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Pharmacology of Mitoxantrone in Cancer Patients

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Summary. *Radioactive mitoxantrone was administered at doses of 1–12 mg/m² by rapid IV infusion to 11 patients. Of the 11 patients, six had normal liver and kidney function tests while the remaining five had abnormal third space and/or hepatic dysfunction. In the former group, the initial $t_{1/2}$ was 13.7 min and terminal $t_{1/2}$ was 37.4 h. The apparent volume of distribution was 13.8 l/kg. The total clearance rate was 230.7 ml/kg/h. The recovery of unchanged mitoxantrone from urine was 6.8% at 24 h and 7.3% at 72 h, while the corresponding recovery of total radioactivity was 9.4% at 24 h and 11.3% at 72 h. In the five patients with abnormal liver function or third space the initial $t_{1/2}$ was variable and ranged from 11.5–63.6 min, and the terminal $t_{1/2}$ ranged from 53.3–173.2 h, whereas the total clearance rate varied from 52.7–170.2 ml/kg/h. However, the cumulative urinary excretion of unchanged mitoxantrone was similar to that of patients with normal hepatic function: 3.9 at 24 h and 5 at 72 h. Biliary excretion was studied in one of these patients, who had jaundice and hepatic impairment; only 2.3% of ^{14}C was excreted in 24 h and 2.7% in 96 h, of which 39% and 41%, respectively, were unchanged mitoxantrone. Our results suggest that mitoxantrone is taken up rapidly by tissue from which it is released slowly. Reduction of mitoxantrone dose is therefore advisable in patients with liver dysfunction or abnormal third space.*

Introduction

Mitoxantrone (NSC-301739), 1,4-dihydroxy-5,8-bis[(2[(2-hydroxyethyl)amino]ethyl)amino]-9,10-anthracenedione dihydrochloride) (Fig. 1), a new anthracenedione derivative, has shown antitumor activity superior or equal to that of doxorubicin in several animal tumor systems, but apparently without cardiotoxicity [4, 7, 8, 11, 12]. Although its mechanism of action remains obscure, preliminary evidence suggests that, like doxorubicin, mitoxantrone intercalates with DNA [2, 3] and is a potent inhibitor of RNA and DNA synthesis of cultured mouse lymphoma L5178Y cells. Compared with doxorubicin on an equimolar basis, mitoxantrone is approximately seven times more potent in inhibiting the incorporation of ^{3}H-uridine and four times more potent in inhibiting the incorporation of ^{3}H-thymidine in these cells [1].

In beagle dogs and cynomolgus monkeys, myelosuppression and toxic gastrointestinal manifestations, such as emesis and bloody diarrhea, appeared to be the major dose-limiting toxic effects of mitoxantrone. Other toxic effects included weakness, weight loss, swollen limbs, labored breathing, hyperthermia, excessive salivation, and lacrimation [1]. Because of its impressive anticancer activity in experimental systems and its apparent lack of cardiotoxicity, mitoxantrone has been selected for phase I/II clinical trial.

Von Hoff et al. recently reported the maximum tolerated dose of mitoxantrone to be 14 mg/m² given by IV infusion every 4 weeks [10]. Myelosuppression was the dose-limiting factor, while other toxic effects,

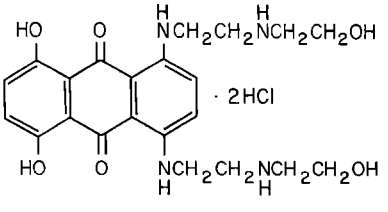

Fig. 1. Structural formula of 1,4-dihydroxy 5-8 bis[(2[(2-hydroxyethyl)amino]ethyl)amino]9,10-anthracenedione dihydrochloride; NSC 301739, mitoxantrone

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such as nausea, vomiting, and diarrhea, were uncommon. There was no evidence of cardiotoxicity, renal failure, or alopecia in the 25 patients studied.

We now describe our clinical pharmacology studies of mitoxantrone in 11 patients with metastatic cancer; the results may be of interest to investigators involved in phase I/II trials of this drug.

Materials and Methods

Mitoxantrone specifically labeled with ^{14}C in all four carbons of the bis-(2-hydroxyethyl) moiety (specific activity 11.2 mCi/mmole, 95% pure chemically and radiochemically) and the unlabeled drug were generously supplied by the Drug Developmental Branch of the National Cancer Institute; they were specifically designated for human use. The drug was formulated in normal saline at a concentration of 50 μg/ml and administered to patients as an IV infusion over 15 min.

