VARIABILITY IN PHARMACOKINETIC OF AMIKACIN IN OPEN FRACTURE ORTHOPAEDIC-TRAUMATOLOGIC PATIENTS

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VARIABILITY IN PHARMACOKINETIC OF AMIKACIN IN OPEN FRACTURE ORTHOPAEDIC-TRAUMATOLOGIC PATIENTS

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ABSTRACT

Amikacin is one of aminoglycoside antibiotic group, distributed in extracellular fluids with low plasma protein bound, and eliminated mainly by renal excretion. But it has reported that this drug has great variability in pharmacokinetic and it concentration achievement in the body. Because of its narrow therapeutic index property, it need individually dosing.

The aimed of this study is to determine pharmacokinetic parameter of amikacin in adults open fracture orthopaedic surgery patients. Amikacin 500 mg was administered by IV bolus injection, blood samples were drawn 2 times in 1 - 8 hours post second injection (post operation). Amikacin in the serum samples assayed by Homogenous Particle-enhanced Turbidimetric Immunoassay (PETIA). Pharmacokinetic parameterization was done by Nonparameteric Expectation Maximization with NPAG-USC*PACK program for elimination rate constant (*K*) and Volume of distribution (*Vd*)

Parameterization in 15 patients, through joint and marginal density probability function showed there are great variability in pharmacokinetic of amikacin with *Vd* values 18.213 ± 6.355 liter (range 10,693 - 31,942 liter), *K* values 0.343 ± 0.108 hours^{-1} (range 0.107 - 0.514 hours^{-1}). This results showed giving amikacin individually in this patients group is needed.

Key words: aminoglycoside, amikacin, pharmacokinetic, vaiability, open fracture, orthopaedic-traumatology.

INTRODUCTION

Amikacin is one of aminoglycoside antibiotics group with a polar nature, distributed in the extracellular fluid, a low protein binding and eliminated mainly by renal excretion (Chambers, 2001). However, it has been reported that this antibiotics have large variability in pharmacokinetics and the achievement of drug concentration in the body (Suprapti et al, 1997; Tod et al, 2001; Conil, et.al., 2006). Amikacin is an antibiotic with concentration dependent properties and has a narrow therapeutic index, therefore dosing individually is required to avoid the occurrence of side effects (Tod et al., 2001; Mc.Evoy, 2002; Craig, 2011).

One of patients population with indication of aminoglycosides are orthopaedic-traumatology surgery patients, especially patients with open fractures type II and III (Gustilo et al, 1990; EAST, 1998). In Clinic, gentamisin has started being resistant, so that anttibiotic use shifted to amikacin. This study aims to determine the pharmacokinetics of amikacin in open fractures orthopaedic-traumatology patients.

MATERIAL AND METHODS

This study was conducted in orthopaedic-traumatology surgery patients with single trauma open fractures type II and III at Intensive Observation Room dr. Soetomo General Hospital Surabaya, Indonesia. Methods used in this study was approved by Hospital Board of Ethics. Inclusion criteria were male/female patient, 17-60 years old, body weight in the normal range, has normal to intermediate creatinine serum level (0.7 to 2 mg%) (Wilson, 1995; Dowling & Comstock, 2005). Exclusion criteria were patients with obese/malnourished, got amikacin therapy in

the first referral without timing administration recorded, with shock condition, with patologic conditions that affect the *Vd* value of amikacin significantly, eg, ascites, peripheral edema, with hemorrhage more than 1500 ml during surgery (30-40% loss of blood volume in the category of severe hypovolemia) (Sunatrio, 2000), patients with other drug therapies which may affect amikacin assay by Fluorescent Polarization Immunoassay (FPIA), (ie is another group that aminoglycosides kanamycin and tobramycin), with therapies that may affect the pharmacokinetics of amikacin, eg. dextran, mannitol (McEvoy, 2002) and furosemide (Lawson et al, 1982; McEvoy, 2002) and patients with a history of allergy to aminoglycosides .

The dosage of amikacin sulfate was given by iv bolus administration with 12-hours intervals. Blood samples were drawn 2 times in 1 - 8 hours post second injection (post operation). Amikacin in the serum samples assayed by PETIA (Abbott Diagnostic, 2006). Pharmacokinetic parameterization was done by Nonparameteric Expectation Maximization with NPAG-USC*PACK program for elimination rate constant (*K*) and Volume of distribution (*Vd*) (USC*PACK version 10.7)

RESULTS AND DISCUSSION

This study was conducted in orthopaedic-traumatologic surgery patients with single trauma open fractures type II and type III, that had amikacin therapy in addition to cephalosporins. In these patients the incidence of infection is quite big, 2% - 7% in type II open fractures, 7% in subtype III-A, 10% - 50% in subtype Hi-fi and 25-50% in subtype III-C (Gustilo et al., 1990; EAST., 1998). The source of contamination in open fractures can be derived from the site of injury, during surgery and during their hospitalization. The majority infection in open fractures caused by gram positive Staphylococcus aureus and gram-negative bacilli with anaerobic (Holtom, 2006; Okike & Bhattacharyya, 2006). Amikacin used to treat gram-negative bacteria, whereas for gram positive bacteria used cephalosporins, especially the first generation that is sefazolin. (Chambers, 2001; Me Evoy, 2002).

