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The pharmacokinetics of quinupristin/dalfopristin in laboratory animals and in humans

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The pharmacokinetics of quinupristin/dalfopristin have been studied in rats, monkeys and humans following intravenous infusion of radiolabelled and unlabelled drug. In rats and monkeys quinupristin and dalfopristin undergo rapid elimination from the blood and wide tissue distribution. Nevertheless, they do not penetrate the central nervous system or cross the placenta to any significant degree and they do not appear to be subject to significant body retention following cessation of administration. The blood elimination half-life of quinupristin was approximately 0.6 h in rats and 0.5 h in monkeys, and that of dalfopristin was approximately 0.6 h and 0.2 h, respectively. Both compounds are primarily eliminated through the bile into the faeces; quinupristin is mainly excreted unchanged whereas dalfopristin is extensively metabolized beforehand. The metabolites include the microbiologically active pristinamycin PIIA for dalfopristin and the microbiologically active glutathione- and cysteine-conjugated derivatives for quinupristin. Quinupristin and dalfopristin appear to be handled in a similar manner by humans. Following intravenous administration both compounds are rapidly cleared from the blood with elimination half-lives of approximately 1 h for quinupristin and 0.4–0.5 h for dalfopristin. The pharmacokinetic profile of quinupristin is dose-independent and so is that of dalfopristin and RP 12536 when considered together. Extravascular diffusion of quinupristin/ dalfopristin has been assessed in human non-inflammatory interstitial fluid.

Introduction

Quinupristin/dalfopristin is a new streptogramin antibiotic, obtained by semisynthesis of compounds naturally produced by *Streptomyces pristinaespiralis* (Figure 1). It comprises the semisynthetic compounds quinupristin and dalfopristin in a 30:70 (w/w) mixture for intravenous use. Synergy between the two constituent compounds confers considerable bactericidal activity against Gram-positive cocci. The pharmacokinetic characteristics of quinupristin, dalfopristin and its active metabolite (RP 12536) have been investigated by studies in rats, monkeys and healthy human volunteers (Rhône-Poulenc Rorer, data on file). Data and observations from these studies are included in this article.

Materials and methods

Animal studies

Pharmacokinetic studies were performed in rats and cynomolgus monkeys using radiolabelled quinupristin/ dalfopristin (Rhône-Poulenc Rorer, data on file).

Preparations. Two radiolabelled forms of quinupristin/dalfopristin were prepared: 30% unlabelled quinupristin with 70% [^{14}C]dalfopristin and 30% [^{14}C]quinupristin with 70% unlabelled dalfopristin both as the methane sulphonate salt (Centre d'Études Nucléaires de Saclay, Gif-sur-Yvette, France). The batches of labelled compounds had specific activities of 18–20 mCi/mmol and the radiochemical purity of the tracer ranged from 89 to 100% when assessed by high performance liquid chromatography (HPLC) and thin layer chromatography (TLC). Solutions of quinupristin/ dalfopristin for intravenous administration were prepared using 5% glucose or 0.9% sodium chloride.

Studies in rats. Both radiolabelled forms of quinupristin/ dalfopristin were administered intravenously via the caudal vein as a single dose of 6 mg/kg to groups of Sprague Dawley or Long Evans rats. The drug was given over 2–4 min using a Harvard pump calibrated to deliver 5 mL/kg at the rate of 15 mL/h. Unlabelled quinupristin/dalfopristin was also administered by the same method to groups of Sprague Dawley rats at the dose of 43 mg/kg over 1 h (10 mL/kg, 2–2.5 mL/h).

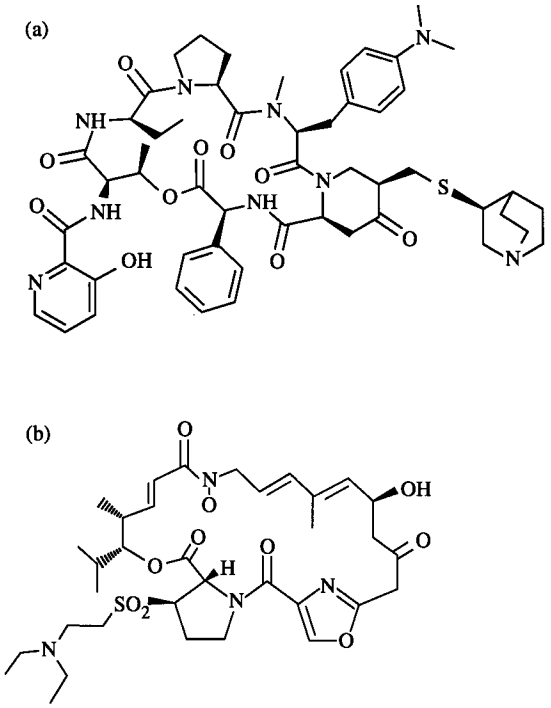

Figure 1. Chemical structures of (a) quinupristin and (b) dalfopristin.

In separate investigations, blood, other fluid and tissue samples were obtained at various times after the end of the infusion period. Whole body autoradiography was used to determine qualitative distribution. Transplacental transfer was assessed in pregnant animals on day 17 of gestation.

