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Pharmacokinetics of Anandron in patients with advanced carcinoma of the prostate

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Summary. The pharmacokinetics of total radioactivity and unchanged drug were studied in patients receiving Anandron (Nilutamide, RU 23908) after a single dose of [^{14}C] Anandron and after q12 h dosings of unlabelled drug for 2–7 weeks. The results indicate that the radioactivity in plasma consists of unchanged drug and metabolites. The plasma decay of Anandron after the absorption phase was biexponential in all patients, with the terminal phase half-life ranging from 23.3–87.2 h. The plasma decay of total radioactivity after the absorption phase was biexponential in 3/12 and monoexponential in 9/12 patients. The calculated terminal phase half-lives for total radioactivity after [^{14}C] Anandron were 34.5–137.3 h. The $AUC_{0-\infty}$ of the unchanged drug in plasma represented 23%–38% of the $AUC_{0-\infty}$ of total radioactivity. Urinary radioactivity consisted primarily of metabolites, the majority of which were chloroform-nonextractable. Urinary excretion of radioactivity at 120 h ranged from 49%–78% of the administered dose; the unchanged Anandron (at 72 h) was 0.6%–1.3% of the dose. In three patients studied, the fecal excretion of Anandron was 1.4%–7.0%. Steady-state plasma levels (4.4–8.5 μg/ml) were attained within approximately 2 weeks from the initiation of twice daily dosing of Anandron. When the plasma pharmacokinetics of radioactivity and unchanged drug after the first single dose were compared with that during steady state, $AUC_{0-12\,h}$ of unchanged Anandron during steady state was significantly higher than the $AUC_{0-\infty}$ after the first single dose, suggesting that the plasma clearance of Anandron is lowered upon chronic administration of the drug, assuming that the bioavailability is constant.

Introduction

Anandron (Nilutamide, RU 23908, 5,5-dimethyl 3-[4-nitro-3 (trifluoro-methyl) phenyl] 2,4-imidazolidinedione) (Fig. 1) is a nonsteroid antiandrogen currently being clinically evaluated for the treatment of carcinoma of the prostate. It blocks the androgen activity by interacting with the cytoplasmic androgen receptor sites at all target sites, namely, the pituitary, hypothalamus, and prostate [12]. The drug, however, is not suitable for inducing chemical castration because it blocks the feedback mechanism that controls the testosterone concentration, causing a progressive increase in testosterone secretion: when the drug was given daily to rats for 14 days, a 17-fold increase in plasma testosterone levels were observed [13]. The increased production of testosterone counteracts the antiandrogen effect in the prostate. Therefore, Anandron has primarily been tested as an adjuvant therapy in orchiectomized patients and in patients receiving LH-RH analogs, since it can counteract the effect of adrenal androgen secretion [4–6, 14]. The first results of the ongoing studies have demonstrated its efficacy on both subjective and objective findings in patients with advanced prostatic cancer [1, 2, 7].

In its clinical evaluation the drug has been given orally twice or three times daily. Its pharmacokinetics have been studied in rats and, in a limited way, in a small number of normal human volunteers [10, 11]. No data were available on the disposition of Anandron in patients receiving this drug either as a single dose or in mulitple dosing schedules. We therefore undertook a detailed pharmacokinetic study of Anandron in patients with advanced carcinoma of the prostate. The study was aimed at understanding (a) the pharmacokinetics of radioactivity and unchanged drug after a single dose of [^{14}C] Anandron, (b) the accumulation kinetics of the drug on repetitive dosing, and (c) the effect of repetitive dosing on the pharmacokinetics of the drug. Reported here are the results of this study. A brief account of the results has previously been published [9].

Materials and methods

Anandron was supplied by Roussel UCLAF (Paris, France) in 50-mg tablets. [^{14}C] Anandron was supplied in 50-mg tablets, each containing 40 μCi. Twelve patients with histologically confirmed diagnosis of stage D carcinoma of the prostate who gave written informed consent were entered into the study, which was carried out under a protocol approved by the Institutional Review Board

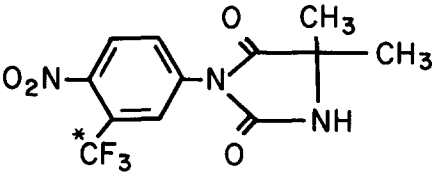

Fig. 1. Structure of Anandron 5,5-diemthyl 3-[4-nitro 3(trifluoromethyl)-phenyl] 2,4-imidazolidinedione). * position of [^{14}C] label

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Table 1. Characteristics of the patients entered into the study

