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Pharmacokinetics Of Flupirtine In Horses

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ABSTRACT

Flupirtine (FLU) after Intravenous(IV) and Per Os (PO) administration in healthy horses was evaluated.

Six mixed breed adult mares were randomly assigned to two groups using cross-over design (2 x 2 Latin-square). Group 1 received a single dose of 1 mg/kg of FLU injected IV into the jugular vein. Group 2 received FLU (5 mg/kg) via nasogastric tube. The wash out period was 1-week. Blood samples (5 mL) were collected at 0.083, 0.25, 0.5, 0.75, 1, 1.5, 2, 4, 6, 8, 10, 24, 36 and 48 h and plasma was analysed by a validated HPLC method.

Some mild and transient adverse effects (that spontaneously resolved within 5 minutes) were observed in 2 out of 6 animals after IV administration. No adverse effects were noticed in the PO administration group. After IV and PO administrations, FLU was detectable in plasma for up to 36 h. The mean elimination half-life was longer after PO (10.27 h) than after IV (3.02 h) administration. The oral bioavailability was about 70%. After in silico pharmacokinetic simulation/modelling, an oral dose of 2.6 mg/kg in horses has been calculated to give C_{max} and AUC values similar to those reported in humans after a clinical dose administration with a theoretical FLU effective plasma concentration of 187 ng/mL. This study could pave the road for the use of this active ingredient in equine medicine as analgesic after pharmacdynamic studies.

Key words: flupirtine; horses; intravenous; oral; pain reliever; pharmacokinetics.

INTRODUCTION

Flupirtine (FLU) is an aminopyridine drug (ethyl {2-amino-6-[(4-fluorobenzyl) amino] pyridin- 3-yl}carbamate) approved in Europe in 1984 for treatment of pain *(1)*. FLU is a centrally acting analgesic with a mechanism of action unlike that of opiates and NSAIDs. It is active with a favourable tolerability and with no antipyretic or antiphlogistic effects *(2)*. It is the first drug to be recognised in the unique class of 'Selective Neuronal Potassium Channel Openers' (SNEPCO) *(3)*. FLU interacts with the G-protein-regulated, Inwardly Rectifying K^+ channels (GIRKs), a novel family of K^+ channels distinct from the voltage-dependent ones. They are regulated by neurotransmitters and are expressed in different parts of the brain. FLU activates GIRKs and stabilizes the membrane resting potential by activating potassium channels KCNQ and thus generating a neuronal hyperpolarizing current (M-current). The increased M-current due to the action of FLU translates to decreased neuronal excitability *(4)*. Moreover, FLU inhibits the N-Methyle-D-Aspartate receptor indirectly by acting as an oxidizing agent at the redox site of the NMDA receptor, maintaining the Mg^{2+} block on the NMDA receptor *(2)*.

FLU can be useful in the treatment of a wide range of pain states in human beings. In line with its mechanism of action promoting neuronal rest, it has been proven useful in conditions involving neuronal hyperexcitability such as chronic pain (non-malignant and malignant), migraine and neurogenic pain *(5-7)*. Furthermore, its effect as a muscle relaxant

represents a great value in painful conditions associated with increased muscle tension, such as musculoskeletal back pain, myofascial pain and tension headaches *(1,8)*.

Although there is a substantial body of evidence on the efficacy of FLU in humans, only a single study on the analgesic effect of FLU in laboratory animals is present in the literature *(9)* and its pharmacokinetic profiles in cats *(10)* and dogs *(10)* have been recently described. Hence, FLU is likely to be launched on the veterinary market in the near future. The aim of this study was to evaluate the pharmacokinetic profiles of FLU after IV and PO administration in healthy horses.

MATERIALS AND METHODS

Chemical and reagents

Pure FLU maleate salt and the Internal Standard trazodone (IS) powders (both >99.0% purity) were supplied by Sigma-Aldrich (St. Louis, MO, USA). HPLC grade acetonitrile (ACN), methanol (MeOH), dichloromethane (CH_2Cl_2) and ethyl acetate (AcOEt) were purchased from Merck (Darmstadt, Germany). Ammonium acetate ($AcONH_4$) was purchased from Carlo Erba (Milano, Italy). Deionised water was produced by a Milli-Q Milli-pore Water System (Millipore, MA, USA). All reagents and materials were of analytical grade and supplied from commercial sources. The LC mobile phase was filtered through 0.2 μm cellulose acetate membrane filters (Sartorius Stedim Biotech S.A., Aubagne Cedex, France) with a solvent filtration apparatus.