Studies in monkeys. Both radiolabelled forms of quinupristin/dalfopristin were administered intravenously as a single dose of 6 or 10 mg/kg to groups of cynomolgus monkeys via the saphenous vein. The drug was given over 12–30 min using a Harvard pump calibrated to deliver 2 or 5 mL/kg at the rate of 30 mL/h. Unlabelled quinupristin/dalfopristin was also administered by the same method to groups of cynomolgus monkeys at the dose of 40 mg/kg over 1 h (10 mL/kg, 30 mL/h).

Blood, other fluid and tissue samples were collected at approximately the same time points after administration as in rats. Whole body autoradiography was used to assess qualitative distribution.

Analytical methods. Radioactivity in blood, other fluid and tissue samples was quantified by liquid scintillation using a spectrometer with a system of external calibration. Whole body autoradiography was performed by exposure of longitudinal sections of frozen rat or cynomolgus monkey to X-ray film for 40 days. Binding to plasma proteins was analysed by ultrafiltration of samples followed by centrifugation and scintillation counting. HPLC was used to assay levels of quinupristin, dalfopristin and RP 12536 in blood, urine and faeces.

As quinupristin and dalfopristin are unstable at physiological pH and are degraded rapidly in whole blood, samples were acidified with 0.05 M hydrochloric acid (3 mL for 1 mL blood) on collection.

Studies in humans

Phase I studies of the pharmacokinetic characteristics of quinupristin/dalfopristin have also been carried out in fasting human volunteers. In these trials, quinupristin/dalfopristin (in the ratio of 30:70) presented as the freeze-dried methane sulphonate, was administered by intravenous infusion after reconstitution and mixing with 5% isotonic glucose solution. Blood samples were acidified on collection with hydrochloric acid (0.5 M or 0.25 M) to prevent the transformation of quinupristin/dalfopristin.

Pharmacokinetics of quinupristin/dalfopristin after single-dose administration. A randomized, double-blind, placebo-controlled safety study was carried out in 26 healthy male volunteers, mean age 28.8 years.[1] The doses were 1.4, 2.8, 4.6, 7.0, 9.8, 12.6, 16.8, 22.4 and 29.4 mg/kg, administered as 250 mL infusions over 1 h. The volunteers were each divided into three groups. Each volunteer group was allocated to receive three dosage regimens of quinupristin/dalfopristin in a sequential fashion. Blood samples were taken immediately before starting infusions and at 30 min (during infusion), 60 min (end of infusion) and 2, 3, 4, 5 and 6 h after the start of infusion. Blood concentrations of quinupristin/dalfopristin expressed as total antimicrobial activity, were measured by bioassay using *M. luteus* as the indicator strain on Bio-Mérieux Agar No. 1, pH 6.6 (limit of detection 0.1 mg/L). Solid phase extraction and HPLC were used to measure blood concentrations of quinupristin, dalfopristin and the active metabolite RP 12536 (limits of detection of 0.1, 0.125 and 0.04 mg/L, respectively).

A further open, randomized, three-way crossover study in 18 healthy male volunteers (mean age 25.3 years) was performed, in which quinupristin/dalfopristin doses of 5, 10 and 15 mg/kg were given as 500 mL infusions over 1 h. Blood samples were collected as described above up to 8 h after the start of each infusion. Plasma concentrations of both compounds were determined by HPLC using solid phase extraction—the lower limit of detection was 0.025 mg/L. Quinupristin was measured by fluorescence, and dalfopristin and RP 12536 by ultraviolet determination.

The disposition of radiolabelled quinupristin/dalfopristin (430 mg) has also been studied in six healthy male volunteers following the administration of a single intravenous infusion of quinupristin/dalfopristin (430 mg) over 1 h.[2]

Penetration into interstitial fluid. Quinupristin/dalfopristin 12 mg/kg was given as a 600 mL 1-h infusion to each of six healthy male volunteers, immediately after the formation of 20 suction blisters on the forearm.[3] Blood samples were collected before and 15, 30, 45, 60, 75, 90, 105, 120, 150, 180, 240, 300 and 360 min after the start of each infusion. Blister fluid samples were collected before starting the infusion and at 60, 120, 240 and 360 min. Concentrations of quinupristin/dalfopristin combined were determined by a global bioassay with antibiotic assay medium no. 1 and *M. luteus* as the indicator strain. Standard curves were plotted using concentration values measured in plasma from human blood samples collected in citrate with added quinupristin/dalfopristin (at the ratio of 30:70). After each dilution the sample was acidified and centrifuged to collect plasma. Standards for suction blister fluid were prepared in 70% human serum in phosphate buffer. Limits of detection were 0.13 mg/L for plasma and 0.25 mg/L for blister fluid.

Results

Animal studies

Blood pharmacokinetics of quinupristin/dalfopristin in rats and monkeys. The blood pharmacokinetics of quinupristin/dalfopristin were determined following a 1-hour infusion to rats and monkeys (Table I). In rats, quinupristin and dalfopristin blood drug concentrations at the end of the infusion (C_{max}) were 2.92 and 6.79 mg/L while values for the area under the plasma drug concentration–time curve (AUC) were 2.22 and 4.45 h/mg/L, respectively. In monkeys, both components achieved higher peak concentrations (C_{max}, 10–11 mg/L) and correspondingly greater AUC values (9–13 h·mg/L). Plasma clearance of quinupristin and dalfopristin was very high in rats (6–7 L·h/kg), exceeding the hepatic blood flow in this species (≈3.3 L·h/kg) by about two-fold. Clearance of both components was lower in monkeys but dalfopristin clearance also exceeded hepatic blood flow (3.12 *vs* 2.6 L·h/kg). In accord with the generally high rate of blood clearance, elimination half-life (t_{β}) for quinupristin and dalfopristin did not exceed 1 h. Volume of distribution (V_d), although five- to seven-fold higher in rats, was similar for dalfopristin and quinupristin within each species (rats, 4.9–5.4 L/kg; monkeys, 0.71–1.08 L/kg).

