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Optimal dose of amikacin in childhood chemotherapy-induced febrile neutropenia: better bet on 20 mg/kg and more in clinical practice

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Thomas Lesieur. Optimal dose of amikacin in childhood chemotherapy-induced febrile neutropenia: better bet on 20 mg/kg and more in clinical practice. Human health and pathology. 2022. dumas-04012788

HAL Id: dumas-04012788

<https://dumas.ccsd.cnrs.fr/dumas-04012788v1>

Submitted on 3 Mar 2023

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UNIVERSITÉ de CAEN NORMANDIE

UFR SANTÉ

FACULTÉ de MÉDECINE

Année 2021/2022

THÈSE POUR L'OBTENTION
DU GRADE DE DOCTEUR EN MÉDECINE

Présentée et soutenue publiquement le : 14 octobre 2022

par

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Né (e) le 26 juillet 1994 à Mont-Saint-Aignan (Seine Maritime)

TITRE DE LA THÈSE :

Pharmacologie de l'amikacine dans les neutropénies fébriles chimio-induites en oncologie pédiatrique : parier sur 20mg/kg

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Remerciements

A Madame la Professeure LELONG-BOULOUARD, je suis et resterai très honoré que vous ayez accepté d'évaluer mon travail de thèse en tant que présidente du jury. Il me semble que c'est la première depuis votre nomination et il y en aura de nombreuses autres. Je vous remercie de votre grande disponibilité pour le service d'oncologie pédiatrique, ainsi que pour m'avoir accordé de votre temps pour l'élaboration et la relecture de ce projet.

A Madame la Professeure SCHNEIDER Pascale, vous m'avez guidé de mon premier jour dans le monde de l'oncologie pédiatrique, dans mon choix ECN, puis en ce jour lors de ma soutenance de thèse. Merci de m'avoir transmis votre appétence pour l'oncologie pédiatrique et merci de votre soutien dans toutes ces épreuves.

A Monsieur le Docteur ROUGER Jérémie, cinq lignes ne suffiront pas. Merci pour ta gentillesse, ta patience, ta douceur envers l'équipe, tes internes, tes patients. Merci pour tes avis éclairés... et merci pour ton temps dont j'ai souvent abusé. Médecin modèle, j'espère que j'aurais la chance de discuter avec toi de futurs projets autour d'une boisson houblonnée.

A Madame la Docteure GOYER Isabelle, merci d'avoir été aux prémices de ce projet, de l'avoir façonné de formules savantes, et d'avoir éclairé les lignes obscures par ton reviewing avisé.

A Monsieur le Docteur BODET Damien, merci de m'avoir toujours soutenu et donné ta confiance, même dans les moments d'incertitude. Tu m'as offert une formation de grande qualité durant l'internat (stages onco/HF/interCHU) et j'espère que je pourrai poursuivre ma formation pour rendre au service les compétences que tu m'as aidé à acquérir.

A Madame la Docteure DEPARIS Marianna, merci de m'avoir inculqué ta version de l'optimisme et merci d'avoir essayé de m'apprendre la rigueur dans l'exercice. Un jour j'y arriverai.

A Monsieur le Professeur PARIENTI Jean-Jacques, pour avoir pris le temps de nous orienter sur la méthodologie et les statistiques.

A ma Mère, mon Père, ainsi qu'à mon Père, ma Mère pour ne pas faire de jaloux. Merci pour ces 28 dernières années, c'était rudement chouette et ce n'est pas fini. Merci de m'avoir poussé toutes ces années à donner le meilleur. J'espère que vous savez que je vous aime même si je ne le dis pas et que vous êtes mes modèles dans la vie. Et merci de m'avoir donné ces 3 rigolos de sœur et frères sans lesquels ce serait moins drôle la vie.

Brolita, Bro, Brolito. J'espère que vous avez bien profité de toutes les voies que j'ai dû ouvrir. Ce n'est d'ailleurs peut être pas terminé. La vie c'était pas juste mais je vous aime bien quand même. J'espère que même si vous partez loin vous viendrez quand même voir ou même appeler votre grand Bro qui vous aime. Un bisou, deux bisous, trois bisous.

A mes Grands Parents qui m'accompagnent et que seront toujours là. Doris, Jean-Pierre, Michel, Marie-Thérèse, merci de tout ce que vous m'avez apporté et m'apportez encore. Vous avez baigné cette famille d'amour et créé les meilleurs parents qu'on puisse rêver d'avoir.

A mon Parrain et ma Marraine, Bertrand et Géraldine, qui me comptent comme leur enfant, et sur qui je peux toujours compter.

A mes Eternels : Léo, Paul, Alex. Des amis comme vous c'est pour la vie.

A mes Boscós avec qui je marche, rie et trinque pour les marins depuis des années. Pour que la dernière décennie soit à l'image des futures. Nous avons encore du chemin à parcourir. A Rouss, Blav, Baud, Nils, BM, PT, Gn.

A mes colocs du 53 : Manu et Greg, qui m'ont appris la bonhomie.

A ma Loupi qui me donne le sourire à chaque réveil. Pour que les matins soient éternels, caramels, bonbons et chocolats.

Abréviations

ANSM	Agence Nationale de Sécurité du Médicament
Cl	Amikacin Clearance
Cl/kg	Amikacin Clearance with respect to weight
C _{max}	Maximal theoretical amikacin concentration
C _{t1}	Amikacin concentration on first dosage
C _{t2}	Amikacin concentration on second dosage
DFI	Drug Free Interval
FN	Febrile Neutropenia
FUO	Fever of unknown origin
GFR	Glomerular Filtration Rate
Ke	Elimination constant rate
PD	Pharmacodynamics
PK	Pharmacokinetics
T _{1/2}	Amikacin half life
%TA	Percentage of Target Attainment
V _d	Theoretical distribution volume
V _d /kg	V _d with respect to weight

