Cancer Chemother Pharmacol (1986) 18: 243–246

Cancer Chemotherapy and Pharmacology

Clinical pharmacology of the biological response modifier maleic anhydride divinyl ether copolymer (MVE-2)

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Summary. The anionic pyran copolymers represent a novel class of high molecular weight biological response modifiers with antitumor activity. Clinical pharmacology studies were performed on MVE-2, a polymer with an average molecular weight of 15.5 Kd. MVE-2 was analyzed in plasma and urine by HPLC. In addition, pharmacology studies were also performed using [^{14}C] labeled MVE-2. The clearance of unlabeled MVE-2 from plasma was monophasic and the $t_{1/2}$ for MVE-2 was extremely short (between 10 and 26 min). The apparent volume of distribution (Vd) varied from 12–18 l. Both the $t_{1/2}$ and the Vd did not appear to be dose-dependent. The plasma clearance for [^{14}C] labeled MVE-2 was studied in seven patients. The clearance of [^{14}C] labeled MVE-2 fit a biphasic mathematical model. The alpha phase half-life was between 11 and 18 min while the beta phase half-life was between 70 and 85 min. Urinary excretion for either unlabeled drug or the [^{14}C] label was between 30 and 45% of the administered dose. These studies show that, in man, the polyanionic macromolecule MVE-2 is cleared rapidly from plasma and excreted extensively in urine.

Introduction

Immunological or biological response modifiers are an important class of antitumor agents, which comprise a proposed new 'fourth modality' complementing surgery, radiation, and chemotherapy for the treatment of cancer. Naturally occurring and synthetic anionic polymers have been noted for their ability to alter biological resistance to tumors by a variety of pleiotropic effects [2, 8]. One of the first totally synthetic biological response modifiers to be evaluated was a copolymer of maleic anhydride and divinyl ether designated maleic anhydride divinyl ether (MVE; DIVEMA, pyran copolymer, NSC-46015). This agent demonstrated antiproliferative activity in a variety of model systems [9, 11]. The antineoplastic activity of pyran copolymer has been largely attributed to its ability to activate macrophages and natural killer cells [7], although its ability to induce synthesis of interferon cannot be excluded as a major source of its activity [5]. Breslow [3] has separated pyran copolymer into five polymer fractions with average molecular weights of 12.5, 15.5, 21.3, 32.0, and 52.6 kilodaltons, designated MVE-1 through MVE-5, respectively. MVE and its congeners were developed based on the observed biological, immunological and anti-tumor properties of a mixture of polymers known as pyran copolymer (Divema). The molecular weight of pyran copolymer was 30 kd on average, but ranged from 5.5 to 100 kd. This drug was found to be an active immunotherapeutic agent which enhanced interferon production or release [6, 10], activates macrophages [6] and the reticulendothelial system [13], and was found to increase resistance to a variety of microbial and viral infections [1]. In animal models, pyran copolymer was found to have antitumor activity against the Lewis and Madison lung carcinomas [18], B-16 melanoma [12], various carcinogen-induced tumors [6], and other hematological and solid tumor models [6, 9, 17].

Because it possesses antitumor and immunomodulatory properties of the parent pyran copolymer mixture and because of its reduced toxicity, MVE-2, a polymer with an average molecular weight of 15500, was chosen for phase I clinical investigation. The results of the clinical trial have been reported elsewhere [15]. Since the pharmacological evaluation of chemotherapeutic agents has greatly affected their clinical use, pharmacological studies of biological response modifiers may also provide new insight into their biology and may result in improved clinical utilization of these agents. With this in mind, we developed a high-performance liquid chromatographic method for analysis of MVE-2 concentrations in plasma and urine [16] and have applied this method to clinical pharmacology studies of MVE-2 in concert with its phase I clinical trial. In addition, we studied the clinical pharmacology of ^{14}C-labeled MVE-2 as an adjunct to the HPLC analytical method, with the aim of determining possible in vivo metabolism of MVE-2 in man.

