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ORIGINAL ARTICLE

Pharmacokinetics and tissue distribution of Kendine 91, a novel histone deacetylase inhibitor, in mice

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Abstract
Purpose The present investigation was undertaken to characterize the pharmacokinetics and oral bioavailability of Kendine 91 in mice and to compare it with other HDAC (histone deacetylases) inhibitors.
Methods After administration of a single intravenous dose (10 mg/kg) or a single oral dose (50 mg/kg) blood and tissues samples were collected and analysed by HPLC/MS/MS.
Results Elimination half-life was higher than that of SAHA (5.87 vs. 0.38 h after intravenous (IV) administration and 10.29 versus 0.75 h after oral administration). Absolute oral bioavailability was found to be 18%. Total body clearance (7.72 l/h/kg) was greater than the hepatic blood flow of 5.4 l/h/kg in mice and larger than glomerular filtration rate in mice (0.84 l/h/kg). Tissue levels and distribution volume indicate a high capacity of Kendine 91 to distribute into tissues.
Conclusions This preliminary pharmacokinetic evaluation prompts us to believe that it is worth pursuing further development of Kendine 91 as an anticancer drug.

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Keywords Kendine 91 · Pharmacokinetics · Mice · Oral bioavailability · HDAC inhibitors

Introduction

The transcriptional activity of certain genes is modulated by the acetylation state of core histones. Histone acetyltransferases (HAT) can stimulate gene transcription by histone acetylation, inducing an open chromatin state. Changes on the chromatin structure promote the access of transcription factors to the promoter regions and result in the activation of gene transcription [1, 2]. Histone deacetylases (HDACs) are catalytic enzymes that control the structure of chromatin via removal of the acetyl inserted in lysine residues of histones [3] by HAT. The most extensively studied post-translational modification of histones is the acetylation of lysine.

Preclinical studies have demonstrated that the use of HDAC inhibitors (HDACis) induces cytodifferentiation, cell cycle arrest, and apoptosis in transformed cells [4] and shows a promising antitumuor activity both in vivo and in vitro, suggesting that the HDACis may be potentially important novel anticancer therapeutics [5].

Among the wide variety of HDAC inhibitors synthesized to date, some of them are already in clinical trials and one of them, suberoylanilide hydroxamic acid (SAHA or Vorinostat) [6], has recently been commercialized. SAHA is a hydroxamic acid–based HDACi that induces differentiation and apoptosis in different cell lines [6, 7]. SAHA inhibits HDAC, which results in the accumulation of acetylated histones of type H2a, H2b, H3, and H4 through a direct interaction with the catalytic site of the enzyme [6]. Unfortunately SAHA has low solubility and low permeability, being classified as class IV by the biopharmaceutics

classification system (BCS), which implies that SAHA may not be well absorbed and may not reach the target receptor [8].

Out of this study we have designed and synthesized a new family of HDAC inhibitors [9], Kendine 91 being the most promising candidate. Its chemical structure is presented in Fig. 1. Among the members of this new family of HDACis, Kendine 91 shows the most promising activity in the treatment of solid tumours and haematologic malignancies. Kendine 91 acts as a potent and specific histone deacetylase inhibitor in HCT 116 and MOLT 4 human cancer cell lines [9].

To appropriately design future clinical trials that will achieve plasma concentrations of Kendine 91 sufficient to induce antitumuor activity, preclinical pharmacokinetic studies are needed. The present investigation was undertaken to characterize the pharmacokinetics and oral bioavailability of Kendine 91 in mice.

Materials and methods

Chemicals and reagents

Kendine 91 was synthesized in the Organic Chemistry group of the University of the Basque Country (San Sebastian, Spain) [9]. Simvastatin, used as internal standard (IS) was purchased from Sigma (St. Louis, MO, USA). Methanol (gradient HPLC grade) was obtained from Scharlau (Barcelona, Spain). Propylene glycol, formic acid, orthophosphoric acid 85%, sodium di-hydrogen phosphate 1-hydrate and tert-butyl methyl ether (MTBE) were purchased from Panreac Química (Barcelona, Spain). Ultrapure water was obtained from a Milli-Q® Plus apparatus (Millipore). Other chemicals were all of analytical grade. Plasma was obtained from Centro Vasco de Transfusiones (Galdakao, Spain). Female balb/c nude mice weighing 18–22 g (5 weeks of age) were purchased from the Harlam Interfauna Ibérica S.L (Barcelona, Spain).