Animals and experimental design

The subjects were Six mixed breeds race horse mares (Italian trotter breed), aged 9 to 13 years and weighing 480 to 590 kg. The horses were determined to be clinically healthy on physical examination, serum chemistry and haematological analyses. Horses were evaluated daily (for 1 week) for visible adverse effects by specialized personnel. Animal care and handling was performed according to the provision of the EC council Directive 86/609 EEC and to Institutional Animal Care and Use directives issued by the Animal Welfare Committee of the University of Pisa, which approved the study protocol.

Horses were randomly assigned to two groups (six slips of paper marked with the numbers 1 to 6 in a box), using cross-over design (2 x 2 Latin-square). Animals were fasted for 12 h overnight before each experiment. During the first phase each horse in group 1 received a single dose of 1 mg/kg B.W of FLU (Katadolon® 100 mg/3 mL vials, FLU D-gluconate AWD Pharma, Radebeul, Germany) injected IV into an indwelling catheter previously inserted in the right jugular vein (flow rate 3 mL/min). Group 2 received a dose of 5 mg/kg B.W via the PO route (Efiret® 100 mg hard capsules, FLU maleate, Meda Pharma S.p.A. Milano, Italy). The oral formulation of FLU was given to all animals via nasogastric tube and consisted of capsules in 500 mL of distilled water. After administration, the nasogastric tube was rinsed with 500 mL of distilled water to ensure complete delivery of the drug into the stomach. A 1-week wash out period was observed between the phases, then the groups were rotated and the experiment was repeated. The left jugular vein was catheterised to facilitate blood sampling. Blood samples (5 mL) were collected at 0.083, 0.25, 0.5, 0.75, 1, 1.5, 2, 4, 6, 8, 10, 24, 36 and 48 h after administration of FLU and placed in collection tubes containing lithium heparin. Samples were immediately centrifuged at 2000 *g* (10 min), and the harvested plasma was stored at -20 °C until use within 30 days from collection.

High performance liquid chromatography

The analytical method was based on a previous method validated in dog plasma *(11)*. In brief, the HPLC system was an LC Jasco (Como, Italy) consisting of quaternary gradient system (PU 980) and an in line multilambda fluorescence detector (FP 1520). The chromatographic separation assay was performed with a Luna $C18_{(2)}$ analytical column (250 mm × 4.6 mm inner diameter, 5 μ particle

size [Phenomenex, Bologna, Italy]) preceded by a security guard column with the same stationary phase ($C18_{(2)}$ [Phenomenex, Bologna, Italy]). The system was maintained at 25°C. The mobile phase consisted of ACN: $AcONH_4$ (20 mM) solution, pH 6.8 (60:40, v/v) at a flow rate of 1 mL/min. Excitation and emission wavelengths were set at 323 and 370 nm, respectively. The elution of the substances was carried out in isocratic mode.

Sample extraction

The procedure was performed in a 15 mL polypropylene vial. A 500 µL aliquot of plasma was added to 100 µL of IS (100 µg/mL) and vortexed for 60 sec. Four mL of AcOEt:CH_2Cl_2 (7:3 v/v) were added, then the sample was vortexed (30 sec), shaken (100 osc/min, 10 min) and centrifuged at 3000 *g* for 10 min at 10° C. Three mL of the supernatant were collected in a separate clean vial. The organic phase was evaporated under a gentle stream of nitrogen at 40 °C and reconstituted with 500 µL of the mobile phase. Twenty µL of this latter solution were injected onto the HPLC-FL.

