CALCULATED WITHDRAWAL TIME BY LAZUARDI EQUATION METHOD

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ABSTRACT

Residues of veterinary drug on consumption animals were giving hazardous for human health. This research aim was to determine calculated of withdrawal time by new concept namely LAZUARDI EQUATION FOR CALCULATE WITHDRAWAL TIME. The lazuardi postulate was using pharmacokinetics bases and analytical bases. The pharmacokinetics bases approximately taking parameter are dosing of the drug and elimination half-life. The analytical base approximately is taking the values of quantitation limit from instrument detection.

Five adult male local Indonesia sheep at about 30 kg were giving clenbuterol HCl 0.02 mg from 0.75 mL of Ventipulmin® intravenously at single dose. The concentrations drug in plasma were assessed by HPLC reverse phase from serial sampling at time of 40., 60., 90., 120., 180., 240., 300., 360., 480., 500., 620., 740 min. Calculated of withdrawal time were using Lazuardi postulate.

Result research apparently that means of elimination half-life and quantitation limit were obtained at 148.0658 min and 0.053 µg/mL. The conclusions of the research are determine of the drug by from lazuardi equation will be find out approximately at 1 d 5 h 28.32 min.

Keywords: β2-agonist, Lazuardi equation for determined withdrawal time, HPLC reverse phase, pharmacokinetics of clenbuterol.

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INTRODUCTION

The measurement of withdrawal time at last decade was still using old theory by calculate from elimination half-life. Some researcher prepared that technique was did not guaranteed that model would be exactly values of withdrawal time (Nanizar Zaman-Joenoes, 1991) Other researcher explained that technique determined of withdrawal time must be updating by added other parameters. The parameters was using parts of pharmacokinetics parameters and multiplication with safety values. The safety factor about 7^{th} to 10^{th} multiplication from the early values (Lazuardi, 2010). At 1985 Aliu and Odegaard was explained that new method will be launched. That method was using sensitivity value form instrument to detected of avalible of the drug (Aliu, Odegaard, 1985). These method was unsuitable for drug with route of administration via extravascular. The new method from Lazuardi equation will be launched and suitable for all of drug with route of administration extravascular or intra vascular. The new

method are correction from Aliu, Odegaard concept but still using same concept from the last researcher. Lazuardi equation was suitable for the drug with first pass effect more than 10% and esay for application.

METHOD

Five male adult sheep from local Indonesia breeder were ready to use as a research subject. The sheep at body weigh approximately 30 kg were examined by veterinarian with target good for research treatment. The animal ethic clearance was obtained from unit animal ethics clearance from faculty of Veterinary Medicine, Airlangga university. Clenbuterol was used for object of the drug with perform as a patent drug. The drug obtained from Netherland Agrovet distribution with specific namely Ventipulmin injection. The active substances was containing 0.02 mg of Clenbuterol HCl each mL ad using recommended dose 2.5 ml each 100 kg clinical subjects via intra vascular. High Performance Liquid Chromatography (HPLC) using a Shimadzu CBM-20A Communication Bus Module for interaction with a Photo Diode Array (PDA) detector Ultra Violet-Visible (UV-Vis) M20A, in which LiChrospher® 100 RP-18 column was a perfect fit:, the following settings were applied for the isocratic method: 223 nm wave-length, 0.5 mL/min flow rate, and 300 kgf/c maximum pump. All chemicals used were of high-purity grade, and the clenbuterol was a certified reference material of the European Pharmacopoeia level CAS No. 21898-19-1. The mobile phase of the fraction used acetonitrile: water (30:70) containing 0.10% phosphoric acid at pH 3.8.

Serial blood sampling at 5 ml from jugular vein were constructed as follows; 40., 60., 90., 120., 180., 240., 300., 360., 480., 500., 620., 740 min after giving intravenously single dose. The sample preparation was adjusted as described by Lazuardi, Bambang (2016) dan Lazuardi, Bambang (2017). The calculate of withdrawal time was using equation at bellow namely Lazuardi Equation.

$$\text{Withdrwal time (t)} = \frac{T1/2\beta \times (\ln R \times \text{Dose} - \ln \text{Clim})}{\ln 2} \qquad \text{Lazuardi Equation}$$

Note:
T1/2β = Elimination half-life
R = accumulated factor = 1.306
Dose = Dose administrated
Clim = Quantitation limit from the sensing detector instrument

