# PROCEEDING

**The 3rd International Conference on**

**Pharmacy And Advanced Pharmaceutical Sciences**

**June 18 – 19, 2013 Yogyakarta, Indonesia**

**Book 2:**

Clinical Pharmacy


**Editors:**

Abdul Rohman

Zullies Ikawati

Tri Murti Andayani

Riris Istighfari Jenie

Marlyn Dian Laksitorini



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# Preface From Editor

On behalf of the Editors, I am deeply grateful to all the reviewers who have been working very hard for reviewing manuscripts submitted during the "3rd International Conference on Pharmacy and Advanced Pharmaceutical Sciences" held in Sheraton Hotel Yogyakarta, by the Faculty of Pharmacy, Gadjah Mada University, Yogyakarta, Indonesia on 18 - 19 June 2013.

We would like to acknowledge to keynote speakers and all the distinguished speakers for their valuable contribution during this conference. Furthermore, we also thank the steering committee for their advice and support. Finally, I would appreciate to all participants, paper and poster presenters who participated in the conference as well as cordially contributed by submitting their full manuscripts published in this proceeding.

Finally, we believe that the presence of this proceeding will significantly contribute to the advance scientific research, especially in the field of Clinical and Social Pharmacy.

Yogyakarta, June 2013,
Chief

**Abdul Rohman**

# Welcome to Yogyakarta

Assalamu'alaikum wr wb
Honorable Rector of Universitas Gadjah Mada, Prof. Dr. Praktino, M.Soc.
Honorable our keynote speaker : dr. Boenjamin Setiawan, PhD
Honorable our distinguished invited speakers, our guests, and all participants

First of all, let us praise to the Almighty Allah SWT, because of His Blessing we are able to attend this opening ceremony of the International Conference on Pharmacy and advanced pharmaceutical sciences today.

This morning, it is a great honor for me to welcome you all in this room in our conference. Welcome to Yogyakarta, and we hope you will enjoy your time here. This conference is the third international conference conducted by Faculty of Pharmacy Universitas Gadjah Mada to facilitate the experts meeting and sharing the knowldege among the researchers, academia, college students, policy makers in corresponding fields, and practitioners.
This year, the theme of The 3rd International Conference on Pharmacy and Advanced Pharmaceutical Sciences (ICPAPS 2013) is : **"Pharmaceutical development towards a sustainable and healthy society".** The conference is conducted in collaboration with Utrecht University the Netherland, Nara Institute of Technology Japan, Mahidol University Thailand, and Cyberjaya University, Malaysia. Thank you very much for our international partners.
As a key note speaker in this conference, we are fortunate to have dr. Boenjamin Setiawan, PhD. He is the founder of Kalbe Farma, one of the big pharmaceutical company in Indonesia. His experience in developing pharmaceutical company as a bussinessman as well as his vision in development of medical and pharmaceutical research in Indonesia will be very inspiring, and hopefully will guide us to develop research in our respective fields. We also invited 12 more experts in various field of pharmacy and pharmaceutical sciences, either from Indonesia or overseas, who will give their lectures.
Here, among 300 participants, there are 175 presenters from 10 countries will present their recent research finding, which are divide into two big topics, Pharmaceutical Science and Technology and Clinical and Social Pharmacy. Our high appreciation and sincere gratitude are delivered to all speakers and presenters who enthusiastically participate in our conference.

The organizing commitee deeply acknowledges The Rector of Universitas Gadjah Mada, Nara Institute of Technology Japan, Mahidol University Thailand, and Cyberjaya University, Malaysia, as well as the sponsors for nice collaboration in conducting the conference. As the chairman of the committee, I personally would like to express our high appreciation and gratitude to all team members for the hard work, dedication, and invaluable efforts for the success of the conference.

Finally, we do hope that all participants could get benefit from this event and have enjoyable moment in Yogyakarta.

Wassalamu'alaikum wr wb.

