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ORIGINAL ARTICLE

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A phase I study of monohydroxyethylrutoside in healthy volunteers

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Abstract The flavonol monohydroxyethylrutoside (monoHER) has demonstrated protection against doxorubicin-induced cardiotoxicity in in vitro and in vivo studies without affecting the antitumor effect. In the present phase I study, the possible side effects and the pharmacokinetics of monoHER were evaluated in healthy volunteers with the aim to develop a safe and feasible dose to be evaluated in cancer patients treated with doxorubicin. The study was performed as a single blind, randomized trial in healthy volunteers (age between 19 and 56 years). At each dose level, six subjects received monoHER and three placebo. MonoHER was solubilized in 100 ml dextrose 5% and administered as an i.v. infusion in 10 min. The placebo consisted of 100 ml dextrose 5%. The starting dose of monoHER was 100 mg/m^2. Dose escalation by 100% of the preceding dose took place after finishing each dose level until the protecting pharmacokinetic values for C_{max} and AUC$^{\infty}$ (as observed in mice after 500 mg/kg monoHER i.p.) were reached and/or serious side effects were observed. The dose was escalated up to 1,500 mg/m^2. The mean values of C_{max} and AUC$^{\infty}$ were 360 ± 69.3 μM and 6.8 ± 2.1 μmol min/ml, respectively. These values were comparable to the C_{max} and AUC$^{\infty}$ observed under the protecting conditions in mice. No serious side effects occurred during the entire study. Thus, 1,500 mg/m^2 is a feasible and safe dose to be evaluated in a phase II study to investigate the protective properties of monoHER against doxorubicin-induced cardiotoxicity in cancer patients.

Keywords MonoHER · Monohydroxyethylrutoside · Doxorubicin · Pharmacokinetics · Clinical phase I study

Preliminary results of this study have been presented as a poster at AACR (Proc. AACR 43 (2002) 2751).

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Introduction

Since the 1960s anthracyclines are used in a wide variety of malignancies. Unfortunately, these extensively used drugs have serious dose-limiting side effects. The cumulative dose-related cardiotoxicity is an important problem [9, 21, 36], particularly in survivors of childhood cancers, who might experience ventricular dysfunction, heart failure, arrhythmias and sudden death, especially in the presence of stressors, such as pregnancy and sports [22, 27].

Anthracycline-induced cardiotoxicity seems to be, at least partly, caused by oxidative stress [22]. Anthracyclines can initiate hydroxyl radical formation, especially after complexation with iron. Owing to a lack of the oxidative defense system in the heart [20, 23], protection can be obtained by protecting compounds, which either scavenge radicals and/or prevent radical formation by iron chelation. ICRF-187 is the only registered and clinically successful cardiotoxicity modulator. By chelating iron, it can inhibit the formation of the oxygen-free radicals. However, in a clinical trial in women with advanced breast cancer, the response rate to doxorubicin-based treatment was significantly lower in the group receiving ICRF-187 (48%) than in the placebo group (63%) [4]. In patients who received ICRF-187, bone marrow suppression was also more severe [33, 35].

Monohydroxyethylrutoside (monoHER) is a potential new protective agent against doxorubicin-induced cardiotoxicity [30, 32]. Inhibition of lipid peroxidation through radical scavenging and iron chelation is supposed to be the mechanism of action [32, 34]. The pro-

tection of monoHER against doxorubicin-induced cardiotoxicity was found to be dose-dependent [31]. In vitro and in vivo experiments showed no influence of monoHER on the antitumor activity of doxorubicin. No side effects were observed in mice treated with monoHER [31].

The present phase I study describes the possible side effects of monoHER and the pharmacokinetics of monoHER were evaluated in healthy volunteers during this study using escalating dose levels with the aim to develop a safe and feasible dose to be evaluated in cancer patients treated with doxorubicin.

Methods

Study population

Volunteers were accrued by advertisement in weekly papers of the Vrije Universiteit and the Vrije Universiteit Medical Center. Volunteers (m/f) had to be healthy and in the age between 18 and 65 years. No medication was allowed since the week preceding the administration of monoHER.

Nine volunteers were entered at each dose level. Characteristics of the volunteers are shown in Table 1. Six subjects received monoHER whereas three subjects received placebo. This study was performed as a randomized, single blind study. Randomization was carried out by drawing a sealed envelope with a volunteer number. This number determined the medication of subsequent dose levels. Replacement of a volunteer meant continuation of the medication indicated in the lane of the respective volunteer number by the replacing volunteer. Because the same volunteers could participate in more than one dose level, the randomization of medication was carried out in a way that every volunteer did get at least one placebo (Fig. 1). Hematology was studied separately at the highest dose in the same volunteers (see Fig. 1).