Materials and methods

Materials. Non-radiolabeled MVE-2 was supplied in sterile 20-ml vials containing 100 mg drug. For clinical use, MVE-2 was reconstituted with 10 ml sterile water for injection (USP) and was further diluted in 250 ml of 5% dextrose in water and then administered i.v. over either 20 min or 1 h.

Radiolabeled [^{14}C]MVE-2 was synthesized from ^{14}C-labeled maleic anhydride and was supplied in sterile 20-ml vials containing 25 mg [^{14}C]MVE-2 with a specific activity of 0.83 μCi/mg. Prior to administration the drug was dis-

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solved in 100 ml of 5% dextrose in water. Sufficient nonradiolabeled MVE-2 was added to bring the total drug dose to that predetermined for each particular patient. The drug was then administered as an i.v. infusion over either 20 min or 1 h.

Patients. As part of the phase I protocol, patients were treated weekly at doses of between 25 and 650 mg/m^2, every other week at doses ranging between 500 and 1200 mg/m^2, and every third week at doses between 1200 and 1500 mg/m^2. The duration of infusion was progressively shortened from 60 min to 20 min in an attempt to circumvent dose-limiting proteinuria associated with the longer duration infusions.

Pharmacokinetic studies were performed on patients during and after the first or fourth treatment with either unlabeled or radiolabeled MVE-2. Heparinized blood samples (10 ml) were drawn at 1 h before infusion start (baseline), infusion midpoint, infusion end (zero), and at 5, 10, 15, 20, 25, 30, 40, 50, 60, 90, 120, and 188 min after the end of infusion. Blood samples were centrifuged at 2500 rpm (Sorvall GLC-2B) for 15 min to remove plasma. After administration of unlabeled MVE-2, the samples were subjected to analysis by HPLC for determination of MVE-2 concentration as described previously [16]. After administration of ^{14}C-labeled MVE-2, plasma aliquots (100 µl) were added to 20-ml scinitillation vials containing 15 ml Aquasol scintillant (New England Nuclear). The samples were analyzed in a Packard scintillation spectrometer for determination of ^{14}C activity.

Urinary excretion of ^{14}C-labeled and unlabeled MVE-2 were determined by scintillation and HPLC analysis of urine collected in 24-h aliquots for 4 days after administration of the agent. Results of plasma disappearance curves for both unlabeled MVE-2 determined by HPLC and ^{14}C-labeled MVE-2 determined by scintillation counting were subjected to nonlinear regression analysis for calculation of standard pharmacokinetic parameters.

Results

The clearance of unlabeled MVE-2 from plasma was studied in 30 patients who received doses of between 400 and 1200 mg/m^2. As shown in Fig. 1, clearance of MVE-2 from plasma as measured by HPLC closely fit ($r^2 > 0.9$) a one-compartment mathematical model. The plasma half-life was extremely short (10.2±2 min), and the limit of sensitivity of the HPLC assay had been reached by 30 min after drug administration in most cases. Nevertheless, this assay was useful for monitoring up to three half-lives in plasma. The summary of MVE-2 pharmacokinetics in 30 patients is shown in Table 1. The calculated plasma half-lives varied from 10 to 26 min and did not appear to correlate with either the dose of drug administered or the infusion duration. The calculated apparent volume of distrubtion (V_d) varied from 10.8±1.2 l to 18±7 l and also did not appear to be dependent upon either the dose administered or the infusion duration.