Drug administration and sample collection

Animals were handled in accordance with the Principles of Laboratory Animal Care (http://www.history.nih.gov/laws). Mice were quarantined for approximately 1 week prior to the study. They were housed under standard conditions and had ad libitum access to water and standard laboratory rodent diet. Kendine 91 was dissolved in a mixture of propylene glycol, ethanol and water. Mice were grouped five per time point and were administered a single intravenous dose (10 mg/kg) through tail vein. At predefined times (pre-dose, 0.08, 0.25, 0.5,1, 2, 3, 6, 8 and 12 h) mice were killed by CO_2 overdose. For oral administration (50 mg/kg dose), animals were maintained in fasted conditions 12 h before dose administration. Four hours after administration, animals were fed with standard laboratory rodent diet. After 0.08, 0.25, 0.5, 1, 1.5, 2, 3, 4, 8, 12, and 24 h, mice were killed by CO_2 overdose. At pre-dose time, samples were also collected. In both cases (intravenous and oral administration) blood samples were collected by cardiac puncture and tissues of interest (liver, heart, lung, kidney and muscle) were extracted. Blood samples were centrifuged for 5 min at 8,000 rpm at 4°C and the plasma and tissues were kept frozen at −80°C until analysis.

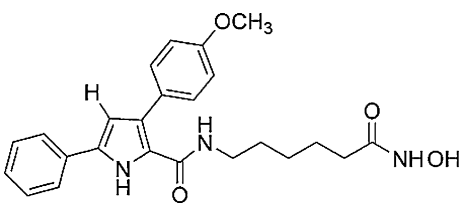

Fig. 1 Chemical structure of Kendine 91

Analytical method for determining Kendine 91 in plasma and tissues

Kendine 91 level in plasma and tissues was determined by HPLC/MS-MS according to a method described and validated previously [10]. Briefly, separation was performed on a C_8 column, with a mobile phase consisting of methanol and aqueous 10 mM formic acid (73:27 v/v). Both analyte and internal standard (simvastatin) were determined using electrospray ionization and the MS data acquisition was via MRM in positive scanning mode. Quantification was performed using the transitions *m/z* 444 → 169 and 441 → 325 for Kendine 91 and simvastatin, respectively. Liquid–liquid extraction was employed for the sample preparation with tert-butyl methyl ether. Tissue samples were accurately weighed and homogenized in phosphate buffer solution pH 7.4. Tissue homogenates were processed as were plasma samples, and analysed by HPLC. Recovery of Kendine 91 in tissue samples relative to plasma samples was obtained by comparing the chromatographic response of Kendine 91 in the tissue samples with the chromatographic response of Kendine 91 in the plasma samples. This factor was later used to calculate the Kendine 91 concentration in unknown tissue samples from calibration curves obtained with plasma samples. Liver, heart, lung, kidney and muscle recoveries were 0.7, 0.67, 0.74, 0.77 and 0.40, respectively. The analytical method was validated with respect to linearity, accuracy, precision, recovery and stability.

Pharmacokinetic analysis

Plasma concentration data of Kendine 91 were obtained from mice and were pooled to provide mean concentration

data. The same was carried out for tissue concentrations. Pharmacokinetic parameters were calculated by a non-compartment method using WinNonlin 4.1 (Professional Version 4.1; Pharsight Corp; Mountain View, CA, USA). Maximum plasma concentration (C_{max}) and the time to reach C_{max} (T_{max}) were estimated directly from the observed concentration versus time profiles. The area under the curve of plasma concentration versus time curve up to the last quantifiable time point, AUC_{0-t} was obtained by the linear trapezoidal method. The AUC_{0-t} was extrapolated to infinity ($AUC_{0-\infty}$) by adding the quotient C_{last}/K_{el}, where C_{last} represents the last measured concentration and K_{el} represents the apparent terminal rate constant. K_{el} was calculated by the linear regression of the log-transformed concentrations of the drug in the terminal phase. The half-life of the terminal elimination phase was obtained using the relationship $t_{1/2} = 0.693/K_{el}$. Systemic clearance was calculated by the relationship $CL = D \times F/AUC_{0-\infty}$, where D is the dose of the compound and F the fraction of dose absorbed.

