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PHARMACOKINETICS OF DICLOFENAC IN PIGS AFTER INTRAMUSCULAR ADMINISTRATION OF A SINGLE DOSE

PEJČIĆ ZORICA*, POKRAJAC MILENA ** and JEZDIMIROVIĆ MILANKA*

**Faculty of Veterinary Medicine, Belgrade; **Faculty of Pharmacy, Belgrade*

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The pharmacokinetics of diclofenac was studied in 10 clinically normal male Yorkshire pigs, following intramuscular (i.m.) administration of a single dose of diclofenac-sodium (2.5 mg/kg body weight). Diclofenac serum concentrations were determined by high-pressure-liquid-chromatography (HPLC), with UV detection (226 nm).

Following i.m. administration all individual diclofenac serum levels best fitted the one-compartment open model for extravascular administration. The maximal diclofenac serum concentration of 5.88 ± 0.934 mg/L was reached after 0.80 ± 0.35 h. The absorption half-life was 0.36 ± 0.25 h, and the area under the concentration vs. time curve ($AUC_{0\rightarrow\infty}$) was 20.32 ± 4.521 mgh/L. A monoexponential concentration decline and small volume of distribution (Vd) of 0.29 ± 0.100 L/kg indicated a rapid, but not extensive distribution of diclofenac between central and peripheral compartment(s). Total clearance was 0.13 ± 0.034 L/h/kg, and elimination half-life was short (1.67 ± 0.743 h), as a result of a rapid distribution and extensive metabolism of diclofenac in the pig's body.

When administered i.m. to pigs, diclofenac is absorbed and distributed rapidly. Distribution is not extensive, suggesting that diclofenac is predominantly retained in the central compartment. The elimination of the drug from the pig's circulation is also rapid, most of it probably being a result of extensive metabolism in the liver.

Key words: diclofenac, pharmacokinetics, serum, pigs, single dose

INTRODUCTON

Diclofenac (DF) is a nonsteroidal anti-inflammatory drug (NSAID), which has been used in human pharmacotherapy for many years. Its use in veterinary medicine is relatively limited, and there is not much data on the pharmacokinetics of DF in target animal species. In veterinary practice, DF is indicated for treatment of various inflammatory and degenerative post-trauma disorders and lameness in horses, cattle and pigs, as well as pre-operative treatment for cataract extraction (Lascelles and Mair, 2001; Booth, 2001).

Diclofenac is an inhibitor of cyclooxygenase (COX) (Menasse *et al*., 1978; Ku *et al*., 1986; Riendau *et al*., 1997), and it has been reported to possess a somewhat greater affinity for COX-2 than COX-1 (Kawai *et al*., 1998). Diclofenac inhibits prostaglandin biosynthesis, but also reduces leukotriene formation, which may contribute to its anti-inflammatory activity (Kothari *et al*., 1987). The drug has a short elimination half-life in most species, including humans, but accumulates at the site of inflammation, where it reaches concentrations higher then in non-inflamed tissues, and similar to those achieved in plasma (Menasse *et al*., 1978).

The pharmacokinetics of DF has been well documented in humans and laboratory animals, but there is not much data concerning domestic pigs.

The purpose of this study was to estimate the pharmacokinetics of unchanged DF in pigs, after i.m. administration of a single therapeutic dose of diclofenac-sodium (2.5 mg/kg).

MATERIALS AND METHODS

Drugs. Diclofenac-sodium and flurbiprofen standards for analyses were provided by ICN Galenika, Belgrade, Serbia and Montenegro. Diclofenac-sodium formulation used for intramuscular administration to pigs was Reuflogin®, 50 mg/mL injectable solution, Fatro, Italy.

Animals. Ten healthy male Yorkshire pigs, which ranged in age from 2 to 3 months and weighed 18.5-28.0 kg were used. The animals were kept on a farm, and fed with corn-soya based feed concentrate. All pigs received a general physical examination, and were weighed just before drug administration.

