Cancer Chemother Pharmacol (1992) 31: 32–36

Cancer Chemotherapy and Pharmacology

Intraperitoneal administration of the antitumour agent *N*-[2-(dimethylamino)ethyl]acridine-4-carboxamide in the mouse: bioavailability, pharmacokinetics and toxicity after a single dose*

Sean M. H. Evans, Deborah Young, Iain G. C. Robertson, and James W. Paxton

Department of Pharmacology and Clinical Pharmacology, University of Auckland School of Medicine, Auckland, New Zealand

Received 1 December 1991/Accepted 27 April 1992

Summary. The pharmacokinetics, tissue distribution and toxicity of the antitumour agent *N*-[2-(dimethylamino)-ethyl]acridine-4-carboxamide (AC) were studied after i.p. administration of [^{3}H]-AC (410 μmol/kg) to mice. The latter is the optimal single dose for the cure of advanced Lewis lung tumours. AC was rapidly absorbed into the systemic circulation after i.p. administration, with the maximal concentration (C_{max}) occurring at the first time point (5 min). There was no reduction in bioavailability as compared with previous i.v. studies, but the shape of the plasma concentration-time profile was considerably different, reflecting a 3-fold lower C_{max} value (20.9 ± 3.6 μmol/l) and a longer $t_{1/2}$ value (2.7 ± 0.3 h) as compared with that observed after i.v. administration (1.6 ± 0.6 h). Model independent pharmacokinetic parameters after i.p. administration were: clearance (C), 17.5 l h^{-1} kg^{-1}; steady-state volume of distribution (V_{ss}), 14.1 l/kg; and mean residence time (MRT), 1.46 h. High but variable tissue uptake of AC was observed, with tissue/plasma AUC ratios being 5.7 for heart, 8.4 for brain, 18.9 for kidney and 21.0 for liver but with similar elimination $t_{1/2}$ values ranging from 1.3 to 2.7 h. All radioactivity profiles in plasma and tissues were greater than the respective parent AC profiles and showed prolonged elimination $t_{1/2}$ values ranging from 21 h in liver to 93 h in brain. However, tissue/plasma radioactivity AUC ratios were near unity, ranging from 0.7 to 1.57, with the exception of the gallbladder (15.6), which contained greater amounts of radioactivity. By 48 h, approximately 70% of the total dose had been eliminated, with the faecal to urinary ratio being approximately 2:1. This i.p. dose was well tolerated by mice, with sedation being the only obvious side effect. No major change was observed in blood biochemistry or haematological parameters. Comparisons of C_{max}, t_{max} and AUC values determined for AC in brain after its i.p. and i.v. administration suggest that the reduction in acute toxicity after i.p. administration is not due to reduced exposure of the brain to AC as measured by AUC but may be associated with the lower C_{max} value or the slower rate of entry of AC into the brain after i.p. administration.

* This study was supported by the Cancer Society of New Zealand. The senior author (S.M.H.E.) is the recipient of a Health Research Council of New Zealand Junior Research Award

Correspondence to: J. W. Paxton, Department of Pharmacology and Clinical Pharmacology, University of Auckland School of Medicine, Private Bad 92019, Auckland, New Zealand

