

The Safety Profile of Single Daily Dose of Aminoglycosides in Comparison with Multiple Daily Dose

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Abstract

To overcome the problems which associated with the standard multiple daily doses (MDD)

of aminoglycosides (AGs) like high incidence of toxicity (nephrotoxicity, ototoxicity) (5-25%) and high cost, an alternative approach was developed which was single daily dose (SDD). This new regimen was designed to maximize bacterial killing by optimizing the peak concentration/minimum inhibitory concentration (MIC) ratio and to reduce the potential for toxicity. The study includes 75 patients selected randomly, 50 of them received SDD regimen of age range of 17-79 years and the remaining received MDD regimen of age range of 13-71 years. The study was designed to evaluate the safety of SDD regimen in comparison with MDD regimen. All the patients in SDD group received a constant dose of 5-mg/kg/day of gentamicin and 20mg/kg/day of amikacin with a drug administration interval based on estimated creatinine clearance (CL_{Cr}): if ≥ 60 ml/min every 24 hours (q24h), 59- 40 ml/min every 36 hours and 39- 30 ml/min every 48 hours. The calculated dose was diluted with 0.9% normal saline or 5% dextrose to 50-100 ml and given as intravenous infusion over 30-60 minutes. In SDD group , the mean length of therapy was 6.4 ± 1.73 days .Gentamicin accounted for 96% of the aminoglycoside use, and the majority (58%) of patients received the drug every 24 hours. The 36- and -48 hours intervals were used for 34 and 8% of the population, respectively. While in MDD group , the mean length of therapy was 5.0 ± 0.91 days. Gentamicin accounted for all (100%) of aminoglycoside use, and all of the patients received the drug every 8 hours. No clinically apparent ototoxicity and nephrotoxicity were observed in the patients in the SDD group, in contrast to the patients in MDD group, in whom 4 patients (16%) were developed nephrotoxicity and 1 patient (4%) was developed ototoxicity. The obtained results indicate that SDD regimen was safer through decreasing the incidence of both nephrotoxicity and ototoxicity. For statistical analysis, ANOVA test was used with $P < 0.01$. Each mean was expressed as mean \pm SEM (Standard Error of Mean).

Key words: Aminoglycosides, Single Daily Dose, Nephrotoxicity and Ototoxicity.

الخلاصة

من اجل تجاوز المشاكل المصاحبة للجرع القياسية المتعددة من دواء الامثيوكلوكوسايد بسبب السمية العالية كتلف الكلى والاذن (5-25 %) والكلف العالية . استحدثت دراسة بديلة في استخدام نظام الجرعة اليومية الواحدة هذا النظام الجديد صمم لزيادة القابلية القاتلة للبكتريا عن طريق زيادة نسبة قيمة التركيز / اقل تركيز مثبط والاقبال من الاعراض الجانبية . تشمل الدراسة على 75 مريض تم اختيارهم عشوائيا ضمنهم 50 مريض كانوا باعمار (17 - 79) سنة استلموا الدواء بنظام الجرعة الواحدة . العدد المتبقي كان بمعدل الاعمار (13 - 71) سنة استلموا الدواء بنظام متعدد الجرع . صممت الدراسة لتقييم سلامة نظام الجرعة الواحدة بالمقارنة بنظام متعدد الجرع جميع المرضى في نظام الجرعة الواحدة استلموا جرعة ثابتة 5 ملغم /كغم /يوم من مادة جنتاميسين و 20 ملغم /كغم /يوم من مادة امي كيسين مع فاصل اخذ العلاج اعتمادا على وضوح الكريبتينين المخمن اذا كان اقل من 60 مل / دقيقة يعطى الدواء كل 24 ساعة , 40 - 59 مل / دقيقة كل 36 ساعة و 39 - 30 مل / دقيقة كل 48 ساعة . الجرعة المسموحة خففت بمحلول الملح الطبيعي 0.9 % او محلول الدكستروز 5 % الى 50 - 100 مل واعطى عن طريق النضوح الوريدي خلال 30 - 60 دقيقة في نظام الجرعة الواحدة كان معدل طول فترة العلاج 6.4 ± 1.73 ايام تم اعطاء الجنتاميسين الى 96 % من المرضى والغالبية منهم (58 %) استلموا الدواء كل 24 ساعة فواصل الـ 36 و 48 ساعة استخدم لـ (34 %) (8 %) من المرضى بالتوالي . بينما في نظام متعدد الجرع كان معدل طول فترة العلاج 5 ± 0.91 ايام جميع المرضى (100 %) استلموا جنتاميسين كل 8 ساعات . لا يوجد ظهور سريري في تسمم الاذن والكلى عند المرضى المستخدمين لنظام الجرعة اليومية الواحدة . بينما في نظام متعدد الجرع حيث ظهرت 4 حالات تلف (16 %) كلى وحالة تلف تسمم الاذن (4 %) . النتائج تؤكد بان نظام الجرعة الواحدة كان اكثر امانا من خلال تقليل الحالات الجديدة من التلف في الاذن والكلى .