Quantitative tissue distribution of radioactivity in rats and monkeys. Quantitative distribution studies in rats and monkeys revealed rapid and extensive tissue uptake of quinupristin/dalfopristin with low or negligible diffusion into the central nervous system. Levels of radioactivity were highest at the earliest sampling point after drug administration in both species (0.25 h in rats; 1 h in monkeys), most notably in tissues and fluids associated with metabolism and elimination (e.g. liver, kidneys, gastrointestinal tissues and secretions). Quinupristin showed an affinity for red blood cells in rats (but not monkeys) and both compounds (mainly quinupristin) showed affinity for venous and arterial walls in rats and monkeys. Levels of radioactivity quickly declined until at the final sampling point (96 h for rats and 168 h for monkeys) only 1–7% of the administered dose remained in rats (mainly kidneys, skin, intestinal contents, blood) and negligible levels remained in monkeys. The quantitative distribution of radioactivity in cynomolgus monkeys administered radiolabelled quinupristin/dalfopristin (up to 24 h post-dose) is presented in more detail in Table II. As described above, radioactivity was greatest 1 h after dose administration. At this time point, radiolabelled dalfopristin and quinupristin achieved greatest levels in bile (1110 and 743 μg equivalent/mL) and the gall bladder (98 and 96 μg equivalent/g) indicating the importance of biliary excretion. Significant penetration into the central nervous system did not occur; levels of both compounds in brain and spinal cord were amongst the lowest of all the organs tested (≤0.01 mg equivalent quinupristin/g, 0.04–0.12 μg equivalent dalfopristin/g). Similarly, dalfopristin/quinupristin showed no specific affinity for melanin as demonstrated by the consistently low levels of radioactivity in the pigmented eye (≤0.06 μg equivalent quinupristin/g and ≤1.06 μg equivalent dalfopristin/g).

Table I. Blood pharmacokinetic parameters for quinupristin/dalfopristin after a 1 h infusion to rats (43 mg/kg) and monkeys (40 mg/kg)

Species/drug	C_{max} (mg/L)	AUC (h/mg/L)	$t_{1/2\beta}$ (h)	Cl (L/h/kg)	V_d (L/kg)
Rat					
quinupristin	2.92	2.22	0.64	6.09	4.9
dalfopristin	6.79	4.45	0.56	6.97	5.4
Monkey					
quinupristin	10.42	12.69	0.51	0.98	0.71
dalfopristin	10.92	9.02	0.24	3.12	1.08

Table II. Levels of total radioactivity in selected tissues and fluids in male cynomolgus monkeys following a single 12 min infusion of radiolabelled quinupristin/dalfopristin 10 mg/kg. Results are expressed as μg equivalent/g of tissue or mL of fluid

Drug/organ	Time after administration (h)		
	1	6	24
[^{14}C]quinupristin			
adrenal	3.94	0.18	0.1
bile	1110	424	43.1
blood	0.59	0.20	0.05
bone marrow	0.56	0.13	0.08
brain	0.01	0.01	0.00
eye pigmented tissue	NA	0.06	0.05
non-pigmented tissue	NA	0.14	0.06
gall bladder	97.8	139.3	8.35
heart	1.39	0.21	0.07
hypophysis	NA	1.15	0.30
kidney	4.34	5.45	3.07
large intestine	1.27	27.96	4.97
liver	11.2	5.48	2.74
lung	1.40	0.43	0.12
lymph nodes	2.37	0.30	0.17
muscle	0.52	0.11	0.03
pancreas	3.31	0.50	0.19
prostate	19.74	0.42	0.08
salivary gland	3.42	0.93	0.28
skin	0.77	0.35	0.15
small intestine	6.70	7.98	0.54
spinal cord	0.02	0.02	0.01
spleen	1.81	0.41	0.12
stomach	4.19	0.28	0.11
testes	0.62	0.21	0.07
thymus	1.65	0.37	0.10
thyroid	0.89	0.15	0.08
urinary bladder	15.8	0.32	0.1
[^{14}C]dalfopristin			
adrenal	1.64	0.44	0.33
bile	743	1781	506
blood	1.97	0.41	0.33
bone marrow	1.00	0.46	0.23
brain	0.04	0.04	0.01
eye pigmented tissue	1.03	0.44	0.44
non-pigmented tissue	0.94	0.31	0.24
gall bladder	96.5	183.7	80.4
heart	1.69	0.50	0.39
hypophysis	3.28	1.00	0.70
kidney	19.44	5.36	5.08
large intestine	2.51	18.6	10.5
liver	19.04	3.20	3.40
lung	1.74	0.43	0.33
lymph nodes	2.12	0.78	0.44
muscle	1.58	0.30	0.36
pancreas	4.95	1.30	0.86
prostate	4.47	0.60	0.42
salivary gland	3.78	1.50	0.67
skin	1.26	0.47	0.31
small intestine	14.7	5.56	1.17
spinal cord	0.12	0.03	0.04
spleen	1.93	0.51	0.47
stomach	2.24	0.54	0.72
testes	1.76	0.52	0.26
thymus	2.28	0.74	0.42
thyroid	1.52	0.63	0.43
urinary bladder	3.15	0.47	0.44

NA, Not available.