Introduction

N-[2-(Dimethylamino)ethyl]acridine-4-carboxamide (AC; NSC 601316) is an experimental antitumour agent [developed in the Cancer Research Laboratories (CRL), University of Auckland Medical School] that is under consideration for phase I clinical trials by the Cancer Research Campaign of the United Kingdom [2, 3]. In our recent studies on the pharmacokinetics of AC after i.v. administration to mice, it appeared that acute toxicity to the central nervous system was dose-limiting [7]. Administration of 165 μmol/kg (60 mg/kg) i.v. was lethal, with seizures and death occurring within 2 min of drug administration; whereas 137 μmol/kg (50 mg/kg) caused seizures and 2 deaths (2/21), and 110 μmol/kg (40 mg/kg) was well tolerated, with sedation being the only obvious side effect. The latter was also the optimal single i.v. dose for the treatment of Lewis lung tumours in mice. High brain concentrations of radioactivity were rapidly achieved after i.v. administration of [^{3}H]-AC in these mice. Other studies using Oldendorf's technique [6] have also shown that AC gains rapid entry into the rat and mouse brain, resulting in a very high brain uptake index similar to that of diazepam [1]. In earlier testing of the antitumour efficacy of AC in BDF_1 mice implanted with a s.c. Lewis Lung tumour, the optimal and maximal single i.p. dose for the cure of advanced disease was 410 μmol/kg (150 mg/kg) [2], which was approximately 4 times the maximum tolerated following administration by the i.v. route. The main aim of the present study was to investigate whether reduced bioavailability or altered distribution might be responsible for the reduced acute toxicity after i.p. administration.

Materials and methods

Materials. The di-hydrochloride salts of AC, the internal standard *N*-[2-(diethylamino)ethyl]acridine-4-carboxamide and the radiochemical starting material (acridine-4-carboxylic acid sodium salt) were synthesised in the CRL. The latter compound was tritiated by Amersham International (Amersham UK) and was further conjugated with 2-dimethylamino-ethylamine to form the di-HCl salt of AC by Dr. W. Denny in the CRL. The confirmation of chemical and radiochemical purity (>98%) has previously been described [7]. The scintillation fluid was Beckman Ready Safe (Beckman Instruments Ltd., California, USA), and Soluene (Packard Instrument Company, Illinois, USA) was used to dissolve tissue before the counting of radioactivity. The solvents were high-performance liquid chromatography (HPLC)-grade acetonitrile and methanol (from Mallinckrodt Inc., Paris, Kentucky, USA). The ammonium acetate, heptane sulphonic acid (sodium salt), triethylamine, glacial acetic acid (all from BDH Chemicals, Poole, UK) and phosphoric acid (J.T. Baker, Inc., New Jersey, USA) were all of Analar grade. All aqueous solutions were prepared using Millipore Milli-Q water.

Animals. Male BDF_1 mice (20–25 g) were used for all experiments. They were bred and maintained under constant temperature and humidity, with sterile bedding, food and water being provided according to institutional guidelines. All animal procedures were approved by the Animal Ethics Committee of the University of Auckland.

Drug formulation and administration. A stock AC solution (82 mM) was prepared in sterile saline and diluted to the required concentration to allow an injection volume of 5 µl/g at the dose of 410 µmol/kg (150 mg/kg). [^{3}H]-AC was included to give a specific activity of 5.43 µCi/µmol. After i.p. administration of [^{3}H]-AC, blood was collected into heparinised tubes by ocular extrusion using ether anestesia at 5, 10 and 15 min and at 1, 2, 4, 6, 8, 24 and 48 h (three mice per time point) and the mice were swiftly killed by cervical dislocation. Thereafter, the liver, gallbladder (when possible), kidneys, heart and brain were rapidly removed and blotted dry before being weighed. After centrifugation of blood, the plasma was removed and both plasma and tissues were stored at –80° C until analysis. The separate collection of urine and faeces was undertaken in nine mice that were held individually in glass or plastic metabolic cages. After 8, 24 and 48 h, the mice were killed and blood and tissues were obtained as described above. A further three mice received 590 µmol/kg (215 mg/kg) i.p. and were killed at t_{max} (15 min) for the determination of brain AC concentrations. Three mice also received a seizure-inducing i.v. dose of 137 µmol/kg and were killed at t_{max} (2 min) for the determination of AC brain levels.

