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Brief Original Article

Effect of aminophylline on the pharmacokinetics of amikacin in Sprague-Dawley rats

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Abstract

Introduction: In most resource-poor settings, amikacin is normally co-administered with aminophylline among preterm newborns with infection and apnea of prematurity. There is the likelihood of an interaction between concurrently administered amikacin that is excreted almost solely via kidneys, and aminophylline, which is known to increase filtration fraction. The aim of this study was to evaluate the effect of aminophylline on the pharmacokinetics of amikacin using an animal model.

Methodology: Twelve male Sprague-Dawley rats (7 – 8 weeks old) were put into 2 equal groups. The test group received amikacin (10 mg/kg/day) with aminophylline (5 mg/kg/day) via the intraperitoneal route, and the control group received only amikacin (10 mg/kg/day) via the same route. On Day 4, after daily administration of drugs, tail vein blood samples were collected at different time points. Serum samples at each time point for each group were pooled and analyzed by fluorescence polarization immunoassay. Non-compartment pharmacokinetic analysis was used to estimate pharmacokinetic parameters. Area under the concentration-time curves (AUCs) were extrapolated from time 0 to infinity ($AUC_{0\rightarrow\infty}$). Elimination rate constant (K_e) and elimination half-life ($t_{1/2e}$) were also estimated.

Results: Pharmacokinetic parameters of the control group (amikacin only) *vis-a-vis* the test group were as follows: C_{max}; 42.4 µmol/L *vs* 19.0 µmol/L, $AUC_{0\rightarrow\infty}$; 84.9 µmol/L/h *vs* 41.4 µmol/L/h, K_e; 0.12 $hours^{-1}$ *vs* 0.24 $hours^{-1}$, and $t_{1/2}$; 5.87 hours *vs* 2.88 hours, respectively.

Conclusion: This study suggests possible interaction between aminophylline and amikacin. However, further studies need to be conducted in humans to ascertain this finding.

Key words: Excretion; infection; interaction; pharmacokinetics.

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Introduction

Newborns, especially those born prematurely or preterm are highly susceptible to infections, and this is partly due to their immature immune system [1]. Antibiotics remain the main therapeutic intervention for these infections. In most newborn intensive care units, a combination of aminoglycosides and beta-lactams are the mainstay in infection treatment. The aminoglycosides are a large group of amine-containing hydrophilic agents that disrupt protein synthesis in bacteria and are primarily eliminated by glomerular filtration. Some clinically important aminoglycosides include gentamicin, kanamycin, amikacin, netilmicin, streptomycin and tobramycin.

Preterm newborns may experience breathing challenges (apnea of prematurity) as a result of underdeveloped respiratory system. Methylxanthines, a group of drugs with bronchodilatory activity, often serve as therapeutic interventions in apnea management among newborns [2]. A proposed mechanism for this bronchodilatory effect of methylxanthines is competitive antagonism of central adenosine receptors, leading to an increase in responsiveness of the respiratory center to carbon dioxide [3]. Furthermore, methylxanthines have been suggested to increase urine output and filtration fraction in patients [4].

In most sub-Saharan African countries, amikacin is the aminoglycoside of choice in the treatment of newborn infections, and aminophylline the methylxanthine in the management of apnea of prematurity. Concurrent administration of amikacin and aminophylline may be required among preterm newborns with infection and apnea of prematurity. There is, however, a dearth of information on possible interaction between amikacin, which is excreted almost solely via the kidneys, and aminophylline that is known to alter filtration fraction. An interaction leading to low serum levels of amikacin after co-administration with

aminophylline could result in sub-therapeutic effect or emergence of resistant strains of microorganisms, and the converse, could result in possible adverse events associated with aminoglycosides, that is, nephrotoxicity and ototoxicity [5].

Hitherto, a study to ascertain possible pharmacokinetic interaction between amikacin and aminophylline in newborns did not find aminophylline to alter the disposition of amikacin [6]. In that particular study, maturational difference between newborn groups was found to be a confounding factor in identifying this pharmacokinetic interaction [6]. Gestational age difference existed between newborns receiving amikacin with aminophylline (preterm) and those receiving amikacin only (full term) [6]. As a follow-up to the aforementioned study [6], we want to use an animal model which could demonstrate possible pharmacokinetic interaction between the two drugs. We, thus, explore the effect of aminophylline on pharmacokinetic parameters of amikacin using Sprague-Dawley rats.