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Introduction générale

La neutropénie chimio-induite est une période à risque d'infections bactériennes, fongiques et virales, source d'hospitalisations inattendues et de mortalité, directement liée à la toxicité hématologique des thérapeutiques utilisées en hématologie et oncologie pédiatrique. Le traitement de la neutropénie fébrile se base sur une antibiothérapie intraveineuse large spectre associant une bêta-lactamine avec inhibiteur de bêta-lactamase, associée fréquemment à un aminoside pour son action bactéricide forte. Dans le département d'hématologie et oncologie pédiatrique au CHU de Caen, l'aminoside utilisé dans cette indication est l'amikacine. L'efficacité de l'amikacine est directement liée au pic plasmatique en fin d'injection et sa toxicité est liée à sa clairance. Un suivi thérapeutique pharmacologique est donc fréquemment réalisé en pratique clinique. Ce dernier a permis d'observer de trop nombreux sous-dosages lors de la première injection en pratique courante dans notre service. Les dernières recommandations de l'ANSM quant à la posologie et l'utilisation de l'amikacine en pédiatrie datent de 2011, et la littérature dans cette population spécifique reste pauvre. C'est alors avec une volonté d'améliorer nos pratiques pour diminuer la mortalité liée à la neutropénie fébrile, au croisement de l'oncologie, de la pharmacologie et de la pharmacie clinique que cette étude a vu le jour. Utilisant des données recueillies en pratique clinique, cette étude vise à déterminer la dose optimale d'amikacine à administrer lors de la première injection pour obtenir un pic dans la zone thérapeutique, tout en étudiant les risques d'effets indésirables (néphro- et oto-toxicités) pour en prévenir l'apparition.

Les cancers pédiatriques restant des pathologies rares et graves, la communauté scientifique des oncologues pédiatres a le devoir de tenir une activité de publications soutenues pour améliorer la vie et la survie de ses patients. C'est alors dans une démarche de publication que cette thèse d'exercice de la médecine a été rédigée sous forme d'article scientifique.

Title page

Optimal dose of amikacin in childhood chemotherapy-induced febrile neutropenia: better bet on 20 mg/kg and more in clinical practice.

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Word count:

- Abstract: 223/250
- Main text: 2799/3500

Number of Tables/Figures:

- Tables: 3
- Figures: 3
- Supplemental files: 2

Short running title: optimal dose of amikacin in pediatric oncology

Abstract

Background and objective. Bacterial infections in critically ill patients must be quickly and effectively treated to avoid death. Thus, target plasma concentration of amikacin should be achieved on the first attempt. To determine the optimal dose to attain target at the first infusion, we conducted a study using pharmacokinetic (PK) parameters of children from our department with chemo-induced febrile neutropenia (FN) who received amikacin at the currently recommended dose (15-30 mg/kg)

Methods. Amikacin PK data from 60 children with chemo-induced FN, corresponding to 126 events were analyzed. Using a mono-compartmental linear model, we calculated theoretical C_{max} for each event to determine percentage of target attainment (%TA) in dosing clusters.

Results. Patients with amikacin < 20mg/kg obtained 56%TA whereas patients with amikacin ≥ 20mg/kg reached 75%TA. Evaluation of patients that reached target (C_{max}>60mg/L) using 15mg/kg regimen showed 44,8%TA. Patients who reached target had significant lower V_d/kg than patients who did not. No ototoxicity was found in our study but 8 potential acute kidney injury were described.

Conclusion. We recommend an upfront dose of 20-30 mg/kg of amikacin in children with chemo-induced FN to achieve the target plasma concentration after the first infusion. Of the eight patients described, only one appeared to have acute kidney injury directly related to amikacin use. Monitoring amikacin plasma concentration remains crucial to insure efficacy and avoid excess of toxicity.

Key words: pediatrics, neoplasm, pharmacokinetics, amikacin, dose, fever, neutropenia, chemotherapy.

Introduction

Pediatric cancer represents 1% of all cancers and still remains a major cause of death in children and adolescents despite advances in treatments(1). Progress in fundamental and clinical research as well as improvements in supportive care led to a better survival these last decades. Limiting the risk of sequelae while maintaining good outcomes is probably the main concern in pediatric oncology today.

One of the biggest dilemmas in supportive care remains the management of infections, which are a major risk after intensive treatments. Occurrence of these infections depends on various factors such as the underlying pathology, the type and the phase of treatment. Their incidence can exceed 50% of patients with an overall avoidable mortality of 6%(2,3). Chemotherapy-induced neutropenia (defined as neutrophils < 0.5 G/L) in particular, exposes patients to bacterial, viral, and fungal infections, which may be life-threatening. Febrile neutropenia (FN) is due to 50-80% of fever of unknown origin(4,5) and the absence of clinical orientation must not delay infusion of broad-spectrum empirical antibiotherapy. This frontline antibiotherapy must cover Gram-negative bacillus including *Pseudomonas aeruginosa* and Gram-positive cocci (especially *Staphylococcus aureus*) such as large spectrum beta-lactam with beta-lactamase inhibitor(6). In severe infections or high-risk infectious situations such as prolonged profound neutropenia, the clinician must rapidly control the infection to avoid septic shock, which can lead to the patient's death. That is why an association with a bactericidal antibiotic (aminoglycosides) is frequently used(7). To be effective, serum concentration of aminoglycosides must be optimal ($C_{max} > 60 \text{ mg/L}$ for amikacin following French guidelines(8)), measured after intravenous infusion. Amikacin is an aminoglycoside that exerts a rapid and potent bactericidal activity, directly correlated to the peak serum concentration. Thus, and as highlighted above, reaching the target plasma concentration at the first infusion is critical in clinical emergency situations. This is challenging insofar as inter-individual pharmacokinetics variability is important and as the efficacy is counterbalanced by the risk of adverse events that are also dose-

dependent. Indeed, nephrotoxicity(9,10) or ototoxicity(11) can occur when there is a renal accumulation due to repeated infusions or overdosage. Therefore, it is commonly admitted that a drug monitoring is necessary.

Multiple studies have evaluated pharmacokinetics of amikacin in various populations but data in pediatric oncology or immunosuppressed children is lacking and there is a need to improve our knowledge in pharmacokinetics(6). Recommended amikacin doses for adults and pediatrics are 15 to 30 mg/kg according to French national drug institute (*Agence nationale de sécurité du médicament et des produits de santé – ANSM*)(12). We therefore conducted a retrospective study in our institution and analyzed the pharmacokinetic parameters of amikacin in children with chemo-induced febrile neutropenia who received amikacin at any dose in line with ANSM recommendations. Our objective was to evaluate the %TA after the 1st amikacin dose in our pediatric oncology population using real life clinical conditions.