HPLC analysis. A specific reversed-phase HPLC method using N-[2-(diethylamino)ethyl]acridine-4-carboxamide as the internal standard has been developed for the quantitation of AC in plasma and urine [7, 9]. This method was modified to measure AC in the following tissues as well: liver, kidney, heart, gallbladder and brain. Briefly, after their removal, all tissues (except liver) were homogenised in Milli-Q water. In the liver, preliminary experiments involving the addition of known amounts of AC indicated the occurrence of significant metabolism during homogenisation with water. To overcome this problem, livers were homogenised immediately after their removal from the animal in a 50% acetonitrile/ammonium acetate buffer solution to stop any further metabolism of AC prior to HPLC analysis. Thereafter, all tissue homogenates were precipitated with acetonitrile and the supernatant was further purified on Extra-Sep C_{18} solid-phase extraction columns (Phenomenex, Torrance, Calif., USA). After elution with acetonitrile/ammonium acetate buffer and evaporation, the final separation was carried out on a C_{18} µBondapak stainless-steel column (30 cm × 0.05 cm inside diameter; Waters Associates, Milford, Mass., USA) using a mobile phase of acetonitrile:water (32:65, v/v) containing 10 mM triethyl-ammonium phosphate. Detection was carried out by fluorescence emission at 475 nm with 358 nm being the excitation wavelength. The addition of the internal standard at the commencement of the analysis corrected for any non-equivalent extraction efficiency. The recovery of known amounts of AC added to tissues ranged from 99.5% to 102.6% for liver, from 95.2% to 109% for brain, from 95.3% to 109% for heart and from 96.4% to 108.8% for kidney.

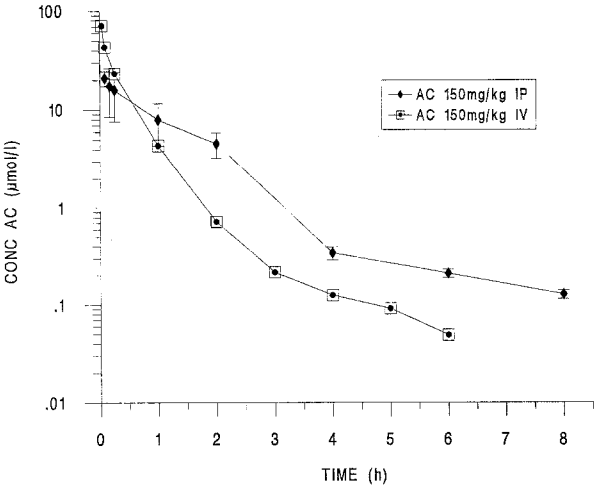

Fig. 1. Mean plasma AC concentration-time profile after the i.p. administration of AC at 410 µmol/kg (◆). *Bars* represent ±1 SD. ●, Equivalent i.v. dose extrapolated (by linear kinetics) from 110 µmol/kg, which is the maximum tolerated i.v.dose

Radioactivity quantitation. Total radiochemical equivalents of AC in plasma, urine, faeces and various tissues were determined using liquid scintillation counting with quench correction as previously described [7].

Toxicological monitoring. Serum biochemical (creatinine, albumin, total protein, aspartate transaminase and alkaline phosphatase) and haematological (haematocrit, haemoglobin, RBC, WBC and platelet counts) tests were carried out using routine methods (Clinical Chemistry Unit and Haematology Department, Auckland Hospital) in 12 healthy control mice and in 21 mice that had been treated with 410 µmol/kg AC i.p. Sampling was carried out in 3 mice on days 1, 2, 3, 5, 7, 10 and 14 after AC administration.

Pharmacokinetic methods. The area under the plasma concentration-time curve (AUC) was computed using the log trapezoidal rule and was extrapolated to infinity by addition of the value C_t/Z, where C_t is the concentration at the last time point and Z is the terminal slope determined by linear regression. The half-life ($t_{1/2}$) was calculated by the equation ln(2)/Z. The terms C_{max} and t_{max} represent the maximal concentration achieved and the time to maximal concentration, respectively. The model-independent pharmacokinetic parameters clearance (C), volume of distribution at steady state (V_{ss}) and mean residence time (MRT) were calculated by the following equations: C = Dose/AUC, V_{ss} = (Dose × AUMC)/AUC^2 and MRT = AUMC/AUC, respectively, where *AUMC* represents the total area under the first moment of the plasma concentration-time curve as calculated similarly to AUC [4]. The concentration-time profile was fitted to a two-compartment model with linear kinetics using MKMODEL, and the models were compared by the Schwarz criterion [5].