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Introduction

Clinical experience over the past 50 years has shown that multiple daily dosing strategy to be both labor and lab. intensive and the Correct multiple daily dosing of aminoglycoside often requires pharmacokinetics expertise, close monitoring of drug serum levels and renal function⁽¹⁾. Currently many centers are adopting the SDD regimen as the standard / preferred dosing method and by the year 2000, about 80% of the hospitals worldwide use SDD regimen.⁽²⁾ The rationales of using aminoglycosides as SDD were due to their concentration dependent killing⁽³⁾, Significant Post – Antibiotic Effect (PAE)⁽⁴⁾, avoidance of the adaptive post – exposure resistance⁽⁵⁾, and aminoglycosides' uptake into renal tubule cells and inner ear is a saturable process⁽⁶⁾. The toxicities of aminoglycosides include nephrotoxicity, ototoxicity (vestibular and auditory). Approximately 8% to 26% of patients who receive aminoglycoside for more than several days develop mild renal impairment which is reversible because the proximal tubular cells have the capacity to regenerate⁽⁷⁾. Aminoglycosides are poly cationic in nature binding to the anionic site on the endothelial cells of the glomerulus leading to reduction in the glomerular filtration rate.⁽⁸⁾ They are almost exclusively filtered by the glomerulus and excreted unchanged. Filtered aminoglycosides undergo proximal tubular reabsorption by binding to anionic phospholipids in the brush boarder, followed by endocytosis and sequestration in lysosomes of the S1 and S2 segments of the proximal tubule.⁽⁹⁾ The earliest lesion observed following clinically relevant doses of aminoglycosides is an increase in the size and number of lysosomes.⁽¹⁰⁾ These lysosomes contain myeloid bodies, which are electron-dense lamellar structures containing undergrated phospholipids. The renal phospholipidosis produced by the aminoglycosides is thought to occur through their inhibition of lysosomal hydrolyases, such as sphingomyelinase and phospholipases⁽¹¹⁾, as a result the lysosomes become progressively distended until they rupture, releasing lysosomal enzymes and high concentration of aminoglycosides into the cytoplasm. The released lysosomal contents can interact with various membranes and organelles that trigger cell death⁽¹²⁾. Aminoglycosides also inhibit various ATPase including Na⁺-K⁺ ATPase, adenylate cyclase; alter the function of mitochondria and ribosome.⁽¹³⁾ Aminoglycosides induce irreversible ototoxicity (Vestibular and auditory) in about 2