Pharmacokinetic evaluation

FLU plasma concentration vs. time curves were modeled for each subject using a mono- or a two-compartment open model ***(12)***. Comparison between competing models was made using the residual plots, visual inspection of the goodness of fit curves and the Akaike's information criterion. The pharmacokinetic calculations were carried out using WinNonLin v 5.3.1 (Pharsight). The PO bioavailability was calculated from the ratio of the areas under the plasma FLU concentration curve after PO and IV administration, respectively, indexed to their respective dose:

$$F(\%) = (AUC_{PO} \times Dose_{IV})/$$

$$(AUC_{IV} \times Dose_{PO}) \times 100$$

Based on the PK analysis of pooled data, computer simulations (WinNonlin 5.3.1) were performed to calculate the oral dose that should be administered to horses in order to achieve the values of C_{max} and AUC reported in humans after oral administration of a clinical dose ***(13)***.

When the theoretical dosage regimen in horses (a PK/PD hybrid variable) was evaluated, the relative effective plasma drug concentration (assumed at the steady state) was calculated according the following formulae ***(14)***:

$$EC = (ED \times Bioavailability)/Clearance$$

where EC is the average effective target plasma concentration needed to obtain the desired clinical response, ED is the dose per dosing interval (amount/time), Bioavailability is the extent of systemic bioavailability (a factor between 0 and 1), and Clearance is the plasma clearance expressed for the given dosing interval.

Statistical analysis

Pharmacokinetic variables were evaluated using the Student's *t* test to determine statistically significant differences between the treatment groups. Both pharmacokinetic parameters and FLU plasma concentrations are presented as means ± standard deviation (normality tested by Shapiro-Wilk test). All analyses were conducted using GraphPad InStat (GraphPad Software). In all experiments, differences were considered significant if $P<0.05$.

RESULTS

The HPLC method was re-validated using horse plasma. Briefly, FLU was linear (r^2 >0.99) in the range 10-1500 ng/mL. When samples exceeded the upper limit of the range, they were re-analysed after appropriate dilution. The intraday repeatability was measured as coefficient of variation and was lower than 5.3 %, whereas accuracy, measured as closeness to the concentration added on the same replicates, was lower than 6.2 %.

Immediately after IV injection of the drug, 2 out of 6 horses showed adverse effects including muscle twitching, head shaking and agitation but they resolved spontaneously within 5 min. No behavioral changes or

alterations in health parameters were observed in the remaining animals during or after (up to 7 days) the study. Physiological signs and parameters were normal.

A bi-compartmental model best fitted the plasma concentrations after IV and PO administrations in all the six horses. Two-compartment with bolus input and first-order output, micro-constants as primary parameters was used for the IV administration while a first-order input, first-order output, no lag time and micro-constants as primary parameters was used for the PO administration. The average plasma concentration vs. time curves after both administrations are reported in Fig.(1). Flupirtine was detectable in plasma up to 36 h, at 48 h, the drug concentrations dropped down the LOQ of the method. After oral administration (5 mg/kg), the FLU plasma concentrations were quite variable, but were detectable over the same range of time. The average C_{max} (1639 ng/mL) was shown at a T_{max} of 2.16 h. The oral bioavailability (F%) was 71.4 ± 33.1%. The half life of elimination (Beta HL) value was 3 times higher in the PO compared to the IV group. The mean values of both clearance and volume of distribution were significantly different between the groups including when normalized for dose and F%. The complete pharmacokinetic parameters are reported in Table (1).

After pharmacokinetic simulation of PO multiple dosing, it was found that if the drug is administered once every 24 h the steady state is achieved after the second administration. The oral dose that theoretically should be administered to horses in order to achieve similar C_{max} and AUC values to those reported with clinical doses in humans, is 2.6 mg/kg (Fig.(2). When the theoretical effective drug plasma concentration (EC) was calculated from the relevant parameters ED, Clearance and bioavailability, it was shown that the expected analgesic effect should be achieved at drug plasma concentrations higher than 187 ng/mL. The average pharmacokinetic profile indicated that this value is exceeded for over 9 and 15 h following administration (Fig.(2) of 2.6 and 5 mg/kg of FLU, respectively.