Methods

We included all patients aged 0-18 years with a malignant diagnosis, hospitalized at CHU de Caen for chemotherapy-induced febrile neutropenia, defined by less than 0.5 G/L of neutrophils with fever, who were treated with at least one amikacin dose, and who had two plasmatic amikacin dosage between November 2018 and December 2021. Patients with nonmalignant diagnosis, patients opposed or whose parents were opposed to participate in the study were not included. We excluded patients for whom there was a lack of data on beginning/duration/end of amikacin infusion, or a lack of data on amikacin blood concentration that did not allow calculation of pharmacokinetic parameters. This study was supported by the local ethic committee, the *Comité Local d'Ethique de la Recherche en Santé* (CLERS) registered under the N° 894/2022.

We collected age, sex, type of malignant disease, weight, height, serum creatinine level before amikacin exposure (the day of infusion) and after exposure (3 to 5 days after the last infusion). Glomerular filtration rate (GFR) before and after infusion was calculated with the Schwartz formula ($\text{Clearance} = K \times \text{Taille (cm)} / \text{Creatinine}$. $K = 36,5$). Acute kidney injury was defined as a GFR $<90\text{mL/min}$ or serum creatinine >1.5 times baseline, after amikacin infusion. We also collected microbiologic documentation during hospitalization, duration of fever and time to microbiologic sample negativity after amikacin target attainment or last amikacin infusion if target plasma concentration was not reached.

An event was defined as a febrile neutropenia episode with the use of amikacin at day 1, blood sample (peak and valley) collection, pharmacokinetics parameters calculation. Multiple events may have occurred in the same patient, only if they corresponded to distinct infectious episodes (apyrexia >1 week after antibiotics discontinuation, and hospital discharge).

Amikacin was administrated once daily as an intravenous infusion. We collected beginning time, duration and end time of each infusion, time and value of plasma dosage. Dosages

greater to 160 mg/L without serum creatinine movement might be explained by technical issues and were therefore considered as outlier values and excluded from final analysis.

Blood was collected from central venous line, after a 10 mL purge.

We considered for amikacin a linear elimination in a one-compartment model as it is commonly accepted in literature(13–16). Therefore, two blood samples at different elimination points were necessary to calculate elimination rate. First concentration measure (Ct1; mg/L) corresponds to T1 (time between beginning of infusion and first blood sample; hour) and second concentration measure (Ct2; mg/L) corresponds to T2 (time between beginning of infusion and second blood sample; hour) (Supplemental Figure 1).

Primary endpoint was to identify patients with theoretical maximum concentration (Cmax; mg/L) > 60mg/L at first infusion, expressed in percentage of target attainment (%TA).

Cmax was calculated to standardize the timing of amikacin serum sampling after infusion.

We therefore calculated amikacin elimination constant rate (Ke) was defined as $[\ln(Ct1) - \ln(Ct2)] / (T2 - T1)$; Drug half-life (t1/2) was defined as $[\ln(2) / Ke]$ (hours).

Drug-free interval (DFI; hour) was defined as time between estimated amikacin complete elimination ($5 * t1/2$; hour) and the next amikacin infusion.

Knowing Ke allowed us to calculate Cmax at the end of injection, corresponding to Tmax (time between beginning and end of infusion; hour).

Cmax was defined as $[Ct1 * \exp(ke * (T1 - Tmax))]$ (mg/L).

Theoretical distribution volume (Vd) was defined by $[\text{amikacin posology} / C_{\text{max}}]$ (L).

We also calculated Vd with respect to weight: $[Vd / \text{weight}]$ (L/kg).

This allowed to calculate Clearance as $Cl (L/h) = Ke (h^{-1}) * Vd (L)$, and clearance with respect to weight as $Cl/kg(L/h/kg) = Cl(L/h) / \text{weight}(kg)$.

We did not calculate the number of subjects required based on hypothesis because of the exploratory nature of this work. From the literature, the numbers in the pediatric population analyzing the amikacin PK data vary from 18(17) to 155(18). To optimize the statistical power of our work, we plan to include 50 subjects retrospectively. Initial patient characteristics are described using numbers and percentages for qualitative and mean with standard deviation for quantitative variables. Regarding primary endpoint, that is, the

proportion of patients with an amikacin C_{max} in the therapeutic area after the first injection, percentage were calculated based on the initial amikacin dosage range and compared with the chi-2 test. We assessed the correlation between values of C_{max} and dose (mg/kg), age and clearance, GFR after amikacin infusion and clearance, age and GFR after amikacin infusion by using Spearman's rank correlation coefficient. The means of quantitative variables for each considered group were compared with a Student t-test (or a non-parametric Mann-Whitney test when the group sizes were too small and/or variables were not normally distributed). A p-value < 0.05 was considered statistically significant. Analyses were carried out by using the JASP software (version 0.16.2).

Results

Of 148 events from 61 patients initially enrolled, a total of 126 events from 60 patients were finally analyzed (Figure 1). The demographic and clinical characteristics for patients are summarized in Table 1.

Amikacin was administered once daily as an intravenous infusion with a mean time duration of 0.5 ± 0.1 hour. First amikacin concentrations were obtained with a mean time after the end of injection of 0.7 ± 0.3 hours with mean values of 48.8 ± 18.5 mg/L. Second amikacin concentrations were obtained after the end of injection with a mean time of 3.9 ± 0.4 hours with mean values of 8.0 ± 4.6 mg/L. These data allowed to assess pharmacokinetics parameters described in Table 2 with calculation of Cmax.

We found a significant correlation between Cmax and dose (mg/kg) (Figure 2). The higher the dose of amikacin administered, the more patients achieved a Cmax within the therapeutic target zone of > 60 mg/L (Figure 3).

With the amikacin dosage regimen of 15 mg/kg or less, we found 44.8%TA. Eighty-five percent of the patients who reached target Cmax had total body weight over 30 kg. Patients attaining target had a mean Vd/kg of 0.2 ± 0.04 L/kg ($p=0.01$).

Patients receiving < 20 mg/kg reached target Cmax in 56% of cases whereas we found 75%TA within patients receiving ≥ 20 mg/kg ($p = 0.026$). Cmax was higher in patients receiving ≥ 20 mg/kg than those receiving < 20 mg/kg (77.1 ± 24.4 vs 67.8 ± 24.0 mg/L respectively; $p = 0.033$).

