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Studies on the intravenous pharmacokinetics of three retinoids in the rat

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Summary

The retinoids are used clinically for the treatment of severe manifestations of psoriasis and acne. In order to examine the pharmacokinetics of these compounds with an aim to increasing our understanding of their absorption, it was necessary to examine the pharmacokinetics of several retinoids. The retinoids chosen were isotretinoin, etretinate, and temaroten which represent three synthetic generations of retinoid. Each retinoid was administered intravenously in a soyabean oil emulsion at two dose levels to male Wistar rats and the plasma concentrations determined by specific HPLC methods. The three retinoids studied display pronounced distribution and their pharmacokinetics appear to be non-linear in terms of their disposition.

Introduction

Retinoids were first produced synthetically in the early 1970s and since that time much effort has been devoted to the study of their pharmacology, pharmacokinetics and toxicological effects. A number of similarities between the clinical manifestations of hypervitaminosis A syndrome (Silverman et al., 1987) and skin alterations in various disease states (keratinisation disorders and certain precancerous conditions) have been observed and have provided a basis for the investigation of the role of vitamin A (retinol) in dermatology and oncology (Bollag, 1970, 1979, 1989; Bollag and Hanck, 1977; Mayer et al., 1978; Sporn and Newton, 1979; Bollag and Matter, 1981; Orfanos et al., 1987; Lippman et al., 1989; Shealy, 1989; Warren and Khanderia, 1989; Natruzzi et al., 1990). Clinical investigations of the antikeratinising properties of vitamin A in such diseases as acne, ichthyosis, lichen ruber planus, Dariers disease and pityriasis rubra pilaris have met with only moderate success. Furthermore, the doses required for therapeutic effect were accompanied by severe adverse reactions, such as changes in skin and mucous membranes, and bone, liver and neurological complications (Silverman et al., 1987; Biesalski, 1989). In an

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attempt to separate the numerous side effects associated with use of the retinoids (including vitamin A) from clinical efficacy, more than 1500 retinoids have been synthesized by chemical manipulation of the vitamin A molecule.

The retinoids possess three main structural features; a cyclic ring, a tetraene side chain and a terminal group which may be polar or non-polar. Modifications to these three regions have enabled the development of three generations of retinoids (Bollag, 1981). These show a range of physicochemical and pharmacological properties. The first generation of retinoids includes vitamin A (retinol) and naturally occurring compounds (metabolites of vitamin A) which have been found in the body. These show similarity in structure to retinol but have modified terminal polar groups. This class includes two acidic compounds, all-*trans*-retinoic acid and 13-*cis*-retinoic acid (isotretinoin, Ro 04-3780). The second generation of retinoids contain an aromatic ring which forms a conjugated system with the tetraene side chain and this therefore increases the lipophilicity of these compounds. This group includes compounds such as etretinate (Ro 10-9359) and Ro 11-5036. The third generation of retinoids are essentially non-polar and are commonly termed arotinoids. They possess both an aromatic ring and a non-polar terminal group produced by the cyclisation of the tetraene side chain. Examples include temaroten (Ro 15-0778) and its sulphone derivative (Ro 15-1570). The structures of these compounds are shown in Fig. 1.

The retinoids selected for the studies reported here were isotretinoin (13-*cis*-retinoic acid, Ro 04-3780), etretinate (Ro 10-9359) and temaroten (Ro 15-0778). These retinoids, representing each of the three synthetic generations referred to above, are, in common with others in the series, highly lipophilic molecules with calculated log *P* (octanol/water) values ranging from ≈ 6.6 for isotretinoin, through greater than 7.0 for etretinate to a value exceeding 8.5 for temaroten (Nankervis, 1992). In order to obtain information relating to the absorption and disposition of the retinoids in the rat, it was essential to have pharmacokinetic information following intravenous dosing. Therefore, the pharmacokinetics of the