Table 1. Pharmacokinetic parameters of flupirtine after IV (1 mg/kg) and PO (5 mg/kg) administrations in healthy horses. Mean± S.D (n = 6)

		IV		PO	
Parameters	**Units**	**Mean**	**SD**	**Mean**	**SD**
AUC	hr*ng/mL	4003	± 1193	13211	± 4914
K01_HL	hr	/	/	1.38	± 0.62
K10_HL	hr	0.84	± 0.44	2.26	± 0.26
Alpha	1/hr	8.19	± 6.44	0.60	± 0.31
Beta	1/hr	0.27	± 0.12	0.07	± 0.03
Alpha_HL	hr	0.12	± 0.06	1.41	± 0.65
Beta_HL	hr	3.02	± 1.30	10.27	± 3.27
Cmax	ng/mL	3706	± 1119	1639	± 643
Tmax	hr	/	± /	2.16	± 0.85
CL‡	mL/hr/kg	269.7	± 83.58	411	± 107.9
V2‡	mL/kg	656.8	± 121.9	1355	± 1273
AUMC	hr*hr*ng/mL	17188	± 12351	/	± /
MRT	hr	3.90	± 1.71	/	± /
V1‡	mL/kg	289.3	± 80.87	1342	± 404.9
K01	1/hr	/	± /	0.61	± 0.30
K10	1/hr	1.06	± 0.66	0.31	± 0.04
K12	1/hr	5.26	± 4.68	0.21	± 0.24
K21	1/hr	2.13	± 1.40	0.15	± 0.10
F%	%			71.4	± 33.1

AUC, area under the plasma concentration–time curve; K01_HL, half-life of the absorption phase; K10_HL, half-life of the elimination phase; Alpha, rate constant associated with distribution; Beta, rate constant associated with elimination; Alpha_HL, distribution half-life; Beta_HL, elimination half-life; C_{max}, peak plasma concentration; T_{max}, time of peak; CL, clearance; V2, volume of compartment 2; AUMC, area under the first moment curve; MRT, mean residue time; V1, volume of compartment 1; K01, absorption rate; K10, elimination rate from compartment 1; K12, rate of movement from compartment 1 to 2; K21, rate of movement from compartment 2 to 1; F%, bioavailability. ‡ For the oral administration these parameters are divided for their bioavailability.

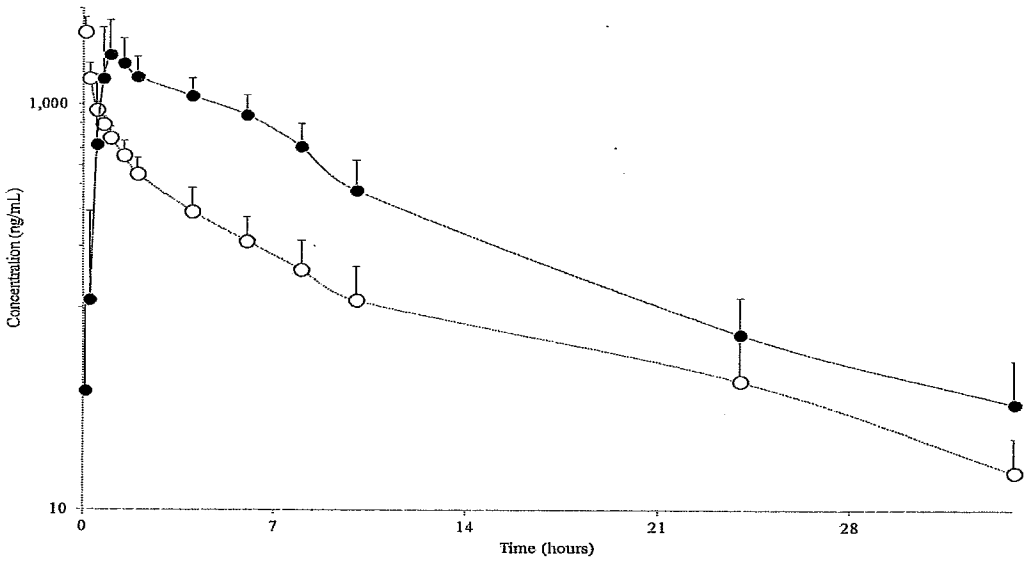

Fig. 1. Mean semi logarithm plasma concentrations of flupirtine vs. time curves following PO (5 mg/kg) (—•—) and IV (--○--) (1 mg/kg) administrations in healthy horses (*n* = 6). Bars represent the standard deviations.

