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## Amikacin Pharmacokinetics and Suggested Dosage Modifications for Cancer Patients

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### ABSTRACT:

**Background/Aim:** Infections in immune compromised neutropenic cancer patients can lead to rapid deterioration, serious morbidity and mortality. Aminoglycosides in association with a  $\beta$ -lactam antibiotic are still commonly prescribed as the first-line combination during prolonged, febrile, severe neutropenia. The optimal peak concentration of amikacin in febrile neutropenic patients is unknown. Objectives were to evaluate pharmacokinetics of amikacin in patients taking cancer chemotherapy for acute lymphoblastic leukemia (ALL) and to individualize amikacin dosage in order to obtain the most effective, non toxic dose for each patient.

**Patients& methods:** The pharmacokinetics of amikacin administered intravenously (1000 mg/24 hrs) over 30 minutes was investigated in 12 oncohematologic patients who experienced neutropenia and fever induced by cancer chemotherapy. The concentration of amikacin in serum was determined by using Abbott TDx system. Then dosage adjustment was performed to achieve a peak concentration of 60  $\mu\text{g} / \text{ml}$  and a trough concentration  $< 5\mu\text{g} / \text{ml}$ .

**Results:** The value for  $V_d$  (L),  $k_e$  ( $\text{h}^{-1}$ ),  $t_{1/2}$  (h), Cl (l/h) were  $19.78 \pm 1.67$ ,  $0.19 \pm 0.01$ ,  $3.59 \pm 0.44$ ,  $3.92 \pm 0.62$ , respectively. The peak and trough serum concentration were  $48.03 \pm 3.94 \mu\text{g} / \text{ml}$  and  $0.51 \pm 0.22 \mu\text{g} / \text{ml}$ . The new dosage is adjusted to achieve  $C_{ss \text{ peak}}$  of 60  $\mu\text{g} / \text{ml}$  using the same dosing interval (24 hrs) and the same  $C_{ss \text{ trough}}$  for each patient was  $1220 \pm 122 \mu\text{g} / \text{ml}$ .

**Conclusion:** 1-The therapeutic drug monitoring of amikacin levels is mandatory for every cancer patient who receives aminoglycosides. 2-The knowledge of the pharmacokinetics of amikacin and accurate dosage adjustment in such patients is needed to avoid possibilities of its ineffectiveness resulting in unnecessary costs and occasionally predisposing patients to a higher risk of toxicity.

**Key words:** Amikacin, pharmacokinetics, acute lymphoblastic leukemia.

### INTRODUCTION

Infections in immune compromised neutropenic cancer patients can lead to rapid deterioration, serious morbidity and mortality <sup>(1)</sup>. With the use of more intensive and potentially curative

chemotherapy regimens, a large number of patients are being immune compromised and subjected to infectious complications which can be life threatening and may limit the benefits of

antineoplastic therapy. This fear led to the establishment of practice of starting empiric broad spectrum antibiotic therapy in such patients to reduce the incidence of morbidity and mortality<sup>(2)</sup>.

Aminoglycosides in association with a  $\beta$ -lactam antibiotic are still commonly prescribed as the first-line combination during prolonged, febrile, severe neutropenia because of their broad-spectrum, peak-dependent bactericidal activities, their marked post antibiotic effects, and their ability to prevent the emergence of resistant mutants<sup>(3)</sup>. The rationale for once-daily (o.d.) dosing of aminoglycosides is well established<sup>(4)</sup>, and several recent studies have documented the clinical and microbiological efficacies of o.d. dosing of amikacin in combination with a  $\beta$ -lactam antibiotic during febrile neutropenia<sup>(5,6)</sup>.

The efficacy of amikacin therapy is determined mainly by achieving the required clinical outcomes, which are shortening in the duration of fever and improvement of the site of infection. These clinical outcomes necessitates that the amikacin peak concentrations should be between 20 to 30 mg / L and trough concentrations < 10 mg /L.<sup>(7)</sup> There are several factors affect the pharmacokinetic parameters ( $k_e$ ,  $t_{1/2}$ ,  $V_d$  &  $Cl$ ) in cancer patients e.g. overhydration, malnutrition, prolonged fever duration and hematologic malignancies itself<sup>(8)</sup>. In addition, the physiologic response to stress in critically ill patients may also leads to increase in volume of distribution and clearance of drugs, as stress increases the basal metabolic energy expenditure, oxygen consumption, cardiac output, blood flow, organ perfusion, urinary urea nitrogen and creatinine excretion during catabolic stress<sup>(9)</sup>.