The apparent volume of distribution was obtained from the equation $Vd_z = D \times F/(AUC_{0-\infty} \times K_{el})$. For intravenous administration, the volume of distribution at the steady-state (V_{ss}) was calculated with the equation $V_{ss} = MRT \times Cl$. Mean residence time (MRT) was determined by division of AUMC (area under the first moment curve) by $AUC_{0-\infty}$. Absolute oral bioavailability (F) was calculated from plasma data using the relationship $F = [dose_{IV} \times AUC_{0-\infty,oral}/dose_{oral} \times AUC_{0-\infty,IV}] \times 100$. From tissue levels, the factor Fr was calculated using the relationship $Fr = [dose_{IV} \times AUC_{0-t,oral}/dose_{oral} \times AUC_{0-t,IV}]$.

Results

Intravenous administration

The plasma concentration-time profile of Kendine 91 after intravenous administration is illustrated in Fig. 2. Following a 10 mg/kg IV dose, plasma concentration reached 3,715 ng/ml at 5 min and then declined triexponentially with time. The compound was detectable in plasma for up to 12 h. Data were analysed according to a noncompartmental analysis using WinNonlin and the relevant pharmacokinetic parameters were computed (Table 1). The elimination half-life was found to be 5.87 h. The mean total body clearance was 7.72 l/h/kg and the volume of distribution at steady-state was 6.3 l/kg. Table 1 also shows the pharmacokinetic parameters of other HDACis (SAHA, EX-2, PXD 101, LBH-589 and SB 639) [8, 11]. In comparison to other HDACis, Kendine 91 shows the highest elimination half-life. Plasma clearance of Kendine 91 was higher than that of SAHA and EX-2, but lower than that of PXD 101, LBH-589 and SB639. Kendine 91 mean residence time (MRT) was 0.82 h.

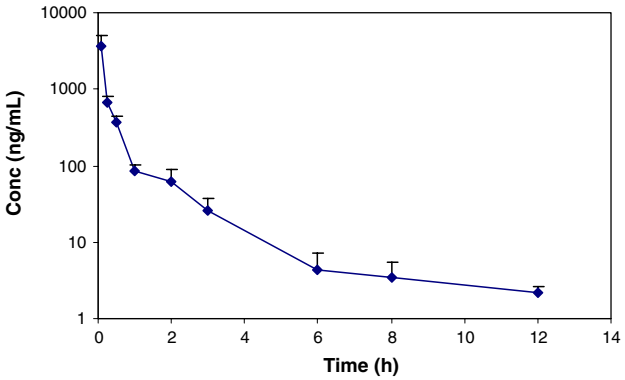

Fig. 2 Plasma concentration-time profile of Kendine 91 after a single IV dose of 10 mg/kg. (*Error bars* represent SD, $n = 5$)

Figure 3 shows the tissue concentrations of Kendine 91 versus time in tissue homogenates after intravenous administration. Kendine 91 was present in liver, heart, lung, kidney and muscle until 8 h after administration. Highest values of AUC_{0-t} of Kendine 91 were found in kidney and heart. The tissue-specific pharmacokinetic parameters are presented in Table 2.

Oral administration

The blood concentration-time profile of Kendine 91 after oral administration is illustrated in Fig. 4. Following oral administration at 50 mg/kg, mean maximal plasma concentration of 4,234 ng/ml was observed. Concentrations were detectable up to 24 h. A second maximum was observed in the plasma level profile, which could be due to enterohepatic circulation although this must be confirmed with additional studies. Comparison of the pharmacokinetic parameters of Kendine 91 and the other HDACis [8, 11] are presented in Table 1. Elimination half-life increased to 10.29 h compared to IV administration. The volume of distribution (Vd_z) reached a value of 114.66 l/kg. The oral bioavailability of Kendine 91 was estimated to be 18%, higher than bioavailability of the other compounds except EX-2. Kendine 91 mean residence time (MRT) was 3.46 h. Concentration-time profiles of Kendine 91 after oral administration in different tissues are shown in Fig. 5. In all tissues, concentrations were detected up to 24 h. The tissue-specific pharmacokinetic parameters are presented in Table 2.

Discussion

Anticancer therapy needs to be improved with new molecules that present higher effectiveness and a more favourable safety profile than the commercialized compounds.