Chairman

**Zullies Ikawati**

# Remark

## Dean, Faculty of Pharmacy, Gadjah Mada University

Firstly, let's thanks to Allah who always blesses to all of us, so that we can get together in this wonderful meeting, the 3rd International Conference on Pharmacy and Advanced Pharmaceutical Sciences (ICPAPS 2013). The Faculty of Pharmacy, Gadjah Mada University (GMU) is very happy to welcome all of you ICPAPS 2013 participants in the meeting and also we welcome all of you in Yogyakarta-Indonesia, the home of the Faculty of Pharmacy GMU.

Secondly, we'd like to give a brief introduction of our institution. Faculty of Pharmacy GMU was erected in September 1946, a year after Indonesian Independence, is noted as the oldest Faculty of Pharmacy in Indonesia. Faculty of Pharmacy GMU has been accredited nationally and internationally as well. In addition, collaboration in research, education, social services with several National and overseas Institutions have been established, intended to achieve our goals, one of those is quality of education. Recently, new regulations on Pharmacist roles in Indonesia have been emphasized as health profession, health promoter and pharmaceutical care. Therefore, theme of this ICPAPS 2013 meeting is selected as 'Pharmaceutical developments towards a sustainable and healthy society' that is parallel to those regulations. Faculty of Pharmacy GMU really hopes that this meeting is fruitful for all participants in general and specifically Pharmacy Institutions to develop to improve their education system.

Finally, Faculty of Pharmacy GMU highly appreciates to the Keynote speakers, invited speakers, all participants for spending your time with us, the Committee [Steering Committee, International partners (Universiteit Utrecht-The Netherland, NAIST-Japan, Mahidol University-Thailand, Cyberjaya University-Malaysia) Organizing Committee] who have been working very hard, and last but not least Faculty of Pharmacy GMU thanks to our sponsors for this meeting. Faculty of Pharmacy GMU realizes that without your participation, this meeting never happens.

Sincerely,

**Subagus Wahyuono**

# Rector Speech

**Rector, Universitas Gadjah Mada**

It gives me genuine pleasure that Universitas Gadjah Mada has the honor of hosting the International Conference on Pharmacy and Advanced Pharmaceutical Sciences, which this year is in its third installment. This Conference, held in collaboration with Japan's Nara Institute of Sciences and Technology, the Netherlands' Universiteit Utrecht, Thailand's Mahidol University and Malaysia's Cyberjaya University, reflects a global commitment maintained by members of prominent think tanks the world over in addressing issues of common concern, which in this year's ICPAPS are Advanced Pharmaceutical Science and Social and Clinical Pharmacy.

Universitas Gadjah Mada, as a leading institution of higher learning in Indonesia, and in its commitment at becoming a World-Class Research University, has long since realized the spinal role of global cooperation in achieving our visions. This is why we welcome any and all effort through which international exchanges of thoughts and expertise can be encouraged. I see this perspective reflected in its entirety in ICPAPS, wherein experts and thinkers from all around the world will gather together and talk of a concerted effort to enhance the quality of pharmacists worldwide, broaden the insights on pharmacy as well as pharmaceutical sciences and technologies, and finally create both a national and international networking system for the dissemination of developments in pharmaceutical sciences and technologies.

Since those are very noble causes we all need to not only address, but also eventually produce into reality, I cannot impress the importance of this Conference for everyone present. Therefore, I can only hope that all the participants, be they researchers, academicians, pharmacists in and outside hospitals, as well as the students, are determined in making the best out of this brief gathering.

I am looking forward to seeing rigorous debates, heated discussions and, most importantly, a result that represents a joint international action held together by scientific truth. Thank you for all your commitment and dedication in organizing and contributing to this conference, and I wish you all the very best of luck.

**Prof. Dr. Pratikno, M.Soc. Sc.**

# Table of Content

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

**Budi Suprapti**
*Clinical Pharmacy Department, Faculty of Pharmacy,*
*Airlangga University Surabaya*
*budiprapti@yahoo.co.id*

## 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 III-B 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; Mc 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.