Low serum aminoglycoside concentrations are associated with a higher risk of clinical failure<sup>(10)</sup> and the selection of resistant strains<sup>(4)</sup>. So far, modifications of aminoglycoside kinetics in febrile neutropenic patients have been reported for conventional dosages administered twice daily (b.i.d.) or three times daily (t.i.d.)<sup>(11-13)</sup>. The use of a high dose of amikacin also raises the question of the linearity of the kinetics<sup>(14)</sup>. The optimal peak

concentration of amikacin in febrile neutropenic patients is unknown, but in nonneutropenic patients, peak concentrations in serum (measured 1 h after the start of the infusion) of <20 mg/liter in patients treated t.i.d. and <40 mg/liter in intensive care unit patients treated o.d. were associated with a less favorable prognosis<sup>(10)</sup>. Hence, a less than proportional increase in the peak amikacin level could affect efficacy.

### AIM OF THE STUDY

The aims of this study were to evaluate pharmacokinetics of amikacin in patients taking cancer chemotherapy for acute lymphoblastic leukemia (ALL) and experiencing neutropenia with febrile episodes and to compare the present results with pharmacokinetic information drawn from the normal population and to individualize amikacin dosage in order to obtain the most effective, non toxic dose for each patient.

### PATIENTS & METHODS

A total of 12 patients taking cancer chemotherapy for acute lymphoblastic leukemia (ALL), 7 males and 5 females were enrolled in this prospective non randomized clinical trial which was conducted at the Medical Oncology Department, National Cancer Institute (NCI), Cairo University, Cairo, Egypt.

#### Inclusion criteria:

1. Febrile neutropenic patients of both sexes (ages >18 years) with an expected duration of neutropenia of >7 days.
2. Patients with a temperature of > 38.5 °C once daily or 38 °C three times a day.

#### Exclusion criteria:

1. Pregnant woman
2. Patients have hypersensitivity to amikacin sulfate or any component of the amikacin formulation.
3. If they had temperature <38 °C

This study was approved and performed according to the institution's local rules. All the patients were also receiving chemotherapy regimen, along with empirical antibiotic therapy for febrile episode (amikacin was co administered with ceftazidime).

Neutropenia was defined as a neutrophil count of  $<500/\text{mm}^3$ , and fever was defined as a body temperature of  $>38.0^\circ\text{C}$  measured twice within 3 h or by an episode of body temperature of  $>38.5^\circ\text{C}$ . During the neutropenic phase a physical examination was performed at least daily for all of these patients.

Initial amikacin dosing regimens were chosen by attending physicians, the patients received a fixed amikacin dose of 1000 mg / 24 hrs as short infusion over 30 minutes then dosage adjustment was performed to achieve a peak concentration of 60  $\mu\text{g} / \text{ml}$  and a trough concentration  $< 5\mu\text{g} / \text{ml}$ .

Amikacin containing amikacin sulfate was diluted in 5% dextrose and infused intravenously over a period of 30 minutes. We assumed that steady-state kinetics was achieved by the fourth dose. Blood samples (6 ml) were collected by a research nurse from the central venous catheter immediately before the fourth dose (time of the trough concentration) and 30 min after the end of 30 min infusion (time of the peak concentration). All the serum samples were stored and kept frozen ( $-20^\circ\text{C}$ ) until analysis.

Amikacin concentration in each 50  $\mu\text{l}$  serum sample was measured with the help of TDx analyzer (Abbott laboratories, North Chicago, USA) by utilizing fluorescence polarization immunoassay technology in hospital's pathology laboratory after calibration and validation of the instrument with amikacin reagents, calibrators and controls, respectively. The intraday coefficient of variation for the assay was  $<5\%$ .

A one-compartment open population model with first-order elimination was used.

Pharmacokinetic parameters were calculated from measured concentrations in serum by using the Sawchuck-Zaske method (15) as follows:

1. Calculation of the elimination rate constant for each patient by using the following equation:  $\ln C_{ss, \max} / C_{ss, \min} = k_e [T - t']$

Where,  $C_{ss, \max}$  is the maximum concentration in the serum and was drawn 30 min after the end of the infusion while the  $C_{ss, \min}$  is the concentration in the serum immediately before the next dose,  $k_e$  is the elimination rate constant, T is the dosing interval

(24hours),  $t'$  is the duration of infusion.