Eleven patients who had histologically proven malignancy and had failed conventional chemotherapy were recruited for the study. Informed consent was obtained in all patients before treatment. Two patients had abnormal liver biochemical test (elevation of serum glutamic oxaloacetic transaminase, alkaline phosphatase, and bilirubin to more than twice normal values), two patients had ascites, and one had massive leg edema secondary to lymphatic obstruction from metastatic cancer. All patients had normal renal function tests (normal blood urea nitrogen and serum creatinine) and normal blood cell count (WBC above 3,000/μl and platelet count above 100,000/μl). Patients' characteristics are listed in Table 1.

Sample Collection. Blood (10 ml) was collected via a heparin lock at 0, 15, and 30 min, and at 1, 2, 4, 6, 12, 24, 48, and 72 h. Plasma was separated by centrifugation for determination of mitoxantrone. Urine was also collected, at 6-h intervals for the first 24 h and then daily up to 72 h.

Radiochemical Technique. Radioactivity was determined with a Packard Tricarb liquid scintillation spectrometer model 2650; quenching was corrected by the external standard channels ratio method; for ^{14}C the counting efficiency was about 90%. Plasma or urine (0.2 ml) was counted in 11 ml PCS, a commercial phase-combining counting solution available from Amersham, Arlington Height, IL.

Determination of Unchanged Mitoxantrone by High-pressure Liquid Chromatography. All plasma samples (10 volumes) were deproteinated with 20% sulfosalicylic acid (1 volume) and the supernatant was adjusted to pH 10 with 8 *N* NaOH; urine samples were also made alkaline to pH 10. The deproteinated plasma or urine was extracted with an equal volume of chloroform-isopropanol (1 : 1, v/v), accompanied by vigorous agitation with a vortex mixer for 5 min, and centrifuged at 12,500 *g* (Sorvall RC2-B centrifuge) for 20 min. The organic phase was removed and evaporated to dryness in a sample concentrator (Brinkman Instrument, Inc., Model SC/48 Westbury, NY, USA) under a stream of nitrogen. The residue was reconstituted with 150 μl distilled water for injection into the high-pressure liquid chromatography (Water Associates Model 204), for which a Waters μ Bondapak C_{18} reverse-phase column (30 cm × 40 mm ID) was used. The elution system consisted of 0.1 *M* acetate buffer, pH 3.96, in 30% methanol, at a flow rate of 2 ml/min under 2,000 psi, with the UV detector set at 254 nm. The location of the unchanged mitoxantrone was ascertained by running unlabeled mitoxantrone through the column. The retention time for mitoxantrone was 16 min. Eluate was collected at 2-min intervals for 20 fractions. The fractions were mixed with 11 ml PCS and the radioactivity was counted in the liquid scintillation counter. The recovery of total radioactivity was greater than 90%.

Computation of the Results. Nonlinear least-square regression analysis of the results was performed with the aid of the PROPHET program. Best fit was obtained on the basis of the conventional open two-compartment model. Pharmacokinetic parameters were computed in the usual fashion.

Results

The pharmacokinetic parameters of mitoxantrone in the first six patients who had normal liver biochemical tests and no abnormal third space is shown in Table 2. The harmonic mean initial half-life of the drug was 13.7 min and the terminal half-life was 37.4 h. The apparent volume of distribution was about 13.8 l/kg, suggesting extensive tissue binding. The mean total clearance was 238.7 ml/kg/h, twice as high as the creatinine clearance in man.

The cumulative urinary excretion of unchanged drug for the first six patients was 7.3% at 72 h, whereas the corresponding recovery of total radioactivity was 11.3% at 72 h (Fig. 2). Therefore unchanged mitroxantrone accounted for 64.6% of the total radioactivity.

Table 3 shows the pharmacokinetic parameters of the remaining five patients who had abnormal liver biochemical tests and/or abnormal third space. The harmonic mean terminal half-life was 70.7 h, which is significantly longer than that of the first six patients, and the mean clearance was 100.7 ml/kg/h, which is significantly lower than that in the six patients of the first group. The computer-generated plasma clearance curve for total unchanged mitoxantrone in a patient with normal hepatic and renal function (patient 4) in comparison with that of a patient with ascites (patient 7) is shown in Fig. 3.