Results

Pharmacokinetics

The mean plasma concentration-time profile obtained for AC after i.p. administration of 410 µmol/kg is shown in Fig. 1. For comparison, the profile obtained following the i.v. injection of 410 µmol/kg is also included. The latter

Table 1. Tissue concentrations of AC measured in mice after an i.p. dose of 410 μmol/kg

Time (h)	Concentrations (μmol/l or μmol/kg)				
	Plasma	Brain	Liver	Kidney	Heart
0.08	20.9 ±3.6	134 ±38	1,046±30	439 ±40	229 ±5.9
0.16	17.4 ±9.0	155 ±89	582 ±235	502 ±285	179 ±109
0.25	15.7 ±8.1	267 ±195	470 ±203	181 ±1.5	116 ±91
1	7.95 ±3.6	40.6±9.0	167 ±51	125 ±32	51.3±39
2	4.57 ±1.3	37.9±14	68.1 ±33	122 ±50	27.0±5.5
4	0.342±0.053	3.60±0.38	2.88 ±0.55	14.9±2.4	3.24±0.99
6	0.211±0.021	1.26±0.27	1.71 ±0.99	6.21±2.3	1.36±0.33
8	0.128±0.011	0.66±0.02	0.86 ±0.21	4.86±1.2	0.93±0.15
AUC (μmol h l^{-1})	23.4	196.4	492.4	442.9	132.7
AUC_I/AUC_P [a]	1	8.39	21.0	18.9	5.67
$t_{1/2}$ (h)[b]	2.7 ±0.29	2.2 ±0.21	1.3 ±0.63	1.3 ±0.16	1.6 ±0.38

[a] Ratio of parent AC AUC in tissue to AUC in plasma
[b] Calculated from the elimination phase of the concentration-time profile

Table 2. Tissue concentrations of radioactivity measured in mice after an i.p. dose of 410 μmol/kg [^{3}H]-AC

Time (h)	Radioactivity (μmol AC equivalents/l or /kg)					
	Plasma	Brain	Liver	Kidney	Heart	Gallbladder
0.08	50.5±5.3	291 ±20.7	1,695±119	575 ±84.6	260 ±100	1,796±385
0.16	67.7±10.8	235 ±130	1,280±425	683 ±287	234 ±113	394 ±244
0.25	82.0±18.4	340 ±213	1,143±384	1,108±792	230 ±116	2,409±1,265
1	64.2±3.4	191 ±96.3	638 ±228	437 ±167	127 ±68.4	3,481±2,472
2	70.6±3.4	159 ±86.4	418 ±64.8	401 ±208	82.8±5.48	2,717±1,265
4	61.8±11.1	51.7±8.6	206 ±39.6	86.4 ±4.5	24.1±9.91	6,653±3,917
6	73.8±3.8	63.1±5.7	223 ±45.9	105 ±25.2	20.8±3.87	5,782±1,785
8	75.2±5.4	70.8±5.4	179 ±9.0	94.5 ±4.5	24.4±5.94	5,873±4,115
24	68.8±5.8	44.3±11.7	93.6 ±20.7	56.1 ±6.5	46.4±2.34	383 ±367
48	41.3±4.4	37.5±13.5	42.3 ±5.4	31.4 ±3.7	28.4±6.93	74.9 ±56.7
AUC (μmol h l^{-1})	4,940	7,785	7,733	5,386	3,308	76,810
AUC_I/AUC_P[a]	1	1.58	1.57	1.09	0.70	15.55
$t_{1/2}$ (h)[b]	32.5±5.16	93.3±14.6	21.3 ±1.6	28.4 ±2.22	32.7±10.6	

[a] Ratio of radioactivity AUC in tissue to AUC in plasma
[b] Calculated from 24 to 48 h

dose is 2.5 times the lethal i.v. dose in mice and was extrapolated by linear kinetics from our previous i.v. studies, which indicated linear kinetics at AC levels up to the maximum tolerated i.v. dose [7].