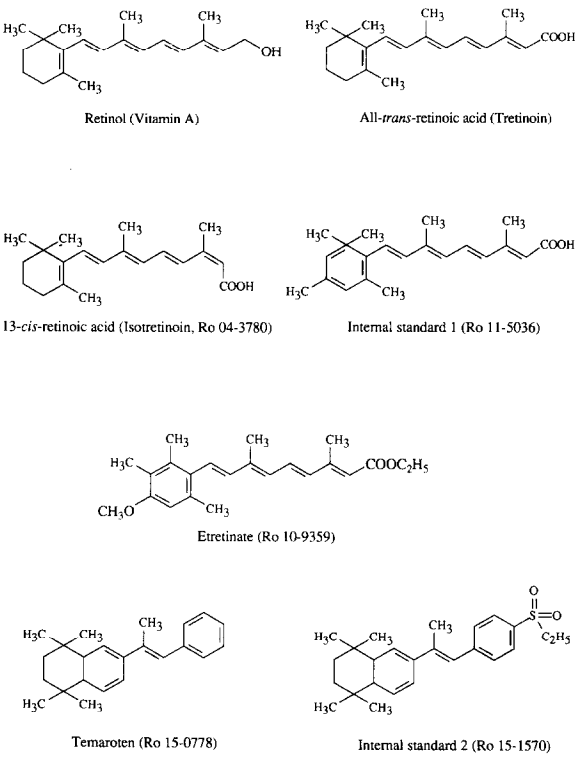

Fig. 1. Chemical structures of the retinoids.

three retinoids stated above were studied at two dose levels in the anaesthetised rat.

Materials and Methods

It has been well established that retinoids are sensitive to light, especially ultraviolet light (Brazzell and Colburn, 1982). Consequently, all samples were protected using aluminium foil wrapping and all unprotected procedures involving the use of retinoids (e.g., weighing) were undertaken under conditions of red/amber illumination.

Chemicals and reagents

All retinoids were supplied by Roche Products Ltd. Egg lecithin as Lipoid E80 was obtained from Lipoid AG, Ludwigshafen, Germany. Pentobarbitone was purchased from Evans, U.K. and acetonitrile from May and Baker, Dagenham,

U.K. All other chemicals were from Sigma, Poole, U.K. and were of analytical grade or better.

Preparation of oily emulsions for intravenous administration

Three soyabean oil-in-water emulsions were prepared. Each emulsion contained one of the three retinoids, isotretinoin (Ro 04-3780), etretinate (Ro 10-9359) or temaroten (Ro 15-0778), for intravenous administration to fasting rats. The retinoid was dissolved in soyabean oil at a concentration of approx. 15 mg/ml. An aliquot of the retinoid solution in soyabean oil (5 ml) was added to a solution of egg lecithin (1.2% Lipoid E80) in double-distilled water (45 ml) and these solutions were homogenised (approx. 5 min) in a micro-fluidiser (Microfluidics Corp., Newton, MA, U.S.A.). The resulting emulsion was transferred into a multi-dosing vial (50 ml), fitted with a rubber septum. The prepared emulsions were stored at room temperature (20°C) and remained stable for several weeks. The exact concentrations of each retinoid in the prepared emulsions were determined by dispensing an accurately weighed sample of each emulsion into a volumetric flask and diluting to volume using tetrahydrofuran. Samples of this mixture were analysed to determine the retinoid concentration using the appropriate HPLC system detailed below.

Pharmacokinetic studies in the rat

Male Wistar rats weighing 200–250 g were used for the study. They were fed standard rat chow with water ad libitum and maintained on a 12-h cycle of day and night. Animals were fasted for 16 h prior to the experimental procedure. Anaesthesia was induced with pentobarbitone (72 mg/kg) administered intraperitoneally. Additional pentobarbitone was administered as and when required to maintain anaesthesia. All rats underwent a tracheotomy and jugular vein and carotid artery cannulation. The drug emulsions were administered intravenously over a period not exceeding 30 s to six groups of six rats (two groups for each retinoid under study). The low dose groups received 0.264 mg/kg isotretinoin, 0.655 mg/kg etretinate or 0.732 mg/kg temaroten. The high dose groups received 0.792 mg/kg isotretinoin, 1.964 mg/kg etretinate or 2.200 mg/kg temaroten. Blood samples (0.2 ml) were collected from the carotid artery of each animal at the following times after drug administration: 5, 10, 20, 30, 45, 60, 90, 120, 150, 180 and 210 min. In studies using etretinate and temaroten additional samples were collected at 240, 270 and 300 min after drug administration. After each blood sample was taken, 0.2 ml of saline was infused intravenously.