There were significant correlations between clearance and weight ($\rho=0.72$; $p<0.001$), Clearance and age ($\rho=0.72$; $p<0.001$), GFR after amikacin and Cl/kg ($\rho=0.42$; $p<0.001$), Cl/kg and age ($\rho=-0.48$; $p<0.001$)(Supplemental Figure 2).

Of the 60 patients, 8 had an audiometry. In these patients, 7 reached the therapeutic target >60 mg/L and 5 had an amikacin concentration > 80 mg/L at least once. One patient had 3 times a Cmax > 90 mg/L in separated events, and one patient had a Cmax at 125mg/L once. These 8 patients had a mean $t_{1/2}$ of 1.2 ± 0.2 hours, Cl/kg of 0.18 ± 0.06 L/h/kg with

mean DFI of 17.7 ± 1.1 hours. No ototoxicity was observed neither in our population undergoing audition test or the 52 other patients for whom we collected sensation of hearing loss.

Acute kidney injury occurred in 8 events (7 patients). We found no difference between the two groups < 20 mg/kg ($n = 3$) and >20 mg/kg ($n = 5$; $p=0.48$) in the occurrence of acute kidney injury. Patients pharmacokinetic characteristics are gathered in Table 3. For these patients, we found a mean Cl/kg of 0.15 ± 0.06 L/h/kg and a mean DFI of 17.2 ± 3.0 hours. In the < 20 mg/kg group: the first patient had a GFR prior to amikacin infusion at 79 mL/min and the second amikacin infusion occurred after a DFI of 9.7 hours, with calculated Cl/kg of 0.04 L/h/kg. The second patient had *Streptococcus mitis* bacteriemia with persistent fever and tachycardia that conducted to central venous catheter ablation. The third patient had isolated viral coronavirus 229E infection without other clinical specifications and GFR varied from 146 to 96 mL/min before and after amikacin infusion. In the > 20 mg/kg group: the first patient had two events of acute kidney injury, first with *Streptococcus mitis* bacteriemia where blood cultures were sterilized within the first amikacin infusion. The patient maintained in this event a GFR after infusion of 138mL/min despite a GFR before infusion of 219mL/min with Schwartz formula. The second event for this first patient was marked by a *Bacillus mycoides* bacteriemia where GFR dropped from 177 to 59 mL/min. Amikacin Cl/kg was calculated at 0.25L/h/kg and a 19.2-hour DFI was respected in this case. The second patient had fever of unknown origin and GFR went from 204 to 132 mL/min after and before amikacin infusion. The third patient had *Streptococcus mitis* infection with prolonged fever (85 hours), ending with central venous catheter ablation. The fifth patient was admitted without bacterial documentation but in a multiorgan failure context due to progressive disease.

Sixty-nine percent of events were described as fever of unknown origin. The documented infections corresponded over the 126 events to 21 viral infections, 16 bloodstream infections and 2 urinary tract infections. Concerning bloodstream infections, blood culture

sterilization occurred at day 1 after amikacin infusion in 12 cases, highlighting the efficiency of the therapeutic strategy and the need to perform quality sampling for bacteriological purposes at the patient admission. The 4 other bloodstream infections required removal of central venous catheter.

Figure 1. Flow chart.

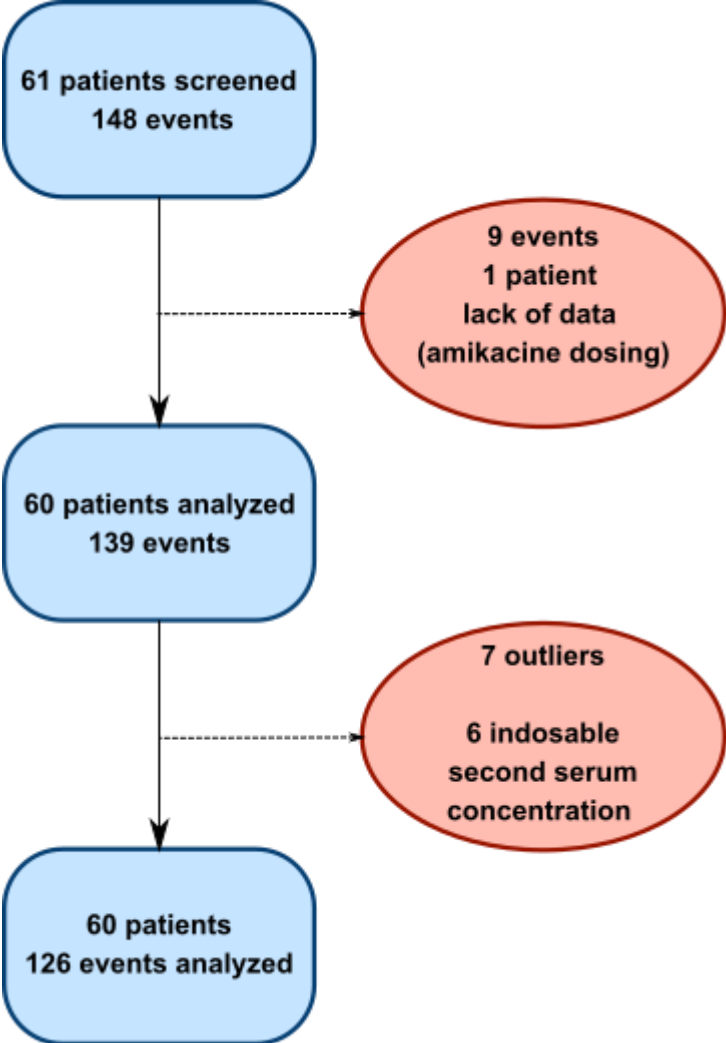


Table 1. Population characteristics

Population characteristics	
Age (years)	
Mean ± SD	7.8 ± 4.4
Minimum – Maximum	0.5 – 16
Weight (kg)	
Mean ± SD	27.9 ± 15.4
Minimum – Maximum	7 – 85
Height (cm)	
Mean ± SD	124.4 ± 28.0
Minimum – Maximum	68 – 182
Dose (mg)	
Mean ± SD	518.9 ± 271.8
Minimum – Maximum	130 – 1500
Dose/kg (mg/kg)	
Mean ± SD	18.9 ± 3.2
Minimum – Maximum	11.9 – 30.4
Sexe M/F	
Number of events (%)	M 86(68%) / F 40(32%)
Pathology	
Hematology	115(91%)
Acute leukemia	98(78%)
Lymphoma	17(13%)
Solid tumors	11(9%)
Embryonnar	5(4%)
Sarcoma	4(3%)
CNS	1(<1%)
GMT	1(<1%)