The mean cumulative urinary excretion of unchanged mitoxantrone in this group of patients was 5.1% at 72 h and the corresponding total ^{14}C was 10.2%, which is not statistically different from that in the first six patients.

Biliary excretion of mitoxantrone was studied in patient 11, who had an indwelling T-tube and presented with jaundice and abnormal liver function tests. The excretion of both total radioactivity and unchanged mitoxantrone in the bile was minimal: only 2.3% of the ^{14}C in 24 h, and 2.7% in 96 h, of which 39% and 41%, respectively, were unchanged drug.

Table 1. Patient diagnosis and characteristics

Patient	Age	Sex	DHAQ dose mg/m^2	Diagnosis
1	59	M	1	Hepatocellular carcinoma
2	68	M	2	Squamous cell carcinoma of the lung
3	61	M	3	Small cell carcinoma of the lung
4	46	M	3	Adenocystic carcinoma of the epiglottis
5	37	F	3	Squamous cell carcinoma of the neck
6	55	M	3	Malignant melanoma
7	52	M	4	Synovial sarcoma with leg edema
8	60	M	3	Adenocarcinoma of the rectum ascites
9	57	F	3	Epidermoid carcinoma of the lung hepatic impairment and ascites
10	56	F	12	Chronic lymphocytic leukemia, ascites
11	66	M	2	Adenocarcinoma of the colon hepatic impairment

Table 2. Mitoxantrone pharmacokinetic parameters

Patient	Half-lives		Vd	Clearance rate	Urinary excretion, % dose			
	Initial	Terminal			Unchanged drug		Total C^{14}	
	(min)	(h)	(l/kg)	(ml/kg/h)	24 h	72 h	24 h	72 h
1	16.9	26.5	7.8	202.9	7.7	10.1	10.1	13.6
2	10.2	32.9	5.7	119.6	12.5	n.c.[a]	14.9	n.c.[a]
3	27.0	46.7	22.6	335.2	5.7	5.1	8.3	10.2
4	28.0	41.9	13.8	228.9	7.5	10.5	9.9	14.1
5	7.9	39.1	21.6	383.3	4.0	5.7	6.9	9.1
6	12.2	46.8	11.0	162.5	3.5	5.1	6.2	9.4
Mean ± SE	13.7[b]± 4.2	37.4[b]± 4.2	13.8 ± 2.9	238.7 ± 41.5	6.8 ± 1.3	7.3 ± 1.2	9.4 ± 1.3	11.3 ± 1.1

[a] Not collected
[b] Harmonic mean

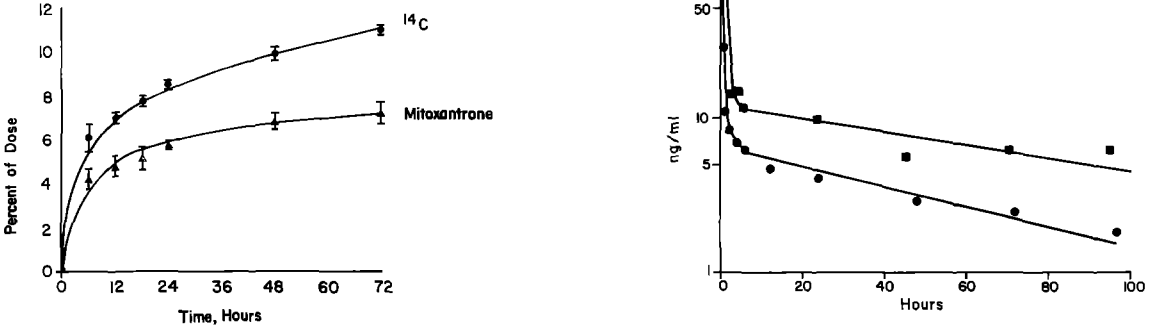

Fig. 2. Cumulative urinary excretion of radioactivity following administration of ^{14}C-mitoxantrone. ●———●, excretion of total radioactivity; ▲———▲, excretion of unchanged mitoxantrone. Values are the means ± SE for six patients

Fig. 3. Plasma disappearance of mitoxantrone postinfusion in patients 4 and 7. The *solid line* is the computer-generated semilogarithmic plot of the non-linear least-square fit of the data; the *closed circles* are the observed values. (■———■, observed values from patient 7; (●———●, observedn values from patient 4; (———) fitted values

Table 3. Mitoxantrone pharmacokinetic parameters in patients with organopathy or third space

