# Single Daily Dose of Gentamicin in the Treatment of Pediatric Urinary Tract Infection

CHALEOMSRI TAPANEYA-OLARN, M.D.*,
VICHIT PITAYAMORNWONG, M.D.*,
KANCHANA TANGNARARATCHAKIT, M.D.*
WIWAT TAPANEYA-OLARN, M.D.*,
THANOM PETCHTHONG, B.Sc.**,

**Abstract**

Fourty-nine patients aged 6 months to 12 years old with suspected urinary tract infection (UTI) were evaluated in this open randomized study. Twenty-seven patients received gentamicin 4.5 mg/kg/d once daily (OD group) and 22 patients received the same daily dose in three divided doses (TID group) for 3 days before being switched to amoxy-clavulanic acid. Ninety-six per cent (26/27) of the OD group had peak gentamicin within therapeutic level while 40 per cent (9/22) of the TID group had peak gentamicin within therapeutic level. One in OD group had high gentamicin level due to technical error in obtaining blood sample. None in neither group had trough level in toxic level. Only 24 patients had confirmed UTI and were evaluated for clinical efficacy and toxicity. Demographic data were the same in both groups except there were more males in OD group (8:3 *vs* 4:9). Patients in OD group became afebrile earlier than TID group (8.69 *vs* 15.31 hours) but no statistically significant difference. All patients had negative urine culture results within 48 hours. None had clinical nephrotoxicity in both groups. More patients in TID group had laboratory nephrotoxicity (5/11 *vs* 2/13) but no statistically significant difference.

We conclude that gentamicin can be given safely and efficiently as single daily dose or thrice daily but more cost effective and less time consuming in once daily dose.

**Key word** : Gentamicin, Pediatric, Urinary Tract Infection

Aminoglycosides (AMG) had been used for several decades with remarkable efficacy in the treatment of gram negative urinary tract infection (UTI). They are the lowest cost parenteral antibiotics in institution's drug formulary(1). The hesitancy about the use of AMG is from concerns over the risks of nephrotoxicity and ototoxicity(2).

* Department of Pediatrics,
** Research Center, Faculty of Medicine, Ramathibodi Hospital, Mahidol University, Bangkok 10400, Thailand.

The rate of killing of gram negative bacteria of AMG is dependent on serum concentration in a linear fashion[3,4] as evident by lower mortality rates from gram negative bacteremia[5], sepsis[6] and pneumonia[7] when peak AMG levels are in the upper therapeutic range. AMG also posses post-antibiotic effect, it can inhibit bacterial regrowth even the AMG concentration falls below a pathogen's minimal inhibitory concentration[8,9].

Toxicity of AMG is best predicted by total area under the concentration time curve as indicated by high trough levels during therapy[10]. Utilizing longer dose interval minimizes accumulation and reduces the risk for nephrotoxicity and ototoxicity. Its toxicity also depends on the duration of therapy[11]. Prolonged use of AMG results in increased renal drug levels and increased risk of nephrotoxicity. In addition, increasing the dose interval and maintaining the standard dose per day will increase the peak and lower the trough level, hence improving the killing properties and lower the incidence of side effects.

Therefore, single daily dose of gentamicin for 3 days while waiting for appropriate choice of oral antibiotic treatment from urine culture and sensitivity results will minimize the nephrotoxicity and effectively treat UTI.

## PATIENTS AND METHOD

### Patients

Pediatric patients aged 6 months to 12 yrs who had fever associated with signs and symptoms suspected of UTI during June 1996 - September 1997 were admitted and enrolled in the study. Patients whose urine culture obtained from cleaned catch urine or cleaned bag with more than $10^5$ colonies/ml of single organism were considered to have UTI. Exclusion criteria were : known allergy to AMG, recently received AMG in the past 2 weeks, on high dose of diuretics or amphotericin B, underlying renal disease prior to studies, history of hearing loss or vestibular dysfunction, immunocompromised host, neutropenia, or renal impairment.

### Methods

Patients were randomized to treatment with intravenous gentamicin 4.5 mg/kg either once daily (OD), or in 3 divided doses (TID) for 3 days. Gentamicin was administered over one hour. Peak gentamicin levels were obtained 30 minutes after the first dose of gentamicin administration, trough gentamicin levels were obtained 30 minutes before the last doses of gentamicin. The levels of gentamicin were analysed by fluorescence polarization immunoassay technic.