Table 2. Pharmacokinetics parameters

C _{max} _(mg/L)	
Mean ± SD [min-max]	72.3 ± 24.5 [23.4 – 133.7]
Ke (h ⁻¹)	
Mean ± SD [min-max]	0.6 ± 0.1 [0.2 – 0.9]
t _{1/2} (hour)	
Mean ± SD [min-max]	1.3 ± 0.3 [0.8 – 2.9]
Cl (L/h)	
Mean ± SD [min-max]	4.2 ± 1.9 [1.1 – 10.8]
Cl/kg (L/h/kg)	
Mean ± SD [min-max]	0.17 ± 0.07 [0.04 – 0.58]
DFI (hour)	
Mean ± SD [min-max]	17.6 ± 2.0 [9.7 – 24.3]
V _d (L)	
Mean ± SD [min-max]	7.6 ± 4.0 [1.9 – 24.0]

Figure 2. Spearman correlation between Cmax (mg/L) and Dose (mg/kg). $p < 0.001$.

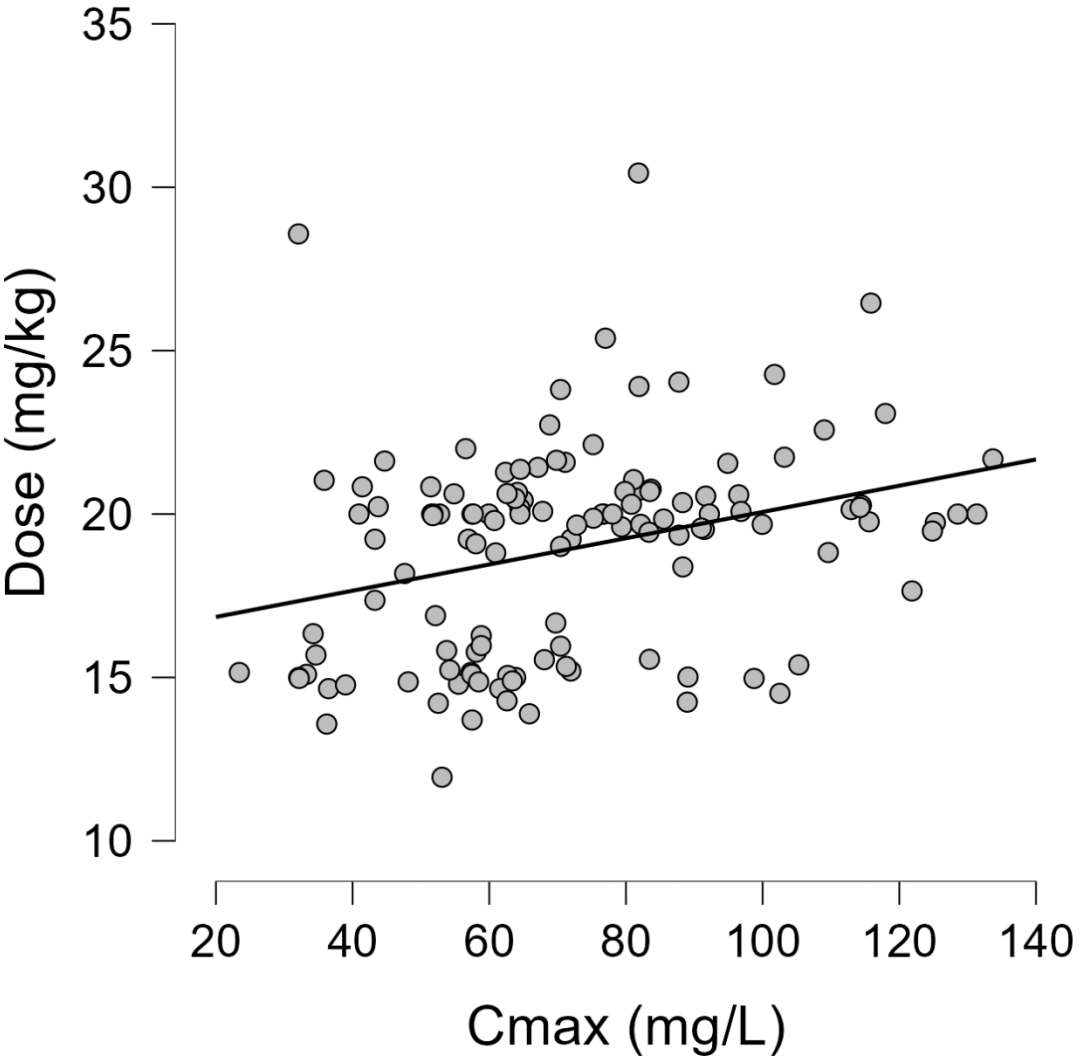


Figure 3. %TA for each dose range (mg/kg)