Methodology

Experimental animals

The study was approved by the Ethical and Protocol Review Committee of the University of Ghana School of Medicine and Dentistry (Protocol ID: MS-Et/M.8-P.5.3/2011-2012). All procedures and techniques used in this study were in accordance with the guidelines published by the National Institute of Health for the Care of Laboratory Animals [7].

Twelve (12) healthy male Sprague-Dawley (SD) rats weighing between 200 – 250 g, and 7 – 8 weeks old, were obtained from the Animal House, School of Biomedical and Allied Health Sciences, College of Health Sciences, University of Ghana. The SD rats were acclimatized to the laboratory environment of the Department of Pharmacology and Toxicology, College of Health Sciences, University of Ghana for a period of one week before the experiment. After acclimatization, the animals were put into 2 groups (Group 1 and Group 2) of 6. Group 1 (test) were co-administered with amikacin and aminophylline, while Group 2 (control) received amikacin only. The animals were kept under a controlled breeding room at 26 ± 2 °C and a 12 hours dark/light cycle throughout the experimental process. Animal feed (Sankofa pellet, Ghana Agro Food Processing Company Limited, Accra, Ghana) and water was *ad libitum* throughout the experiment.

Drug administration

Amikacin (250 mg/mL; Amikin®- Bristol-Myers Pharmaceuticals, Middlesex, England) and aminophylline (250 mg/10 mL; Aminophylline injection USP, Pfizer Pharmaceutical Company, New York, USA) were each diluted separately with distilled water. A dose of 10 mg/kg of amikacin was administered intraperitoneally as a single push to SD rats in Group 1. This was followed immediately by the administration of 5 mg/kg of aminophylline, administered in a different syringe to same SD rats in Group 1. SD rats in Group 2 were administered with only amikacin (10 mg/kg) via the intraperitoneal route. Doses for the two Groups were administered every 24 hours for 3 consecutive days, with drug administration at the same time on each day. Tail vein blood samples were collected after 1, 2, 4, 8, and 15 hours following drug dose administered to SD rats on the 4th day. Blood sampling was performed on the 4th day since both amikacin and aminophylline would normally reach steady state 3 days after their administration. To obtain serum, blood samples were collected into separator microtainer tubes and centrifuged at 1500 rpm for 10 minutes. Serum samples were transferred into Eppendorf tubes and stored at -80 ^{o}C until analysis for levels of amikacin.

Serum amikacin measurement

Volumes of serum samples obtained from SD rats were insufficient for the assay available for determination of levels of amikacin. This limitation was therefore overcome by pooling together serum samples from SD rats at each time point to obtain sufficient serum volume required for the assay of amikacin. Thus, one pooled-sample was obtained for each time point for Groups 1 and 2. Usually, challenges associated with low sample volume during pharmacokinetic studies can be circumvented by sample-pooling [8]. Amikacin in serum was measured by fluorescence polarization immunoassay (FPIA), using COBAS INTEGRA 400 (Roche Diagnostic Limited, Basel, Switzerland). FPIA is based on competition for antibody binding sites between drug in sample and drug labeled with an enzyme. The coefficient of variation over the entire calibration range during assay process was less than 4%.

Pharmacokinetic analysis

A non-compartmental analytical approach was used to estimate pharmacokinetic parameters of amikacin for the two groups. Levels of amikacin of rats within the two groups were used to plot concentration-time curves.

The linear trapezoidal rule was applied in extrapolating area under the concentration-time curves (AUCs) for the two groups. AUCs were from time 0 hours till the last measurement point (15 hours), and further extrapolated to infinity ($AUC_{0\rightarrow\infty}$). Elimination rate constant (K_e) was assessed by linear regression of the terminal part of the log concentration-time curves. Elimination half-life ($t_{1/2e}$) was calculated as; $t_{1/2e} = 0.693K_e^{-1}$.

Results

Concentration-time curves

Amikacin samples were pooled at the various pre-determined times in the SD rats, and concentration-time curves were obtained for each group (Figure 1).