2. Calculation of the half life by using the following equation.

$$t_{1/2} = \frac{0.693}{k_e}$$

4. The volume of distribution ( $V_d$ ) was determined by using the following equations:

$$V_d = \frac{\text{Dose (mg)}}{t' k_e (C_{ss, \max} - C_{ss, \min} e^{-k_e t'})}$$

4. Calculation of the total body clearance (CL) by using the following equations:  $Cl = k_e V_d$

5. The dosage interval will be constant for all patients = 24 hrs.

6. Determine the dose required to achieve  $C_{ss, \text{peak}}$  of 60  $\mu\text{g} / \text{ml}$  &  $C_{ss, \text{trough}} < 5 \mu\text{g} / \text{ml}$  because the study will use the extended dose interval regimen.

$$K_0 = \frac{C_{ss, \max, (\text{desired})} k_e V_d (1 - e^{-k_e T})}{1 - e^{-k_e t'}}$$

Where  $K_0$  is the infusion rate

Peak amikacin levels obtained with the new dosage regimen were then compared with those obtained with the recommended doses by Chi-square analysis.

## RESULTS

Twelve patients including 7 males and 5 females were included in this study. All patients had acute lymphoblastic leukemia and experiencing neutropenia episodes. The age of the patients ranged from 23 to 65 years of old. Mean body weight was  $72.08 \pm 5.86$  kg. The characteristics of these 12 patients are shown in table (1) the mean

pharmacokinetic parameters for amikacin are shown in table (2).

Mean peak and trough amikacin levels obtained after administration of the recommended dosage, 1000 mg (14.5 mg/kg/day) were  $48.0 \pm 33.94$  and  $0.51 \pm 0.22$  respectively. The new dosage is adjusted to achieve  $C_{ss \text{ peak}}$  of 60 ug/ml using the same dosing interval (24 hrs) and the same  $C_{ss \text{ trough}}$  for each patient was  $1220 \pm 122$  as shown in table 3.

**Table 1. Patient characteristics**

Parameters	Values (mean $\pm$ SD)
Age	$42.83 \pm 13.29$
Body weight	$72.08 \pm 5.86$
Serum creatinine	$0.76 \pm 0.34$

**Table 2. Amikacin pharmacokinetic parameters after intravenous infusion in 12 cancer patients.**

Parameters	Values (mean $\pm$ SD)
$V_d$ (L)	$19.78 \pm 1.67$
$k_e$ ( $h^{-1}$ )	$0.19 \pm 0.01$
$t_{1/2}$ (h)	$3.59 \pm 0.44$
Cl (l/h)	$3.92 \pm 0.62$
Peak (ug/ml)	$48.03 \pm 3.94$
Trough (ug/ml)	$0.51 \pm 0.22$

**Table 3. Comparison of the dose and mean peak concentration after the old and new dose administration.**

Parameters	Old dose	New dose
Dose (mg/day)	1000	1220
Mean peak (ug/ml)	$48.03 \pm 3.94$	$60.15 \pm 6.12^*$

\*  $P < 0.001$

## DISCUSSION

Information on drug disposition in target populations allows clinicians to optimize the design of dosage regimens both 'a priori' and later in the course of therapy. Individualization of dosage requirements is especially necessary in high-risk populations, such as patients with malignancies, due to the life-threatening nature of infections in neutropenic patients and the narrow therapeutic index of aminoglycosides. Increased aminoglycoside distribution volumes and clearances have been noted in patients with malignancies (16,17). However, these kinetic alterations are not uniform in all subgroups of malignancies and cannot be attributed to any single variable such as malignancy type, degree of neutropenia, disease state, total exposure or type of chemotherapy. Furthermore, no combination of factors has been described to accurately predict which patients will require larger dosages of aminoglycosides (18,19).

Our patients had lower CL and a higher or equal  $V_d$  of amikacin which resulted in longer  $t_{1/2}$  when compared to health subjects. The present value for  $t_{1/2}$  ( $3.59 \pm 0.44$ ) is in agreement with the reported range of  $3.6 \pm 2.2$  and  $3.8 \pm 2.4$  hrs in patients with hematologic malignancies (11,17). The current value for CL was  $3.92 \pm 0.62$  L/h which is lower than the cited value in normal population. The normal reported value for this parameter is  $6.18$  (7). Poor nutritional status was associated with decreased amikacin CL. This is similar to results from other investigators. Dickerson et al. observed a significant decrease in gentamicin CL in healthy volunteers after fasting compared with that in a protein loaded state (20).