Experimental protocol. A single therapeutic dose of diclofenac-sodium (2.5 mg/kg body weight) was administered to pigs intramuscularly in the neck. Food was restricted 12 h before and 4 h after, and water 1 h before and 2 h after drug administration. With exception of these intervals, food and water were available ad libitum. Animals were kept in a group, and allowed to move freely inside the farm-box. They were separated from the group only during blood sampling, and were returned shortly afterwards. Blood samples (about 5 mL) were collected from vena subcutanea abdomonis dex. et sin. at 0; 0.5; 1; 1.5; 2; 3; 4; 6; 9; 12 and 24 h post dosing. Blood samples were allowed to clot, centrifuged (1000 g for 20 min) the serum was separated and stored at -18^{o}C until assayed.

Analytical method. Serum samples were analyzed by reversed phase UV/HPLC method, after one-step liquid-liquid extraction, that had previously been developed and validated by the authors (Jevtić *et al*., 1998; Pejčić *et al*., 1999; Pejčić *et al*., 2002).

Extraction. Serum samples (1 mL aliquots) were spiked with internal standard (flurbiprofen), acidified with 2 mL of phosphoric acid (2.5 mol/L), and 5 mL of mixture of hexane-isopropylalcohol (9:1, v/v) was added. Since the calibration curve was not linear above 1.8 mg/L, when shown that DF concentrations were greater than that limit, aliquots of serum samples smaller than 1 ml were used, and then diluted up to 1 mL with the blank serum. Serum samples prepared as previously described, were then mixed by end-over-end rotation for 15 minutes, and centrifuged for 10 min (1000 g). The organic layer was

transferred to a clean test tube and evaporated to dryness under a stream of nitrogen, in a water bath at 50°C. The residues were dissolved in 200 μL of the mobile phase by vortexing during 30 seconds, and 20 μL of the reconstituted solution was injected into a chromatographic system.

Chromatographic conditions. The chromatographic separation was performed using the Supelcosil LC-18 column (250 x 4.6 mm; 5 μm), and UV detector set at 226 nm. The mobile phase consisted of acetonitrile-methanol-0.1 mol//L sodium acetate (25 : 30 : 45, v/v), pH 7.3 (pH adjusted with glacial acetic acid). The mobile phase flow rate was 1 mL/min. The peaks obtained for DF and internal standard were narrow, sharp and symmetrical, separated from each other, as well as from the components of the biological material. The retention times for DF and the internal standard were about 6 and 8 minutes respectively, and total analysis time was about 10 minutes. Linearity of the analytical method for determination of DF in pig serum was obtained within the concentration range of 0.02-1.80 mg/L ($r>0.99$). Quantification and detection limits for DF in the serum were <0.02 mg/L and <0.01 mg/L, respectively. Mean recovery value for DF from serum was 94% ($n = 5$). Intra-day and inter-day precision (CV%, $n = 5$) were <7% and <12%, respectively.

Pharmacokinetic analysis. The individual DF serum levels were analyzed by a least-squares non-linear regression analysis, using the computer program (NONLIN, version 2.5, Phillip H. Sherrod, Association of Shareware Professionals, USA). One- and two-compartment models for extravascular drug administration were tested, and the best fit was determined by the application of Akaike's information criterion (Yamaoka *et al*., 1978). The pharmacokinetic parameters were obtained for each individual pig, and then combined to derive mean pharmacokinetic parameters.

The maximum DF serum concentration (C_{max}) and the time (t_{max}) to reach C_{max} were obtained from the individual concentration-time curves. The absorption constant (K_{abs}), the elimination constant (K_{el}) and the theoretical DF serum concentration at zero time (C_0), were obtained directly from the equation given below. The other parameters were calculated as follows:

Absorption half-life: $t_{1/2abs}=0.693/K_{abs}$; elimination half-life: $t_{1/2el}=0.693/K_{el}$; area under the C-t curve: $AUC_{0\rightarrow\infty}=C_0(1/K_{el}-1/K_{abs})$; total clearance: $Cl= D/AUC_{0\rightarrow\infty}$ (where D is the dose administered); apparent volume of distribution: $V_d = CL/K_{el}$ (Gibaldi and Perrier, 1982).

RESULTS

The mean (± SD) serum concentration-time (C-t) profile of DF after i.m. administration to pigs is shown in Figure 1. Data are presented in linear (A) and semi-logarithmic (B) plots.