AC was rapidly absorbed into the systemic circulation after i.p. administration as indicated by the plasma C_{max} value (20.9±3.6 μmol/l) occurring at the first time point (5 min). The plasma AC elimination profile fitted a two-compartment model, but the absorption was so fast that it was not possible to distinguish between first-order and zero-order rate input. Assuming 100% bioavailability after i.p. administration (see Discussion), the model-independent pharmacokinetic parameters were: C, 17.5 l h^{-1} kg^{-1}; V_{ss}, 14.1 l/kg; and MRT, 1.46 h. High but variable AC concentrations (coefficient of variation (CV) range, 0.8%–78%] were observed in the tissues, with the tissue/plasma AUC ratios being 21.0 for liver, 18.9 for kidney, 8.4 for brain and 5.7 for heart (Table 1). AC concentrations in the tissues declined at a similar rate ($t_{1/2}$ range, 1.3–2.2. h) as those in plasma ($t_{1/2}$ = 2.7±0.3 h).

Radioactive profiles in plasma and tissues

All plasma and tissue radioactivity profiles (expressed as μmol AC equivalents/l or kg) were greater than the respective parent AC profiles, with prolonged $t_{1/2}$ values ranging from 21 h in the liver to 93 h in the brain (Table 2). The AUC ratio of radioactivity/AC parent was highest in plasma (206) and lowest in kidney (12). At the first time point (5 min), plasma radioactivity concentrations were 50.5±5.3 μmol/l as compared with AC concentrations of 20.9±3.6 μmol/l, indicating that significant biotransformation had occurred by this time. Peak radioactivity concentrations (82.0±18.4 μmol/l) occurred in the plasma at 15 min and remained relatively constant for 24 h thereafter, followed by a slow decline from 24 to 48 h ($t_{1/2}$ = 32.5±5.2 h). By 48 h, the radioactivity in the plasma and tissues appeared to have equilibrated, with concentrations ranging from 28.4 to 42.3 μmol/kg (mean, 36.2±5.5 μmol/kg). In contrast to AC, radioactivity AUC tissue/plasma ratios were near unity, ranging from 0.7 to 1.6.

Table 3. Excretion of radioactivity after i.p. administration of [^{3}H]-AC to mice at 410 μmol/kg

Excretion period (h)	Mean of dose cumulation (%)[a]	
	Urine	Faeces
0– 8	15.0±1.9	5.33±6.0
0–24	21.7±4.8	40.9±19
0–48	23.8±2.2	47.0±0.79

[a] Data represent mean values ± SD for 3 mice

Excretion of radioactivity

The urinary and faecal elimination of radioactivity over 48 h after i.p. administration is shown in Table 3. The ratio of faecal to urinary radioactivity output was approximately 2:1. By 48 h, 70% of the total dose had been eliminated in the urine and faeces. Measurement of unchanged AC in urine indicated that after a dose of 410 μmol/kg i.p.; less than 1% of the total dose was eliminated unchanged.

Toxicity

An i.p. dose of 410 μmol/kg was well tolerated by the mice, with some sedation being the only obvious side effect. No significant change in body weight was observed over 28 days after AC administration. Over 14 days, the mean haematological parameters (in 3 mice) on each day remained within ± 2SD of the mean value calculated for the 12 control mice (Table 4). Similarly, all biochemical parameters remained within this range with the exception of aspartate transaminase (elevated at 24 h but returning to normal by 48 h) and albumin (reduced at 48 h but returning to normal by 72 h).

After i.p. administration of 410 μmol/kg, brain AC concentrations were very variable with the C_{max} (267±195 μmol/kg) occurring at 15 min and the brain AUC being 196 μmol h kg^{-1}, whereas mice that had received 137 μmol/kg i.v. experienced seizures and showed a brain C_{max} value of 507±288 μmol/kg at 2 min and an AUC value of 65 μmol h kg^{-1}. Increasing the i.p. dose to 590 μmol/kg resulted in brain concentrations of 571±201 μmol/kg at 15 min; this was associated with clonic seizures and sedation.