Analysis of samples

The HPLC system consisted of a pump and variable-wavelength UV detector (LKB Models 2150 and 2151, respectively, LKB-Produkter, Bromma, Sweden), a Gilson auto-sampling injector (Model 231–401, Gilson International, Villiers-le-Bel, France) and a Spectra-Physics data integrator (Model SP4290, Spectra-Physics, San Jose, CA, U.S.A). Blood samples containing isotretinoin were analysed under the following conditions: the HPLC column was a Spherisorb (Phase Separations, Queensferry, U.K.) ODS2 (15 cm × 4.6 mm i.d.) with a 5 μm particle size; the mobile phase consisted of acetonitrile (70% v/v) and 0.1 M ammonium acetate adjusted to pH 6.0 (30% v/v). The flow rate was 1.0 ml/min, the injection volume was 20 μl and the compounds were detected by their UV absorbance at 350 nm. Plasma samples containing isotretinoin were extracted using a direct protein precipitation method involving the addition of acetonitrile (200 μl), acetonitrile (100 μl) containing the internal standard (Ro 11-5036, 7.5 ng) to plasma (100 μl). The mixture was, after a thorough mixing, centrifuged (13 000 × g, 10 min) and the supernatant removed by aspiration.

Blood samples containing temaroten were analysed by HPLC under the following conditions: the column was a Spherisorb ODS2 (15 cm × 4.6 mm i.d.) with a 5 μm particle size; the mobile phase consisted of acetonitrile (90% v/v) and 0.1 M ammonium acetate adjusted to pH 6.0 (10% v/v). The flow rate was 1.0 ml/min, the injection volume was 20 μl and the compounds were detected by their UV absorbance at 280 nm. Blood samples containing temaroten were extracted using the direct protein precipitation

method described above for isotretinoin but using Ro 15-1570 (200 ng) as the internal standard.

Blood samples containing etretinate were analysed by normal phase HPLC using the following conditions: the column was a Spherisorb CN column (15 cm × 4.6 mm i.d.) with a 3 μm particle size; the mobile phase consisted of hexane (99.15% v/v), methyl benzoate (0.6% v/v) and propionic acid (0.25% v/v). The flow rate was 1.0 ml/min, the injection volume was 20 μl and the compounds were detected by their UV absorbance at 360 nm. Blood samples containing etretinate were extracted using the direct protein precipitation method described above for isotretinoin but using isotretinoin (200 ng) as the internal standard. All assay methods were linear over the range used in these studies ($r^2 > 0.995$) and demonstrated good recovery, precision (variability < 10%) and accuracy.

Pharmacokinetic analysis

The plasma concentration vs time data from each rat were treated as follows. The area under the plasma concentration vs time curve (AUC) was calculated using the trapezoid approximation method. An estimate of AUC from the last data time point to infinite time was obtained by dividing the final concentration data point by the terminal elimination rate constant. The terminal elimination rate constant (k) was determined from the gradient of the terminal log.-linear section of the concentration time curve. The area under the first moment of the plasma concentration time curve (AUMC) was calculated similarly after multiplying each plasma concentration by its time. The terminal half-life ($t_{1/2}$) of the respective retinoid was determined by dividing the logarithm of 2 by the elimination rate constant. Clearance, mean residence time and the volume of distribution at steady state were calculated using standard non-parametric methods (Gibaldi and Perrier, 1982).

Results and Discussion

The pharmacokinetic data for isotretinoin (Table 1 and Fig. 2), demonstrate a non-proportional increase in AUC with increasing dose, resulting from a decrease in both the total body clearance (from 6.0 ± 3.4 ml/min per kg at 0.264 mg/kg to 2.5 ± 0.2 ml/min per kg at 0.792 mg/kg) and the volume of distribution at steady state (438 ± 199 ml/kg at 0.264 mg/kg to 197 ± 48 ml/kg at 0.792 mg/kg). These data are consistent with other animal studies which report a steady-state volume of distribution in rats of 230 ml and total clearance of 2.1 ml/min (Liu et al., 1990)) and in dogs (volume of distribution = 2020 ml and clearance = 5.2 ml/min (Cotler et al., 1983)). The elimination half-life also increased with increasing dose. The mean half-life for isotretinoin was found to be 48 ± 5 min at the lower dose and 61 ± 7 min at the higher dose. Both of these values are slightly shorter than data reported in