Pharmacokinetic parameters of amikacin of the two groups

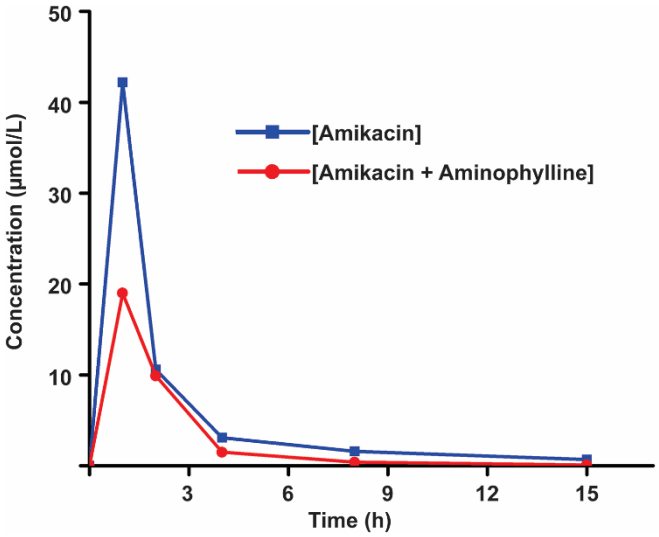
The pharmacokinetic parameters obtained for each group was based on calculation/extrapolation from respective concentration-time data (Table 1).

The maximum amikacin concentration (C_{max}) for the control group was about two-fold higher than the test group. Total drug exposure from time 0 hours to last sampling time (15 hours), and to infinity ($AUC_{0\rightarrow\infty}$), was greater for the control group compared to the test group. Elimination of amikacin (K_e) was faster in the test group compared to the control group, and this resulted in a shorter elimination half-life for the former.

Discussion

Concomitant drug administration is often necessary when patients present with more than one clinical condition. This therapeutic approach can lead to drug-drug interactions which may be pharmacokinetic or pharmacodynamic in nature. The current study evaluated the potential pharmacokinetic interaction between amikacin and aminophylline concomitantly administered to Sprague-Dawley rats. In a previous study, no interaction was found between amikacin and aminophylline in newborns [6]. Maturational differences among the test and control subjects was cited as a confounding factor that may explain the lack

Figure 1. Concentration-time curves of amikacin with and without aminophylline in Sprague-Dawley rats.



of interaction observed in that study [6]. The current study, however, ensured that rats of similar maturational ages (7 – 8 weeks) were used, so that confounders like kidney and liver maturational differences were eliminated.

Total drug exposure for Sprague-Dawley rats in the test group was about two-fold lesser than that of the control group. The decrease in amikacin exposure in animals concomitantly administered with aminophylline could be due to the increased rate of elimination observed in this group. Methylxanthines are known to increase urine output and glomerular filtration fraction [4,9], and it is possible that this effect may have contributed to the increased elimination of amikacin.

Furthermore, the half-life of amikacin in rats co-administered with amikacin and aminophylline was shorter compared to rats administered with amikacin only. This was expected, as half-life and rate of elimination are inversely related. Indeed, if decreased drug exposure and elimination half-life pertain to concurrent administration of amikacin and aminophylline in newborns, then, there could be sub-therapeutic consequences and/or possible emergence of

Table 1. Summary of amikacin pharmacokinetic parameters among two groups of rats.

PK parameter (Units)	Amikacin only	Amikacin + aminophylline
C_{max} (µmol/L)	42.4	19.0
$AUC_{0\rightarrow15}$ (µmol/L/h)	79.0	41.0
$AUC_{0\rightarrow\infty}$ (µmol/L/h)	84.9	41.4
K_e (h^{-1})	0.12	0.24
$t_{1/2}$ (h)	5.87	2.88

amikacin resistance among pathogenic microorganisms over time.

A study that investigated the effect of concomitant administration of non-steroidal anti-inflammatory drugs (NSAIDs) with amikacin in newborns reported that NSAIDs reduced amikacin clearance on the first day of life [10]. A recommendation from that study was a dosing modification among newborns co-administered NSAIDs and amikacin. Thus, the relevance of such similar studies.

Although the current study using an animal model showed some level of interaction between amikacin and aminophylline, a limitation was the inadequate sample volumes at each time point, which led to pooling of serum. Therefore, mean pharmacokinetic parameters within each group could not be obtained for statistical comparison. Notwithstanding, comparison of pharmacokinetic parameters of traditional versus pooled samples have found no statistical significant difference between the two sets of parameter estimates. Thus, results from the current study still has scientific significance [11].

Conclusions

In summary, data from this study suggest possible interaction between aminophylline and amikacin in Sprague-Dawley rats. The way forward, based on findings from this study, is to conduct a similar study among newborns, eliminating possible confounders such as gestational age.

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