Table 1 Pharmacokinetic parameters of Kendine 91, SAHA, EX-2, PXD 101, LBH-589 and SB639 in mice plasma after IV and oral administration

	Kendine 91	SAHA [11]	EX-2 [11]	PXD 101 [11]	LBH-589 [11]	SB639 [8]
IV at 10 mg/kg						
$AUC_{0\rightarrow\infty}$ (ng h/ml)	1,295	1,486	1,987	862	546	634
$t_{1/2}$ (h)	5.87	0.38	1.54	1.21	1.37	1.67
C_{max} (ng/ml)	3,715	–	–	–	–	–
CL (l/h/kg)	7.72	6.73	5.03	11.6	18.3	15.8
Vd_z (l/kg)	65.4	3.7	11.2	20.2	36.1	38.1
V_{ss} (l/kg)	6.3	–	–	–	–	–
MRT (h)	0.82	–	–	–	–	–
Oral at 50 mg/kg						
$AUC_{0\rightarrow\infty}$ (ng h/ml)	1,169	619	6,118	287	126	412
$t_{1/2}$ (h)	10.29	0.75	4.21	1.34	2.90	1.64
C_{max} (ng/ml)	4,234	501	6,565	489	116	–
CL (l/h/kg)	7.72	–	–	–	–	–
Vd_z (L/kg)	114.7	–	–	–	–	–
MRT (h)	3.5	–	–	–	–	–
F (%)	18.05	8.33	61.6	6.66	4.62	13

AUC area under curve, $t_{1/2}$ elimination half-life, Vd_z volume of distribution, V_{ss} volume of distribution at steady-state, C_{max} observed maximum concentration, *CL* plasma clearance, *MRT* mean residence time, *F* bioavailability

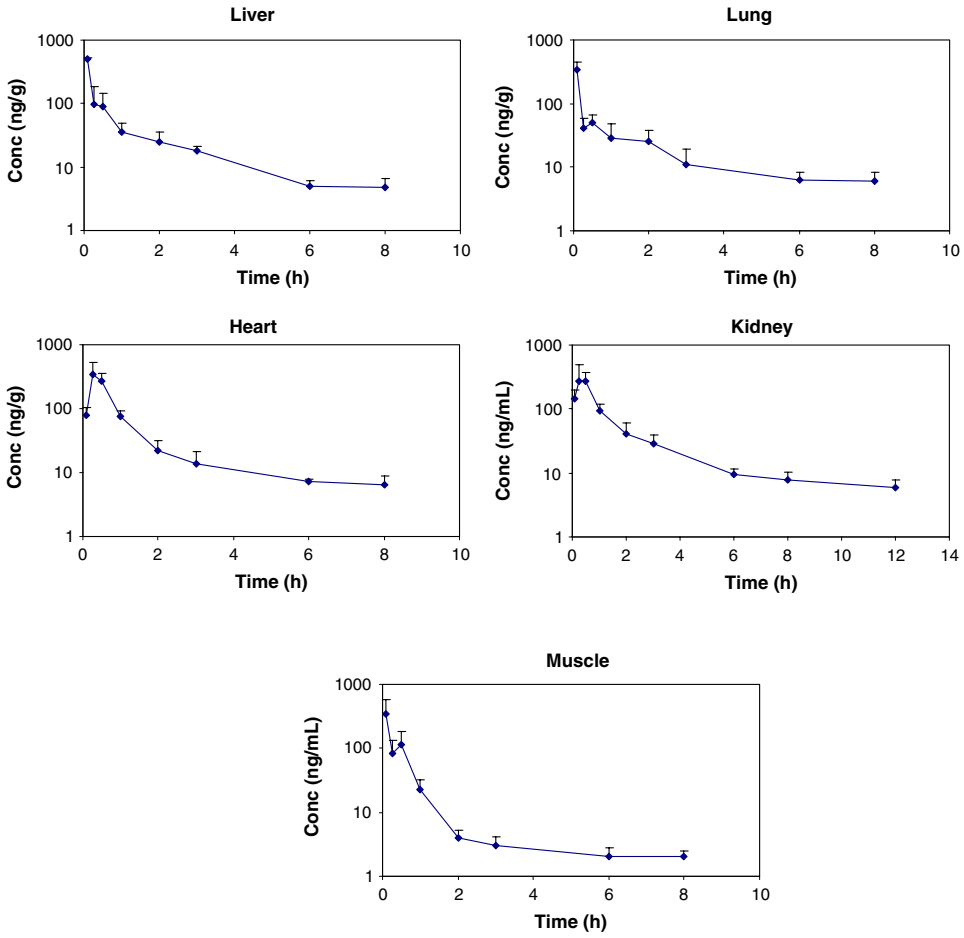

Fig. 3 Concentration-time profiles in liver, heart, lung, kidney and muscle tissue homogenates after IV administration of Kendine 91 to mice with a dose of 10 mg/kg (*Error bars* represent SD, $n = 5$)