The present value for  $V_d$  was  $0.27 \pm 0.04$  l/kg the normal value for this parameter have been mentioned as  $0.26$  l/kg (7). From other reports, the value of  $V_d$  has been varied from  $0.38$  and  $0.41$  l/kg in cancer patients (11,17). The  $V_d$  of amikacin is reported to be markedly elevated in hematologic malignancies compared with normal (17). This has been attributed to substantial changes in extracellular fluid compartment in patients with

severe sepsis as a result of changes in state of hydration (21,22). Davis et al (11) attributed this increased  $V_d$  due to lower serum albumin concentrations by a mechanism. But, according to them, it may be due to low venous oncotic pressure that results in increased extracellular fluid. Since aminoglycosides are distributed readily to that space, the  $V_d$  would be increased in sepsis-induced hypoalbuminemia. The  $V_d$  of amikacin is reported to have a substantial effect on its effect on its peak serum concentration and consequently, the dosage requirements of amikacin (23). In patients with contracted volume, lower dosages while for that with expanded volumes larger dosages of amikacin are needed to achieve desired peak levels (24).

The goal was to adjust the amikacin dosing to obtain 1-h peak and 24-h trough serum amikacin levels of  $60$  and  $<5$   $\mu\text{g/liter}$ , respectively (6,25).

With regard to the peak value, it is known that a peak concentration/MIC ratio of  $>6$  is required to obtain the highest probability of a favorable outcome in immunocompetent patients (26). Although we did not assess the relationship between peak amikacin concentration and short-term outcome, it has been reported that neutropenic patients with gram-negative bacterial infections require higher peak bactericidal concentrations than nonneutropenic patients to improve the outcome (27). Moreover, the post-antibiotic effect of aminoglycosides is dependent on the peak concentration and time of exposure, but it is markedly reduced in neutropenic animals (4,28). Finally, adaptive resistance to aminoglycosides (i.e., the increase in the MIC after the first exposure to the antibiotic) is decreased by a factor of 2 to 3 when the peak concentration/MIC ratio increases from 8 to 24 (29). Therefore, the value of  $40$  mg/liter that holds for intensive care unit patients might be too low for neutropenic patients. Since the MICs at which 90% of strains susceptible to amikacin are inhibited are  $<8$  mg/liter, a peak amikacin level of  $>60$  mg/liter seems to be a reasonable goal for

avoiding inefficacy in severely neutropenic patients.

### CONCLUSION

1. The therapeutic drug monitoring of amikacin levels should be available for every cancer patient who receives this aminoglycoside.
2. Modification of dosage guidelines cannot replace therapeutic drug monitoring for the individual patient.
3. The knowledge of the pharmacokinetics of amikacin and accurate dosage adjustment in such patients is needed to avoid possibilities of its ineffectiveness resulting in unnecessary costs and occasionally predisposing patients to a higher risk of toxicity.
4. Further studies with more number of patients are needed in target patients in order to ensure conclusive results.

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## حركية دواء "الأميكاسين" وإمكانية تعديل الجرعة لمرضى السرطان

منال الحمامصي

قسم الصيدلة الإكلينيكية - كلية الصيدلة - جامعة عين شمس

إن العدوي في المرضى الذين يعانون من نقص المناعة قد يؤدي إلى التدهور السريع وارتفاع معدل الوفيات بينهم. مازال استخدام أدوية "الأمينوجليكوسيد" مع "البنتا لاكتام" يوصف كخط دفاع أول في حالات ارتفاع درجات الحرارة المصحوب بنقص شديد في عدد كرات الدم البيضاء (النيوتروفيل).