## REFFERENCES


Abbott Diagnostic, 2006. Multigent$^{R}$ Amikacin REF 6L35-20 – package insert.

Bayard DS., Milman MH., Schumitzky A., 1994. Design of dosage regimens: a multiple model stochastic control approach. *International Journal of Bio-Medical Computing*, 36: 103-115

Bauer LA, 2001. *Applied Clinical Pharmacokinetics*. New York: McGraw-Hill Medical Publishing Division, pp. 93 -179

Bressolle F., Gouby A., Martinez J., Joubert P., Saissi G., Guillaud R., Gomeni R., 1996. Population Pharmacokinetics of Amikacin in Critically Ill Patients. *Antimicrobial Agents and Chemotherapy*, 40 (7): 1682-1689.

Bustad A, Terziivanov D, Leary, Port, Schumitzky, Jelliffe, 2006. Parametric and Nonparametric Population Methods: Their Comparative Performance in Analysing a Clinical Data Set and Two Monte Carlo Simulation Studies. *Clinical Pharmacokinetics*, 45: 365-383.

Chambers HF., 2001. Antimicrobial Agent, The Aminoglycosides. In (Hardman J.G., Limbird LE., Goodman Gilman A., Goodman & Gilman's). *The Pharmacological Basis of Therapeutis*, 11th ed. New York: Mc Graw-Hill Medical Publishing Division, pp. 1219-1238.

Conil J.M., Georges B, Breden A, Segonds C., Lavit M., Seguin T., Coley N., Samii K., Chabanon G., Houin G., Saivin S., 2006. Increased Amikacin Dosage Requirements in Burn Patients Receiving a Once-Daily Regimen. *International Journal of Antimicrobial Agents*, 28 : 226-230.

Craig WA., 2011, Optimizing Aminoglycoside Use. *Critical Care Clinic*, 27: 107-121.

Downing TC. & Comstock TJ, 2005. Quantification of Renal Function. In (Dipiro JT et al). *Pharmacotherapy A pathophysiologic Approach.* New York: Mc Graw Hill-Medical Publishing Division, pp 760-780.

EAST (Eastern Association for the Surgery of Trauma), 1998. Practice Management Guideline Parameter for Prophylactic Antibiotics in Open Fracture. www.east.org/tpg/archive/html/ chap10body.html, 21 Januari 2008.

Goytia L.G & Hermandes C. G, 2000. Bayesian Approach to Control of Amikacin Serum Concentrations in Critically Ill Patients with Sepsis. *Annals Pharmacotherapy*, 34: 1389-94.

Gustilo RB., 1989. Management of Open Fractures, in (Gustilo R.B., Gruninger R.P.

Gustilo R.B., Merkow R.L., Templeman D., 1990. Current Concepts Review. The Management of Open Fractures. *The Journal of Bone and Joint Surgery American*, 72 (2): 299-304.

Okike K & Bhattacharyya T., 2006. Trends in the Management of Open Fractures. A Cirtical Analysis. *The Journal Bone and Joint Surgery American.*, 88: 2739-48.

Holtom PD., 2006. Antibiotic Prophylaxis: Current Recommendations. Journal of the American Academy of Academic Orthopaedic Surgeons. , 14: S98-S100.

Jelliffe R.W., Schumitzky A., Guilder M.V., Liu M., Hu L., Maire P., Gomis P., Barbaut X., Tahani B., 1993. Individualizing Drug Dosage Regimen: Role of Population Pharmacokinetic and Dynamic Models, Bayesian Fitting, and Adaptive Control. *Therapeutic Drug Monitoring,* 15: 380-393

Jelliffe R.W., Schumitzky A., Bayard D., Leary R., Thomson A., Botnen A., Guilder MV., Bustad A., Neely M., 2009. Pharmacometric Tools to optimize control of drug PK/PD models for best patients care. www.lpak.org/pubsinfo/teaching-topic .php, 10 April 2009.