Patient number	Age	Performance status (ECOG)	SGOT* (IU/l)	Alkaline phosphatase* (IU/l)	LDH* (IU/l)	Bilirubin* (mg/dl)	BUN* (mg/dl)	Serum creatinine* (mg/dl)
1	73	2	31	1370	186	0.4	16	0.8
2	75	2	47	175	287	1.3	35	1.4
3	64	2	20	206	–	0.3	16	0.9
4	69	2	30	272	259	0.5	13	1.0
5	76	2	57	>480	256	0.6	25	1.0
6	82	2	23	625	411	0.4	15	0.5
7	57	3	19	490	226	0.3	16	0.6
8	66	1	31	84	242	0.5	10	0.9
9	75	1	24	211	257	0.4	16	1.1
10	77	1	15	108	174	0.2	33	1.1
11	74	1	16	246	281	0.6	16	1.0
12	62	1	21	174	173	0.8	16	1.1

* Upper limit of normal: SGOT, 50 IU/l; Alkaline phosphatase, 115 IU/l; LDH, 225 IU/l; Bilirubin, 1.5 mg/dl; BUN, 26 mg/dl; serum creatinine, 1.4 mg/dl

(Table 1). All patients were hospitalized and received [^{14}C] Anandron on day 1 (150 mg/120 μCi in ten patients, 200 mg/160 μCi in two patients). Patients fasted for 10 h before and 4 h after receiving the dose. The pharmacokinetics of the unchanged drug were studied for 72 h after this initial single dose and that of radioactivity for 144 h or more. Following the study of the single-dose pharmacokinetics, 11 patients began a 12 h dosing of unlabelled Anandron, starting either on day 4 (eight patients) or on day 8 (three patients). One patient (patient 1, Table 1) received a single dose of [^{14}C] Anandron. He subsequently had a disease-related hemorrhage and was withdrawn from the study before the initiation of repetitive dosing. Patients 2–4 received 150 mg b.i.d., which was well tolerated. The dose was then escalated to 200 mg b.i.d., but because of gastrointestinal side effects in the first patient treated at this dose (patient 5), all subsequent patients received 150 mg b.i.d. The drug was given for 2–7 weeks and the kinetics of Anandron accumulation were studied. At the end of 5–7 weeks, six patients were again hospitalized and received a second dose of [^{14}C] Anandron (150 mg/120 μCi) while continuing on a q12h dosing of unlabelled Anandron. The pharmacokinetics of radioactivity and unchanged drug were studied and compared with those after the first single dose.

Sample collection. Sampling of blood was typically carried out at 0.5, 1, 2, 4, 6, 12, 24, 36, 48, 60, and 72 h after the first single [^{14}C] Anandron dose. Urine samples were collected in 6- to 12-h pools through day 7. At the initiation of twice daily dosing of Anandron, blood samples were taken every 12 h immediately prior to the drug intake, while the patients were hospitalized, and at 1- to 2-week intervals subsequently on an outpatient basis. Blood and urine sampling after the second dose of [^{14}C] Anadron was similar to that after the first.

Measurement of total radioactivity in plasma, urine, and feces. Radioactivity measurements were made by liquid scintillation counting. An external standard method was used for quench correction of radioactivity in plasma and urine, whereas an internal standard method was used for that in feces.

Measurement of unchanged Anandron from plasma and urine. Anandron was measured by an isocratic reverse-phase high performance liquid chromatography (HPLC) method developed for this purpose. The HPLC system consisted of a Waters (Milford, Mass.) M590 or M600A pump, 441 UV detector, an automatic sample injector model 710 WISP, and a Varian (Walnut Creek, Calif.) 402 chromatography data system. The column was an IBM C18 (5-μm particle size, 25 cm), the mobile phase was 70% methanol set at a flow rate of 1.2 ml/min, with UV detection at 254 nm and detector sensitivities set at 0.005 or 0.02. An external standard method was used for quantitation of Anandron. Anandron was extracted from 1 ml plasma or urine with 2 ml chloroform. A measured volume of the chloroform was separated and evaporated. The residue was reconstituted to the original concentration in mobile phase and a 10- to 20-μl sample was injected into the HPLC. The method was specific for Anandron and, under our assay conditions, had a retention of ~4.5 min. The detection limit was 50 ng/ml. The extraction efficiency of Anandron with chloroform was >98%. In Figs. 2 and 3,