Whole body radiography in rats and monkeys. Qualitative determination of radioactivity in rats and monkeys using whole body radiography revealed a distribution pattern similar to that observed in the studies detailed above. Representative whole body autoradiographs are presented in Figure 2. In Sprague Dawley (albino) rats, quinupristin/dalfopristin achieved good tissue and fluid penetration at 0.25 and 3 h post-dose, particularly in intestinal contents, liver, kidney, blood, salivary gland, spleen, bone marrow and adrenals. Quinupristin radioactivity rapidly declined after 24 h, although some general retention of dalfopristin radioactivity was observed. In Long Evans (pigmented) rats, dalfopristin was slightly retained by melanin but quinupristin showed no affinity for this compound. In monkeys, the highest levels of radiolabelled quinupristin and dalfopristin were seen in the liver and kidneys. There was no persistent retention of radioactivity in melanin-containing tissues, the haemopoetic system or glandular tissues.

Ex vivo protein binding in rats and monkeys. Plasma protein binding of quinupristin was 78–80% in rats and 85–96% in monkeys 0–6 h post-infusion. Over the same time-frame, dalfopristin binding to plasma proteins increased from 48 to 98% in rats and from 45 to 90% in monkeys. This increase in plasma protein binding is probably due to binding of drug-derived products.

Metabolism and excretion in rats and monkeys. Quinupristin was not extensively metabolized in either rats or monkeys—about 38% and 25% of the administered dose was recovered unchanged in the urine and faeces 1–2 days after infusion. The main metabolites in both species were an in-vitro active glutathione-conjugated derivative (RP