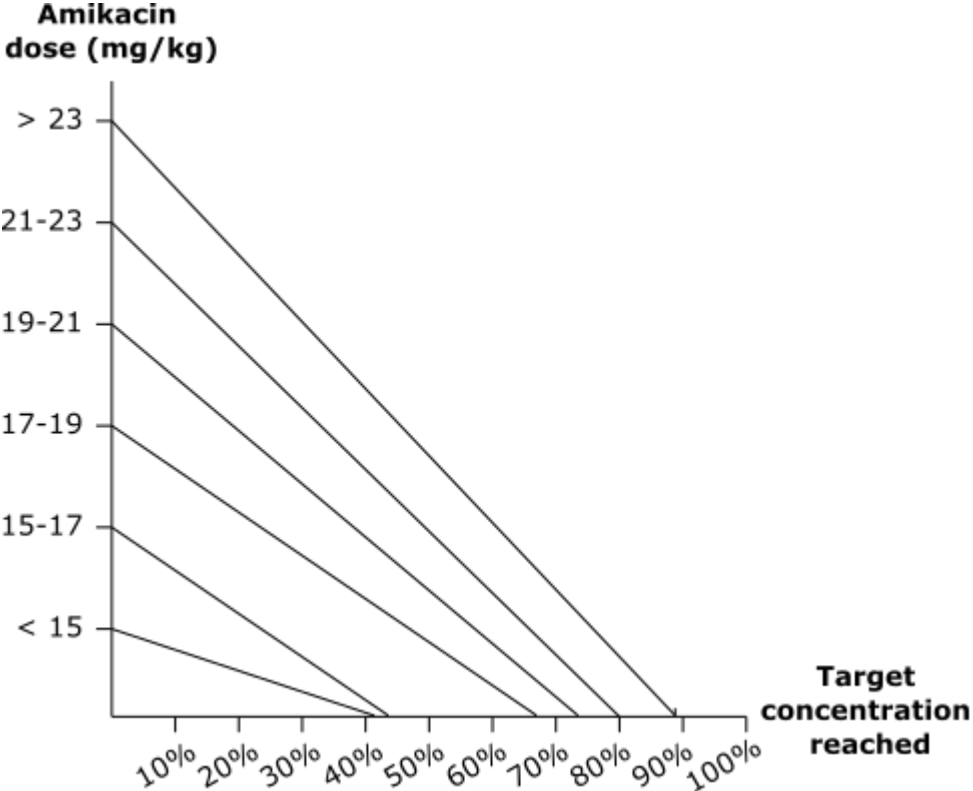


Table 3. Nephrotoxicity cases pharmacokinetics characteristics

N	Dose/kg (mg/kg)	Cmax (mg/L)	T1/2 (hour)	Cl/kg (L/h/kg)	DFI (hour)	Clinical context
1	21,4	67,1	1,2	0,19	18,6	Bacteriemia
2	20,0	57,5	0,9	0,25	19,2	Bacteriemia
3	14,2	89,0	2,9	0,04	9,7	Preexisting DFG <90mL/min
4	23,8	70,4	1,3	0,19	17,7	Unspecific
5	23,9	82,0	1,1	0,18	18,5	Bacteriemia
6	15,0	98,7	1,0	0,11	19,1	Bacteriemia
7	21,7	103,2	1,1	0,13	18,5	Multi-organ failure (progressive disease)
8	15,8	53,8	1,5	0,13	15,9	Unspecific

Discussion

Amikacin is an aminoglycoside antibiotic with a concentration-dependent bactericidal activity that is widely prescribed in pediatrics and adults, with a large variability in pharmacokinetics regarding to clinical situations(19–22). Pediatric use is mostly recommended in sepsis treatment in critical ill conditions(23,24), empirical antibiotherapy with burn injuries(20,25), and FN in pediatric oncology(17,26–28). Despite some PK analysis in pediatrics(18,19,29–31), data in the pediatric oncology specific situation remains limited. Even if their analyses were carried out in only 13 patients, Krivoy *et al.*(28) found benefits of once daily dose compared to infusion twice a day; higher peak, lower trough and longer elimination half-life leading to a better post-antibiotic effect. Alhadab *et al.*(27) performed pharmacokinetics/pharmacodynamics (PK/PD) simulations in 34 patients and concluded that 15 mg/kg is a safe but suboptimal dosage. Dewandel *et al.*(26) described PK covariates including within-patient covariates in time in a large population (114 children, 188 amikacin treatment episodes) contributing with clinical features to a better understanding of amikacin PK/PD. Clinical implications remain limited in literature and to our knowledge, our study is the first one evaluating dosage in actual clinical conditions in pediatric oncology. Being in real life conditions first expose to drug monitoring difficulties. Indeed, although it would have been required, monitoring with blood sampling in a different line of those used for infusion was not acceptable because of the painful nature of the blood sampling in patients already receiving heavy treatments. This might have lead to outlier values thereby adding inaccuracy to therapeutic drug monitoring. Moreover, a total of 6 events could not have been included in this study due to unmeasurable second serum concentration despite maximum time after infusion of 5 hours. This reinforces the idea that elimination in our population is rapid and thus that the linear model is applicable.

Our study demonstrates that choosing 20 to 30 mg/kg on the first infusion leads to better peak concentration than < 20mg/kg, obtaining a $C_{max} > 60\text{mg/L}$ 75% of the time and more. Patients with total body weight > 30kg and $V_d/\text{kg} < 0.25\text{L/kg}$ can more easily reach

target concentration with a lower dose but no excess toxicity was found in this population, which leads us to propose a reference dose of 20 mg/kg even with those patients.

Due to sarcopenia in oncological context, GFR was probably often overestimated. Acute kidney injury appeared to have multiple etiologies in our population. As demonstrated by De Broe *et al*(16) cortical kidney accumulation may lead to real nephrotoxicity cases. Thus, prolonged elimination (low Cl/kg) and short DFI situations increase nephrotoxicity risk. Our study only reported 8 nephrotoxicity events, but only one seemed to be directly correlated with amikacin toxicity (event n°3) with prior renal failure, low Cl/kg and short DFI. Due to poor data in literature, we could not find any data defining normal values of DFI limiting acute kidney injury risk. DFI and Cl/kg monitoring may have to be included in further amikacin use to reduce nephrotoxicity risk and may be more informative than calculated GFR variations, which are highly inaccurate in pediatric oncology clinical practice. Drug monitoring still remains crucial to detect overdoses and avoid acute kidney injury risk by inciting to adapt dosing and especially dose-interval for the subsequent infusions.

Amikacin dose adaptation was systematically proposed by our pharmacology department, but finally left to the clinician discretion. Due to poor number of events registered following pharmacologists proposal, we didn't manage to evaluate dose adaptation formula in our study.

Microbiological documentation was lacking in 69 % of cases (FUO), which is consistent with what is described in the literature(32,33). In 75 % of bloodstream infections, beta-lactamin use with amikacin led to blood culture sterilization at day 1, highlighting that antibiotics use was efficient and the need to perform quality sampling for bacteriological purposes at the patient admission.

In our study population, no patient was transferred in critical care unit due to uncontrolled sepsis, even patients who were under the C_{max} target. Better patient information, therapeutic education and easier emergency access led to less septic shock presentation(34). In addition, amikacin indication in our department was broader than those

commonly described(6) (signs of sepsis or septic shock). Those included all febrile neutropenia with predictable length over 7 days, and all febrile neutropenia with abdominal functional complaint. The absence of severe infectious complication in our population and particularly in those who did not reach the target suggests that amikacin may not have been necessary to control the infection, or that the bacterial species involved were particularly sensitive.