Dosage regimen (dose and interval of administration) designed to assure the achievement of effective levels. Achievement blood levels of the drug is determined by the behavior drug in the body or pharmacokinetics of the drug. In addition to effectiveness, individual regimen is required because this drug has a narrow therapeutic index with great inter-individual variability in the pharmacokinetics (Bressolle, 1996; Tod et al., 1998; Goytia & Hermandes, 2000). So that it is necessary to determine the pharmacokinetics of amikacin in patients population whose taking the drug.

As clinical procedure amikacin was given to the patient with the dose of 500 mg intravenously (1-2 minutes), twice a day with 12 hours administration interval. The first dose was given before surgery, the second and further dose was given after surgery. Blood samples were drawn two times between 1 to 8 hours after injection . This sampling time is based on the disposition of amikacin in the body that has 3 phases and dose adjustment was done with pharmacokinetic parameter in the second phase that regard to renal function, which occurs at 1-8 hours after injection (Shentag, 1981; Bauer, 2001) .

Pharmacokinetic parameterization was conducted using NPEM with NPAG-USC*Pack Program. In this approach the pharmacokinetics parameters are considered as random variables, so have distribution. There is no asumpsion about the shape of parameter pharmacokinetic distribution, the overall population distribution estimated from population data, making it possible to find the distribution that is not normal even multimodal. Depiction of the distribution of pharmacokinetic parameter is an important to determine the central tendency parameter for the accuracy of the model estimates in the determination of initial regimen (Jelliffe et al., 1993; Bustad et al., 2006). In individualization with Multiple Models Bayesian approach (Bayesian MM), the model with the overall population

point of NPAG output, used as Bayesian priors (Bayard et al., 1994; Jelliffe et al., 2009).

In accordance with the inclusion and exclusion criteria was obtained samples of 15 patients, comprising 13 male and 2 female, aged 20-54 years, rates of serum creatinine 0.5-1.5 mg / dL. Pharmacokinetic parameterization results from 15 patients for *K* and *Vd* obtained 15 points, could be seen in join probability density function on Figure 1. Each point represent values pairs of pharmacokinetic parameters (*K* and *Vd)* and the chance/probability of occurrence. Results showed each patient has a different of estimated pharmacokinetic parameters values, none of patients has the same values and it has considerable variability in the pharmacokinetics

Figure Number 1

Figures 2 and 3 showed the marginal probability density function of elimination rate constant (*K)* and volume of distribution *(Vd),* more clearly showed there are great variability in *K* or *Vd* parameters. These are demonstrated by the wide spread of the parameters values. *K* values in the range of 0.107 $hour^{-1}$ to 0.514 $hour^{-1}$with a mean value of 0.343 $hour^{-1}$, median 0.357 $hour^{-1}$, mode of 0.106 $hour^{-1}$ and a standard deviation 0.108 $hour^{-1}$. *Vd* value in range of 31.942 Liters to 10.693 Liters, with a mean value of 18.213 Liters, median 15.845 Liters, mode 10,643 Liters and standard deviation 10.643 Liters (Table 1).

Figure number 2

Figure number 3

Large variability of amikacin pharmacokinetic parameters in this study is consistent with the pharmacokinetic data available in the literature (Tod et al., 1998; Bleyzac et al., 2000; Goytia & Hermandez, 2000; Treluyer et al., 2002). The conditions and procedure in handling the trauma may contribute to the variability of the pharmacokinetics of amikacin. Trauma with severe pain and psychological stress can cause vasoconstriction of blood vessels and the release of a number of hormones such as renin-angiotensin, vasopressin, antidiuretic hormone, growth hormone, glucagon, cortisol, epinephrine and norepinephrine. Resuscitation/fluid therapy can cause hyperdynamic conditions (Dutton, 2008). All of the above conditions can lead to changes in the kinetics of the drug in the body, both in volume of distribution and elimination.