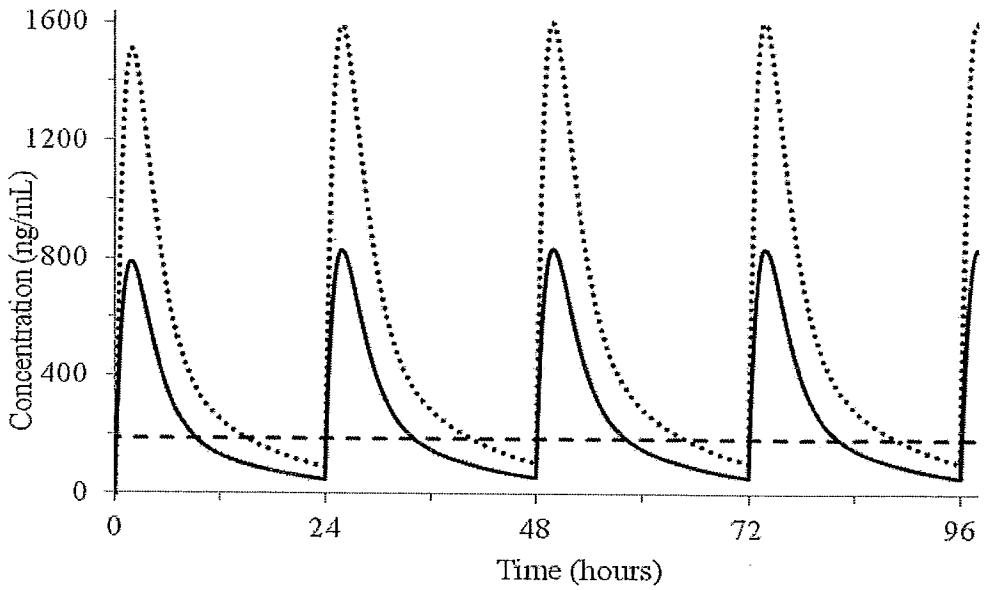

Fig. 2. Mean plasma concentrations of flupirtine vs. time curves following a simulated PO multiple dose rate at 5 mg/kg/day (dotted line) and a simulated PO multiple dose rate at 2.6 mg/kg/day (solid line). The dashed line represents the theoretical effective concentration.

DISCUSSION

Flupirtine is a centrally acting, non-opioid analgesic that is available in a number of European countries for the treatment of a variety of pain states *(15)*. The therapeutic benefits seen with FLU relate to its unique pharmacological properties. Recently its potential for use in veterinary medicine has been explored *(16)*.

Flupirtine produced an efficacy profile superior to that of tramadol for cancer-associated pain *(4,17)*. FLU produced a significant 5 fold increase in morphine antinociception when the two drugs were administered in combination in different rat models of pain *(18,19)*. If the sparing opioid effect is also evident in horses, this active ingredient could play an important role in combinatorial analgesic therapy in order to avoid moderately high regimens of opioids. FLU might be also an attractive alternative for patients with a history of adverse drug reaction to NSAIDs *(20)*. In fact it does not induce the gastrointestinal side effects evoked by classical NSAIDs or the cardio-/cerebrovascular and renal side effects evoked with chronic therapy with COX-2 selective inhibitors *(21)*.

Allometric scaling is an approach for dosage selection that can be used in the absence of either species-specific pharmacokinetic data or prior drug experience in the target species *(22)*. In the present study, an evidence-based approach rather than an allometric calculation of the dose was preferred. Both approaches share the assumption that species differences in pharmacodynamics are clinically negligible. The oral dose administered in the present study (5 mg/kg) was about 3 times higher than the minimum dose reported in human clinical practice (100 mg/subject/day). However, it is still within the recommended human clinical range (100-400 mg/subject/day) *(15)*. The rationale for dose selection of 5 mg/kg is based on earlier preclinical studies in dogs and cats. The ED_{50} of FLU after oral administration in the electrical tooth pulp stimulation test in dogs and cats was 3.5 mg/kg *(23)* and 3 mg/kg *(9)*, respectively. Additionally, recent pharmacokinetic studies carried out with this dose regimen did not show any adverse effects after oral administration *(10,11)*.