The clearance of ^{14}C-labeled MVE-2 was studied in seven patients who received either 100 or 400 mg/m^2 MVE-2 containing a consistent dose of ^{14}C label (100 µCi). As shown in Fig. 2 [^{14}C]MVE-2 was cleared from plasma biphasically. The alpha phase for clearance varied between 11 and 18 min and was similar to that found for unlabeled MVE-2 analyzed by HPLC. A terminal plasma phase was found for [^{14}C]MVE-2 which varied between 70 and 85 min. This phase may have become apparent because of the higher sensitivity of monitoring with radiolabeled MVE-2 than of the HPLC method. The (V_d) calculated for radiolabeled MVE-2 was between 18±3 and 13.5 l and was similar to that found for unlabeled MVE-2 measured by HPLC. The urinary excretion of unlabeled MVE-2 measured by HPLC and [^{14}C]MVE-2 measured by scintillation counting is shown in Fig. 3 and 4, respectively. In both cases, most of the drug was excreted in urine in the first 24 h after administration. Approximately 45% of the radiolabel was excreted, while only 30%–40% of the intact

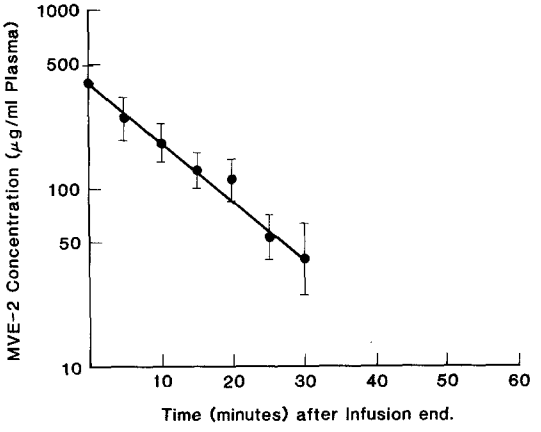

Fig. 1. Clearance of unlabeled MVE-2 from plasma of patients ($n=6$) at a dose of 500 mg/m^2 infusion over 60 min. *Line* shown is the least-squares fit line ($r>0.05$) for an open, one-compartment mathematical model for clearance ($t_{1/2}$ = 10.2±1.9 min)

Table 1. Summary of MVE-2 pharmacokinetics

No of patients	Dose (mg/m^2)	Infusion duration (min)	$t_{1/2}$ (min)	V_d (l)	Cxt (mg/ml × min)
4	400	20	9.9±1	11.9±2.3	1.1±0.3
1	400	60	9.6	15	0.51
6	500	20	15.9±3	10.8±1.2	1.4±0.8
4	500	60	10.2±1.9	13.5±1.4	0.7±0.23
8	650	20	14 ±1	12.2±2	1.4±2.0
3	650	60	25.9±13	18 ±7	3.3±2.0
4	1200	60	10.2±2	16 ±3	2.1±0.4

* Values shown are means ± SEM

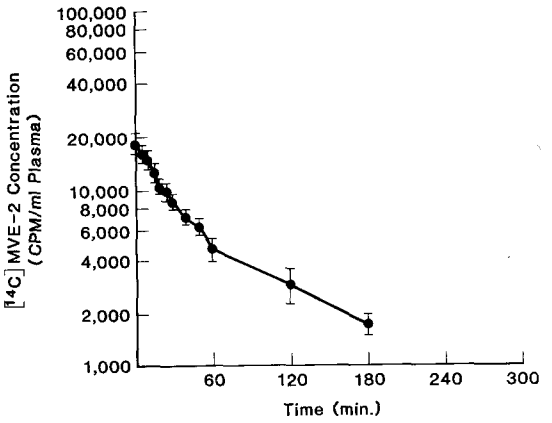

Fig. 2. Clearance of ^{14}C-labeled MVE-2 from plasma of five patients. The data closely fit ($r^2 > 0.99$) an open two-compartment mathematical model for clearance ($t_{1/2\,\alpha} = 11 \pm 1.5$ min, $t_{1/2\,\beta} = 85 \pm 12$ min)

