may be the case in born patients, plasma concentrations car reach 4 µg/ml, and 2% to 5% of the drug may appear in the urine [1].



Gentamicin molecular structure (molecular weight = 477.603 grams/mole)

Literature search

The literature search was performed electronically using the PubMed database as a search engine and the following keywords were used: "gentamicin efficacy safety", "gentamicin toxicity", "gentamicintissue concentration",

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"gentamicin pharmacokinetics", "gentamicin prophylaxis", "gentamicin treatment", "gentamicin trials", gentamicin CSF", "gentamicin meningitis", "gentamicin placental transfer", and "gentamicin breast-milk". In addition, the book "The pharmacological basis of therapeutics" [1] has been consulted.

Results

Efficacy and safety of gentamicin

Once-daily gentamicin is effective and safe in malnourished children and effectively treats serious infections [2]. Gentamicin is efficacy and safe in 89% of hospitalized children receiving a single-daily dose of gentamicin [3]. In 55 patients who received gentamicin, the cure-rates was 96% suggesting that gentamicin is effective and safe in these patients [4]. Gentamicin, administered once daily, is efficacy and safe in the treatment of patients with severe infections [5]. Gentamicin is efficacy and safe in the treatment of patients with severe infections caused by gram-negative bacteria [6].

Toxicity induced by gentamicin

Gentamicin causes acute renal failure as it is accumulates in the kidney [7]. Two-hundred-fifty-eight patients were treated with gentamicin and the auditory toxicity developed in 10% of patients and the nephrotoxicity developed in 26% of patients [8]. Gentamicin induced acute kidney injury in patients undergoing orthopedic surgery [9]. Gentamicinadministered subconjunctivally is highly toxic to the corneal endothelium and anterior chamber structures [10]. A single dose of gentamicin-induced minimal nephrotoxicity and ototoxicity compared to multiple doses of gentamicin [11]. Gentamicin ototoxicity occurred in two-thirds of patients and cochlear toxicity occurred in one-third of patients [12]. Gentamicin dose of 1.5 mg/kg induced ototoxicity and vestibular dysfunction specifically when the cumulative dose exceeds 17 mg/kg [13].Gentamicin induced ototoxicity especially in patients with renal failure who had high plasma concentrations of gentamicin [14].

Diffusion of gentamicin into body-tissues

Gentamicin penetrates in significant amounts in bone during total hip arthroplasty and knee arthroplasty [15]. The concentration of gentamicin in peripheral subcutaneous tissue was 0.7 times the concentration in skeletal muscle tissue. Gentamicin showed the greatest penetration in male patients without the peripheral arterial disease [16]. Concentrations of gentamicin were measured in serum and in wound tissueof 30 patients after the topical administration of 260 mg gentamicin. The median gentamicin concentration was 304 µg/ml in the wound tissue and 2.05 µg/ml in serum [17]. Sixteen patients with ischaemic foot ulcers received 284±116 mg of gentamicin. The median gentamicin concentration in ischemic foot ulcers was 9.4 µg/ml 1 hour after gentamicin administration [18]. Gentamicin was administered intravenously at a dose of 240 mg to 7 healthy volunteers. The peak gentamicin concentration in subcutaneous tissue was 6.7±2.0 µg/ml and the area under the concentration-time curve was 1,281±390 µg*min/ml. Thus gentamicin reached a concentration higher the minimum inhibitory concentration of the common bacteria causing the infections [19].

Pharmacokinetics of gentamicin in febrile neutropenic patients and in healthy subjects

Bianco et al. [20] studied the pharmacokinetics of gentamicin in 34 febrile neutropenic patients, aged 57.7±13.7 years, weighing 68.7±18.6 kg, with an initial serum creatinine of 1.0±0.4 mg%, and a creatinine clearance, corrected by surface body area, of 70.1±33.8 ml/min/1.73 m^2, and in 40 healthy subjects, aged 57.7±13.6 years, weighing 67.5±12.5 kg, with an initial serum creatinine of 1.1±0.4 mg%, and a creatinine clearance, corrected by surface body area, of 61.7±23.9 mg/min/1.73 m^2. In each patient and in each healthy subject, the gentamicin dose was adjusted to provide 1-hour peak concentration of 5 to 10 µg/ml and trough concentrations of less than 2 µg/ml.