After 3 days of gentamicin treatment, the antibiotic was switched to oral amoxy-clavulanic acid 50 mg/kg/d in three devided doses for 7 days for both groups or to other appropriate oral antibiotics according to urine culture results if patients had allergy to ampicillin, or if it was resistant to amoxy-clavulanic acid.

### Evaluation of efficacy

Signs and symptoms were evaluated and recorded at 0 hour, and every 4 hours for 3 days. Urinalysis, urine culture, urine-N-acetyl-D-glucosaminidase (NAG) by modified Leaback and Walker method[12], serum creatinine by Jaffe reaction method were done at 0 hour, 48 hours and 10 days. Patients were considered afebrile if their temperatures were less than 37.8°C for more than 24 hours.

### Evaluation of nephrotoxicity

Clinical nephrotoxicity was evaluated by serum creatinine. Laboratory nephrotoxicity was evaluated by urine NAG. Serum creatinine and urine NAG were measured at 0 hour, 48 hours and 10 days after therapy. Twenty-five per cent or 0.5 mg/dl increased in serum creatinine from baseline was defined as clinical nephrotoxicity. One fold rising of urine NAG/creatinine ratio from baseline was considered as laboratory nephrotoxicity.

### Statistics

Statistical analysis were done by using median and range for demographic data, Chi-squared test, and Fisher's exact test for qualitative analysis, Student's *t* test and Wilcoxan Ranksum test for quantitative analysis, Kapmir log rank test for duration of fever, and Chi-squared test for comparison of gentamicin level.

## RESULTS

There were 49 patients enrolled in this study, 25 patients were excluded due to negative urine culture in 18, mixed organisms from urine culture result in 6, and neutropenia in one. Only 24 patients fulfilled the criteria. Thirteen patients received gentamicin once daily, 11 patients received gentamicin thrice daily. There were no significant differences in demographic data between the two

**Table 1. Demographic data and causative agents.**

| Regimen | TID (n=11) | OD (n=13) |
|---|---|---|
| Age (month) | 10 (3-118) | 24 (3-163) |
| Male* (%) | 8 (72.7) | 4 (30.7) |
| Serum creatinine (mg/dl) | 0.4 (0.4-0.6) | 0.5 (0.4-0.8) |
| Temperature (°C) | 39 (38-40.2) | 38.8 (38-40.2) |
| *E.coli* UTI | 11 (100%) | 12 (92.3%) |

* p = 0.041

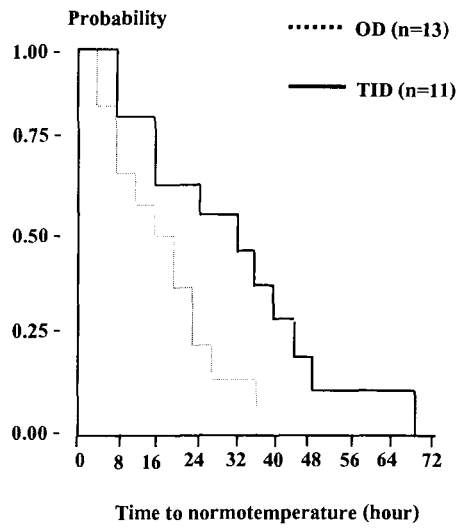


**Fig. 1. Life table of probability and time to normotemperature.**

groups except there were more males in TID group (8:3 *versus* 4:9). Twenty-three patients had *E. coli* and one patient in OD group had *Corynebacteria* spp (Table 1). All were sensitive to gentamicin.

Clinical efficacy was shown in Fig. 1. Most patients in OD group became afebrile by 24 hours (mean 8.69 hours) as compared to TID (mean 15.31 hours). However, there were no statistic significant differences (p = 0.067). All urine cultures were negative by 48 hours and 10 days after the treatment.

Clinical toxicity indicated by serum creatinine was assessed. There were no significant changes in serum creatinine at any time in both groups [0.5 (0.4-0.8), 0.5 (0.3-0.9), 0.4 (0.3-0.8) mg/dl at 0, 48 hours and 10 days respectively in OD group and 0.4 (0.4-0.6), 0.4 (0.4-0.8), 0.4 (0.3-0.6) mg/dl at 0, 48 hours and 10 days respectively in TID group].

Concerning renal tubular toxicity as detected by one fold rising of urine NAG/creatinine ratio[13], 5 out of 11 patients in TID group had one fold increase in urine NAG as compared to 2 of 13 in OD group. There were no statistically significant differences (p = 0.182).