Patient	Half-lives		Vd	Clearance rate	Urinary excretion, % dose			
	Initial	Terminal			Unchanged drug		Total C^{14}	
	(min)	(h)	(l/kg)	(ml/kg/h)	24 h	72 h	24 h	72 h
7	25.8	53.3	5.4	70.1	6.5	7.9	9.2	13.9
8	11.5	173.2	15.2	60.8	4.3	5.3	8.2	10.4
9	24.4	69.3	17.0	170.2	2.9	3.4	3.9	5.6
10	63.6	57.7	4.4	52.7	2.5	n.c.[a]	2.7	n.c.[a]
11	37.1	69.3	15.0	149.6	3.3	3.8	9.4	10.8
Mean ± SE	23.9[b] ± 2.2	70.7[b] ± 23.4	11.4 ± 2.7	100.7 ± 24.5	3.9 ± 0.7	5.1 ± 1.0	6.7 ± 1.6	10.2 ± 1.7

[a] Not collected
[b] Harmonic mean

Discussion

The clinical pharmacokinetics of mitoxantrone have certain unusual features. The elimination of the drug from the plasma was relatively slow, with a terminal half-life of about 37 h, compatible with the low urinary excretion of 7% of the administered dose in 72 h (Table 2). The hepatobiliary excretion rate of this agent in man remains largely unknown, although we observed that very little of it was found in the bile of a patient, who, however, had extensive liver disease. Since in the dog the rate of biliary excretion of mitoxantrone was slow [5], if man resembled the dog in this regard, mitoxantrone is expected to be excreted only slowly in the bile of man also. In both species, measurable amounts of mitoxantrone metabolites were detected in the bile as well as in the urine, but the extent of metabolism was limited. In other words, in man, the renal, hepatic, and metabolic clearance rates of mitoxantrone were all low. To reconcile these findings with the comparatively high total clearance of the drug, which was at least twice the creatinine of man, the conclusion appears to be inevitable that elimination from the plasma must be principally by tissue uptake and binding. This is consistent with the exceedingly large apparent volume of distribution of the drug. Moreover, recent results from our laboratories suggest that mitoxantrone was not only highly bound to plasma protein but also taken up quickly and in high concentrations by blood cells [6].

Regarding the hepatobiliary excretion of mitoxantrone, although the rate was probably slow, the extent of excretion by this route could nevertheless be significant. As mentioned above, in our studies with beagle dogs [5], we observed that the excretion of the drug was slow by either the biliary or the urinary route; unfortunately in these experiments we were unable to collect the bile beyond 5 h. However, in one study we recovered 63% of the administered dose, representing mitoxantrone and metabolites, in the feces of a dog in 24 h. Extrapolating this finding to man, we contend that the predominant route of mitoxantrone excretion in man must be fecal. To confirm this, further studies are now in progress.

Comparing mitoxantrone pharmacokinetics in the two groups of patients, the values of apparent volumes of distribution are not significantly different. However, in patients with hepatic impairment or third space, the average total clearance of mitoxantrone was decreased to less than one-half of that in patients with normal liver function, whereas the terminal half-life of the drug was almost doubled. Similar changes have been reported with many drugs in diseased states involving the liver [9], notwithstanding the fact that the effect of diseased liver on pharmacokinetics is far from simple. In the present study, because renal clearance was not significant in mitoxantrone elimination, the reduction of total clearance of this agent in patients with impaired liver function or third space is most probably attributable to either decreased hepatic clearance or impaired intrinsic metabolic clearance, particularly since we have no evidence that in these patients the tissue deposition of mitoxantrone has been changed.

All but one of our patients were given uniformly low doses of mitoxantrone; the exception was patient 10, who received the drug at a dose of 12 mg/m^2. However, we have elected to include the results obtained in this patient in our report, because even at this seemingly high dose no dose-dependent mitoxantrone pharmacokinetics were apparent. In comparison with the remaining four patients of this group, none of the pharmacokinetic parameters of patient 10 deviated widely from those of the others.

Our studies have amply demonstrated that knowledge of the pharmacokinetics of a drug is of paramount importance in planning its clinical trial. Patients with moderate liver impairment or abnormality of the third space, such as ascites, are at greater risk for mitoxantrone toxicity. Judicious dosage modifications and frequent monitoring of plasma drug concentrations are advised in these patients to avoid serious consequences of prolonged exposure to mitoxantrone, a drug shown by us to localize and persist in the body.

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