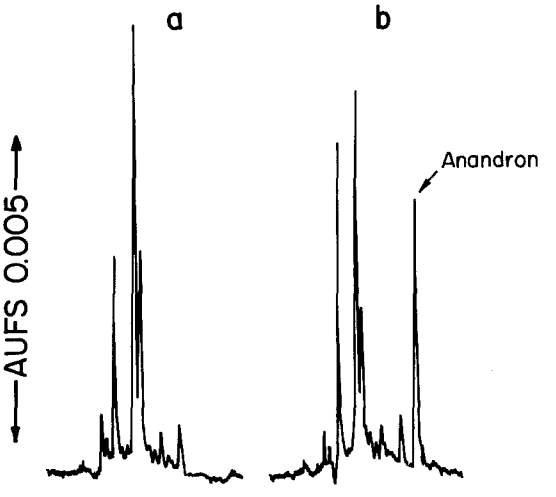

Fig. 2. HPLC separation of Anandron in the plasma of a patient. *a*, Pretreatment sample; *b*, sample obtained 2 h after Anandron administration

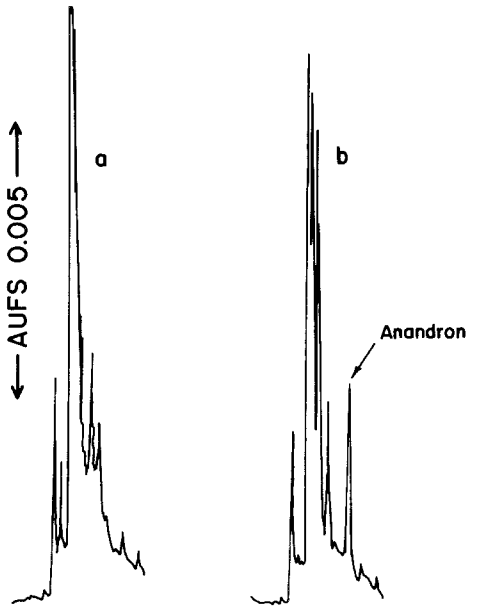

Fig. 3. HPLC separation of Anandron in the urine of a patient. *a*, Pretreatment sample; *b*, sample obtained 18 h after Anandron administration

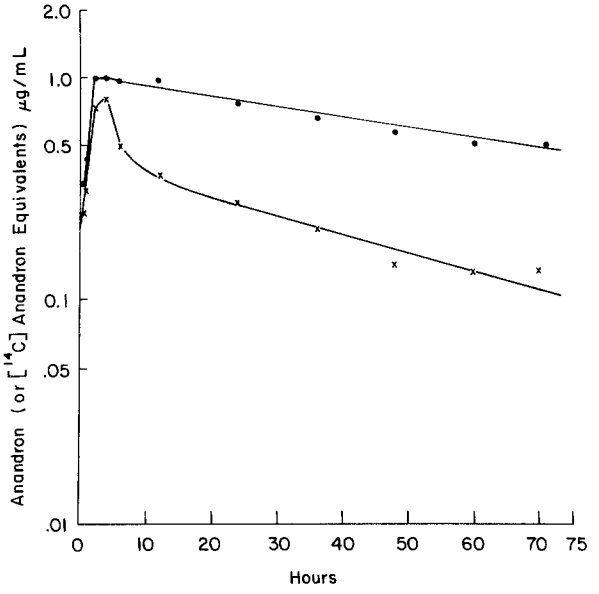

Fig. 4. Plasma profiles of radioactivity (–o–) and unchanged Anandron (–x–) in a patient receiving 150-mg dose

the separation of Anandron in plasma and urine are shown.

Nature of metabolites. From each sampling period 1 ml urine was extracted with 2 ml chloroform, and the radioactivity remaining in the aqueous phase was determined. This radioactivity represents the hydrophilic metabolites of Anandron.

Plasma protein binding of Anandron. The protein binding of Anandron was measured by centrifugal ultrafiltration after the addition of [^{14}C] Anandron to human plasma, to given final concentrations of 200, 100, 50, 20, 5, and 1 µg/ml. After Anandron was added to the plasma, each dilution was placed in a 30° C water bath for 10 min. Duplicate 1-ml samples of each concentration were ultrafiltered using Amicon Centrifee ultrafiltration devices in a fixed angle rotor (IEC CRU 5000 Centrifuge) at 2000 *g* for 10 min. A 0.25-ml sample of plasma before ultrafiltration and a 0.25-ml sample of plasma ultrafiltrate were counted in 10 ml of ACS II scintillation fluid.

A control experiment was carried out to evaluate the nonspecific binding of Anandron to the ultrafiltration membranes. This experiment was carried out in a manner identical to that above, except that Anandron was added to phosphate-buffered saline (PBS) to make final concentrations of 1 and 5 µg/ml, which were then ultrafiltered using the Amicon Centrifree devices.