Conclusion

20-30 mg/kg of amikacin is a more appropriate dose to reach concentration target on first infusion in our pediatric oncology population. Infants may need greater dose with respect to weight whereas there is a need for close monitoring with adolescents if C_{max} is higher than expected after the first infusion. Monitoring DFI and Cl/kg may help to detect amikacin-related acute kidney injury but prospective studies with larger population are needed.

Conclusion générale

Cette étude a permis de revoir à la hausse les posologies d'amikacine dans la population d'oncologie pédiatrique avec une dose recommandée en première intention de 20 à 30 mg/kg. Le monitoring rapproché des paramètres pharmacocinétiques, notamment d'élimination du médicament (Cl, DFI, $t_{1/2}$) reste clef dans la prévention de la survenue d'effets indésirables, en particulier du risque d'insuffisance rénale aiguë. Bien que cette étude soit rétrospective et monocentrique, le nombre important de sujets inclus a permis à l'étude d'obtenir une puissance suffisante pour l'obtention de résultats significatifs. Au-delà de proposer une mise à jour des posologies d'amikacine, ce travail souligne l'importance de la pluri- et interdisciplinarité dans la pratique courante de l'hématologie et oncologie pédiatrique.

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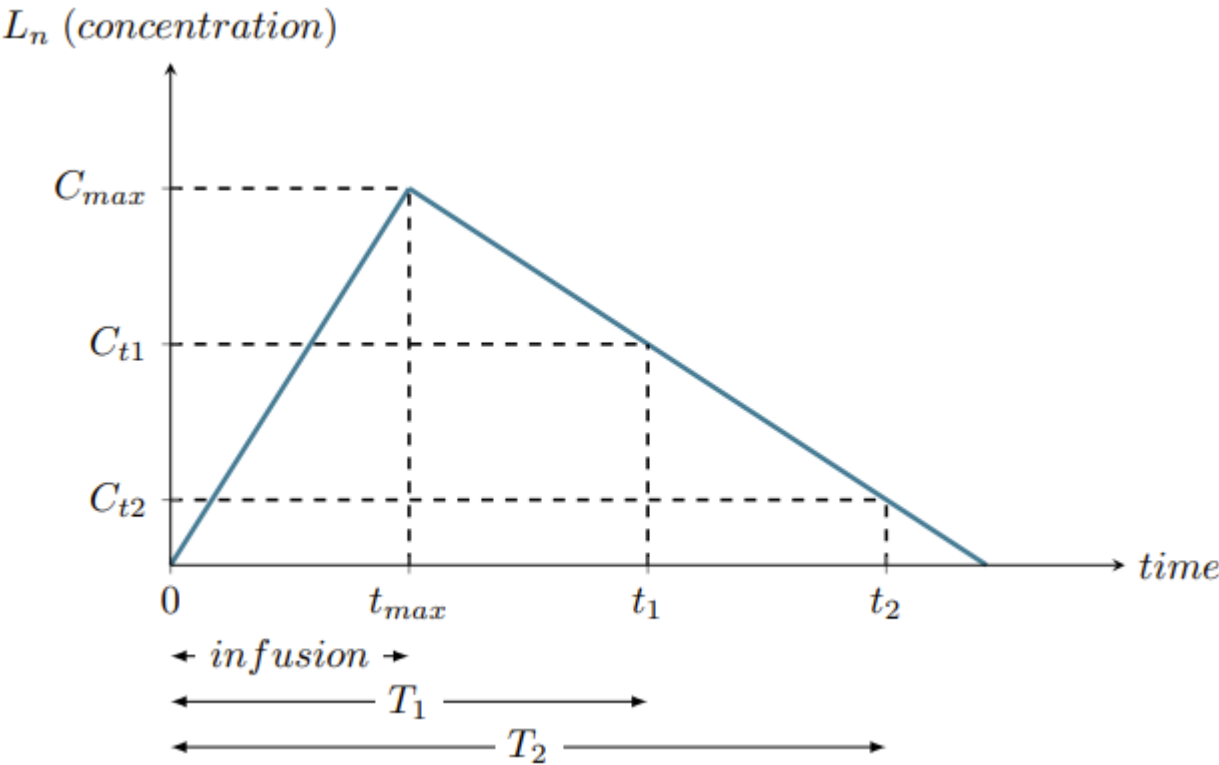
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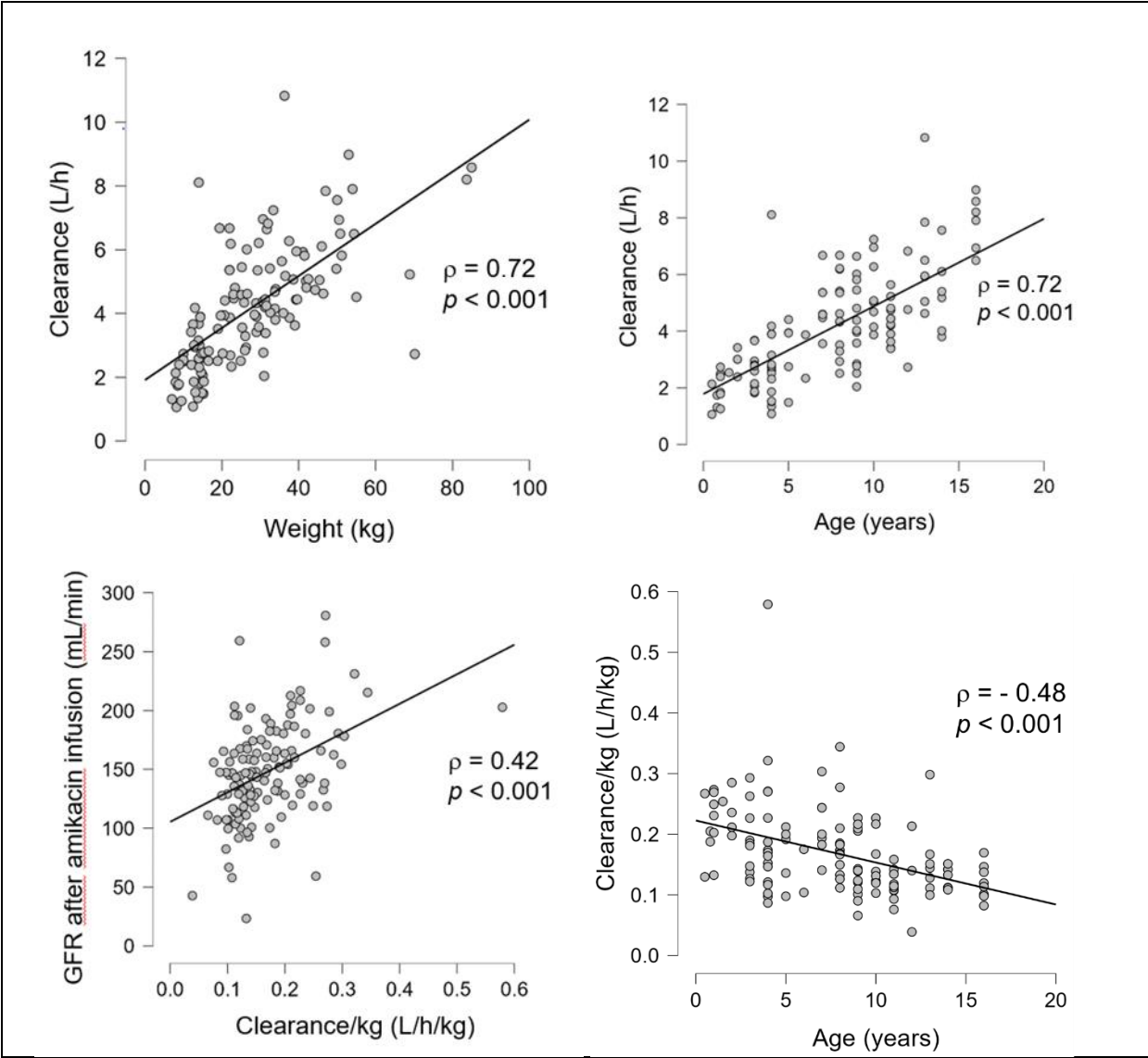
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Annexes