to 25% of the patients⁽¹⁴⁾. The precise mechanism of hair cell destruction in both forms of ototoxicity is unclear, but it has been suggested that aminoglycosides interfere with active transport system essential for the maintenance of the ionic balance of the endolymph⁽¹⁵⁾. This would lead to alteration in the normal concentration of ions in the labyrinthine fluid with impairment of electronic activity and nerve conduction. Eventually, the electrolyte changes, or perhaps the drugs themselves damage the hair cell irreversibly. Several factors have been associated with a higher incidence of ototoxicity including duration of therapy (>8 days), cumulative dose, total daily dose, trough serum drug concentration, concurrent diuretic therapy, underlying disease state, previous exposure to aminoglycoside therapy, age, specific aminoglycosides⁽¹⁶⁾. SDD regimen was suitable for all patients requiring aminoglycoside therapy except those having great changes in aminoglycoside pharmacokinetics like pregnant patients, children etc.... The drug dosage in SDD regimen was by fixing the dose of the drug with changing the interval of drug administration according to the estimated CLcr⁽⁶⁾ and this consist of giving a constant dose of 5mg/kg/day for gentamicin and tobramycin, 20mg /kg/day for amikacin and 15 mg/kg/day for streptomycin⁽¹⁷⁾. The interval of drug administration will depend on the estimated CLcr calculated by using Cockcroft equation⁽¹⁷⁾. The dose is calculated based on Actual Body Weight (ABW) unless the patient is ≥ 20 % more than the IBW. For obese patients, a dosing weight (DW) should be calculated. Monitoring of renal toxicity was done through measurement of basal and every 2-3 days of serum creatinine concentration (S.cr)⁽⁶⁾. The standard measurement of peak and trough level is not required due to the high peak level and drug –free interval obtained with SDD regimen. In patients with adequate renal function (CLcr >60ml/min), the trough aminoglycoside level would be near zero (<< 1mg/L) so, the initial dosing interval would be maintained and no further drug level determination was necessary as long as CLcr remains unchanged⁽¹⁸⁾. In general, monitoring of the SDD regimen can be achieved by taking a single random blood sample through 6-14 hours. after starting of the infusion and the level will be evaluated on a nomogram. Even this single random drug concentration may no longer be necessary to be measured for the following classes of patients⁽¹⁷⁾ :-Patients receiving SDD every 24 hours, Patients without concurrently administered nephrotoxic

agents, Patients without exposure to contrast media, Patients not in the intensive care unit, Patients less than 60 years age. A baseline and weekly audiometry are recommended for patients who require greater than 2 weeks of therapy⁽⁷⁾.

Materials and Methods

This comparative study was done in Al-Kirkuk General Hospital in Kirkuk city on (75) patients admitted to surgery, medicine and gynecology wards under medical supervision by the specialist physician in each ward. The patients were selected randomly and they were classified in to two groups, SDD group (50 patients, age 17-79 years) and MDD group (25 patients, age 13-70 years). The Patients that were eligible for the study include all the patients requiring aminoglycoside therapy except those with great change in AG pharmacokinetics. The Patients in SDD group were received aminoglycoside antibiotic (whether gentamicin or amikacin) in a dose depending on their Actual body weight (ABW) unless their ABW is >20% above their Ideal body weight (IBW). For these patients, a dosing weight (DW), which is based on the IBW plus 40% of the estimated adipose tissue mass, was calculated for dosage determination. The interval of drug administration is based on the calculated creatinine clearance (CLcr) according the Cockcroft Equation, which is equal to:-

CLcr (male) = $IBW (kg) (140 - Age) / 72 [S.cr \text{ mg/dl}]$
 CLcr (female) = $0.85 IBW (kg) (140 - Age) / 72 [S.cr \text{ mg/dl}]$

Where: - IBW is ideal body weight. Therefore,

If CLcr is ≥ 60 ml/ min, the interval of drug administration would be 24 hours,

CLcr is 59-40 ml/ min; the interval of drug administration would be 36 hours,

CLcr is 39-30 ml / min; the interval of drug administration would be 48 hours,

CLcr is < 30 ml/ min, aminoglycosides would not be recommended and other alternative antibiotics should be used.

Culture and sensitivity test was done before starting therapy using modified Kirby-Bauer Method to know the reason of failure (if occur) whether due to drug resistance or due to the regimen itself. The following laboratory tests and parameters were monitored for all patients who enrolled in the study including:- Basal and every 2-3 days measurement of serum creatinine concentration, White Blood Cell count(WBC) and general urine examination (G.U.E)(For those having UTI), Basal and daily recording of body temperature. Monitoring of nephrotoxicity was

done through basal and periodic measurement of S.cr, while ototoxicity was monitored through baseline audiometry and documentation of auditory function, and daily monitoring of any changes in hearing status under the supervision of specialized physician.