Pharmacokinetics of gentamicin was studied in all 49 cases, 22 in TID and 27 in OD group. Peak gentamicin levels were 7.79 ± 2.28 μg/dl in OD group as compared to 3.25 ± 1.73 μg/dl in TID group (p = 0.001). Ninety-six per cent (26/27) of OD group had peak gentamicin level within therapeutic range of 4 to 12 μg/dl while 40 per cent (9/22) in TID group were in therapeutic range. Only one patient in OD group had peak gentamicin level above 12 μg/dl due to technical error in obtaining the blood sample at the end of drug administration instead of thirty minutes later. In addition, the trough gentamicin levels were 0.20 ± 0.27 μg/dl in OD group and 0.29 ± 0.23 μg/dl in TID group (p = 0.068). None were in toxic level.

## DISCUSSION

Our study results showed that the efficacy of daily dose gentamicin treatment as assessed by clinical improvement was not different from conventional treatment and may be better as indicated by early disappearing of fever (8.69 hours *vs* 15.31 hours), but there is no statistically significant difference which is due to small sample sizes. All cases had microbiological cures by 48 hours of treatment in both groups. Our clinical efficacy data supported the studies of gentamicin treatment in adult patients by Prins et al[14] and in pediatric patients by Elhanan et al[15], Shanka[16] and other aminoglycoside studies[17,18]. We briefly used gentamicin for only 3 days, which lessened the gentamicin exposure time and lessened the side effects.

We found no clinical nephrotoxicity in neither groups. OD group had even less biochemical nephrotoxicity than TID group (2/13 *vs* 5/11, p = 0.18), although it was not significantly different. These might be due to small sample size and tendency to have very low side effects of gentamicin even in TID group. Additionally, pharmacokinetic studies of gentamicin confirm the theory of higher peak and lower trough level in OD group. These might explain early clinical improvement in OD group and tendency to have less nephrotoxicity.

Therefore gentamicin may be given as once daily dose in treatment of urinary tract infection in pediatric patients. It is as safe and effective as conventional thrice daily dose but has more advantage to nursing staff in minimizing the time consuming and more cost effective.

(Received for publication on October 15, 1999)

## REFERENCES


1. Deamer RL, Dial LK. The evolution of aminoglycoside therapy : a single daily dose. Am Fam Physician 1996; 53:1782-6.
2. John JF Jr. What price success? The continuing saga of the toxic: therapeutic ratio in the use of aminoglycoside antibiotics. J Infect Dis 1988; 158: 1-6.
3. Kapusnik JE, Hackbarth CJ, Chambers HF, Carpenter T, Sande MA. Single, large, daily dosing versus intermittent dosing of tobramycin for treating experimental pseudomonas pneumonia. J Infect Dis 1988; 158:7-12 [Published erratum appears in J Infect Dis 1988; 158:911].
4. Davis BD. Mechanism of bactericidal action of aminoglycosides. Microbiol Rev 1987; 51:341-50 [Published erratum appears in Microbiol Rev 1988;52:153].
5. Moor RD, Smith CR, Lietman PS. The association of aminoglycoside plasma levels with mortality in patients with gram-negative bacteremia. J Infect Dis 1984; 149:443-8.
6. Noone P, Parsons TM, Pattison JR, Slack RC, Garfield-Davies D, Hughes K. Experience in monitoring gentamicin therapy during treatment of serious gram-negative sepsis. Br Med J 1974; 1:477-81.
7. Moore RD, Smith Cr, Lietman PS. Association of aminoglycoside plasma levels with therapeutic outcome in gram-negative pneumonia. Am J Med 1984; 77: 657-62.
8. Vogelman BS, Craig WA. Postantibiotic effects. J Antimicrob Chemother 1985; 15(Suppl):37-46.
9. MacKenzie FM, Gould IM. The post-antibiotic effect. J Antimicrob Chemother 1993; 32:519-37.
10. Chan GL. Alternative dosing strategy for aminoglycosides: impact on efficacy, nephrotoxicity, and ototoxicity. DICP 1989; 23:788-94.
11. Mattie HM, Craig WA, Pecheir JE. Determinants of efficacy and toxicity of aminoglycosides. J Antimicrob Chemother 1989; 24:281-93.
12. Leaback DH, Walker PG. Studies on glucosaminidase. Biochem J 1961; 78: 151-6.
13. Assadamongkol K, Tapaneya-Olarn W, Chatasingh S. Urinary N-acetyl-beta D-glucosaminidase (NAG) in aminoglycoside nephrotoxicity. J Med Assoc Thai 1989; 2(Suppl 1):42-5.
14. Prins JM, Buller HR, Kuijper EJ, Tange RA, Speelman P. Once versus thrice daily gentamicin in patients with serious infections. Lancet 1993; 341:325-9.
15. Elhanan K, Siplovich L, Raz R. Gentamicin once-daily versus thrice-daily in children. J Antimicrob Chemother 1995; 35:327-32.
16. Shanka AJ, Sharma S. Gentamicin as daily dose therapy in recurrent urinary tract infection in children. Curr Ther Res 1987; 41:599-603.
17. Viscoli C, Dudley M, Ferra G, et al. Serum concentrations and safety of single daily dosing of amikacin in children undergoing bone marrow transplantation. J Antimicrob Chemother 1991; 27(Suppl C):113-20.
18. Trijillo H, Robleclo J, Robeldo C, et al. Single daily dose amikacin in pediatric patients with severe gram-negative infections. J Antimicrob Chemother 1991; 27(Suppl C):141-7.