Supplemental Figure 1. Representation of dosages performed in clinical practice in a linear elimination model



Supplemental Figure 2. Spearman correlations between clearance and weight, Clearance and age, GFR after amikacin and Cl/kg, Cl/kg and age.



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VU, le Doyen de la Faculté

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du Conseil d'Université
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Pour le Président
de l'Université de CAEN et P.O

Le Doyen

ANNEE DE SOUTENANCE : 2022/2023

NOM ET PRENOM DE L'AUTEUR : LESIEUR THOMAS

TITRE DE LA THESE :

Pharmacologie de l'amikacine dans les neutropénies fébriles chimio-induites en oncologie pédiatrique : parier sur 20 mg/kg

RESUME DE LA THESE EN FRANÇAIS :

Contexte et objectif. Les infections bactériennes graves doivent être traitées rapidement et efficacement. Ainsi, la concentration plasmatique cible d'amikacine doit pouvoir être atteinte dès la première administration. Afin de déterminer la dose optimale pour atteindre la cible lors de la première perfusion, nous avons mené une étude sur les paramètres pharmacocinétiques (PK) d'enfants de notre service, atteints de neutropénie fébrile (FN) chimioinduite qui ont reçu de l'amikacine à la dose actuellement recommandée (15-30 mg/kg).

Méthodes. Les données pharmacocinétiques sur l'amikacine de 60 enfants atteints de neutropénie fébrile, correspondant à 126 événements, ont été analysées. À l'aide d'un modèle linéaire monocompartimental, nous avons calculé la C_{max} théorique pour chaque événement afin de déterminer le pourcentage d'atteinte de la cible (%TA) dans différents groupes de posologie.

Résultats. Les patients recevant < 20 mg/kg ont atteint la cible dans 56 % des cas, contre 75 % chez ceux recevant plus de 20 mg/kg. L'étude des patients atteignant la cible avec 15 mg/kg a révélé une TA de 44,8 %. Ces patients avaient un V_d/kg significativement plus faible que les patients qui n'atteignaient pas la cible. Aucune ototoxicité n'a été trouvée dans notre étude, mais 8 insuffisances rénales aiguës potentielles ont été décrites.

Conclusion. Nous recommandons une dose initiale de 20 à 30 mg/kg d'amikacine chez les enfants traités pour une neutropénie fébrile chimio-induite pour atteindre la concentration plasmatique cible dès la première perfusion. La surveillance de la concentration plasmatique d'amikacine demeure cruciale pour limiter le risque d'effets indésirables.

MOTS CLES :

Pédiatrie, cancer, pharmacocinétique, amikacine, fièvre, dose, chimiothérapie, neutropénie

TITRE DE LA THESE EN ANGLAIS :

Optimal dose of amikacin in childhood chemotherapy-induced febrile neutropenia: better bet on 20 mg/kg and more in clinical practice.

RESUME DE LA THESE EN ANGLAIS :

Background and objectives. Bacterial infections in critically ill patients must be quickly and effectively treated to avoid death. Thus, target plasma concentration of amikacin should be achieved on the first attempt. To determine the optimal dose to attain target at the first infusion, we conducted a study using pharmacokinetic (PK) parameters of children from our department with chemo-induced febrile neutropenia (FN) who received amikacin at the currently recommended dose (15-30 mg/kg).

Methods. Amikacin PK data from 60 children with chemo-induced FN, corresponding to 126 events were analyzed. Using a mono-compartmental linear model, we calculated theoretical C_{max} for each event to determine percentage of target attainment (%TA) in dosing clusters. Results. Patients with amikacin < 20mg/kg obtained 56%TA whereas patients with amikacin ≥ 20mg/kg reached 75%TA. Evaluation of patients that reached target (C_{max}>60mg/L) using 15mg/kg regimen showed 44,8%TA. These patients had significant lower V_d/kg than patients who were not reaching target. No ototoxicity was found in our study but 8 potential acute kidney injury were described.

Conclusion. We recommend an upfront dose of 20-30 mg/kg of amikacin in children with chemo-induced FN to achieve the target plasma concentration after the first infusion. Of the eight patients described, only one appeared to have acute kidney injury directly related to amikacin use. Monitoring amikacin plasma concentration remains crucial to avoid excess of toxicity.

KEY WORDS:

Pediatrics, neoplasm, pharmacokinetics, amikacin, dose, fever, neutropenia, chemotherapy.