All individual DF serum levels best fitted a one-compartment open model for extravascular administration. After i.m. administration of DF to pigs, serum levels increased monoexponentially until maximal concentrations were achieved, which was followed by a slower, but also monoexponential concentration decline. The

equation which best fitted the data, and was therefore chosen for pharmacokinetic parameters estimation, was as follows:

$$C_t = C_0 (e^{-Kel \cdot t} - e^{-Kabs \cdot t})$$

In two individual cases, prominent secondary peaks on the C-t curve occurred, both between 2nd and 4th hour after drug administration.

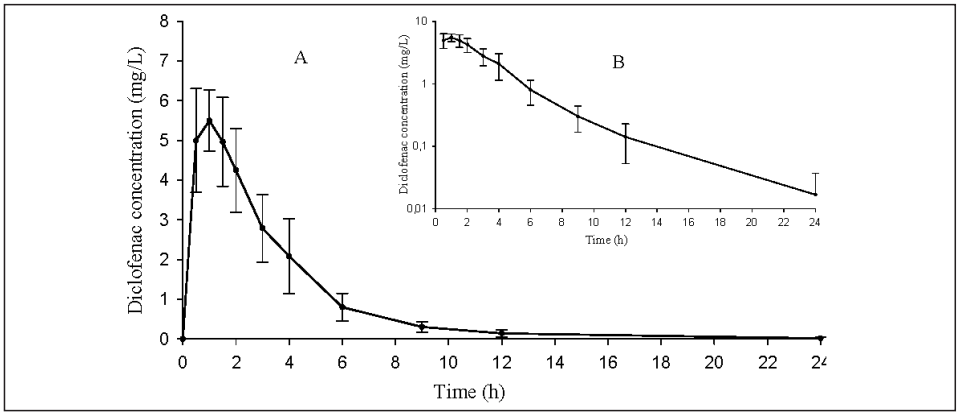

Figure 1. Concentration-time curve (mean ±SD, n=10) of diclofenac in serum of pigs after i.m. administration of a single dose of diclofenac-sodium (2.5 mg/kg body weight) (A). Inserted is the semi-logaritmic plot (B)

Table 1. The pharmacokinetic parameters (mean ±SD, n = 10) after i.m. administration of a single dose of diclofenac-sodium (2.5 mg/kg body weight) to pigs

Parameter	Units	Mean ± SD
C_{max}	mg/L	5.876 ± 0.994
t_{max}	h	0.80 ± 0.35
C_0	mg/L	17.27 ± 12.97
K_{abs}	h^{-1}	3.08 ± 2.54
$t_{1/2abs}$	h	0.36 ± 0.25
K_{el}	h^{-1}	0.50 ± 0.23
$t_{1/2el}$	h	1.67 ± 0.74
Cl	L/h/kg	0.134 ± 0.034
Vd	L/kg	0.292 ± 0.101
$AUC_{0\rightarrow\infty}$	mg·h/L	20.32 ± 4.52

C_{max}, maximum serum concentration; t_{max}, time to reach C_{max}; C_0, theoretical DF serum concentration at zero time; K_{abs} and K_{el}, absorption and elimination constants; $t_{1/2abs}$ and $t_{1/2el}$, absorption and elimination half-lives; Cl, total clearance; V_d, apparent volume of distribution; $AUC0_{\rightarrow\infty}$, area under the C-t curve

The mean (± SD) values of pharmacokinetic parameters of DF after i.m. administration to pigs, estimated as previously described, are presented in Table 1.

DISCUSSION

After i.m. administration to pigs, DF was absorbed rapidly, with a mean absorption half-life of approximately 20 min. Time to reach maximal serum concentrations was 30 min., in 5 of 10 pigs studied, and 90 min. in one case. Absorption of DF after i.m. administration is rapid in man also, where absorption starts 3-4 minutes after dosing, and C_{max} is reached after 20-30 minutes (Kurowski, 1988). In rats, C_{max} is reached 45 min. after i.m. drug administration (Peris-Ribera *et al*., 1991). The results obtained in this experiment indicate marked inter-individual variations in the absorption phase, particularly in the absorption rate (CV% of $t_{1/2abs}$=69%), with much less variations in C_{max} (CV%=17%) and $AUC_{0\rightarrow\infty}$ (CV%=22%). In humans, DF absorption has also been reported to be the most variable pharmacokinetic phase, even after p.o. administration of the drug solution (Culig *et al*., 1986; Brune, 1985). It had been shown that once absorbed in the circulation, DF concentrations increase rapidly and reache C_{max} in a short time (Willis *et al.*, 1979, Chan *et al*., 1990). Some findings indicate that administration into the neck musculature may lead to greater variations in drugs' absorption, compared to the administration into the gluteal muscle (Delmas *et al*., 1997). In this investigation, the neck musculature was chosen for drug administration, regardless of the fact that it might increase inter-individual variations in drug absorption, since this is the injection site most commonly used in practice when administering drugs to pigs.