Pharmacokinetic data analysis. A noncompartmental pharmacokinetic analysis of the data was carried out using the computer program Lagran [15] on a Sperry PC. The AUC and the terminal phase half-life were calculated for each patient with the use of this program. The apparent t_{max} and C_{max} reported were the values observed for each patient. Comparisons of pharmacokinetic parameters were carried out by a paired *t*-test using the computer program "Epistat" on a Sperry PC.

Results

Single-dose pharmacokinetics

Plasma decay of radioactivity and unchanged drug. In Figs. 4 and 5, the typical plasma decay profiles of radioactivity in Anandron equivalents and that of unchanged Anandron after the [^{14}C] Anandron dose for two representative subjects are shown. As seen in these figures, the profile of plasma radioactivity varied: three patients showed the profile indicated in Fig. 5, with a distinguishable distribution phase prior to the terminal elimination phase, whereas the remaining patients showed no distinguishable distri-

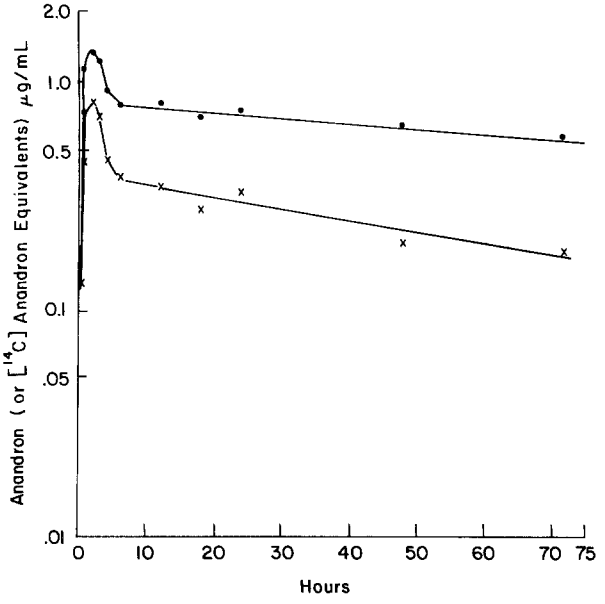

Fig. 5. Plasma profile of radioactivity (–o–) and unchanged Anandron (–x–) in another patient receiving 150-mg dose

bution phase (Fig. 4). The plasma decay of radioactivity was slow and measurable for 144 h or more from the time at which the first [^{14}C] dose was given (Fig. 6). The multiple dosing of the patients start on day 4 or 8 did not affect the slope of this curve. The profile of Anandron in plasma after a single dose of Anandron was similar in all 12 patients, showing an absorption phase followed by distribution and elimination phases. In Table 2, the observed C_{max} and t_{max} values and the calculated $AUC_{0-\infty}$ and terminal phase $t_{1/2}$ values for radioactivity and unchanged drug for all patients, along with the dose adjusted on a mg/m^2 basis, are shown. The C_{max} for unchanged drug (150-mg dose) ranged from 0.52 to 1.17 μg/ml, representing 49%–90% of the C_{max} for radioactivity. The t_{max} for Anandron was 1–4 h and that for radioactivity, 2–12 h. The AUC for radioactivity (150-mg dose) ranged from 103.2 to 169.4 μg·ml^{-1}·h. The AUC for Anandron ranged from 25.2–54.5 μg·ml^{-1}·h, representing 23%–38% of the total radioactivity. The terminal phase half-life for the radioactivity was 34.5–136.3 h, and that for the unchanged drug was 23.3–87.2 h. The pharmacokinetic parameters (C_{max}, AUC, and $t_{1/2}$) for radioactivity were significantly different from those for unchanged Anandron (paired *t*-test: $P < 0.01$). The AUC, a parameter that can be related to the dose of the drug (for drugs showing linear kinetics), was examined more closely in relation to the adjusted dose (mg/m^2). Since doses are not widely variable, linear regression analysis with the fit constrained through zero was chosen. The results indicate that the data on both radioactivity and the unchanged drug correlate linearly with the dose, with *r* values of 0.952 and 0.959, respectively. The AUCs of both radioactivity and the unchanged drug for patients 5 and 6 showed the most deviation from the fitted curve (patient 5, higher AUC; patient 6, lower AUC).

At early times after drug administration, Anandron accounted for the major portion of the total radioactivity in plasma, as shown in Table 3. At 2 h after drug intake, 79% of the total radioactivity was unchanged drug, declining to 32% at 72 h.