On the other hand, as an IV dose, administration of 5 mg/kg FLU produced some adverse effects in dogs *(11)*. In the present study the IV dose was reduced to 1 mg/kg to minimise potential adverse effects. Although the dose was reduced, some mild and transient adverse effects were visible in two subjects. This is in line with the unexpected sensitivity of horses to certain drugs when they are injected IV *(24)*. No information about the minimal effective concentration in animal species is available for FLU. Hence, if the plasma level of FLU reported in humans after administration of a clinical dose is assumed to also be effective in the horse, the 1 mg/kg IV administration of FLU is quite a way from reaching that plasma level. If the IV dose was increased, more severe adverse effects might be expected. Hence, although other studies need to be undertaken to clarify the FLU safety issue, IV administration is not recommended in this species.

FLU is a water soluble compound in the form of maleate salt (pKa 5.3) that is rapidly absorbed from the human gastro intestinal tract *(25)*. The T_{max} found in this study (2.16 h) is in between the T_{max} reported for dogs (1.42 h) and humans (range 1.6-1.8 h), and cats (2.78 h). A number of factors may be responsible for this difference: the large variation in this parameter in the horse, different absorption or other species-specific factors. In contrast, while the maximal plasma concentrations of FLU after PO administration in humans (100 mg/subject) *(26)* and in cats *(10)* were comparable when normalized for the administered dose and F%, in horses they showed a lower average value compared to that reported for dogs *(11)*. A large difference has been shown in oral F% between humans (90%) and animals (cat and dog) (about 40%). In horses the oral F% was 71%. Large differences in F% between humans and animals (carnivorous vs. herbivorous) have previously been demonstrated, indicating that F% values derived in an animal species cannot always be extrapolated to humans or other animal species *(27-29)*. Values of apparent CL and V2 after PO administration including following

normalization for F% and dose, were different from those after IV administration. This suggests that other phenomena such as the different pharmaceutical composition used in the IV and PO routes (D-gluconate vs. maleate, respectively) or a saturation of the metabolic enzymes (triggered by the prolonged high drug concentrations in the PO group), might have generated these differences.

Although FLU has been used in the treatment of acute and chronic states in humans for 25 years, no minimal effective concentration for pain relief has been reported yet. However, it is noteworthy that in horses (despite the low oral F%) a dose of 5 mg/kg PO produced FLU plasma concentrations higher than the plasma concentrations produced by the PO clinical dose (100 mg/subject/day) reported in humans *(13)*. After in silico modelling/simulation, the calculated dose that produces in horses C_{max} and AUC values (critical parameters for the evaluation of bioequivalence) similar to those reported in humans as effective, is 2.6 mg/kg/day. This dose (the equianalgesic dose of human clinical dose) is in line with the ED_{50} values experimentally calculated earlier in cats and dogs *(9, 23)*. The drug plasma EC calculated after the simulation is exceeded for over 9 h and 15 h, after 2.6 and 5 mg/kg FLU oral administration, respectively, suggesting a long lasting therapeutic effect of the drug. Both the theoretical dose and EC need to be evaluated/confirmed with further PK/PD studies.

Following PO administration of FLU, horses showed mean terminal plasma elimination half-lives in between those reported in cats (13.6 h) and dogs (7.1 h) *(10,11)*. This is in line with the clearance value of FLU in horses which is smaller than that reported in dogs (604 mL/h/kg) and larger compared to that reported in cats (195 mL/h/kg) *(10,11)*. A likely explanation for the difference in half life values could be the difference shown to occur in cats, being that while FLU is bio-transformed in the N-acetylated analogue D13223 in humans *(30)*, this transformation could be slower or could occur to a lesser extent in horses. Indeed, horses are well known as being poor acetylators *(31)*.

FLU is predominantly excreted in urine: (about 72% in humans *(13)*. Although the CL value of FLU did not significantly change in patients with mild renal impairment compared to healthy patients, the half-life almost doubled *(26)*. Hence, caution should be used in horses with presumed renal impairment. It has also been proven that old age is associated with increased half-life of the drug in humans *(26)*. Hence, this should be taken into consideration if FLU is to be administered to elderly horses.