Secondary peaks observed in a few C-t curves, occurred between 2nd and 4th hour after dosing, and were always smaller then the primary C_{max} peaks. These extra-peaks could have been caused by slower and delayed absorption of DF form the injection site. Similar findings were reported in rats after i.m. administration, and suggested by the authors to have been caused by DF precipitation in the muscle due to its pH-dependent solubility (Peris-Ribera *et al*., 1991). In minipigs, extra-peaks were observed after p.o. administration, but also after i.v. administration of DF, indicating enterohepatic recirculation of the drug (Oberle *et al*., 1994). Enterohepatic recirculation of DF has been reported in rats (Stierlin and Faigle, 1979; Fukuyama *et al*., 1994) and dogs (Stierlin and Faigle, 1979; Tsuchiya *et al*., 1980), but is negligible in humans (Stierlin and Faigle, 1979; Davies and Anderson, 1997). In domestic pigs, the possible existence of enterohepatic recirculation of DF requires further investigations.

Monoexponential concentration decline, as well as visual inspection of the C-t curves, indicated a rapid distribution of DF after i.m. administration to pigs. The distribution phase appeared to be overlapped with the absorption phase, and as such couldn't have been recorded without more frequent blood sampling throughout the first few hours post-dosing. After i.v. administration of DF to humans (Willis *et al*., 1979) and minipigs (Oberle *et al*., 1994), when no drug absorption process interfered, rapid distribution of DF was clearly visible. Based

on our results, the volume of distribution of DF in pigs was estimated to be small (0.292 L/kg). Such a small volume of distribution has been expected, and probably was reflecting a high degree of plasma protein binding of the drug (Chamouard *et al*., 1985; Chan *et al*., 1987; Borga and Borga, 1997). Small DF volume of distribution have previously been reported in humans (Davies and Anderson, 1997), minipigs (Oberle *et al*., 1994), rats, dogs, monkeys (Riess *et al*., 1978) and rabbits (Said and Sharaf, 1981).

Considering the small volume of distribution and a high degree of plasma protein binding of DF, we suggest that in pigs, similarly to humans (Willis *et al*., 1979) DF is retained mostly in the central compartment, without extensive distribution to peripheral compartment(s). Studies in mice revealed that the highest DF concentrations were achieved in the liver, kidneys and bile, and somewhat lower concentrations in the lungs and heart, indicating that these tissues were probably a part of the central compartment. (Riess *et al*., 1978).

Serum DF concentrations declined rapidly in pigs, thus being less then 10% of C_{max} after 6-9 h, but still detectable after 24 h post dosing. The short elimination half-life (1.67 h) also indicated rapid elimination of DF from the plasma of pigs. With the exception of rats, where DF elimination half-life was longer (15 h) due to its enterohepatic recirculation (Torres-Lopez *et al*., 1997), short elimination half-lives have also been reported in other species: 1.3 h in dogs (Tsuchiya *et al*., 1980), 2 h in rabbits (Said and Sharaf, 1981), 2.4 h in minipigs (Oberle *et al*., 1994) and 1.1 h-1.8 h in humans (Willis *et al*., 1979; Kendall *et al*., 1979; Kurowski, 1988). Total clearance in pigs (0.134 L/h/kg) was found to be lower than reported in humans (0.2-0.6 L/h/kg) (Davies and Anderson, 1997), but greater then reported in minipigs (0.057 L/h/kg) (Oberle *et al*., 1994). It could be presumed that total DF clearance obtained in pigs is mainly hepatic clearance, since in other animal species as well as in humans, DF was shown to be eliminated predominantly by metabolism in the liver (Menasse *et al*., 1978, Stierlin and Faigle, 1979; Degen *et al*., 1988; Oberle *et al*., 1994; Riess *et al*., 1978).