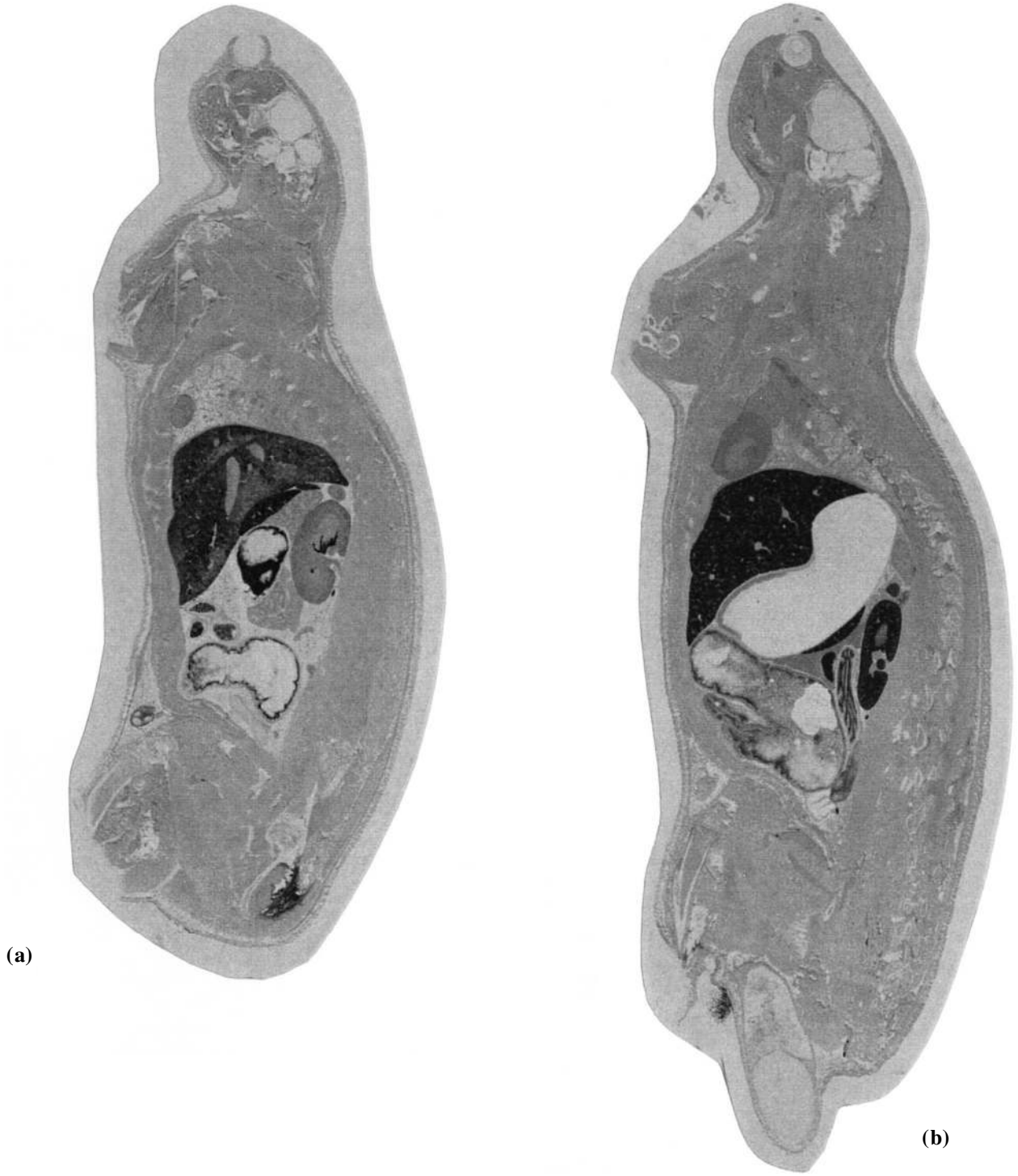

Figure 2. Representative longitudinal section whole body autoradiographs of rats and monkeys killed 15 min after iv infusion of quinupristin/dalfopristin 6 mg/kg: (a) female rat given [^{14}C]quinupristin/dalfopristin; (b) male rat given quinupristin/[^{14}C]dalfopristin; (c) female monkey given [^{14}C]quinupristin/dalfopristin; (d) female monkey given quinupristin/[^{14}C]dalfopristin. Key: 1, spleen; 2, adrenal gland; 3, hypophysis; 4, kidney; 5, kidney basin; 6, muscles; 7, bile duct; 8, gall bladder; 9, liver; 10, uveal tract; 11, arterial wall; 12, aorta; 13, bone marrow; 14, pancreas; 15, kidney cortex; 16, uterus; 17, eye; 18, submaxillary gland; 19, lung; 20, spinal cord; 21, cervix; 22, blood; 23, myocardium; 24, vagina; 25, skin; 26, intestinal mucosa; 27, bone; 28, bladder; 29, stomach content; 30, stomach wall; 31, small intestine content; 32, stomach; 33, thoracic vertebra; 34, parotid gland; 35, left ventricle; 36, middle ear; 37, urine; 38, caecum; 39, brain; 40, carotid artery; 41, thymus; 42, cerebellum; 43, sternebra; 44, cervical vertebra; 45, tongue; 46, oesophagus; 47, trachea.