Table 1. Pharmacokinetic parameters of gentamicin which have been obtained in 34 febrile neutropenic patients and in 40 healthy subjects. Values are the mean±SD, by Bianco et al. [20].

		Distribution volume (L)				Initial steady-state conc. (µg/ml)	
Group	$T_{1/2}$ (h)	Per kg of total body weight	Per kg of ideal body weight	TBC (ml/min/1.73 m^2)	Daily dose (mg/kg of total body weight)	Peak conc.	Trough conc.
Patients	3.3±2.7	0.31±0.11	036±0.33	87.1±30.8	4.8±1.5*	4.8±1.5**	0.6±0.5
Healthy subjects	3.7±2.2	0.31±0.10	0.32±0.17	81.1±36.7	3.2±1.4	4.1±1.5	0.6±0.6

$T_{1/2}$ = elimination half-life. TBC = total body clearance. *P-value = 0.02. **P-value = 0.04 (Student t test for umpired data).

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This table shows that the elimination half-life of gentamicin is about 3 hours in patients and in healthy subjects indicating that gentamicin is rapidly eliminated. The distribution volume of gentamicin is lower than the water volume. The total body clearance is similar in patients and in healthy subjects. The daily dose of gentamicin is lower in healthy subjects than in patients thus the peak concentration of gentamicin is lower in healthy subjects than in patients.

Pharmacokinetics of gentamicin in tetraplegic and paraplegic patients and in healthy subjects

Segal et al. [21] investigated the pharmacokinetics of gentamicin in 7 tetraplegic patients, in 7 paraplegic patients, and in 7 healthy subjects aged 20 to 60 years and gentamicin was intravenously infused at a dose of 1.5 mg/kg.

Table 2. Pharmacokinetic parameters of gentamicin which have been obtained in 7 tetraplegic patients, in 7 paraplegic patients, and in 7 healthy subjects. Values are the mean±SD, by Segal et al. [21].

			Distribution volume		
Gentamicin dose (mg)	Kel (h^{-1})	Half-life (h)	L	L/kg	TBC (ml/kg/min)
Tetraplegic patients					
121±17	0.323±0.07	2.2+0.4	28.4±6.5*	0.36±0.08*	1.91±0.58*
Healthy subjects					
106+14	0.341±0.03	2.1±0.1	28.4±6.5*	0.26±0.02*	1.46±0.08*
Paraplegic patients					
106+28	0.340±0.13	2.2±0.7	25.0±4.5*	0.37±0.11*	2.31±1.6*

Kel = elimination-rate constant. TBC = total body clearance. *P-value < 0.05 (Student t test for umpired data).

This table shows that gentamicin is rapidly eliminated as the mean elimination half-life is about 2 hours in patients and in healthy subjects. The distribution volume is lower that the water volume, the distribution volume is larger in the tetraplegic and paraplegic patients than in healthy subjects, and the total body clearance is higher in tetraplegic and paraplegic patients than in healthy subjects.

Prophylaxis with gentamicin

Gentamicin is efficient as quinolones in the prevention of urinary tract infections [22]. A single dose of gentamicin is a safe option for perioperative prophylaxis in patients undergoing orthopedic surgery [23]. Prophylactic gentamicin-containing collagen implants prevent infections in patients undergoing orthopaedic surgery[24]. Intramuscular gentamicin is a safe and effective prophylactic antibiotic in reducing the incidence of infections in patients undergoing prostatic biopsy [25]. Single-dose combination of metronidazole and gentamicin reduces surgical site infections in patients undergoing uncomplicated appendectomy [26]. Intravenous gentamicin is an effective prophylaxis for sternal wound infections [27]. Long-term prophylaxis with inhaled gentamicin effectively treats Pseudomonas aeruginosa infection in children with cystic fibrosis [28], and prophylaxis with gentamicin prevents infections in patients undergoing cardiac surgery [29].