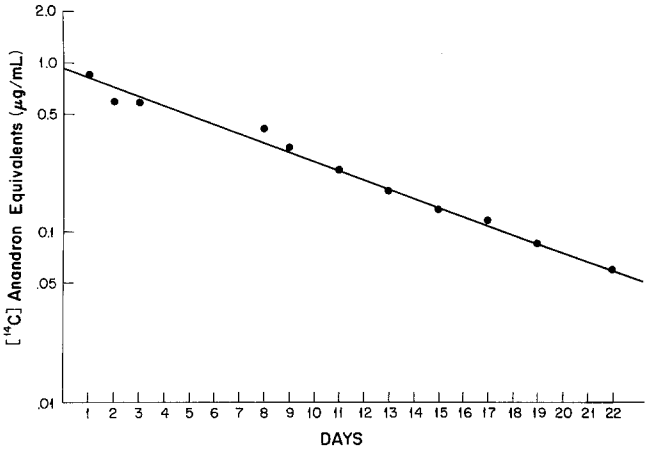

Fig. 6. Plasma decay of radioactivity in a patient after 150-mg dose of [^{14}C] Anandron. This patient started receiving q12h dosings of unlabelled Anandron starting from day 8

The in vitro plasma protein-binding experiments indicated a 72%–85% binding at the concentrations tested (Table 4). A significant change in protein binding was observed only at concentrations higher than 20 μg/ml. At the Anandron concentration we typically measured in plasma, 84% binding was obseerved.

Urinary excretion of radioactivity and the unchanged drug. The cumulative urinary excretion of radioactivity and Anandron after drug administration is shown in Fig. 7 for a representative patient. The excretion was slow and continuing at 120 h. The percentage of the dose excreted as radioactivity and unchanged drug for each of the patients is shown in Table 5. Although up to ~78% of the radioactivity was recovered in urine at 120 h (Table 5), the unchanged

Table 2. Pharmacokinetic parameters of plasma radioactivity and unchanged. Anandron after the first single dose of [^{14}C] Anandron

Patient number	Dose (mg/m^2)	C_{max} (μg/ml)		t_{max} (h)		$AUC_{0-\infty}$ (μg · ml^{-1} · h)		Terminal phase $t_{1/2}$ (h)	
		Total radioactivity	Unchanged drug	Total radioactivity	Unchanged drug	Total radioactivity	Unchanged drug	Total radioactivity	Unchanged drug
1	89.2	1.34	1.17	6.0	2.0	151.5	38.5	74.1	51.7
2	77.7	1.36	0.82	2.0	2.0	151.7	35.8	137.3	61.2
3	94.9	1.51	0.98	6.0	1.0	156.5	35.5	94.1	48.2
4	75.0	1.06	0.52	6.0	3.0	111.5	33.4	106.7	79.1
5[a]	104.2	2.28	1.45	4.0	2.0	293.1	73.6	95.2	61.1
6[a]	122.6	2.26	1.94	4.0	2.0	106.7	37.4	34.5	23.3
7	89.2	1.76	1.33	4.0	4.0	123.7	33.4	48.9	34.3
8	75.0	1.03	0.81	12.0	4.0	129.1	49.5	82.4	53.5
9	79.8	1.38	0.70	12.0	4.0	169.4	54.5	100.8	87.2
10	70.4	1.03	0.82	4.0	4.0	103.2	25.2	72.5	39.3
11	79.8	1.13	0.84	4.0	2.0	135.8	40.0	99.8	60.2
12	68.2	1.25	1.07	2.0	2.0	127.6	40.4	96.5	75.9
Range		1.03 – 1.76	0.52 – 1.17	2.00 – 12.0	1.00 – 4.0	103.2 – 169.4	25.2 – 54.5	34.5 – 137.3	23.3 – 87.2
Mean[b] ± SD		1.29 ± 0.24	0.91 ± 0.24	5.80 ± 3.68	2.80 ± 1.14	136.0 ± 21.0	38.6 ± 8.4	86.9 ± 27.1	56.3 ± 18.8

[a] 200 mg dose

[b] Mean ± SD of t_{max} and $t_{1/2}$ for all patients. Mean ± SD of C_{max} and AUC are for patients receiving 150-mg dose

Table 3. Proportion of Anandron to total radioactivity in plasma at specific times after the addition of [^{14}C] Anandron

Time (h)	Ratio of Anandron/total radioactivity in plasma (mean ± SD)[a]
1	0.83 ± 0.14
2	0.79 ± 0.14
6	0.49 ± 0.09
12	0.40 ± 0.07
24	0.36 ± 0.04
72	0.32 ± 0.05

[a] Average for all patients

drug accounted for < 1% of the total dose, indicating that urine consisted only of metabolites. In urine, 75%–100% of the radioactivity was found in the aqueous phase by chloroform extraction, revealing the hydrophilicity of the Anandron metabolites (Table 4).

Excretion of radioactivity in feces. In three patients, the proportion of radioactivity excreted at the end of 4–5 days was 1.4%–7.0% of the total dose given (Table 6).