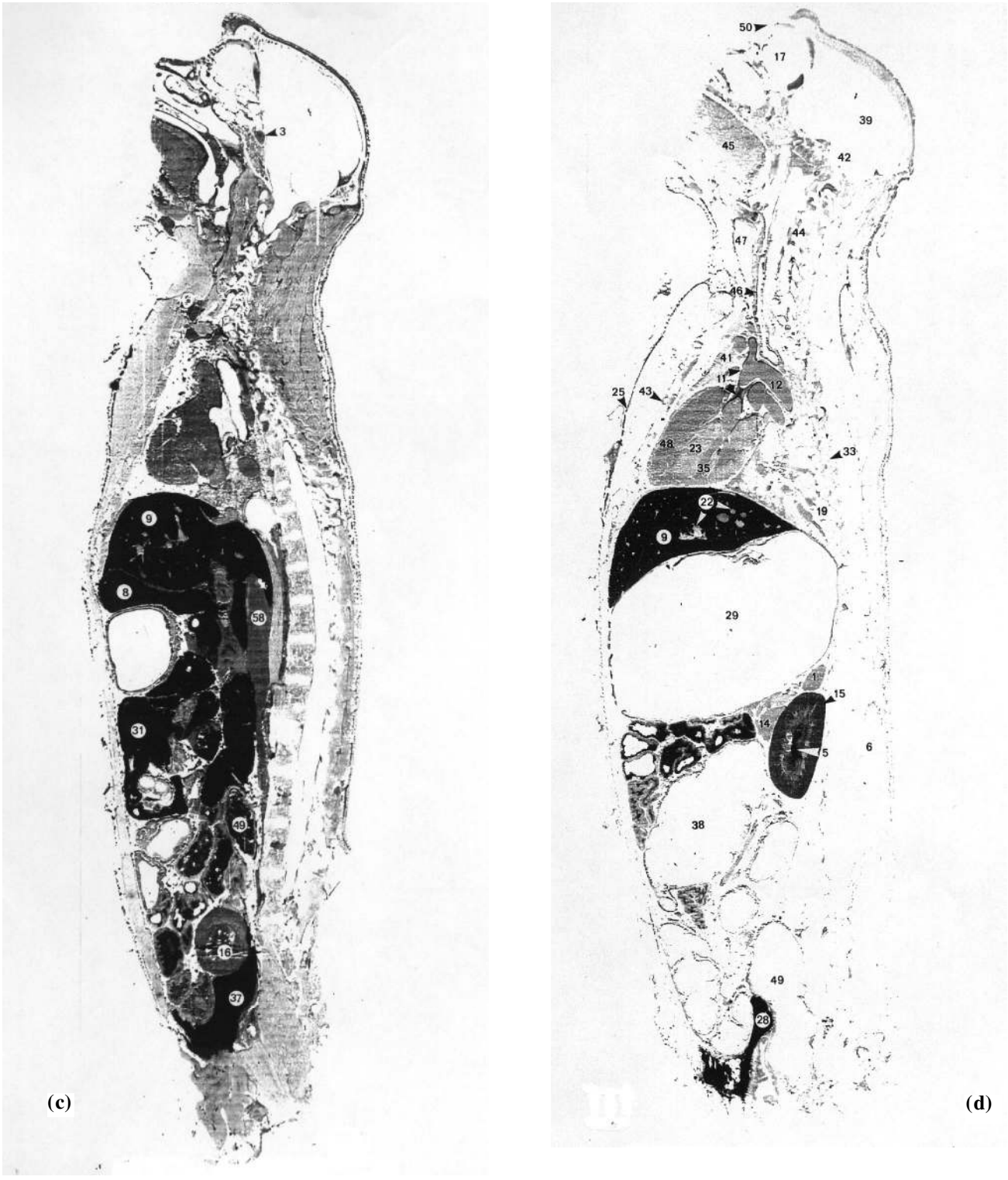

Figure 2. *Continued*

69012) and an in-vitro active cysteine-conjugate (RP 100391); an unidentified metabolite was also recovered in rats. Dalfopristin was extensively metabolized in both rats (≈99%) and monkeys (≈92%) to the natural pristinamycin PIIA (RP 12536), its glutathione conjugate and to numerous by-products.

Quinupristin and dalfopristin are both primarily excreted in the faeces. In rats and monkeys, 73–89% of

quinupristin and 67–83% of dalfopristin were recovered in the faeces following intravenous administration; urinary recovery accounted for <13% in rats and 18–24% in monkeys. The high faecal recovery of both compounds reflects extensive excretion in bile (quinupristin 84%, dalfopristin 70% when determined in rats), although significant enterohepatic recycling does not occur.

Studies in humans

The maximum blood concentration (C_{max}) of quinupristin/dalfopristin at the end of a 1 h infusion in 26 healthy volunteers ranged from 0.95 mg/L at a dose of 1.4 mg/kg to 24.2 mg/L at 29.4 mg/kg (Table III).[1] Linear correlations between dose and C_{max} were observed for quinupristin and dalfopristin. At higher doses (12.6–29.4 mg/kg), antimicrobial activity (blood levels ≥0.1 mg/L) of quinupristin/dalfopristin was detectable for up to 6 h after the infusion. At these doses t_{β} values were 1.27–1.39 h for quinupristin/dalfopristin, 0.56–0.61 h for quinupristin and 0.75–0.84 h for RP 12536.

A more detailed pharmacokinetic evaluation of quinupristin and dalfopristin was carried out by Montay *et al*.[4] The mean plasma concentrations of quinupristin, dalfopristin (each administered in single doses of 5, 10 and 15 mg/kg) and the metabolite RP 12536 in 18 healthy volunteers are shown in Figure 3. Quinupristin and dalfopristin showed biphasic plasma elimination. Values of the initial and terminal elimination half-lives ranged from 0.17 to 0.23 h and 0.93 to 0.96 h for quinupristin, and from 0.11 to 0.23 h and 0.39 to 0.91 h for dalfopristin, respectively. A statistically significant increase in final elimination half-life with increasing dose was observed with dalfopristin, and variation between individuals was greater for this compound. High plasma clearance (Cl) values were observed for both compounds: 1.1 L/h/kg for quinupristin and 1.0–1.2 L/h/kg for dalfopristin. These values were independent of the administered dose and similar to the value for hepatic blood flow (1.2 L/h/kg). V_d and V_d at steady state (V_{ss}) were approximately 1.4 L/kg and 0.8 L/kg, respectively. However, V_d (0.54–1.80 L/kg) and V_{ss} (0.33–0.70 L/kg) increased with increasing doses of dalfopristin. This phenomenon could not be explained by the saturation of plasma protein binding, as the extent of dalfopristin binding is below 30% in humans (data on file, Rhône-Poulenc Rorer).

C_{max} and $AUC_{0-\infty}$ for RP 12536 increased disproportionately relative to increases in the dose of quinupristin/dalfopristin over the range 5–15 mg/kg. However, dose-proportionality was obtained with the sum of AUC values for dalfopristin and RP 12536 (expressed as dalfopristin equivalent). Terminal $t_{1/2}$ of RP 12536 also increased with dose while total clearance decreased. The mean pharmacokinetic parameters of quinupristin, dalfopristin and RP 12536 are summarized in Table IV.

In six healthy volunteers, total levels of radioactivity for [^{14}C]quinupristin and for [^{14}C]dalfopristin were comparable both in blood and in plasma.[2] Both agents were excreted mainly in the faeces and to a lesser extent in the urine. Faecal recovery accounted for 74.7% of the quinupristin dose and for 77.6% of the dalfopristin dose: urinary recovery accounted for 15.1% and 18.7% of the administered dose, respectively (mainly within 3 h of administration). As in animal studies, a significant proportion of the quinupristin dose was excreted unchanged (35% of total radioactivity in urine, 15% of extractible radioactivity in faeces), although notable excretion as a cysteine conjugate (RP 100391) also occurred (38% of total radioactivity in urine, 7.5% of total radioactivity in faeces). No unchanged dalfopristin was detected in faeces although non-extractable metabolites were present. In

Table III. Mean blood C_{max} (mg/L) values of quinupristin/dalfopristin, its individual components and RP 12536 at the end of a 1 h infusion in 26 healthy volunteers. Blood concentrations of quinupristin/dalfopristin measured by bioassay and concentrations of quinupristin, dalfopristin and RP 12536 measured by HPLC.