Lawson DH, Tilstone WJ, Path MRC, Gray JMB, Srivastava PK, 1982. Effect of Furosemide on the Pharmacokinetics of Gentamicin in Patients. *Journal of Clinical Pharmacology*, 22, 254-258.

Mc.Evoy GK., 2002. Aminoglycosides. *AHFS, American Hospital Formulary Service 2002*, American Society Health System Pharmacists, pp 65 – 80.

Shentag JJ,1981. Aminoglycosides. In (William EV, Shentag JJ, William JJ). *Applied Pharmacokinetics. Principles of Therapeutics Drug Monitoring*. San Francisco: Applied Therapeutics, Inc, pp 174-209.

Sunatrio S., 2000. *Resusitasi Cairan*. Jakarta: Media Aesculapius-Fakultas Kedokteran Universitas Airlangga, hal 43-57.

Suprapti B., Basori A., Suhartono B., Sajmsiah S., 1997. Population Pharmacokinetic Models of Gentamicin with Nonparametric Method. *Jurnal Pascasarjana Universitas Airlangga*, 6 (3): 147-152.

Tod MM., Padoin C., Petitjean O., 2001. Individualising Aminoglycoside Dosage regimens after Therapeutic Drug Monitoring. Simple or Complex Pharmacokinetic Methods? *Clinical Pharmakokinetics,* 40 (11):: 803-814.

Wilson LM., 1995. Gagal Ginjal Kronik In (Price SA, Wilson LM), *Patofisiologi Konsep Klinis Proses-proses Penyakit* ed.4. Penerbit Buku Kedokteran-ECG, hal. 812-847.