Results and Discussion

Age was considered an important factor in aminoglycosides toxicities since with increasing age there was a decrease in renal function and subsequent reduction in aminoglycosides excretion and hence there accumulation. Table(1) showed Percent of patients in respect to their age distribution.

Table (1): Percent of patients in respect to their age distribution.

Group	≤ 40 years	41-50 years	51-60 years	61-70 years	>70 years
SDD	40%	18%	26%	12%	4%
MDD	52%	20%	20%	8%	0%

Figure (1) showed that in the SDD group, majority (58%) of patients received the drug (gentamicin and amikacin) every 24 hours. The 36- and -48 hours intervals were used for 34 and 8% of the population, respectively. While all the patients in MDD group were received therapy every 8 hours, Renal function is an important criteria in aminoglycosides therapy since it determines the dose and interval of drug administration because they are mainly renally excreted⁽¹⁹⁾. Renal function status was reflected by normal serum [S.Cr] and creatinine clearance⁽²⁰⁾. The normal range of serum creatinine was 0.7-1.2 mg/dl (70-150 $\mu\text{mol/L}$) and of creatinine clearance was 60-125 ml/min⁽²¹⁾.

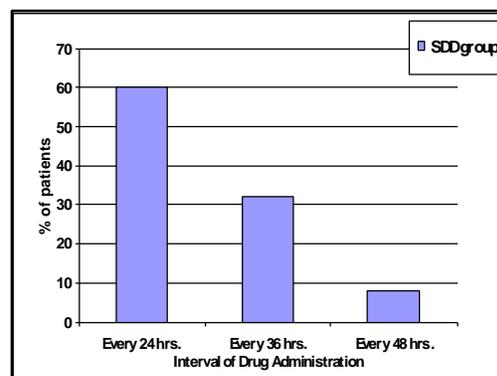


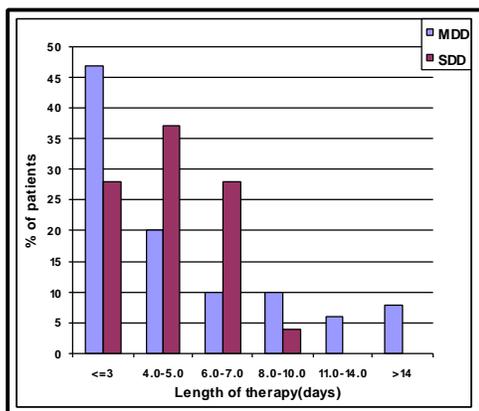
Figure (1) : Percent of patients (SDD) group in respect of interval of drug administration

Table(2): The mean pre and post treatment serum creatinine concentration [S.Cr] for SDD and MDD group.

Groups	Pretreatment mean [S.Cr](mg/dl)	Post treatment mean serum [S.Cr] (mg/dl)
SDDgroup	1.0±0.09 ^a	0.97±0.09 ^a
MDD group	1.15±0.32 ^b	1.7±0.33 ^c

Each value represents mean±SEM, Values with non identical superscripts (a,b,c) are considered significantly different (p<0.01) .

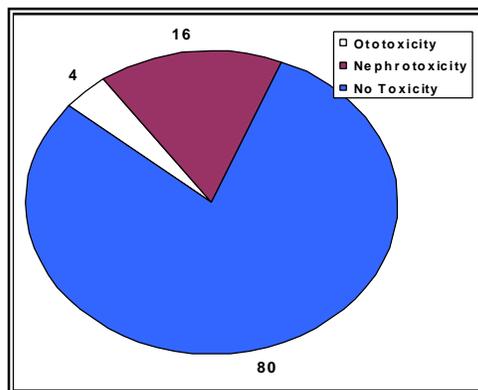
Table (2) showed that the pre treatment renal function in both SDD and MDD group was normal (reflected by the normal [S.Cr]) while the post treatment was abnormal in MDD group (reflected by the elevated [S.Cr]) which indicate the occurrence of nephrotoxicity. Statistical analysis (P>0.01) revealed that there was no significant difference between the mean pre and post treatment [S.Cr] in SDD group while there was a significant difference (P<0.01) in MDD group. This indicates the superiority of SDD regimen over MDD regimen since the incidence of nephrotoxicity with MDD regimen was higher and occur in a wide number of patients (5-25%) as many studies reported⁽²²⁾ Duration of therapy (>8 days) was one of the most important determinant risk factor in aminoglycosides toxicity⁽²³⁾ and they receive therapy for various duration ranging from ≤3 days to > 14 days, figure (2).