TABLE 1

Pharmacokinetic data for isotretinoin (Ro 04-3780), etretinate (Ro 10-9359) and temaroten (Ro 15-0778) in the rat (n = 6) after intravenous administration

Isotretinoin (Ro 04-3780)		
Dose (mg/kg)	0.264	0.792
AUC (μg ml^{-1} min)	55 ± 31	317 ± 34 [a]
Half-life (min)	48 ± 5	61 ± 7 [a]
MRT (min)	73 ± 16	79 ± 3
Clearance (ml/min per kg)	6.0 ± 3.4	2.5 ± 0.2 [a]
V_{ss} (ml/kg)	438 ± 199	197 ± 48
Etretinate (Ro 10-9359)		
Dose (mg/kg)	0.655	1.964
AUC (μg ml^{-1} min)	114.6 [b]	579.6 ± 130.3
Half-life (min)	ND	ND
MRT (min)	10 ± 7	38 ± 20
Clearance (ml/min per kg)	5.72 [b]	3.53 ± 0.64
V_{ss} (ml/kg)	57 ± 15 [b]	134 ± 133
Temaroten (Ro 15-0778)		
Dose (mg/kg)	0.732	2.200
AUC (μg ml^{-1} min)	195 ± 37	852 ± 100 [a]
Half-life (min)	111 ± 38	114 ± 45
MRT (min)	111 ± 68	62 ± 14
Clearance (ml/min per kg)	3.9 ± 0.6	2.6 ± 0.4 [a]
V_{ss} (ml/kg)	432 ± 269	325 ± 349

[a] Statistically significantly different ($p < 0.05$) from the corresponding low dose by unpaired t-test.

[b] Insufficient data for statistical analysis.

ND, not determined; AUC, area under the plasma concentration time curve; MRT, mean residence time; V_{ss}, volume of distribution at steady state.

the literature (half-life = 76 min) (Liu et al., 1990), however, these data were obtained from studies in Sprague-Dawley rats of much larger body weight (383 ± 33 g) than those used in our studies. The mean residence time, MRT, an estimate of the average time a molecule of drug spends in the body (Gibaldi, 1991), was 73 ± 16 and 79 ± 3 min at the lower and higher doses, respectively, and was consistent with the observed elimination half-life.

Isotretinoin is used widely in the treatment of acne and acneform conditions and a number of pharmacokinetics studies have been performed in man, especially after oral dosing. The non-linear nature of the pharmacokinetics observed here in the rat has not been seen previously in man even at higher doses. When advanced cancer patients received 0.5 mg/kg per day isotretinoin initially, increasing stepwise over 4 weeks to 8 mg/kg per day, a linear correlation of plasma concentration with dose was observed with large inter-individual variation in peak plasma concentrations (Kerr et al., 1982). It should be appreciated that this study relied on data obtained after oral administration and that low bioavailability and high intersubject variation in blood concentrations in humans after oral administration have been previously reported (Khoo et al., 1982; Colburn et al., 1983a). These observations may have been the result of degradation of the retinoid in the gut lumen, extensive first-pass metabolism or poor absorption (Brazzell and Colburn, 1983). Pharmacokinetic studies performed by Khoo et al. (1982) demonstrated that after oral administration of 100 mg isotretinoin to 12 healthy human volunteers, the drug appeared in the blood after a lag time of 0.5 to 2 h. Peak blood concentrations (74–511 ng/ml) were found at between 1 and 4 h after administration, falling to below 5 ng/ml at 72 h; secondary peaks were observed between 6 and 24 h after dosing. These secondary peaks were said to reflect enterohepatic circulation of the drug; such peaks were not seen in a similar study conducted by Colburn et al. (1983b) and