Quinupristin/dalfopristin dose (mg/kg)	Quinupristin/ dalfopristin	Quinupristin	Dalfopristin	RP 12536
1.4	0.95	0.61	0.54	0.07
2.8	1.90	NA	1.17	0.11
4.6	3.31	1.92	1.62	0.38
7.0	4.96	3.00	4.16	0.45
9.8	6.83	3.85	3.90	0.55
12.6	10.70	8.54	7.15	1.27
16.8	12.82	10.93	4.82	1.47
22.4	14.05	13.53	4.36	1.68
29.4	24.20	19.93	6.90	2.44

NA, Not available.

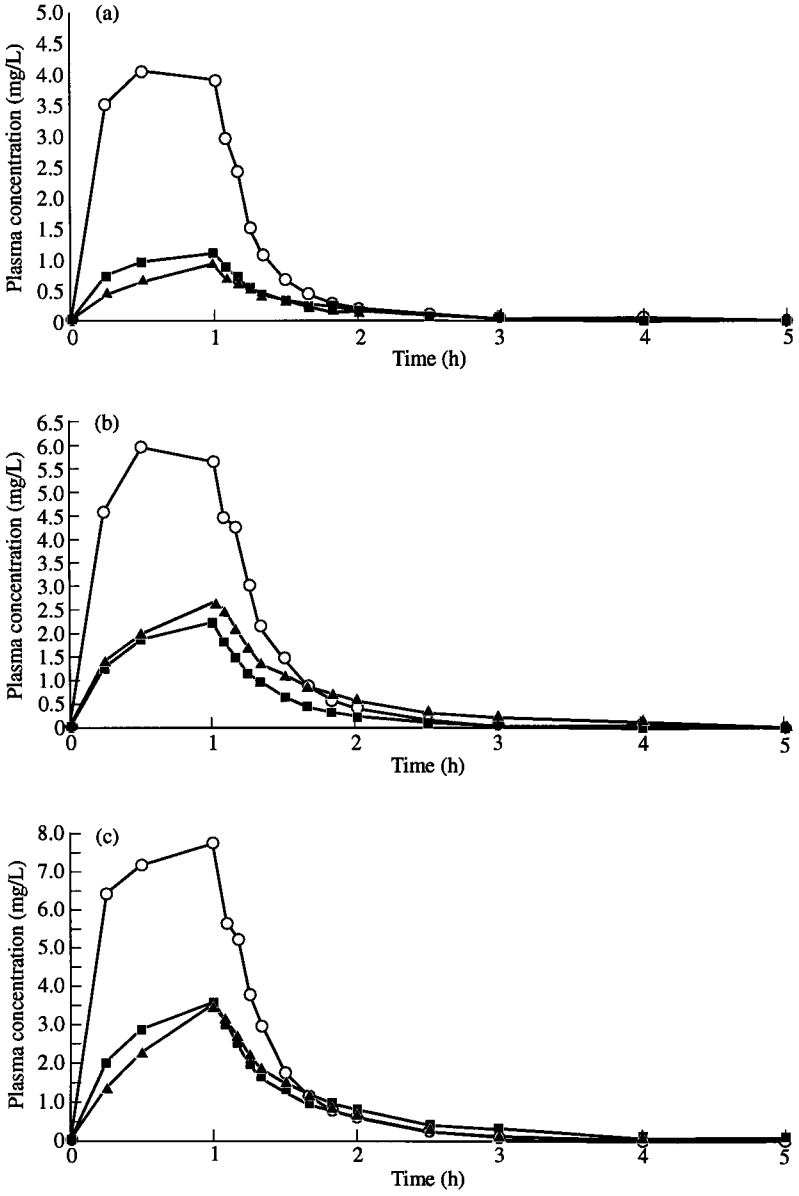

Figure 3. Mean plasma concentrations (HPLC assay) of quinupristin (■), dalfopristin (◯) and RP 12536 (▲) in up to 18 healthy volunteers after 1 h infusion of quinupristin/dalfopristin (a) 5, (b) 10 or (c) 15 mg/kg (data on file, Rhône-Poulenc Rorer).

urine, dalfopristin was mainly recovered as pristinamycin IIA (RP 12536) (59%) and as probable cysteine and glutathione derivatives of this metabolite.

Bernard *et al*[3] showed, in a microbiological assay of blister fluid from six healthy volunteers, 82.5% of quinupristin/dalfopristin penetrated into interstitial fluid. The percentage penetration was calculated from the ratio of AUC values between suction blister fluid and plasma for the interval from 0 to 6 h. The combination was still detectable (at a mean concentration of 0.92 mg/L) 6 h after a single intravenous dose of 12 mg/kg. Other pharmacokinetic data from these volunteers are shown in Table V.

Discussion

Preliminary in-vitro studies revealed that quinupristin/dalfopristin was unstable at physiological pH (7.4) but stable at pH 3–4 in various media (data on file, Rhône-Poulenc Rorer). Specific conditions for blood sample collection were therefore validated to ensure the stability of both components in subsequent investigations.