# การรักษาโรคติดเชื้อทางเดินปัสสาวะในเด็กด้วยยาเจ็นตะมิซิน ฉีดวันละครั้ง

*เฉลิมศรี ตปนียโอฬาร, พ.บ.*, วิวัฒน์ ตปนียโอฬาร, พ.บ.*,*
*วิจิตร พิทยาอมรวงศ์, พ.บ.*, ถนอม เพ็ชรทอง, วท.บ.**, กาญจนา ตั้งนรารัชชกิจ, พ.บ.**

ได้ศึกษาผู้ป่วยเด็กอายุ 6 เดือน – 12 ปี จำนวน 49 ราย ที่ได้รับการวินิจฉัยเบื้องต้นว่าเป็นทางเดินปัสสาวะอักเสบ สุ่มตัวอย่างผู้ป่วยออกเป็น 2 กลุ่มคือ กลุ่มที่ได้ยา gentamicin ขนาด 4.5 มก./กก./วัน หยดทางหลอดเลือดดำวันละครั้ง (OD group) จำนวน 27 ราย และกลุ่มที่ได้ยาขนาดเดียวกันแต่แบ่งเป็นฉีดยาวันละ 3 ครั้ง (TID group) จำนวน 22 ราย ให้ยา gentamicin รวม 3 วัน แล้วเปลี่ยนเป็น amoxy–clavulanic acid กินต่อจนครบระยะเวลารักษา ใน OD group ยาถึง therapeutic level ร้อยละ 96 ขณะที่ TID group มีเพียงร้อยละ 40 หลังได้ยาครั้งแรก ผู้ป่วย 1 รายใน OD group มีระดับยา gentamicin สูงมากจากความผิดพลาดในการเจาะเลือด ไม่มีผู้ป่วยรายใดในทั้ง 2 กลุ่ม มี gentamicin trough level ในระดับเป็นพิษต่อไต มีผู้ป่วยเพียง 24 รายที่มีการติดเชื้อทางเดินปัสสาวะจริง ในกลุ่มนี้ได้ศึกษาผลการรักษาทางคลินิกและพิษต่อไตของยา ไม่พบความแตกต่างใน demographic data เว้นแต่ใน OD group มีผู้ป่วยเพศชายมากกว่า (8:3 *vs* 4:9) OD group มีไข้ลงเร็วกว่า TID group (8.69 *vs* 15.31 ชั่วโมง) แต่ไม่แตกต่างทางสถิติ ผู้ป่วยทุกรายเพาะเชื้อจากปัสสาวะไม่ขึ้นหลัง 48 ชั่วโมง ไม่พบพิษต่อไตที่แสดงออกทางคลินิก แต่พบพิษต่อไตจากการตรวจทางห้องปฏิบัติการใน TID group พบ 5 ใน 11 ราย ใน OD group พบ 2 ใน 11 ราย ซึ่งไม่มีความแตกต่างกันอย่างมีนัยสำคัญทางสถิติ

โดยสรุป การให้ยา gentamicin หยดทางหลอดเลือดดำวันละครั้ง มีความปลอดภัยและมีประสิทธิภาพเท่ากับการแบ่งให้ฉีดยาวันละ 3 ครั้ง แต่สามารถให้ได้สะดวกและประหยัดกว่า

**คำสำคัญ** : Gentamicin, Pediatric, Urinary Tract Infection

* ภาควิชากุมารเวชศาสตร์,
** สำนักงานวิจัย, คณะแพทยศาสตร์โรงพยาบาลรามาธิบดี, มหาวิทยาลัยมหิดล, กรุงเทพ 10400