Conclusion

This is the first study on FLU in horses. The pharmacokinetic profiles of FLU in the horse were different compared to FLU disposition in humans, cats and dogs. IV administration is not advisable in horses because it is most likely to produce adverse effects. Although the oral F% of FLU was lower than that in humans, a 5 mg/kg administration gave plasma concentrations exceeding those reported in humans after clinical dosing. An oral dose of 2.6 mg/kg in horses has been calculated to give C_{max} and AUC values similar to those after clinical dose administration in humans. This study could pave the road for the use of this active ingredient in equine medicine. Further studies are need to be undertaken to assess if this drug is suitable for horses.

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الملخص العربى

المسار الحركى لعقار الفلوبرتين فى الخيول

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يعد عقارالفلوبرتين من الادويه المسكنه للألم غير الافيونيه والتى تستخدم منذ عقود طويله فى الأنسان لعلاج كثير من حالات الألم وهدفت هذه الدراسه الى معرفه الحركيه الدوائيه لهذا العقار فى الخيول ولقد استخدمت فى هذه التجربه عدد ٦ من اناث الخيول مختلطه الانساب يتراوح اعمارهم من ١١-١٣ سنه واوزانهم من ٤٥٠-٥٩٠ كيلوجرام وتم تقسيمهم الى مجموعتين كل منهما تحتوى على ثلاثه حيوانات تم تصويمهم ١٢ ساعه قبل التجربه واجريت التجربه على مرحلتين الاولى تم فيها تجريع ٣ خيول بواسطه الانبوب المعوى عن طريق الفم الفلوبرتين كبسولات ١٠٠ ملجم بجرعه ٥ ملجم/كجم وتجريع الثلاث خيول الاخرى عن طريق الوريد الودجى بجرعه ١ ملجم/كجم وبعد حوالى اسبوع كفتره خروج للدواء من الدم تم تبادل المجموعات واعاده التجربه وتم سحب عينات الدم من الوريد فى الاوقات المحدده حسب الجدول الزمنى لسحب العينات بعد٥ دقائق،١٥ دقيقه،٣٠ دقيقه،٤٥ دقيقه ،وساعه ، وساعه ونصف و٢و٤و٦و٨و١٠و٢٤و٣٦و٤٨ ساعه.ووضعت عينات الدم فى انابيب تحتوى على ماده الهيبارين وسرعان ماتم فصلها بجهاز الطرد المركزى وتجميع البلازما وحفظها تحت درجه تساوى -٢٠ درجه سيليزيه حتى تم تحليلها بواسطه طريقه أثبت صحتها معمليا وتم تحليلها بواسطه جهاز الكروماتوجرافيا السائله عاليه الاداء.

تم تحليل النتائج بواسطه استخدام برنامج Winolin المخصص لحساب الحركيه الدوائيه للادويه بأستخدم bicompartmental model وتم اختبار صحه النتائج عن طريق Ackick`s criteria للموديل وكذلك الرؤيه العينيه لتمثيل النتائج على المنحنيات البيانيه.

فقد اوضحت النتائج ان فتره نصف العمر مختلفه بالنسبه للتجريع بالفم والوريد للشكلين (الفمى والوريدى) متمثله فى 1.30±3.02ساعه بالنسبه للفم و 3.27±10.27ساعه للوريد وان اتاحيه الدواء تساوى حوالى 33.1±71.4% وان اعلى تركيز للدواء كان 1639 ng/ml وشوهد بعد 2.16ساعه وان الطريقتين المستخدمتين للتجريع اخذتا نفس الشكل فى مرحله انسحاب الدواء من الجسم وكذلك ظل تركيز الدواء بعد التجريع من الفم موجود حتى ٣٦ ساعه وانخفض بعد ٤٨ ساعه عن الحد الذى يستطيع الجهاز اكتشافه.

تمثل هذه الدراسه الخطوه الاولى التى قد تمهد الطريق لاستخدام هذه الماده فى الطب البيطرى