Accumulation of Anandron after multiple dosing

Patients treated with Anandron q12h showed the typical accumulation kinetics shown in Fig. 8. Steady-state levels were attained in an approximately 2-week period, as assessed from 8/11 patients who received the drug for a period larger than 2 weeks. At 150 mg q12h, the steady-state levels ranged between 4.4 and 8.5 μg/ml.

Pharmacokinetics of radioactivity and unchanged drug after the second radioactive dosing during steady state

Six patients received a second 150-mg dose of [^{14}C] Anandron between 38 and 51 days after the initiation of multiple dosing. The plasma AUCs and $t_{1/2}$ for both radioactivity and unchanged Anandron were calculated after the second [^{14}C] Anandron dosing for all these patients. Since plasma decay of radioactivity is not affected by continued q12h dosing with the unlabelled drug, the $AUC_{0-\infty}$ and terminal phase $t_{1/2}$ were calculated using all the data. For the unchanged drug, the AUC and terminal $t_{1/2}$ were determined with data obtained from intense sampling in one dosing interval, i.e., $AUC_{0-12\,h}$ and $t_{1/2}$ through 12 h data. In Tables 7 and 8, the comparison of these data to those obtained after the first [^{14}C] dosing in the same patients are shown. When a paired *t*-test was used to compare each pa-

Table 4. Plasma protein binding of Anandron

Anandron concentration (μg/ml)	Protein-bound (%)
1.0	84.5
5.0	84.4
20.0	84.0
50.0	80.8
100.0	78.9
200.0	71.9

Control experiments performed in phosphate-buffered saline have indicated > 96% recovery of Anandron in ultrafiltrate

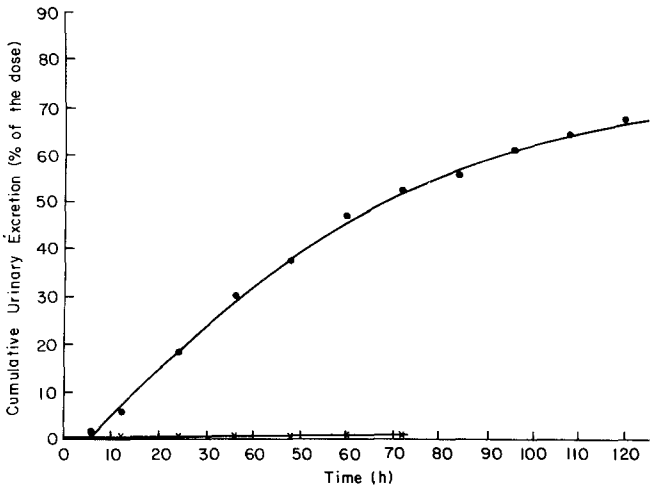

Fig. 7. Cumulative urinary excretion of radioactivity (–o–) and unchanged Anandron (–x–) in a patient receiving 150-mg dose of [^{14}C] Anandron. This patient started receiving q12h dosings of unlabelled Anandron starting from day 4

Table 5. Urinary excretion of radioactivity and the unchanged drug after the first single [^{14}C] Anandron dose and the nature of urinary metabolites

Patient number	Urinary excretion (% of dose)		% Radioactivity that is $CHCl_3$-nonextractable[b]
	Total radioactivity (at 120 h)	Unchanged drug (at 72 h)[a]	
1	20.5[c]	–	89 – 96
2	48.8	0.73	75 – 87
3	71.2	1.13	82 – 99
4	66.4	0.48	92 – 100
5	54.5	0.94	80 – 92
6[d]	–	–	87 – 96
7	77.9	1.21	89 – 94
8	68.4	1.17	91 – 98
9	49.0	1.09	88 – 96
10	53.7	0.49	89 – 93
11	64.4	0.63	86 – 99
12	61.5	0.14	89 – 94
Mean ± SD	61.6 ± 9.8	0.80 ± 0.36	

[a] Values only up to 72 h are reported since the multiple dosing regimen began after this in 8/12 patients
[b] The values shown are the range of percentage of nonchloroform-extractable radioactivity present in all urine tested after the first [^{14}C] Anandron dose in each of the patients
[c] Up to 24 h
[d] Incomplete collections
–, No data