In the plasma of minipigs, only a small portion of one DF metabolite was observed (Oberle *et al*., 1994), and some evidence of enterohepatic recirculation was present, while humans were shown to metabolize DF extensively to six metabolites, with no enterohepatic recirculation of the drug (Degen *et al*., 1988; Blum *et al*., 1996). This difference in metabolic pattern was suggested to be the possible cause of lower clearance and longer elimination half-life of DF in minipigs than in humans (Oberle *et al*., 1994). Taking the previously mentioned data into account, as well as the proven similarities between pigs and humans in physiological functions and activity of cytochrome P 450 system (Oberle *et al*., 1994; Witkamp and Monshouwer, 1998), it could be presumed that the metabolic pattern of DF in domestic pigs may be somewhere between humans and minipigs. Pigs are shown to have a small capacity for sulfoconjugation and predominantly form glucuronic acid conjugates of drugs, which are well known to be degradable in the gastrointestinal tract (Baggot, 1988). Thus, enterohepatic recirculation of DF in pigs could be presumed, but needs further investigation.

There are very little data in literature concerning DF pharmacokinetics in target animal species. In this study, DF pharmacokinetics was assessed in pigs,

following i.m. administration of a single therapeutic dose of diclofenac-sodium. Our findings suggest that when administered i.m. to pigs, DF is absorbed, distributed and eliminated rapidly. Diclofenac appears not to distribute extensively into tissues, and is predominantly retained in the central compartment. The metabolism of diclofenac was not investigated in the present study, but from the data reported for other species, it could be assumed that rapid drug elimination from the circulation, which was found in our investigation, was primarily a result of its extensive metabolism in the liver.

Address for correspondence:
Mr Zorica Pejčić,
Faculty of Veterinary Medicine,
Department of Pharmacology and Toxicology,
Bul. Oslobođenja 18, 11000 Belgrade,
Serbia
e-mail: zorica@vet.bg.ac.yu

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FARMAKOKINETIKA DIKLOFENAKA KOD SVINJA POSLE JEDNOKRATNE INTRAMUSKULARNE PRIMENE

PEJČIĆ ZORICA, POKRAJAC MILENA i JEZDIMIROVIĆ MILANKA

SADRŽAJ

Farmakokinetika diklofenaka ispitivana je na 10 zdravih svinja rase jorkšir, posle jednokratne intramuskularne (i.m.) primene diklofenak-natrijuma u dozi od 2,5 mg/kg telesne mase. Koncentracija diklofenaka u serumu određivana je tečnom hromatografijom (HPLC) sa UV detekcojim (226 nm).

Posle i.m. primene, koncentracija diklofenaka u serumu najbolje se može opisati jedno-prostornim farmakokinetičkim modelom za ekstravaskularnu primenu leka. Maksimalna koncentracija diklofenaka u serumu (5.88 ± 0.934 mg/L) postignuta je posle 0.80 ± 0.350 h. Poluvreme resorpcije bilo je 0.36 ± 0.250 h, a površina ispod C-t krive ($AUC_{0\rightarrow\infty}$) was 20.32 ± 4.521 mgh/L. Monoeksponencijalno opadanje koncentracije diklofenaka, kao i mali volumen distribucije (0.29 ± 0.100 L/kg) ukazuju na brzu, ali ne i obimnu raspodelu leka između centralnog i perifernog prostora. Klirens diklofenaka iz plazme iznosio je 0.13 ± 0.034 L/h/kg. Poluvreme eliminacije bilo je kratko (1.67 ± 0.743 h), verovatno kao posledica brze raspodele i metabolizma leka.

Posle i.m. primene kod svinja, resorpcija i raspodela diklofenaka odvijaju se brzo. Raspodela nije obimna, što ukazuje na zadržavanje leka pre svega u centralnom prostoru. Eliminacija diklofenaka iz cirkulacije takođe je brza, verovatno kao posledica njegovog intenzivnog metabolizma u jetri ovih životinja.