نقص تركيز أدوية "الأمينوجليكوسيد" في الدم قد يؤدي إلى فشل العلاج كما يؤدي إلى ظهور ميكروبات مقاومة لتأثير الدواء. إن أقصى مستوى لتركيز دواء "الأميكاسين" في الدم للمرضى المصابين بارتفاع درجات الحرارة و المصحوب بنقص شديد في عدد كرات الدم البيضاء (النيوتروفيل) غير معروف و لكن في المرضى المصابين بارتفاع درجات الحرارة الغير مصحوب بنقص شديد في عدد كرات الدم البيضاء (النيوتروفيل) فإنه وجد عندما يكون أقصى مستوى لتركيز الدواء في الدم بعد ساعة من بداية الحقن الوريدي أقل من ٢٠ ميكروجرام/مل بعد أخذ الجرعة مقسمة على ثلاث مرات يوميا و أقل من ٤٠ ميكروجرام/مل بعد أخذ الجرعة مرة واحدة في اليوم للمرضى الذين يعالجون في غرف الرعاية المركزة لا يؤدي إلى التحسن المطلوب. لذلك فإن زيادة مستوى تركيز الدواء في الدم عن ٤٠ ميكروجرام/مل بعد أخذ الجرعة مرة واحدة في اليوم قد يؤدي إلى زيادة فعالية الدواء في هؤلاء المرضى.

تهدف هذه الدراسة إلى تعيين و تقييم حركية دواء "الأميكاسين" في الدم في المرضى المصابين بسرطان الدم و يأخذون العلاج الكيميائي و يعانون من نقص شديد في عدد كرات الدم البيضاء (النيوتروفيل) مصحوب بارتفاع درجات الحرارة ثم مقارنة نتائجهم مع الأصحاء لتحديد جرعة دواء "الأميكاسين" لكل مريض على حده للحصول على أقصى فعالية للدواء و أقل أعراض جانبية.

و لقد أجريت هذه الدراسة على ١٢ مريض بسرطان الدم يعالجون بالمعهد القومي للأورام - جامعة القاهرة و يعانون من ارتفاع درجات الحرارة ( $>38^{\circ}\text{C}$ ) و أيضا نقص شديد في عدد كرات الدم البيضاء (النيوتروفيل) ( $<500/\text{mm}^3$ ) نتيجة تعاطيهم للأدوية الكيميائية لعلاج السرطان و يأخذون دواء "الأميكاسين" ١٠٠٠ مجم/اليوم كجرعة واحدة كما وصفه الطبيب المعالج. ثم تم أخذ عينات من دم كل مريض قبل أخذ الدواء مباشرة لتحديد أقل مستوى لتركيز الدواء بالدم ثم بعد ساعة من بداية الحقن عن طريق الوريد لتحديد أقصى مستوى لتركيز الدواء بالدم و ذلك بعد الجرعة الرابعة من أخذ الدواء لضمان وصول تركيز الدواء في الدم إلى حالة الثبات و لقد تم تعيين تركيز الدواء في الدم باستخدام نظام "Abbot TDx" و لقد وجد أن أقصى مستوى تركيز للدواء في الدم هو " $48.03 \pm 3.94 \mu\text{g} / \text{ml}$ " و أقل مستوى تركيز للدواء في الدم هو " $0.51 \pm 0.22 \mu\text{g} / \text{ml}$ " ولقد وجد في الدراسات السابقة إن هذا التركيز للدواء في الدم أقل مما هو مطلوب لتحقيق الشفاء لهؤلاء المرضى الذين لهم ظروف خاصة نتيجة النقص الشديد في عدد كرات الدم البيضاء (النيوتروفيل) و الذين يحتاجون إلى مستوى تركيز أعلى للدواء بالدم لذلك تم تعديل الجرعة لكل مريض لكي تصل إلى "60 ug/ml" كأقصى مستوى لتركيز الدواء بالدم وبناء عليه تم تعديل الجرعة من ١٠٠٠ مجم/اليوم كجرعة واحدة إلى ١٢٢٠ مجم/اليوم كجرعة واحدة.

من هذه الدراسة نخلص إلى النتائج الآتية:

١. تعيين مستوى تركيز دواء "الأميكاسين" في الدم في المرضى المصابين بسرطان الدم و يأخذون العلاج الكيميائي و يعانون من نقص شديد في عدد كرات الدم البيضاء (النيوتروفيل) لابد أن يتم لكل مريض على حده.
٢. تعديل الجرعة حسب الإرشادات الموضوعية مسبقا (guidelines) لا تحل محل تعيين مستوى تركيز الدواء في الدم و ضبط الجرعة لكل مريض على حده حسب ظروفه المرضية الخاصة.
٣. معرفة و تعيين حركية دواء "الأميكاسين" و تحديد الجرعة لكل مريض يزيد من فعالية الدواء و يقلل التكلفة و الأعراض الجانبية الخطيرة.
٤. إجراء المزيد من الدراسات المستقبلية على عدد أكبر من المرضى لتأكيد هذه النتائج.