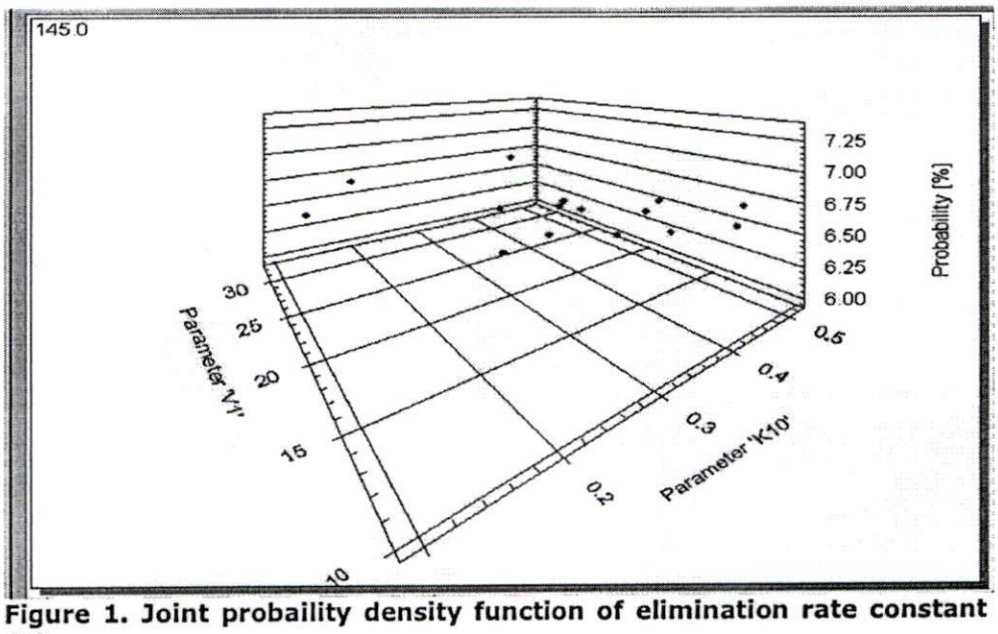


**Figure 1. Joint probaility density function of elimination rate constant (K) and Volume of distribution (VD)**

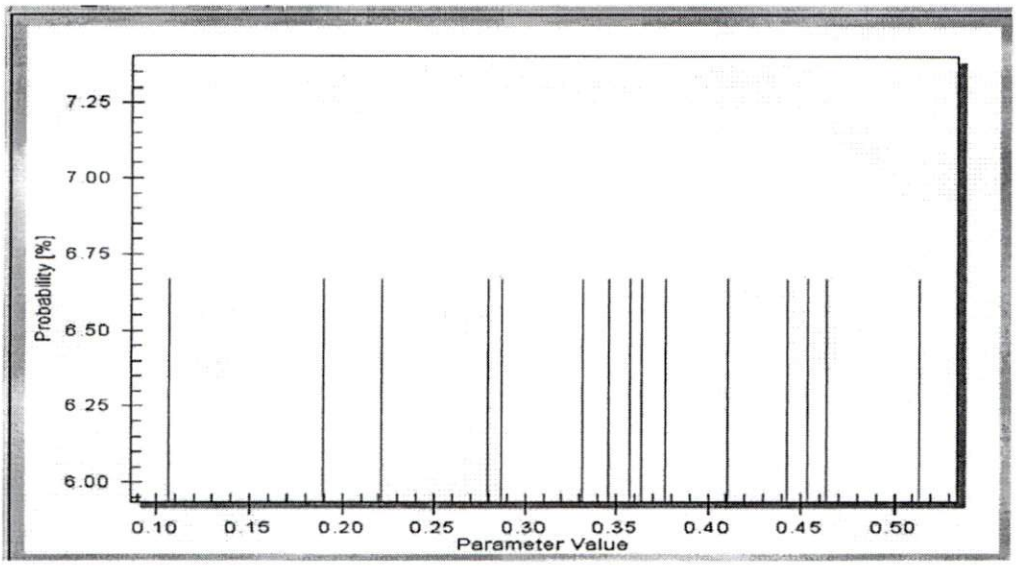


**Figure 2. Marginal probaility density function of elimination rate constant (K)**

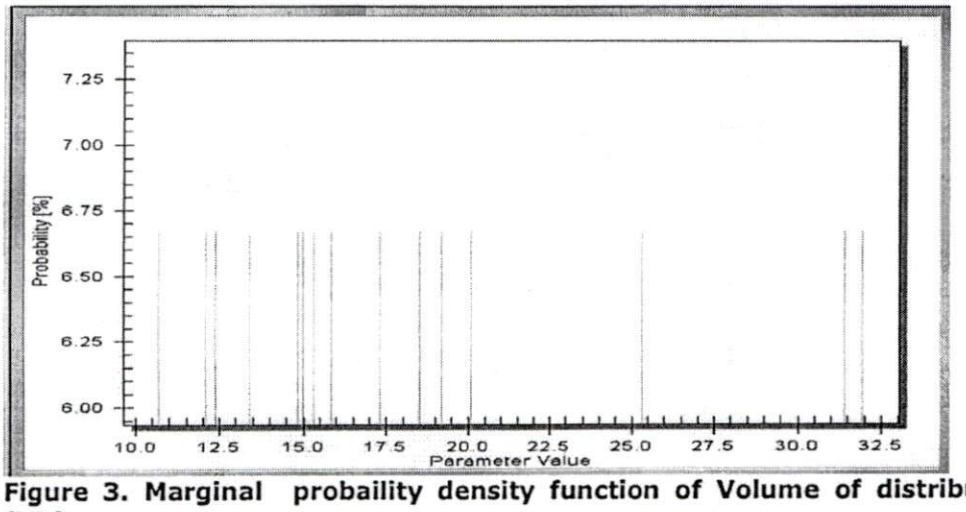


**Figure 3. Marginal probaility density function of Volume of distribution (VD)**

| | 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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