Development of candidates in anticancer therapy needs a careful exploration and understanding of the pharmacokinetic disposition. This is important since the in vivo pharmacokinetic behaviour and PK-PD correlation can act as surrogates for the clinical effectiveness of the compounds [8]. In the process of optimization of new candidates, the pharmacokinetic profile has to be either equal to or better than those attributed to existing drugs. Vorinostat (SAHA)

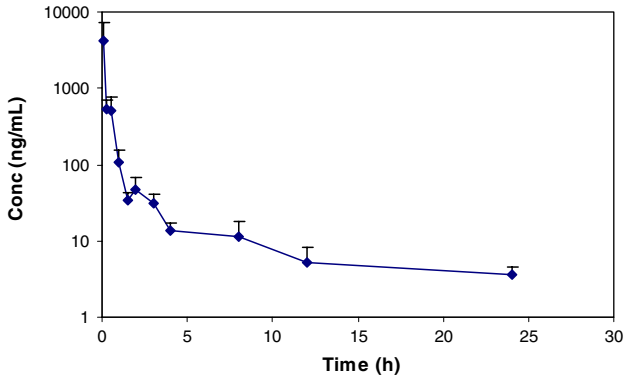

Fig. 4 Plasma concentration-time profile of Kendine 91 after an oral dose of 50 mg/Kg. (*Error bars* represent SD, $n = 5$)

is a HDAC inhibitor recently approved by the FDA. However, this compound presents a limited oral bioavailability and a very short elimination half-life in animals [11] and humans [12]. It is desirable to find another molecule in the HDAC inhibitor class, with improved physicochemical, pharmacokinetic and pharmacodynamic properties with respect to SAHA.

The present work represents the first report of the in vivo pharmacokinetics of Kendine 91 in an animal model, the mouse. Intravenous and oral administrations were performed and the oral bioavailability was calculated. Moreover, time correlation profiles of Kendine 91 levels were obtained in liver, heart, lung, kidney and muscle. The pharmacokinetic parameters of Kendine 91 were compared to other HDAC inhibitors [8, 11] SAHA, EX-2, PXD 101, LBH-589 and SB693. The pharmacokinetic comparison of these compounds indicates that after IV and oral administration, elimination half-life of Kendine 91 (5.87 and 10.29 h after IV and oral administration, respectively) was much longer than that of SAHA (0.38 and 0.75 h after IV and oral administration), EX-2 (1.54 and 4.21 h after IV and oral administration), PXD 101 (1.21 and 1.34 h after IV and oral administration), LBH-589 (1.37 and 2.90 h after IV and oral administration) and SB693 (1.67 and 1.64 h after IV and oral administration) (Table 1). MRT, which better describes the drug's time course, was 0.82 and 3.46 h for intravenous and oral administration, respectively. No data about MRT of the other compounds are available. Plasma clearance of Kendine 91 after IV administration was equivalent to that of SAHA (7.72 vs. 6.73 l/h/kg), but lower than that of PXD 101 (11.6 l/h/kg), LBH-589 (18.3 l/h/kg) and SB639 (15.8 l/h/kg). After oral administration, no data of plasma clearance were reported for SAHA and the