Treatment of bacterial infections with gentamicin

Intra-vesical gentamicin instillation reduces the episodes of urinary-tract infection and the degree of antimicrobial resistance [30]. Topical gentamicin is an effective treatment of Nagashima-type disease [31]. Topical and intradermal gentamicin suppresses dystrophic epidermolysis bullosa [32]. Subcutaneous gentamicin injection is a well-tolerated and effective agent for treating cutaneous infections [33]. Gentamicin is an effective antibiotic option for empirical therapy of women with community-onset complicated acute pyelonephritis [34]. Ten patients with brucellosis were treated with azithromycin and gentamicin and 7 patients (70%) had an excellent therapeutic response at the end of therapy [35]. Gentamicin was administered at a dose of 4 mg/kg daily and amikacin was administered at a dose of 9 mg/kg daily and amikacin gives results essentially equivalent to gentamicin in adults with urinary-tract infections [36]. Gentamicin was administered at a dose of 3 to 27 mg/kg daily for 7 to 12 days (mean, 10 days) and gentamicin treats the infection caused by Staphylococcus aureus [37]. Gentamicin was administered at a dose of 5 mg/kg daily and treated 16 infections caused by Staphylococcus aureus and 6 infections caused by Staphylococcus albus. The minimum inhibitory concentration of Staphylococcus aureus and Staphylococcus albus were 3.1 and 0.78 µg/ml, respectively [38]. Four-hundred-four isolates of Salmonella serovar typhi were obtained from the blood of patients. The isolates were sensitive to gentamicin showing a minimum inhibitory concentration of 0.01 to 4µg/ml and

gentamicin eradicated this organism from the blood of patients [39].

Trials with gentamicin

Eighty-eight patients with infected diabetic foot ulcers were treated with gentamicin and 46 (52%) showed total eradication of all pathogens. The gentamicin was well-tolerated and treated the infection in diabetic foot ulcers [40]. A trial demonstrated that intra-tympanic gentamicin is an effective and safe treatment of Ménière's disease [41]. Fifteen randomized controlled trials, encompassing a total of 6,979 patients, were included in the study and gentamicin-collagen implants significantly reduced the surgical site infections [42]. Implantable gentamicin-collagen sponges significantly reduced the risk of sternal wound infection after cardiac surgery [43]. Gentamicin collagen sponges reduced the infection of the sternal wound in patients undergoing cardiac surgery [44]. A prospective, randomized, controlled monocentric trial was performed to evaluate the efficacy and safety of once-daily ceftriaxone 2 grams plus gentamicin 5 mg/kg in comparison to cefepime 2 grams thrice-daily plus gentamicin 5 mg/kg in the treatment of neutropenic fever. Once-daily ceftriaxone plus gentamicin was not inferior to cefepime plus gentamicin in the empirical treatment of neutropenic fever [45]. Once-daily gentamicin dosing with twice-daily clindamycin dosing is efficacious and safe as thrice-daily dosing of gentamicin and clindamycin for peripartum uterine infection [46]. Amikacin and gentamicin are effective against severe gram-negative infections and amikacin is not more ototoxic or nephrotoxic than gentamicin [47].

Penetration of gentamicin into the cerebrospinal fluid (CSF)

Intraoperative gentamicin serum concentration ranged from 3.9 to 9.4 µg/ml (mean, 4.8±2.0). In all surgeries, CSF gentamicin concentrations were about 2 µg/ml, thus gentamicin reached significant amounts in the CSF and treated meningitis caused by Candida albicans or by Citrobacter freundii [48]. Gentamicin concentrations in serum and CSF were measured in 8 patients suffering from meningitis and gentamicin concentrations in CSF ranged from 0.4 µg/ml to 5.66 µg/ml and CSF to serum ratio ranged from 7.4 to 57.6% (mean, 25.8) [49]. Gentamicin was administered intraventricularly at a mean dose of 2.5 mg/kg to 52 infants with meningitis caused by Escherichia coli or Salmonella species. The concentrations of gentamicin in ventricular and lumbar CSF 1 and6 hours after administration ranged from 10 to 130 µg/ml and from 8 to 85 µg/ml, respectively [50]. The intraventricular administration of 1 mg of gentamicin to 5 children with meningitis resulted in ventricular CSF concentrations greater than 20 µg/ml 1hour after dosing and ranged from 5 to 14 µg/ml 36 hours after administration [51]. Gentamicin concentrations in CSF were measured in 21 adult patients who were treated with gentamicin for meningitis due to gram-negative enteric bacilli. Patients received 3 to 12 doses of 4 mg of gentamicin intrathecally. Within 8 hours after an intrathecal injection in the lumbar area of 4 mg, CSF samples contained 19 to 46 µg/ml of gentamicin after 20 hours of administration [52].