Discussion

We have previously reported that the elimination kinetics of AC after tail-vein i.v. bolus doses in BDF_1 mice were linear over the dose range of 8–110 μmol/kg, i.e. up to the maximum tolerated dose [7]. Pharmacokinetic studies at higher i.v. doses were not possible due to seizures and death. Using the linear relationship between the AC dose used and the plasma AUC and C_{max} values obtained in that study, an i.v. dose of 410 μmol/kg was predicted to give an AUC value of approximately 21 μmol h l^{-1} and a C_{max} value of 71 μmol/l. The plasma AUC observed after an i.p. dose of 410 μmol/kg was 23 μmol h l^{-1}, indicating that the i.p. bioavailability of AC is 100%. Thus, there is no apparent reduction in the systemic availability of AC after i.p. administration. Although AC is absorbed rapidly into the systemic circulation after i.p. administration, the shape of the plasma concentration-time profile is considerably different, resulting in a 3-fold lower C_{max} value and a longer $t_{1/2}$ value as compared with the i.v. route.

Extensive tissue uptake of AC was observed, with the greatest accumulation occurring in the liver and kidney, which appear to be the main organs involved in the elimination of AC. The brain also accumulated AC, resulting in an AUC value that was 8 times the corresponding plasma value. This i.p. dose of 410 μmol/kg did not result in any serious acute toxicity, although the brain's exposure to AC (AUC, 196 μmol h kg^{-1}) was 3 times the predicted AUC value (65 μmol h kg^{-1}) following a seizure-inducing i.v. dose of 137 μmol/kg. In addition, the rate of entry of AC into the brain after i.p. administration appeared to be slower, with the C_{max} value (267 μmol/kg) occurring at 15 min as compared with 2 min after the i.v. dose. Increasing the i.p. dose to 590 μmol/kg induced mild clonic seizures and sedation in these mice and resulted in a brain C_{max} value of 571 μmol/kg at 15 min, which is similar to the seizure-inducing i.v. value (563 μmol/kg). These suggest that the reduction in acute CNS toxicity after i.p.

Table 4. Biochemical and haematological values obtained in control mice and following i.p. administration of AC at 410 μmol/kg

Days after administration	Parameter[a]								
	AST (IU/l)	ALP (IU/l)	Total protein (g/l)	Albumin (g/l)	Haematocrit (%)	Haemoglobin (g/l)	RBC (×10^{12}/l)	WBC (×10^9/l)	Platelets (×10^9/l)
Control (n = 12)	98.7±28	141±32	49.6±2.1	27.2±1.1	40.6±3.9	145±6.9	8.69±0.8	3.38±1.3	803 ±185
1	181 ±12*	133±31	47 ±2.5	25 ±2.5	38.8±2.0	137±6.0	8.31±6.0	3.2 ±0.2	982 ±140
2	124 ±24	77 ±9.0*	48 ±0	23 ±0.5*	38.5±2.0	139±3.0	8.4 ±0.2	2.7 ±1.2	1,042±80
3	92 ±25	87 ±15*	49 ±2.0	25.3±1.3	37.8±1.4	141±4.0	8.4 ±0.1	3.3 ±0.6	828 ±138
5	101 ±34	165±2.5	50.5±2.5	28.5±1.5	37.9±3.0	135±9.0	8.2 ±0.6	4.3 ±0.6	798 ±81
7	106 ±29	139±7.0	50.5±0.5	29.5±0.5	36.7±0.1	112±30	6.5 ±2.2*	4.6 ±2.1	528 ±180*
10	74 ±11	149±16	51 ±1.5	28.3±1.3	36.8±0.2	130±0.5	8.0 ±0.1	3.4 ±0.1	1,036±119
14	70 ±8.4	163±25	51 ±2.0	28 ±1.0	36.4±0.7	135±2.5	7.9 ±0.1	5.2 ±2.0	1,000±0