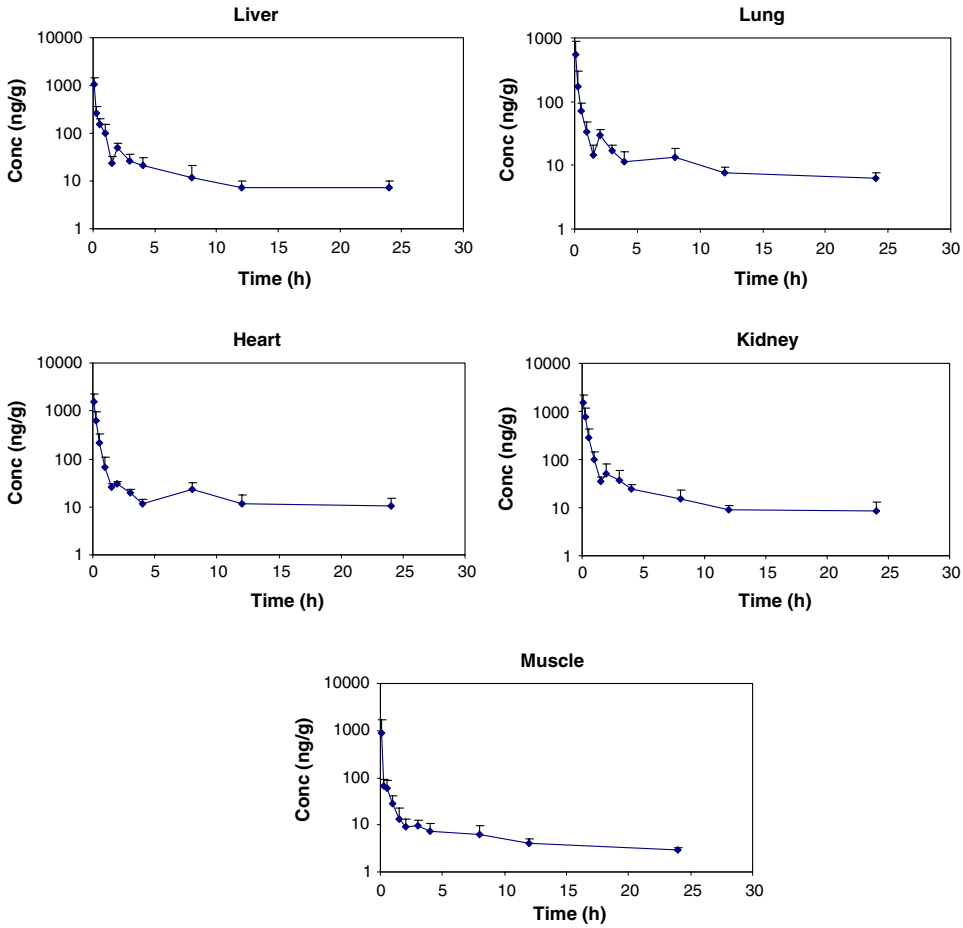

Fig. 5 Concentration-time profiles in liver, heart, lung, kidney and muscle tissue homogenates after oral administration of Kendine 91 to mice with a dose of 50 mg/Kg (*Error bars* represent SD, $n = 5$)

Table 2 Pharmacokinetic parameters of Kendine 91 in tissues after intravenous (10 mg/kg) and oral administration (50 mg/kg) to mice

Organ	C_{max} (ng/g)	$t_{1/2}$ (h)	$AUC_{0\rightarrow t}$ (ng h/g)	$MRT_{0\rightarrow t}$ (h)	Fr
IV (10 mg/kg)					
Liver	502.66	2.21	266	1.22	
Lung	346.14	5.42	199	1.49	
Kidney	271.95	8.98	412	2.11	
Heart	345.47	4.39	316	1.30	
Muscle	343.04	6.16	163	0.73	
ORAL (50 mg/kg)					
Liver	1028.14	11.80	569	4.59	0.43
Lung	539.73	19.76	374	6.21	0.38
Kidney	1492.10	14.93	840	3.83	0.41
Heart	1589.86	18.38	775	4.77	0.49
Muscle	908.39	12.91	282	4.24	0.35

$Fr = [dose_{IV} \times AUC_{0-t,oral} / dose_{oral} \times AUC_{0-t,IV}]$

AUC area under curve, *MRT* mean residence time, $t_{1/2}$ elimination half-life

other inhibitors [8, 11]. Nevertheless, from the reported plasma concentration-time profile, it seems that it was not possible to calculate due to its fast concentration decrease in plasma levels. However, the levels of Kendine 91 remained above the limit of quantification up to 12 h post doses after intravenous administration and up to 24 h post doses after oral administration. Results suggest that Kendine 91 presents improved features with respect to other inhibitors.