Table 6. Excretion of radioactivity in feces after [^{14}C] Anandron

Patient number	Dose excreted in 5 days (%)
2	1.6
3	7.0
4	1.4*

* 4 days

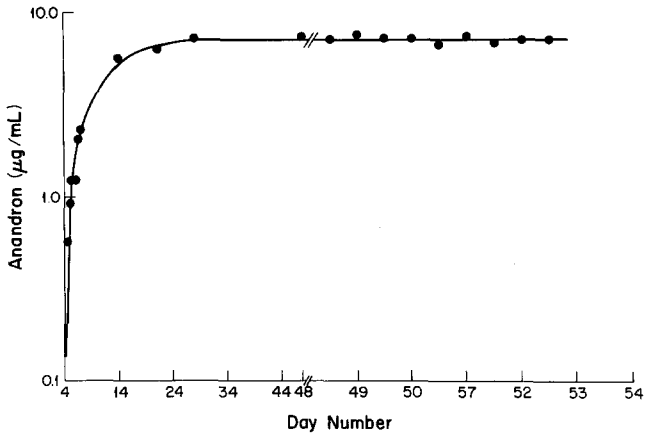

Fig. 8. Accumulation of Anandron in a patient receiving 150-mg q12h dosings of unlabelled drug

Table 7. Half-life and AUC of radioactivity after first [^{14}C] Anandron dose and during steady state

Patient number	First dose		Steady state	
	$t_{1/2}$ (h)	$AUC_{0-\infty}$ ($\mu g \cdot ml^{-1} \cdot h$)	$t_{1/2}$ (h)	$AUC_{0-\infty}$ ($\mu g \cdot ml^{-1} \cdot h$)
6[a]	34.5	106.7	61.6	105.7
7	48.9	123.7	100.2	192.2
9	100.8	169.4	76.0	128.3
10	72.5	103.2	91.1	111.8
11	99.8	135.8	145.6	183.4
12	96.5	127.6	76.0	82.8
Mean ± SD	76 ± 29	132 ± 24	92 ± 30	140 ± 47

[a] This patient received 200 mg [^{14}C] Anandron at the first dose and 150 mg at the second. The AUC comparison was therefore confined to the remaining five patients

Table 8. Half-life and AUC of Anandron after the first single dose and during steady state

Patient number	First dose		Steady state	
	$t_{1/2}$ (h)	$AUC_{0-\infty}$ ($\mu g \cdot ml^{-1} \cdot h$)	$t_{1/2}$ (h)	$AUC_{0-12\,h}$ ($\mu g \cdot ml^{-1} \cdot h$)
6[a]	23.3	37.4	31.9	65.8
7	34.3	33.4	31.3	92.5
9	87.2	54.5	47.8	108.6
10	39.3	25.2	46.4	73.3
11	60.2	40.0	47.0	81.3
12	75.9	40.4	27.8	93.1
Mean ± SD	53 ± 25	39 ± 11	38.7 ± 9.3	90 ± 13

[a] This patient received 200 mg [^{14}C] Anandron at the first dose and 150 mg at the second. The AUC comparison was therefore confined to the remaining five patients

rameter after the first dose with that at steady state for both radioactivity and unchanged drug, a highly significant difference ($P = 7 \times 10^{-5}$) was found only for the AUC of Anadron, the $AUC_{0-\infty}$ for Anandron after the first dose being significantly lower than the $AUC_{0-12\,h}$ during steady state.

Discussion

The bioavailability and pharmacokinetics of Anandron have been studied in the rat and the dog [7, 8]. The bioavailability was complete in the rat and 70% in the dog, and the half-lives were 7 h and 11.6 h, respectively. The present study was carried out to understand the disposition of this drug in man and revealed an important difference between the species in terms of the half-life of the drug. We found that the half-life of Anandron in patients is extremely long (23–87 h) compared with that in animals. The half-life for radioactivity after treatment with [^{14}C] Anandron was also longer in patients (35–137 h) when compared to the 11 h previously observed in the rat [11]. The species differences in half-lives of Anandron is not attributable to differences in protein binding, because 80% protein binding has been reported for Anandron in both rat and dog plasma, and we observed a similar 84% protein binding for the drug in human plasma.

The bioavailability of Anandron could not be determined in this study because a parenteral from was not available. However, the negligible excretion of radioactivity in the feces and the high recovery in the urine indicate that Anadron is well absorbed from the GI tract. Judging from the values of the AUCs for Anandron and total radioactivity, it is apparent that the exposure to metabolites accounted for about 70% of the total body exposure after Anandron. It should be noted, however, that unchanged Anandron predominated in the first 2 h after [^{14}C] Anandron (~80% of the total radioactivity at 2 h), gradually declining to 50% at 6 h and to 32% at 72 h. Thus, metabolism of Anandron appears to be a relatively slow process, which is consistent with the observation of slow excretion of radioactivity in the urine. Our data showed that only negligible amounts of Anandron are excreted in the urine, while the Anandron metabolite(s) is the predominant renal excretion product. The slow metabolism of Anandron has also been observed in the rat, where 70–95% of radioactivity was associated with unchanged drug in the first 6 h [11].

