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# Effect of Growth and Development on Pharmacokinetics of Antipyrine in Swine

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**Abstract:** The aim of this study was to analyze the effect of growth and development on the pharmacokinetics of antipyrine in swine. Four animals of 16 days old were used for the study. Pharmacokinetic (PK) studies were performed at ages 16, 29, 58, 72, 116, 131, 146, 160, 191, 220 days to cover the different life stages of animals from birth to adulthood, after IV administration of 16 mg $kg^{-1}$ of antipyrine. Blood samples were obtained at 0.0, 1.0, 2.0, 4.0, 6.0, 8.0 and 12 h post-administration and serum concentrations of drug were determined by validated method. Pharmacokinetic parameters as elimination half-life ($t_{1/2el}$), Volume of distribution (VD) and Clearance (Cl), showed variations in different ages of the study groups. The model that best fit $t_{1/2el}$ was the sum of sines and cosines in the periods 204, 102 and 51 days. For Cl, it was at 204, 102, 68 and 51 days and for Vd, it occurred at 204, 102, 68 and 40 days. As $t_{1/2el}$ increased, there was a reduction in Cl and vise versa. To explain these variations, the presence of an endogenous biological rhythm is proposed where periods of rapid growth may affect elimination and metabolic rates. These observations could explain some of the interindividual variations in PK of certain drugs that are eliminated by oxidation reactions. These observations bring into manifestation the close relationship existing between physical growth and drug elimination. Periodic variations observed in the half-life time and metabolic clearance rate of antipyrine probably reflect biologic variations resulting from the existence of biological endogenous rhythms that are common properties of all living beings and perhaps, one of the factors that most influence interindividual variation.

**Key words:** Antipyrine, pharmacokinetics, animal model

## INTRODUCTION

Biological, anthropological and biochemical changes occur throughout the lifespan (Huang *et al*., 2004). Such changes could affect the pharmacokinetics of many therapeutic drugs. For this, it is necessary to consider the effects of rapid growth, sexual maturation and physiological reorganization on pharmacokinetics of drugs. In recent years, the necessity to know the way a drug is eliminated by an organism has increased. This knowledge is of paramount importance since it could provide the basis for an adequate drug dose prescription (Hattis *et al*., 2003). In experimental animals and humans, it was demonstrated that biochemical compositions underwent certain changes due to growth, normal maturation and nutritional state (Lares-Asseff *et al*., 1999; Zahn and Kim, 2007; Morris *et al*., 2009). Therefore, it is convenient to study the effect or relationship which these kinds of changes may have on drug pharmacokinetics in humans. Some reports showed that there is a great interindividual variability of pharmacokinetic values and that some of the most important factors of this interindividual variation correspond to weight and age (Lares-Asseff *et al*., 2006; Lazzerini and Tickell, 2011).

Animals can be useful predictors of drug pharmacokinetics in humans. Growth and development take place in a shorter period in animals. This makes interpretation of tests in animals inherently easier to perform than in humans. However, similar events occur as in humans than in laboratory animals that cover the full period of animal development which can reasonably be considered as appropriate surrogate for human development (Dourson *et al*., 2002; Brent, 2004; Meyer *et al*., 2005).

Physical growth is associated with changes in tissue composition, meaning that each organ at each given time is characterized by a body composition and that human develops changes in biochemical and enzymatic processes that take place in each organ (Kim *et al*., 2005). The presence of rhythmic fluctuations in drug metabolism implies that drug metabolism is under internal regulation (Baraldo, 2008), for example, changes in drug metabolism correspond also to a change in the level of plasma corticosterone (Zhang *et al*., 2011). Studies by Gachon

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and Firsov (2011), suggest that adrenal glands may be involved in short-term regulation of hepatic drug metabolizing enzymatic activity.

Liver plays an important role in mammalian metabolic homeostasis and biochemical development and differentiation of this organ have been the most extensively studied in the recent years with the discovery that the enzyme capacity for drug biotransformation changes with age (Postic *et al*., 2004).

Ginsberg *et al.* (2004) and Kanamori *et al.* (2002) brought into evidence the existence of a number of important factors which determine certain physiological differences between neonates and adults, both in the extreme ages of life, that affect pharmacokinetics of therapeutic drugs. Among these factors are immature function of renal and hepatic function and blood flow to these organs. These two factors among others act to decrease the clearance of many drugs. In this context, growth and development processes which affect pharmacokinetic processes play an important role.

In studies separately carried out by Peter *et al.* (1991) and Matzke *et al.* (2000), antipyrine was shown to be an important biochemical marker of oxidative metabolism. They pointed out the importance and participation of CYP450 enzymes in the determination of 4-hydroxyantipyrine, 3-hydroxymethylantipyrine and norantipyrine formation with the implication of hepatic enzymes-CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C18 and CYP3A4 in the transformation of antipyrine.