After oral administration, absorption of Kendine 91 from mouse gastrointestinal tract was rapid; Kendine 91 was detected in plasma from the first blood sampling point (0.08 h). Absolute oral bioavailability was found to be 18% at 50 mg/kg oral dose which was higher than that of SAHA (8%) [11], PXD 101 (7%) [11], LBH-589 (5%) [11] and SB639 (13%) [8]. Although these values correspond to mice, oral bioavailability of SAHA in human at doses of 200 and 400 mg administered during the fasting state was 43% [13]. The modest oral bioavailability of Kendine 91 in mice could be due to a poor absorption in the gastrointestinal tract and/or small intestine or hepatic first-pass metabolism when administered orally. Kendine 91 presents very low water solubility and the dissolution process in the gastrointestinal fluid could limit the intestinal absorption. Phase I metabolism involves hydrolysis, reduction, and oxidation of drugs. These reactions expose or introduce a functional group (–OH, $–NH_2$, –SH, or –COOH) to drugs and usually results in an increase in the hydrophilicity of drugs [14]. Phenyl groups are present in Kendine 91; thus theoretically, one may expect that these groups would be modified and could justify a first-pass effect in the intestine and/or the liver. Further studies are needed to know if the low bioavailability is caused by poor absorption or first-pass metabolism or both.

Examination of the concentration versus time curve for Kendine 91 following oral administration suggests an enterohepatic circulation since several maximums in plasma levels were detected. The enterohepatic circulation of drugs may play an important role in the kinetic behaviour [15, 16], since it determines a greater portion of the AUC and an increase in half-life. However, enterohepatic circulation must be confirmed with additional studies, such as the use of bile duct cannulated animals.

Kendine 91 total body clearance (7.72 l/h/kg) was greater than the hepatic blood flow of 5.4 l/h/kg in mice [17] and larger than glomerular filtration rate in mice (0.84 l/h/kg) [18]. This suggests that clearance could be attributed to a combination of different elimination pathways such as degradation/metabolism, glomerular filtration and/or others, like bile excretion. Tissue levels of Kendine 91 in liver and kidney support the idea of the contribution of these organs to the drug elimination from the body.

After IV administration, Kendine 91 tissue levels (Fig. 3) were still detected up to 8 h in liver, heart, lung and muscle and up to 12 h in kidney. Tissue levels were detected up to 24 h in all assayed tissues after oral administration (Fig. 5). Fr values (Table 2) show the relative bioavailability, measured in terms of tissue levels, ranging from 0.35 h in muscle to 0.49 h in heart. The higher half-life of Kendine 91 after oral administration that could be due to enterohepatic circulation, could justify higher bioavailability when measured from tissue levels than when measured from plasma levels. The highest concentrations of Kendine 91 were found in the kidney, which suggests that this new drug could be eliminated via this organ. The second highest concentration was found in heart tissue, followed by liver, lung and muscle. This pattern was found for both IV and oral administration. In almost all tissues, the elimination rate paralleled rather closely than in plasma, which indicates that unexpected accumulation should not occur in these tissues with repeated administration.

Distribution volume and tissue levels of Kendine 91 indicate extensive drug distribution in specific tissues. The high lipid solubility of this new molecule could favour its

access to tissues. This is highly convenient for increasing exposure of cancer and premalignant cells to optimal concentrations of drug, suggesting that this antitumour compound could be useful for the treatment not only of haematologic malignancies but also of solid tumours, for whose Kendine 91 presents biologic effects.

Tissue homogenates have been extensively used to determine drug concentration in tissues, although this does not take into account the fact that tissues are made of distinct compartments: interstitial fluid, cells and cell compartments in which the drug is not necessarily distributed in a homogeneous fashion. Moreover, measurements in tissue homogenates do not give any information on whether the drug is actually available for activity [19]. In addition, it is very difficult to determine the concentration of a drug at the receptor site. However, whole tissue concentrations can be of value in initial studies during drug development to overall distribution of the drug. This study is the first pharmacokinetic evaluation of this new molecule, and the information provided by the tissue concentration-time profile is highly useful for gaining knowledge on the capacity of Kendine 91 to access different organs, and therefore to be considered in a plausible treatment of solid tumours located in those tissues.

In summary, the present study describes the pharmacokinetics of Kendine 91, a novel HDAC inhibitor, in mice. After IV and oral administration to mice, elimination half-life of Kendine 91 was higher than that of SAHA, a recently FDA approved HDAC inhibitor. After oral administration, plasma concentrations-time profile indicates a possible enterohepatic circulation although this must be confirmed with additional studies. Tissue levels and distribution volume indicate high capacity to distribute into tissues. Antitumour activity of Kendine 91 and this preliminary pharmacokinetic evaluation prompts us to believe that it is worth pursuing further development of Kendine 91 as an anticancer drug.

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