Treatment of bacterial meningitis with gentamicin in infants

Two-hundred-nine infants were aged ≤2 months of age. Sixty isolates were obtained from newborns aged ≤7 days old, in whom the most common pathogens were group B Streptococcus (27/60; 45.0%), and Streptococcus pneumoniae (13/60; 21.7%) and non-typhoid Salmonella enterica (7/60; 11.7%). Gentamicin provided less coverage for gram-negative than gram-positive isolates (74/86; 86.0% vs. 155/163; 95.1%, P-value = 0.012) [53]. Group B β-haemolytic streptococci and Escherichia coli strains accounted for approximately two-thirds of all cases of neonatal meningitis and gentamicin is recommended for the initial empiric therapy of newborns with meningitis caused by these pathogens [54]. Twenty-one infants with purulent meningitis were treated with gentamicin. Two infants died and another one developed hydrocephalus but the remaining 18 infants were cured [55].

Transfer of gentamicin across the human placenta

Gentamicin was administered intravenously at a dose of 80 mg followed by an infusion of 18.5 mg per hour to 6 women with a gestational age of 18 to 23 weeks undergoing an elective abortion. Maternal and foetal concentrations of gentamicin were obtained 30 min after the loading dose and hourly during the infusion period and the foetal weight ranged from 238 to 515 grams [56].

Table 3. Gentamicin concentrations in the maternal serum, foetal serum, foetal urine, amniotic fluid, and maternal urine which have been obtained in 6 mothers and 5 foetuses. Values are the minimum, maximum, and mean±SD, by Kauffman et al. [56].

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ISSN: 2582-9181

Value	Infusion time (min)	Maternal serum during infusion (µg/ml)	Foetal serum (µg/ml)	Cord serum (µg/ml)	Foetal urine (µg/ml)	Amniotic fluid (µg/ml)	Maternal urine (µg/ml)
Minimum	140	2.10	0.50	0.60	1.90	0	83
Maximum	350	6.20	1.40	1.50	3.50	0	920
Mean	241	3.85	1.05	1.08	2.71	0	417
±SD	36.5	0.55	0.12	0.12	0.21	0	114

This table shows that the mean maternal and foetal concentrations of gentamicin are 3.85 and 1.08 µg/ml, respectively, suggesting that gentamicin poorly crosses the human placenta.

A single intramuscular dose of 40 mg of gentamicin was administered to 37 pregnant women before delivery. Maternal and umbilical cord blood concentrations of gentamicin were determined at the time of delivery. The mean peak concentration of gentamicin was 3.65 µg/ml in the maternal serum which was reached within 30 min after dosing and the mean peak umbilical cord serum was 1.25 µg/ml which was reached within 60 to 120 min after dosing. The mean peak concentration in the cord serum corresponded to 34.5% of that in the maternal serum indicating that gentamicin poorly crosses the human placenta [57].

Migration of gentamicin into the breast-milk

Ten lactating women received a single dose of 80 mg of gentamicin intramuscularly in the early postpartum period, average gentamicin concentrations were 157 ng/ml 1 hour after the dose, 156 ng/ml at 3 hours after the dose, 137 ng/ml at 6 hours after the dose, and 3 ng/ml at 12 hours after the dose [58]. After implantation of 90 gentamicin-impregnated beads into the femur of one mother with osteomyelitis, the breast-milk concentration ranged from 70 to 190 ng/ml at various times of gentamicin administration [59]. Ten nursing newborns received prophylactic gentamicin intramuscularly at a dose of 80 mg thrice-daily. On the 4th day of treatment, the concentration of gentamicin in the breast-milk was 420 ng/ml 1 hour after the dose, 480 ng/ml 3 hours after the dose, 490 ng/ml 5 hours after the dose, and 410 ng/ml 7 hours after the dose [60]. These results are consisting with the view that gentamicin is poorly migrated into the breast-milk.