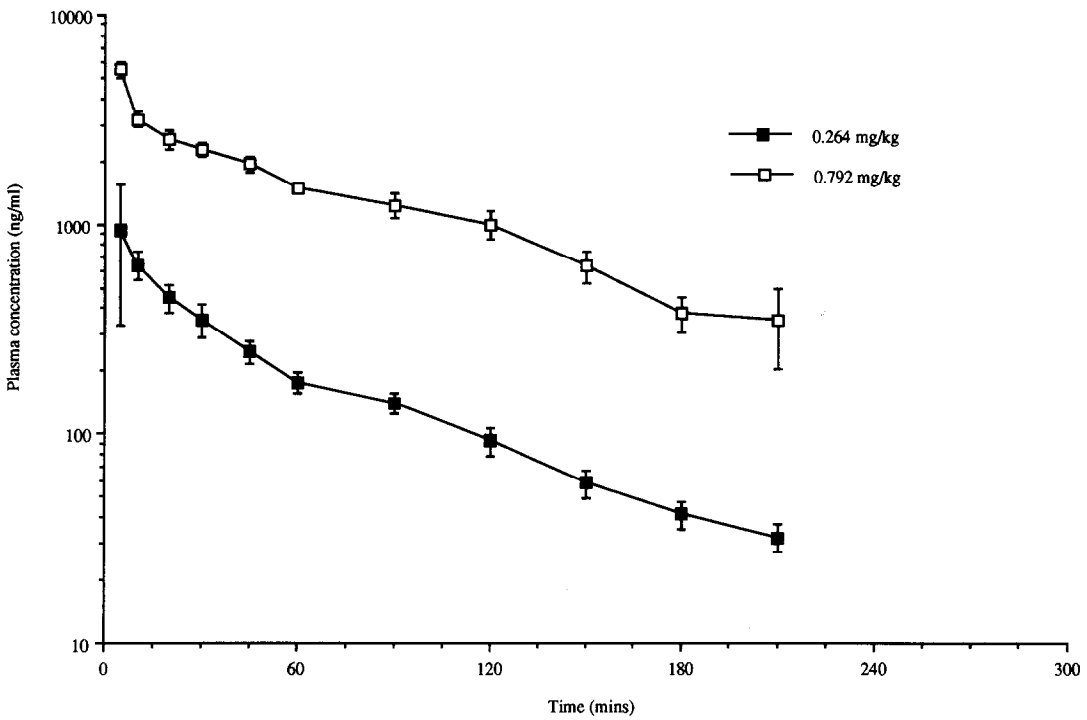

Fig. 2. Plasma concentration-time profile for isotretinoin (Ro 04-3780) in the rat after intravenous dosing in a soyabean oil emulsion.

were not observed following intravenous drug administration in our studies.

After intravenous administration of etretinate at the higher dose (1.964 mg/kg) to rats (Fig. 3), plasma concentrations fell rapidly from 33000 ng/ml at 5 min post dose to less than 100 ng/ml after 150 min and below the assay limit of detection (20 ng/ml) at 180 min. At the low dose (0.655 mg/kg), a similar rapid fall in plasma concentrations from approx. 5000 ng/ml at 5 min post dose to less than 40 ng/ml after 45 min post dose and below the limit of detection at 60 min (Fig. 3) was observed. As a consequence of these observations, it was believed that it would be fallacious to calculate an elimination half-life. Clearance was estimated to be 5.7 ml/min per kg at the lower dose and 3.5 ± 0.64 ml/min per kg at the higher dose; the volume of distribution at steady state was 57 ± 15 ml/kg at the low dose and 134 ± 133 ml/kg at the higher dose. The data obtained indicate that a prolonged distribution phase is seen for etretinate and that the terminal elimination phase had not been observed in our studies. This prolonged distribution phase presented problems in accurately measuring the resulting low retinoid concentrations in plasma samples after 180 min post dose. It has been suggested (Paravicini et al., 1981) that, using the graphical method of residuals, there are at least three phases of decline in drug concentration following a single intravenous dose of etretinate to man (half-life of the phases: 5–10 min, 30–60 min, and 6–12 h). Evidence of at least one other longer phase was present but the sensitivity limits of the assay method did not permit visualization, however, the presence of significant plasma levels of etretinate 140 days after cessation of chronic therapy suggests a long elimination phase (half-life approx. 100 days) (Bollag, 1981; Paravicini et al., 1981). These data were obtained from a trial study in psoriatic patients undergoing chronic therapy with 10–25 mg/day etretinate for more than a year (Paravicini et al., 1981).