DISCUSSION

From the validated method of analysis, we were found that limit of quantitation 0.053 µg/mL. The chromatogram analyte was showed at figure 1. The result research was explained at Table 1. From table 1 was find the elimination rate constant (K_{el}) from sheep-1 to sheep-5 was different at $P>0.05$. From the table was known that K_{el} for sheep-1 to sheep-5 as follows; 0.0057 min^{-1}., 0.007 min^{-1}., 0.003 min^{-1}., 0.006 min^{-1}., 0.004 min^{-1}. The mean of elimination half-life sheep-1 to sheep-5 were obtained at 148.0658 min by detailed as follows; sheep-1 at 121.597 min., sheep-2 at 99 min., sheep-3 at 231 min., sheep-4 at 115.5 min., sheep-5 at 173.25 min. We

are agree if the result research at described above indicate that drug have a two model compartment. The first compartment is central compartment and the second are periphery compartment. The periphery compartment is following to excretion about time 300 minutes or more at serial sampling times (Lazuardi, 2016).

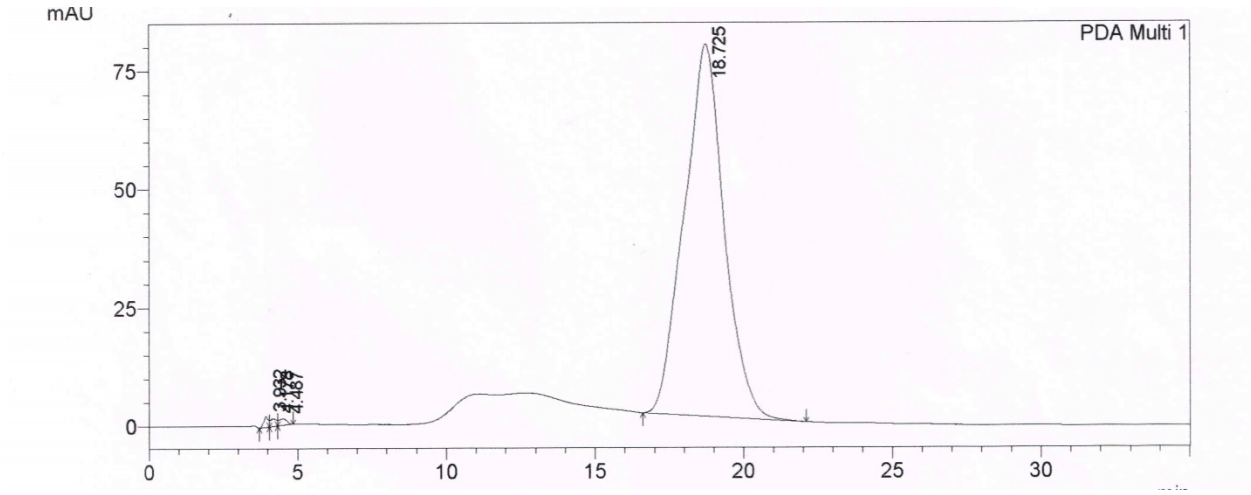

Figure 1. Chromatogram clenbuterol on the mobile phase of the fraction used acetonitrile: water (30:70) containing 0.10% phosphoric acid at pH 3.8.

Table 1. Concentration of clenbuterol after dosing 0.02 mg single dose administration

Time (min)	Sheep-1 (µg/mL)	Sheep-2 (µg/mL)	Sheep-3 (µg/mL)	Sheep-4 (µg/mL)	Sheep-5 (µg/mL)
40	781.06	819.00	766.00	771.010	762.00
60	755.11	800.00	727.00	715.010	741.00
90	711.00	720.00	711.04	698.120	718.00
120	600.00	618.00	664.25	577.100	521.00
180	587.00	511.00	517.00	519.000	478.00
240	482.51	455.00	481.21	497.010	418.33
300	420.00	329.00	311.19	398.220	311.00
360	401.01	311.00	217.13	287.440	229.00
480	319.02	289.54	151.11	218.330	219.00
500	111.00	89.08	118.21	176.110	118.03
620	84.00	60.00	109.00	87.030	98.00
740	65.00	15.00	64.02	21.050	55.66

K_{el}^{a} K_{el}^{b} K_{el}^{c} K_{el}^{d} K_{el}^{e}

Superscript a,b,c,d,e diferent each other $p>0.05$ by one way ANOVA

CONCLUTION

The conclusion of the result research were as follows; (1) the lazuardi equation suitable for calculate for determined withdrawal time (2) the with withdrawal times of clenbuterol on sheep at 29.467 h or 1 d 5 h 28.32 min.

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