Data represent mean values ± SD. AST, Aspartate transaminase; ALP, alkaline phosphatase

[a] Serum creatinine concentrations were either 0.03 or 0.04 g/l in normal mice and did not differ in treated mice

* Sifnificantly different (P <0.05)

administration may be due to a reduction in the AC C_{max} in the brain or to the rate of entry of AC into the brain rather than to the overall exposure of the brain to AC as measured by the AUC. An alternative, albeit less likely, explanation of the route-dependent acute CNS toxicity is the involvement of an AC metabolite. Rapid and extensive metabolism of AC occurs in the mouse and high concentrations of metabolites occur in all tissues, including the brain, yielding prolonged elimination $t_{1/2}$ values [7, 8]. Although plasma radioactivity profiles are similar after AC administration by the i.p. and i.v. routes, the possibility exists that the synthesis of a specific metabolite or, indeed, its concentration-time profile may be route-dependent. In addition, the possibility that AC causes acute cardiovascular changes associated with high peak concentrations following i.v. bolus administration, which may precipitate a seizure, cannot be dismissed and warrants further investigation.

In summary, the ability to increase AC's efficacy by giving a larger single dose to mice by the i.p. route was not accompanied by any increase in serious toxicity. Of particular interest is that this i.p. dose, which was the optimal single dose that consistently cured 85% of mice with advanced s.c. implanted Lewis lung tumours [2], did not result in any apparent toxicity to the haematopoietic system. In addition, slow i.v. infusion (or perhaps oral dosing) may be the method of choice in the clinic to avoid any possible acute toxic effects of AC in patients.

Acknowledgement. The authors would like to express their gratitude to the CRL for supplying the AC.

References

1. Cornford EM, Young D, Paxton JW (1992) A comparison of blood-brain barrier and liver penetration of acridine antitumour drugs. Cancer Chemother Pharmacol 29 (6): 439–444
2. Finlay GJ, Baguley BC (1989) Selectivity of *N*-[2-(dimethylamino)ethyl]acridine-4-carboxamide towards Lewis lung carcinoma and human tumour cell lines in vitro. Eur J Cancer Clin Oncol 25: 271–277
3. Finlay GJ, Rewcastle GW, Baguley BC, Denny WA (1987) Potential antitumour agents: 50. In vivo solid tumour activity of derivatives of *N*-[2-(dimethylamino)ethyl]acridine-4-carboxamide. J Med Chem 30: 664–669
4. Gibaldi M, Perrier D (1982) Noncompartment analysis based on statistical moment theory. In: Gibaldi M, Perrier D (eds) Pharmacokinetics. Marcel Dekker, New York, pp 409–417
5. Holford NHG (1985) MKMODEL, a modelling tool for microcomputers – a pharmacokinetic evaluation and comparison with standard computer programs (abstract). Clin Exp Pharmacol [Suppl] 9: 95
6. Oldendorf WH, Braun LD (1976) [^{3}H]Tryptamine and [^{3}H]water as diffusable internal standards for measuring brain extraction of radiolabelled substances following intracarotid injection. Brain Res 113: 219–227
7. Paxton JW, Young D, Evans SMH, Robertson IGC, Kestell P, Cornford EM (1992) Pharmacokinetics and toxicity of *N*-[2-(dimethylamino)ethyl]acridine-4-carboxamide in the mouse after i.v. administration. Cancer Chemother Pharmacol 29 (5): 379–384
8. Robertson IGC, Palmer BD, Officer M, Lawson V, Paxton JW, Bland T (1992) Metabolism of the experimental antitumour agent acridine carboxamide (AC) in the mouse. Drug Metab Dispos (in press)
9. Young D, Evans PC, Paxton JW (1990) Quantitation of the antitumour agent *N*-[2-(dimethylamino)ethyl]acridine-4-carboxamide in plasma by high performance liquid chromatography. J Chromatogr Biomed Appl 528: 385–394