In order to determine the plasma concentrations of etretinate over a prolonged time period

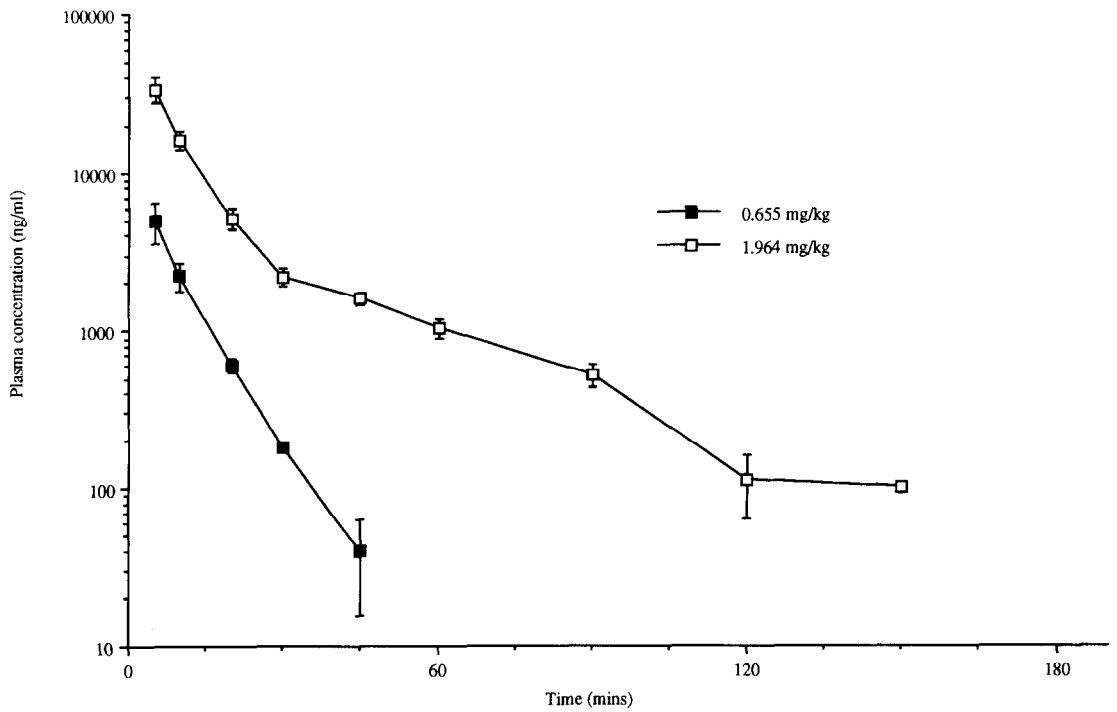

Fig. 3. Plasma concentration-time profile for etretinate (Ro 10-9359) in the rat after intravenous dosing in a soyabean oil emulsion.

in the rat, it would have been necessary to increase greatly the plasma concentrations of the drug. It would be possible to achieve this by administering a much larger dose of retinoid to the animal (up to a dose of 20 mg/kg may have been necessary). However, it was felt inappropriate to exceed the volume of intravenous soyabean emulsion beyond the 0.6 ml dose size chosen (which represents approx. 5.5% of the total blood volume in a 250 g rat). It was also found to be impractical to administer a higher dose of retinoid in other physiologically acceptable vehicles because of the limited solubility of etretinate in these solvents. The proposed high dose would have also greatly increased the potential toxicity of the drug to the animal and would have far exceeded the upper therapeutic limit for man (2 mg/kg). Other alternative procedures would have been to use much greater blood sample volumes at each data point, extracting the whole animal blood volume (10–12 ml) for each data point. This procedure was, however, considered unacceptable.