The factors/reasons related variability in the pharmacokinetics of amikacin until now can not be explained clearly with the patient's condition. This is due to the complexity of biological systems that not all the data can be quantified in the laboratory and clinic to be correlated with the pharmacokinetics (absorption, distribution, metabolism and excretion) of the drug. Given the large variability of pharmacokinetic amikacin and it have a narrow therapeutic index would require individual dosage regimen, required population pharmacokinetic modeling in group of patients

CONCLUSION

There are great variability in pharmacokinetic of amikacin This results showed giving amikacin individually in this patients group is needed.

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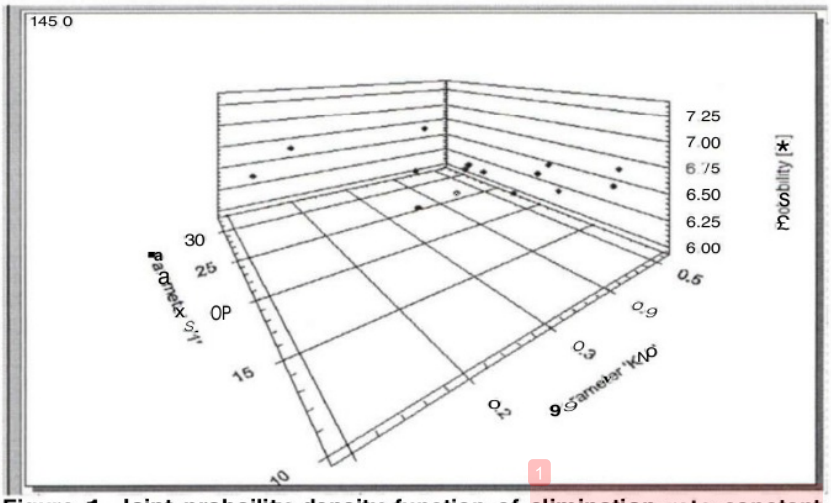

Figure 1. Joint probaility density function of elimination rate constant (K) and Volume of distribution (VD)

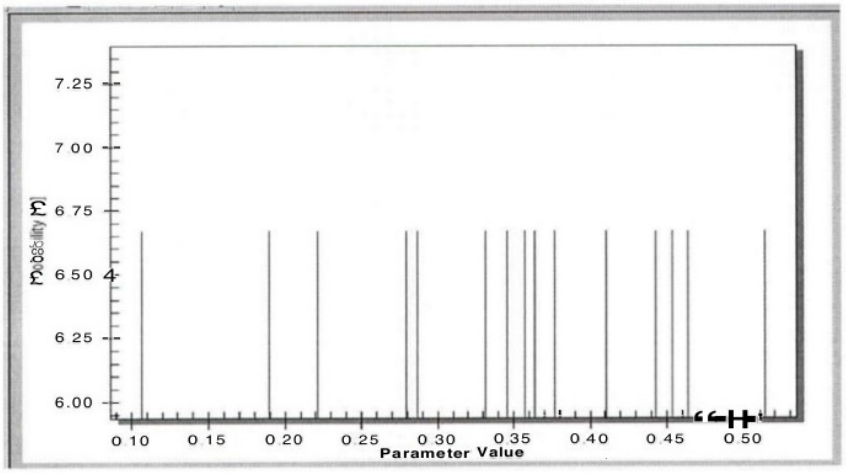

Figure 2. Marginal probaility density function of elimination rate constant (K)

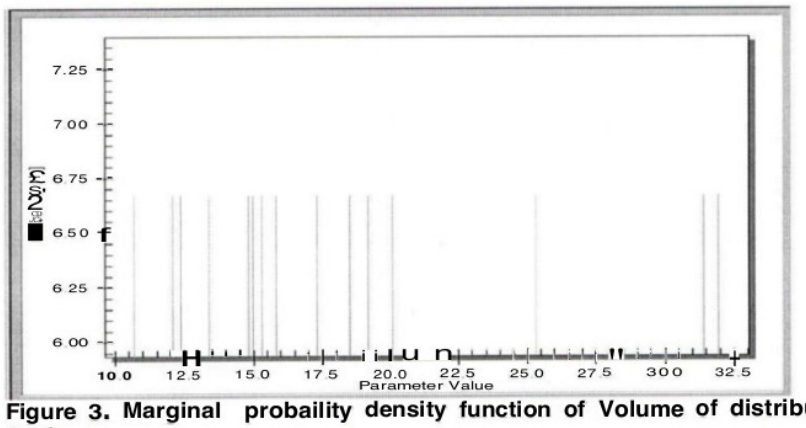

Figure 3. Marginal probaility density function of Volume of distribution (VD)

	Mean	Median	Modus	SD	Min	Max
K (hours)	0,343	0,357	0,106	0,108	0,107	0,514
Vd (liters)	18,213	15,845	10,643	6,355	10,693	31,942

Table 1. Statistic values of K and Vd in 15 patients open fractures othopaedic-traumatologic patients

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