It was found that on administration of antipyrine, there was a steady decrease in the volume of distribution (Vd) and in the elimination half-life in the first three months of life while the systemic clearance increased in the first 12 weeks of postnatal life (Janus and Suszycka, 1996). Nevertheless, these authors found that age is a determinant factor in the excretion of 4-hydroxyantipyrine on discovering that in 12-week-old calves, the excretion of this compound is significantly higher than in one-week-old calves.

There was an age-related change in partial clearances of antipyrine metabolites when expressed per unit body weight. The aim of this study was to assess the effect of growth and development on the pharmacokinetics of antipyrine in swine.

## MATERIALS AND METHODS

For the characteristics of the study, a longitudinal study was conducted in a batch of swine. Four animals from the cross-breed of York and Landrace strains were used. Pharmacokinetics studies were performed at ages 16, 29, 58, 72, 116, 131, 146, 160, 191, 220 days to cover the different life stages of animals from birth to adulthood. At the age of 220 days old, the animal is considered to have reached its adult stage (Reiland, 1978). This species was selected because it is a useful experimental model in biomedical research due to its similarities with humans not only in their anatomical, physiological and nutritional but also in their metabolic aspects (Schook *et al*., 2005).

**Ethical statements:** The study was approved and carried out under the rules established by Institutional Committee for Care of Laboratory Animal at National Politechnic Institute, CIIDIR- Durango, Mexico (named CICUAL in Spanish). Animals were not sacrificed and were maintained under bioterium conditions (food and water ad libitum throughout the study period). Affectations were only those related to blood samples obtainment.

Antipyrine was administered intravenously at a dose of 16 mg $kg^{-1}$ of body weight. Before each pharmacokinetics study, the swine were weighed and measured from the tip of the horn to the tail origin. Blood samples with heparin as anticoagulant were obtained at 0.0, 1.0, 2.0, 4.0, 6.0, 8.0 and 12 h post-administration of the drug. Antipyrine concentration in the serum obtained was determined using the method of Brodie *et al*. (1949).

Spectral analysis is a statistical technique that decomposes a time series into spectra of cycles of different lengths by means of Fourier series (Gonzalez, 1997; Wagner, 1998).

The following pharmacokinetics values were calculated: Elimination half-life of antipyrine ($t_{1/2el}$), elimination rate constant (kel), metabolic clearance (CL) and volume of distribution (Vd) using one compartment model (Gibaldi and Perrier, 1975). Spectral analysis was performed on the swine data to simulate the above variables.

## RESULTS

Figure 1 displays the evolution of elimination half-life of as a function of chronological age. As it is shown, there are two regular variations of this in time series. Elimination half-life increases from 0-30 days, then, gradually decreases in a negative exponential curve that reaches its minimum at 100 days of age. At this moment, the half-life increases again and reaches its maximum at 130 days of age and then gradually decreases until totally eliminated.

It was observed that the same variations in every swine although, with little differences from one animal to another which exactly correspond to the age of the animals.

These results suggest the existence of some similarities in the biorhythm. To test this, Spectral

Analysis was applied by means of least square method using a sine function (y = a+b sine (X)) as well as cosine function (y = a+b cosine (X)) (Bogomolny, 1994). This was the model that best fit the data obtained for every swine.