Figure(2) : Percent of patient in respect to their length of therapy

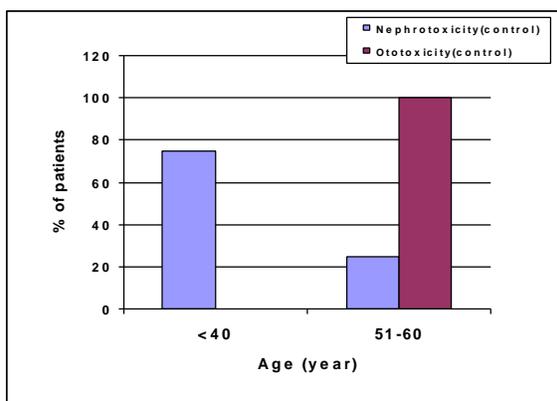
The mean length of therapy in SDD group was 6.4±1.73 days while 5.0±0.91 days in MDD

group. The results of statistical analysis indicated that there was no significant difference (P>0.01) in the mean length of therapy between the SDD and MDD group. 24% of the patients in SDD group received therapy for ≥ 8 days compared to only 8% in group indicating the safety of SDD regimen since no toxicity was observed in spite of higher percent of patients who received longer duration of therapy due to the safety profile of SDD regimen⁽²⁴⁾ figure (2) . Ninety six percent of the patients in SDD group received gentamicin and 24% received amikacin, while all the patients in the MDD group received gentamicin only. The total number of the patients who received gentamicin and amikacin in SDD group were > 50 because most of the patients were first treated empirically with gentamicin then converted to amikacin according to the results of culture and sensitivity test which revealed gentamicin resistant bacteria and amikacin sensitive bacteria. The mean dose of gentamicin was 282.9±6.8 {range, 212.5 - 438.4} mg in SDD group and 235.2±4.8 {range, 120- 240} mg in MDD group, while for amikacin it was 182±71.3 . {range, 914-1680} mg. The results of statistical analysis showed that there was a significant difference (P<0.01) in the mean dose of gentamicin between SDD and MDD group. This proves the safety of SDD regimen because no incidence of toxicity despite the use of higher dose, in contrast to development of toxicity in MDD group⁽²⁵⁾. All patients who are given the SDD and MDD regimen either had improved or complete resolution of their infections except two patients given MDD regimen had failures. Concerning the toxicity (nephrotoxicity and ototoxicity) of both SDD and MDD regimen, no toxicity was observed in any patients received SDD regimen While 20% of the patients who received MDD regimen developed toxicity, figure(3).



Figure(3) : Percent of patients MDD group in respect of drug toxicity occurrence

Nephrotoxicity was defined as an increase in S.cr. of ≥ 0.5 mg/dL above the baseline value. Patients were not evaluated for nephrotoxicity if they had been treated with aminoglycoside in the previous week, treatment with aminoglycoside was resumed within one week of stopping treatment, hemodialysis was started within 48 hour after the start of therapy and if the patient met the criteria for nephrotoxicity within the first 24 hour of therapy since in that case the decline in renal function is unlikely to be the result of the aminoglycoside treatment⁽²⁶⁾. Nephrotoxicity was not detected in any of the patients who received SDD regimen. This agree with other study which also indicate no nephrotoxicity with SDD regimen⁽²⁷⁾, but David P. Nicolau study showed that SDD regimen may be associated with small percent (1.2%) of nephrotoxicity⁽⁶⁾. Sixteen percent of the patients in MDD group met the criteria of nephrotoxicity in our study, figure (3). Figure (4) show the age distribution of the patients in whom toxicity occurred. All the patients who developed nephrotoxicity in MDD group were male and 75% were of age of ≤ 40 years with mean age of 35 ± 9.5 years and mean dose 210 ± 20.0 mg. This agree with other studies that revealed 5-25% of nephrotoxicity with MDD regimen^(28,29). The mean length of therapy in those who developed nephrotoxicity was 9.3 ± 2.9 since duration of therapy was of the most important determinant factor in nephrotoxicity⁽³⁰⁾,