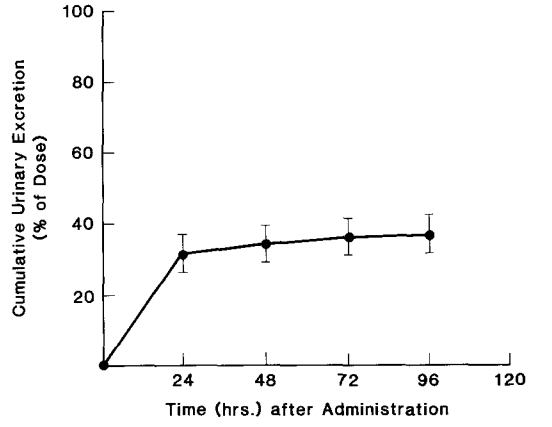

Fig. 3. Urinary excretion of MVE-2 measured by HPLC analysis of urine collected from patients who received 500 mg/m^2 MVE-2 infusion over 60 min. As shown, most of the drug was excreted in the first 24 h after administration

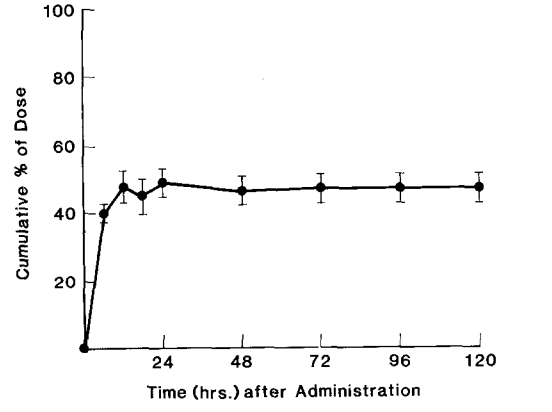

Fig. 4. Urinary excretion of ^{14}C-labeled MVE-2 in patients who received 400 mg/m^2 (100 μCi) of drug

drug was excreted according to HPLC. Analysis of stool specimens collected after [^{14}C]MVE-2 administration showed that less than 1% of the total ^{14}C dose was excreted over 72 h (data not shown).

Discussion

The pharmacokinetics and tissue disposition of MVE-2 have been reported in several animal model studies [4, 14]. Significant amounts of MVE-2 were found to be absorbed by tissues early after administration. However, amounts of drug were still detectable at 2 weeks after dosing of the animals. These studies showed that ^{14}C-labeled MVE-polymers or radiolabeled metabolites were found in the liver (8%–9% of the total administered dose), carcass (10%–11%), tail (5%–6%), skin (1%–2%), kidneys (1%), and spleen (0.5%–1%) at 28 days after administration. The combined urinary and fecal excretion of MVE-2 was approximately 20% of the administered dose over 48 h. Insignificant amounts (0.1% or less) of $^{14}CO_2$ were recovered at all sampling times.

The initial clearance of both unlabeled and ^{14}C-labeled MVE-2 from plasma of patients appeared to be extremely rapid, suggesting extensive clearance by extravascular sites. Since previous animal model studies have shown clearance of MVE-2 primarily by the liver, the rapid alpha-phase plasma t½ may be the result of first-pass clearance by the liver in man. In contrast to the animal model studies, MVE-2 was excreted extensively in urine (30%–45% of the dose). In addition, while patients were found to excrete less than 1% of the total administered dose in the stool over 72 h, the fecal excretion of MVE-2 in rats was substantially higher (5%–9% of the injected dose) [4].

In summary, these studies show that the polyanionic macromolecule MVE-2 is cleared rapidly from plasma and excreted extensively in urine within 24 h after administration. If animal tissue distribution studies accurately reflect the tissue disposition in man, the rapid plasma clearance may be due primarily to absorption by hepatic clearance mechanisms.

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Table 2. Summary of [^{14}C] MVE-2 pharmacokinetics (1-h infusion)

No of patients	Dose (mg/m^2)	$t_{1/2\alpha}$ (min)	$t_{1/2\beta}$ (min)	V_d (l)	Cxt CPM × 10^6/ml × min
5	400	11 ± 1.5	85 ± 12	18 ± 3	1.5 ± 0.0058
2	100	18	70	13.5	2.0

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Received April 30, 1986/Accepted June 24, 1986