A non-proportional increase in AUC was observed for temaroten (Table 1 and Fig. 4), with increasing dose, resulting from a decrease in total body clearance from 3.9 ± 0.6 ml/min per kg at 0.732 mg/kg to 2.6 ± 0.4 ml/min per kg at the 2.2 mg/kg dose. There was considerable inter-subject variability in the data for the volume of distribution at steady state (432 ± 269 ml/kg and 325 ± 349 ml/kg for the 0.732 and 2.20 mg/kg doses, respectively). The MRT at the lower dose (111 ± 68 min) was consistent with the elimination half-life observed at the lower dose (111 ± 38 min), however, the MRT at the higher dose was much lower (62 ± 14 min) than either the MRT at the lower dose or the elimination half-life at either dose. These differences, however, were not significant ($p > 0.05$) because of the considerable inter-subject variation in the data.

Temaroten is an arotinoid and in contrast to the other retinoids has no polar terminal carboxyl group. After oral administration of 96 mg of temaroten in an oil filled gelatin capsule to fasted healthy human subjects the mean peak plasma

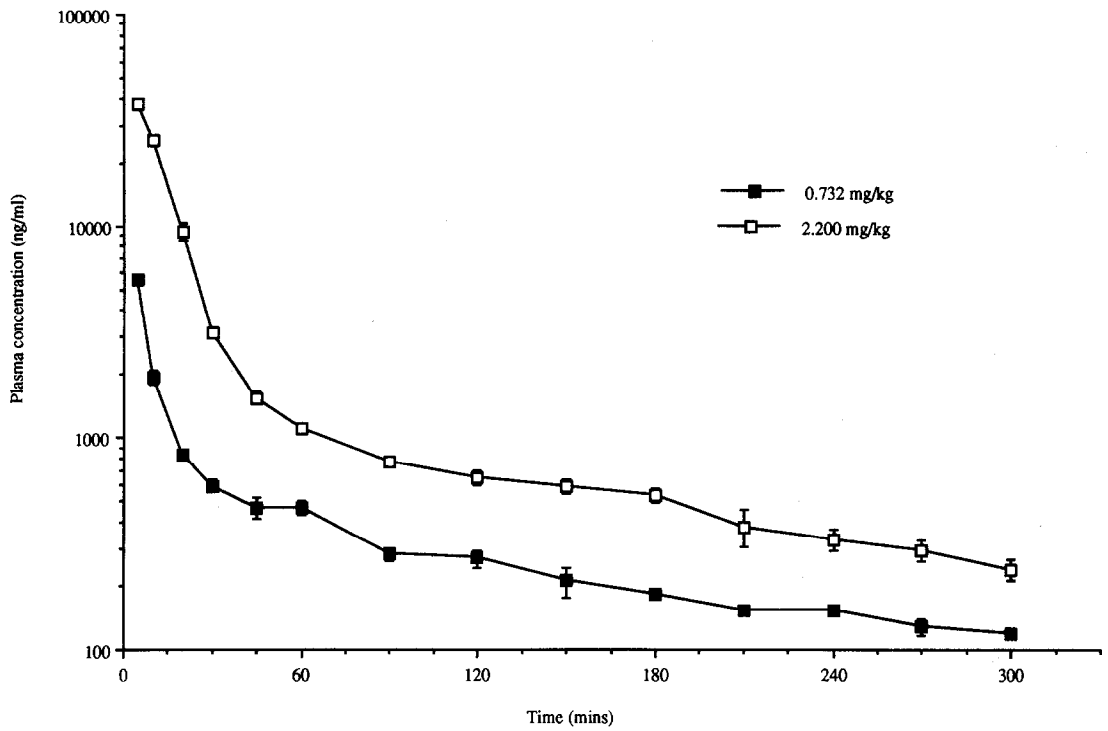

Fig. 4. Plasma concentration-time profile for temaroten (Ro 15-0778) in the rat after intravenous dosing in a soyabean oil emulsion.

concentration was achieved after 6.9 h, with a harmonic mean elimination half-life of 24.1 h (Holazo et al., 1990). We were unable to find in the literature any other reported pharmacokinetic data in animals relating to this compound.

We have examined the pharmacokinetics of three retinoids after intravenous administration to fasted male Wistar rats. These data are essential in order to define the disposition of these compounds and we have identified such common features as pronounced distribution which clearly affects the plasma concentration-time profile after drug administration. We have also observed that the pharmacokinetics of all three retinoids appear to be non-linear in terms of their disposition. This is despite the doses being chosen to lie within the linear pharmacokinetic range of those used previously in man.

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