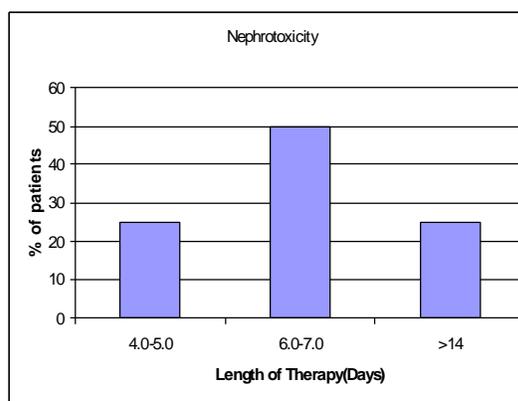
Figure(4) : Percent of patient MDD group in whom toxicity occur in respect to age distribution

Figure(5) . No significant difference in the mean age and dose was observed between the patients in MDD group who developed nephrotoxicity and those who did not, but there was a significant difference ($P < 0.01$) in the

mean length of therapy, 5 days compared to 9.3 days, indicating the importance of duration of therapy on toxicity. Ototoxicity, in the form of vestibular manifestation, was not observed in any of the patients in SDD group as in Benjman M. Limson *et al* study which also revealed no ototoxicity with SDD regimen⁽³¹⁾ while other study revealed only 0.14% ototoxicity⁽⁶⁾. Four percent of the patients in MDD group developed ototoxicity with age > 50 years old, and duration of therapy of > 14 days as Bates, D.E. study indicate a high percent of ototoxicity with MDD regimen ranging from 5-25%⁽³²⁾.

In spite of the presence of greater risk factors for aminoglycosides toxicity in SDD group including :-

- elderly patients (> 70 years) were found in SDD group but not in MDD group;
- the percentage of patients who received therapy for ≥ 8 days were greater in SDD group;
- administration of amikacin in SDD group for a median length of therapy of 13 days (range 3 to 42 days) which is greater than the recommended duration of therapy for amikacin (i.e., 7 to 10 days);
- greater median dose of gentamicin in SDD group;
- use of SDD regimen in diabetic and hypertensive patients with impaired renal function;



Figure(5) : Percent of patients MDD group in whom nephrotoxicity occur in respect of length of therapy

with no appearance of toxicity in SDD regimen indicates it's safety over MDD regimen. This safety was due to the new pharmacodynamic data of aminoglycosides which is the saturability of aminoglycosides accumulation in renal tubular cells and inner

ear at low concentration (threshold concentration) and the time above this threshold concentration was the determinant of toxicity^(6, 33). The threshold for toxicity was corresponds to a plasma concentration of 2 mg/L. The once-daily regimen produces a threefold higher plasma concentration, which enhance efficacy that otherwise might be compromised due to the prolonged sub-MIC concentration later in the dosing interval compared with every-8-hour regimen. Once-daily regimen provides a 12-hour period during which plasma concentration are below the threshold for toxicity, thereby minimizing the toxicity that otherwise might result from the early high plasma concentration. The every-8-hour regimen, in contrast, provides only a brief period (< 3 hours) during which plasma concentrations are below the threshold for toxicity^(33,34), (figure 5).

Conclusion

On the basis of the obtained results, one can conclude that SDD regimen appears to be safer than the conventional MDD regimen through reduction in the incidence of nephrotoxicity and ototoxicity.

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