Discussion

Gentamicin is an important agent for the treatment of many serious gram-negative bacillary infections and gentamicin is the aminoglycoside of first-choice because of reliable activity against all but the most resistant gram-negative aerobes. Gentamicin preparations are available for parenteral, ophthalmic, and topical administration. The intramuscular or intravenous dose of gentamicin sulfate is 5 to 7 mg/kg in patients with normal renal function and in patients with renal dysfunction the gentamicin dose should be reduced. The dose schedule is 3 mg/kg once-daily for newborns more than 35 weeks of gestation; 5 mg/kg daily in two divided doses for infants with severe infections; and 2 to 2.5 mg/kg thrice-daily for children up to 2 years of age. Gentamicin is absorbed slowly when it is applied topically in an ointment and somewhat more rapidly when it is applied as a cream [1]. The efficacy and safety of gentamicin have been reported [3-6] and gentamicin may cause nephrotoxicity or ototoxicity [7-14]. Gentamicin penetrates into bone and knee [15], skeletal muscle [16], wound tissue [17], ischemic foot ulcer [18], and in subcutaneous tissue [19] in significant amounts. The pharmacokinetics of gentamicin have been studied in febrile neutropenic patients and in healthy subjects and the mean elimination half-life of gentamicin is about 3 hours in patients and healthy subjects [20]. The pharmacokinetics of gentamicin have been investigated in tetraplegic and in paraplegic patients and in healthy subjects and the elimination half-life of gentamicin is about 2 hours in patients and in healthy subjects [21]. The prophylaxis [22-29], treatment [30-39], and trials [40-47] with gentamicin have been extensively studied. Gentamicin penetrates into the cerebrospinal fluid in significant amounts [48-52]. In literature, there are no studies on the treatment of bacterial meningitis with gentamicin in adults, whereas the bacterial meningitis was cured in infants [53-55]. The transfer of gentamicin across the human placenta is documented in 2 studies and gentamicin poorly crosses the human placenta [56, 57]. The migration of gentamicin into the breast milk has been reported in 3 studies and gentamicin poorly migrates into the breast-milk [58-60].

In conclusion, gentamicin is an important agent for the treatment of many serious gram-negative bacillary infections. The intramuscular or intravenous dose of gentamicin sulfate is 5 to 7 mg/kg in patients with normal renal function and the dose should be reduced in patients with renal dysfunction. The efficacy and safety of gentamicin have been reported but gentamicin may induce nephrotoxicity and ototoxicity and gentamicin diffuses into body tissues in significant amounts. The pharmacokinetics of gentamicin have been studied in febrile neutropenic patients and in healthy subjects and the mean elimination half-life is about 3 hours. The pharmacokinetics of gentamicin have been investigated in tetraplegic and in paraplegic patients and in healthy subjects and the mean elimination half-life of gentamicin is about 2

hours. The prophylaxis, treatment, and trials with gentamicin have been extensively studied. Gentamicin penetrates into the cerebrospinal fluid in significant amounts, and gentamicin treated bacterial meningitis in infants. Gentamicin is poorly transferred across the human placenta and poorly migrates into the breast-milk. The aim of this study is to review the clinical pharmacology of gentamicin.

Conflict of interests

The authors declare no conflicts of financial interest in any product or service mentioned in the manuscript, including grants, equipment, medications, employment, gifts, and honoraria.

This article is a review and drugs have not been administered to men or animals.

Acknowledgments

The author thanks Dr. Patrizia Ciucci and Dr. Francesco Varricchio, of the Medical Library of the University of Pisa, for retrieving the scientific literature.

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2(5): 01-08
ISSN: 2582-9181

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