Pharmacokinetic studies of quinupristin and dalfopristin in rats and monkeys indicate that following intravenous infusion, the compound is rapidly cleared from the blood (t_{β} = 0.24–0.64 h) and is widely distributed in the

Table IV. Mean pharmacokinetic parameters for quinupristin, dalfopristin and RP 12536 after 1 h infusions of 5, 10 and 15 mg/kg quinupristin/dalfopristin in up to 18 healthy volunteers (data on file, Rhône-Poulenc Rorer). Plasma concentrations of compounds determined by HPLC.

Quinupristin/ dalfopristin dose (mg/kg)	C_{max} (mg/L)	$AUC_{0-\infty}$ (mg/L.h)	$t_{1/2\alpha}$ (h)	$t_{1/2\beta}$ (h)	Cl (L/h/kg)	V_d (L/kg)	V_{ss} (L/kg)
Quinupristin							
5	1.20 (30)[a]	1.41 (20)	0.17 (26)	0.93 (21)	1.13 (34)	1.37 (30)	0.83 (50)
10	2.32 (21)	3.01 (17)	0.19 (27)	0.97 (21)	1.03 (20)	1.44 (29)	0.79 (51)
15	3.58 (21)	4.69 (20)	0.23 (48)	0.96 (31)	0.99 (19)	1.37 (33)	0.81 (42)
Dalfopristin							
5	4.55 (51)	4.57 (44)	0.11 (29)	0.39 (38)	0.99 (70)	0.54 (60)	0.33 (109)
10	6.38 (43)	7.27 (42)	0.15 (41)	0.52 (41)	1.19 (54)	0.88 (60)	0.43 (68)
15	8.46 (31)	9.71 (37)	0.23 (22)	1.09 (34)	1.23 (40)	1.80 (35)	0.70 (49)
RP 12536							
5	0.94 (18)	1.24 (18)	0.22 (15)	0.91 (18)	2.76 (18)		
10	2.54 (33)	3.70 (24)	0.39 (66)	1.63 (41)	1.53 (26)		
15	3.75 (43)	5.14 (38)	0.39 (26)	2.17 (16)	1.83 (45)		

[a] Values in parentheses are coefficients of variation (%).

Table V. Mean pharmacokinetic parameters in plasma and interstitial (suction blister) fluid of quinupristin/dalfopristin after a 1 h infusion of 12 mg/kg.[3] Concentrations of quinupristin/dalfopristin determined by bioassay.

	C_{max} (mg/L)	t_{max} (h)	AUC_{0-6h} (mg/L.h)	$AUC_{0-\infty}$ (mg/L.h)	Cl (L/h)	Percentage penetration (0–6 h)	$t_{1/2}$ (h)
Plasma	8.65		11.11	11.42	74.01		1.48
Interstitial fluid	2.41	1.66	9.19			82.49	

t_{max} = time to C_{max} in interstitial fluid.

Table VI. Balance recovery (% of dose) of radiolabelled quinupristin/dalfopristin in rats, monkeys and humans (data on file, Rhône-Poulenc Rorer). All values are for mean recovery except where indicated

	Quinupristin			Dalfopristin		
	rat (4 male, 4 female)	monkey (2 female)	human (6 male)	rat (4 male, 4 female)	monkey (2 female)	human (6 male)
Urine	8.4 (M), 7.2 (F)	17.7/24.0	15.1	12.0 (M), 7.2 (F)	18.0/24.1	18.7
Faeces	79.9 (M), 84.9 (F)	72.5/89.1	74.7	66.1 (M), 67.1 (F)	71.5/82.5	77.4
Total	88.7/92.4	98.6/109.0	89.8	88.7 (M)[a], 82.9 (F)[a]	96.3/101.0	96.2

[a] Includes expired $^{14}CO_2$.

body (V_d = 0.71–5.4 L/kg). Nevertheless, it does not appear to cross the blood–brain barrier or the placenta to any significant degree. The major route of elimination is through bile into faeces. Quinupristin is notably excreted unchanged whereas dalfopristin undergoes extensive metabolism which includes the formation of the natural pristinamycin PIIA (RP 12536). This derivative possesses in-vitro antimicrobial activity similar to that of the parent

compound and their pharmacokinetics appear to be related.

Clinical pharmacokinetic studies indicate similar handling of quinupristin/dalfopristin by humans. The compound is rapidly eliminated from the plasma ($t_{\beta} \approx$ 0.1–1.5 h) and appears to be widely distributed (V_d = 0.54–1.8 L/kg). Furthermore, balanced recovery studies show that radiolabelled quinupristin/dalfopristin is eliminated mainly in the faeces and to a lesser extent in the urine (as in rats and monkeys). In the close plasma level relationship study that has been conducted quinupristin and dalfopristin showed biphasic elimination. A dose-independent pharmacokinetic profile emerged for quinupristin, but not for dalfopristin or RP 12536 when these moieties were examined separately. With increasing doses of dalfopristin, there was a significant increase in its volume of distribution without a change in clearance—its elimination half-life therefore increased accordingly. Interestingly, the sum of the AUCs for dalfopristin and its metabolite RP 12536 showed dose-proportionality. This is important as the antimicrobial activity of quinupristin/dalfopristin has been correlated with AUC values in experimental models of infections (data on file, Rhône-Poulenc Rorer).

Finally, the results of the experiments with suction blister fluid of Bernard *et al.*[3] show that quinupristin/dalfopristin penetrates rapidly and well into non-inflammatory interstitial fluid.

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