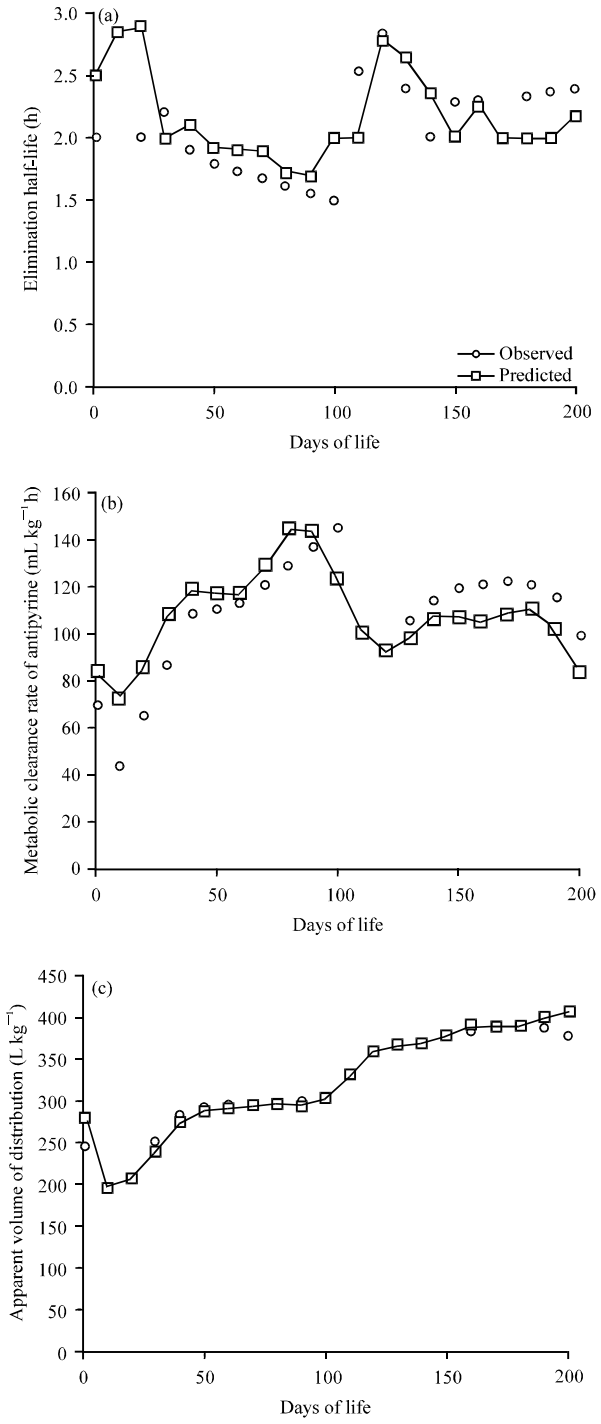


Fig. 1(a-c): Regular variations as time series of the (a) Elimination half-life (h), (b) Metabalic clearance and (c) Apparent volume of distribution of antipyrine in swine

In order to identify biological variations, the model that best fit the elimination half-life of antipyrine was the sum of sine and cosines with $R^2 = 0.89$ and goodness of fit $\chi^2 = 0.46$ $p>0.50$.

Figure 1b shows evolution of the metabolic clearance rate of antipyrine as a function of the chronological age. There is a regular variation in time series suggesting a biorhythm however, inversely to what was obtained in the half-life time. Initially the metabolic clearance rate decreased from 0-16 days, then gradually increased in an exponential curve until it reached the maximum at 100 days of age and after began to decrease and got to the minimum at 120 days. The second variation began after the 120th day of age with a gradual increase that got to a steady level until totally eliminated at adult age. The model that best fit metabolic clearance rate of antipyrine was the sum of sine and cosines with $R^2 = 0.90$ and goodness of fit $\chi^2 = 15.39$ $p = 0.75$.

Figure 1c shows the evolution of the apparent volume of distribution as a function of chronological age. It is clear that there was a polynomial relation that is evident when the apparent volume of distribution increased because of the increase in age. This is even clearer when expressed in milliliters/kilogram of body weight.

It is worthwhile to note that from 0-16 days there was a decrease in the apparent volume of distribution which gradually decreased in an exponential manner after this age. The model that best fit the evolution of apparent volume of distribution was the sum of sine and cosines with $R^2 = 0.96$ and goodness of fit $\chi^2 = 8.16$ $p = 0.99$. There were no significant differences between the observed and the calculated curve. Based on this, this model was considered as being the best fit for the data in this parameter.

## DISCUSSION

As observed, there is an important biological relationship with regular variations in time series among the physical growth factors as age, weight and body size with the parameters obtained from pharmacokinetics of antipyrine. This relationship was obtained using a longitudinal study of these parameters.

The results obtained by Gilman *et al.* (2003) and Bartelink *et al.* (2006) bring into evidence the necessity to modify treatment schemes as a consequence of changes in the kinetic processes of drug absorption, distribution and metabolism during the maturity processes of organogenesis. Changes in body composition taking

place along with growth and development processes are other important aspects that could alter the volume of drug absorption and distribution. Moreover, it is worthwhile to point out the pharmacokinetic changes originated as a consequence of pathophysiologic processes giving rise to differences between children and adults.

The plasmatic elimination half-life is the half-life time of a drug in an organism. This is relevant because it reflects drug disposition in the organism which is mainly related to renal and metabolic clearance as was reported previously (Alcorn and McNamara, 2002; Johnson *et al*., 2006). The regular variations in time series with an ascending tendency seen in this study are a clear demonstration of this relevance.

The regular variations approximately correspond to periods of fast growth in the animals which approximate to the periods of lactation, puberty and adolescence in humans (Brent, 2004). These results are important because they could explain some possible causes of interindividual variation in pharmacokinetics of drugs and therefore contribute in correct treatment scheme.

Metabolic clearance rate shows similar behavior as that seen in the plasmatic elimination half-life time, however, with an inverse relationship to this parameter. Increase in apparent volume of distribution as a function of age, weight and body size, expressed in L $kg^{-1}$ of body weight, reflects a broader drug distribution as the physical growth increases in accordance with the age (Hines, 2013).

## CONCLUSION

These observations bring into manifestation the close relationship existing between physical growth and drug elimination. Periodic variations observed in the half-life time and metabolic clearance rate of antipyrine probably reflect biologic variations resulting from the existence of biological endogenous rhythms that are common property of all living beings and perhaps, one of the factors that most influence interindividual variation.

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