We saw a large variability in all the pharmacokinetic parameters after [^{14}C] Anandron. However, some of the apparent variability, such as that in AUCs is reduced when one considers this parameter in relation to the dose adjusted to the body surface area rather than to the total dose. The deviations observed in the AUCs for radioactivity and Anandron in patients 5 and 6 cannot be explained on the basis of their history or clinical course. Although patient 5 had high values for SGOT and alkaline phosphatase, the SGOT value was only slightly greater than the upper limit of normal, and subsequent values were in the normal range. The alkaline phosphatase value in this patient was probably related to bony metastases. The unusually long half-life of radioactivity in patient 2 might be related to a slight impairment of renal function, as BUN was 35 in this patient and serum creatinine was at the upper limit of normal (Table 1). However, in general, the type of variability observed here is not unusual because of a number of compounding variables that exist in such a patient population, with other medications and intrinsic variability in plasma protein binding. Despite this variability, the data does show that the disposition of Anandron in cancer patients is not different from that in normal individuals who received the drug. Pottier et al. [11] have studied the pharmacokinetics of Anandron in 12 human volunteers and found that the drug shows linearity in kinetics and has an

average half-life of 46 h. The mean $t_{1/2}$ observed for Anandron in this study is 56.3 ± 18.8 h (Table 2).

There is only limited pharmacokinetic information on other antiandrogens. Flutamide (trifluouro-2-methyl-4'-nitro-*m*-propionotoluidide), another nonsteroid antiandrogen and structural analog of Anandron, appears to be a prodrug, giving rise to a metabolite with active antiandrogenicity [8]. Flutamide is rapidly metabolized in humans, as is evident from the observation that only ~2% of the total radioactivity has been accounted for by the unchanged drug in plasma as early as 1 h after drug administration [3]. The drug is metabolized to many compounds, and the proportion of the presumedly active metabolite represented 23% and 10%, respectively, of the total radioactivity in plasma at 1 and 8 h after drug administration. The half-life of this active flutamide metabolite appears to be about 6 h, but this cannot be said with certainty because of the limitation of measurement to 8 h posttreatment [3].

The accumulation kinetics of q12h dosing of Anandron indicated that it takes ~2 weeks for the steady state to be attained, the steady-state levels at a dose of 150 mg being 4.4–8.5 μg/ml. It is quite interesting that, although linearity in kinetics was observed in our own study between the adjusted dose of 68.2– 122.6 mg/m^2 and that of Pottier et al. at three different single doses (100, 200, and 300 mg), we found that upon chronic administration the pharmacokinetics deviated from linearity: $AUC_{0-12\,h}$ (AUC in one dosing interval) of Anandron is significantly higher than $AUC_{0-\infty}$ after the single dose. Assuming that the bioavailability of the drug has not changed during this repetitive dosing, this observation indicates that the clearance of the drug decreased. Whether this is related to a change in the distribution of the drug or to a change in the activity of the drug-metabolizing enzymes is not known at this time. The former seems more probable since no difference was observed between the half-life after the first dose and that after repeated doses. However, it is of interest to note that in a large study (total, 184 patients) carried out in France [2], where a radioimmunoassay was used to determine the steady-state levels of the drug in patients taking 150 mg/day or 300 mg/day as capsules over a period of 12 months, concentrations were constant over time and the observed steady-state levels were proportional to the dose. Thus, while our studies indicate that the predictability of steady-state levels based on single-dose pharmacokinetics may not be valid for this drug, the studies of Brisset et al. [2] have indicated that steady-state levels may be predicted for other repetitive doses if steady-state levels are known for a given chronic dosing. From our study we cannot assess the dose proportionality for steady-state levels, because only one patient received 200 mg b.i.d., while all others received 150 mg (patient 5, who received chronic dosing of Anandron at 200 mg, had a steady-state level of 13.0 μg/ml, whereas patients receiving 150 mg had 6.33 ± 1.28 μg/ml).

In conclusion, Anandron, an active antiandrogen, is well absorbed from the GI tract and is slowly metabolized. The overall exposure the body receives is due more to the metabolite fraction than to Anandron. However, Anandron is in the plasma for a prolonged period and appears to be cleared only by metabolism. There are changes in its pharmacokinetics with chronic administration of the drug, which are not understood at this time. Based on the very long half-lives of unchanged Anandron and on the fact that it is only the unchanged Anandron and not the metabolite(s) that has antiandrogen activity [11], it seems that Anandron can be given less frequently than in this study and that perhaps a q24h administration of the drug would be appropriate.

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