Study	Dose mg/m²	Volunteer numbers								
Phase I	100	1	2	3	4	5	6	7	8	9
	200	1	2	10	4	11	6	7	8	9
	400	12	2	15	4	13	6	7	8	9
	800	1	2	15	4	12	6	7	8	9
	1500	1	2	15	4	12	6	16	8	9
Hematology	1500	1		15	-	-	6	16	8	9

Fig. 1 Randomization schedule used in the phase I study and the hematology study (*filled square* placebo; *open square* monoHER). *Number* identifies the volunteer

Ethical considerations

This study was approved by the medical ethical review committee of the Vrije Universiteit Medical Center. The outline of the study was explained to the volunteers before obtaining their written informed consent.

Data analysis

Concentration-time curves of monoHER were obtained from three volunteers at each dose level. At the highest dose level (1,500 mg/m^2), six curves were analyzed. The area under the concentration–time curve (AUC$^\infty$), mean residence time (MRT), clearance (Cl), volume of distribution and half-lives were determined by using a NONLIN fit with two or three exponential terms using the pharmacokinetic computer program WinNonlin, version 1.5 (Pharsight Corporation, Mountain View, USA).

Treatment

MonoHER

Unformulated drug was provided by Novartis Consumer Health, Nyon, Switzerland.

Table 1 Characteristics of the volunteers participating in the study

Volunteer number	Gender	Age (years)	Weight (kg)	Body surface area (m^2)	Number of participated dose levels
1	Female	19	56	1.6	4
2	Female	37	68	1.86	5
3	Male	20	62	1.82	1
4	Male	32	83	2.06	5
5	Female	23	73	1.87	1
6	Male	28	60	1.75	5
7	Female	27	73	1.94	4
8	Male	46	69.5	1.87	5
9	Female	56	73	1.82	5
10	Female	19	–	–	1 (placebo)
11	Male	52	75	1.96	1
12	Male	44	84	2.15	3
13	Male	23	83	2.05	1
14	Female	42	73	1.93	0
15	Male	28	92	2.25	3
16	Female	43	56	1.54	1

Formulation of the drug The drug was formulated under aseptic conditions by the Department of Pharmacy, Vrije Universiteit medical Center, Amsterdam, The Netherlands. The required amount of monoHER was dissolved in 100 ml dextrose 5% for intravenous use, adjusted to pH 9.3 using sodium hydroxide 4 M. After dissolution of the drug, the solution was readjusted to pH 8.4 with hydrochloric acid 1 M. The final solution was filtered through a sterile 0.2 μm filter and transferred into a sterile 100 ml IVAC infusion system (Alaris Medical BV, Amersfoort, The Netherlands). The solution was chemically stable for at least 24 h at room temperature [2]. MonoHER or placebo were administered to the volunteer within 24 h after preparation.

Administration of the drug MonoHER was administered as an intravenous infusion during exactly 10 min. Because 10% of the registered drug Venoruton is monoHER and 1,500 mg of Venoruton could be administered intravenously to patients without any side effect [26], the starting dose of monoHER was 100 mg/m^2. After finishing a dose level the dose was escalated by 100% (of the preceding dose) until values of C_{max}≥131 μM and AUC$^{\infty}$≥6.3 μmol min/ml were obtained under the protecting conditions in mice after administration of 500 mg/kg i.p. [3] and/or serious side effects were observed. Although monoHER is yellow-colored the placebo was not colored, because of possible side effects of the additive. Instead, the IVAC infusion system was wrapped in aluminum foil and the infusion links were covered with a yellow extension tube for blinding. Hundered milliliters of placebo was administered in the same way as monoHER.

Safety parameters

Before administration of monoHER blood pressure, pulse frequency, liver function (serum bilirubin, SGOT, SGPT, γ-GT) and renal function (serum creatinine) were measured and a routine 12-lead ECG was performed. Blood pressure and pulse frequency were repeated directly after the infusion and 1, 2 and 3 h thereafter. An ECG was also repeated 3 h after administration. Measurements of renal and liver function were repeated 24 h and 3 days after the end of the infusion.

After the phase I study, hematology was checked in six healthy volunteers receiving 1,500 mg/m^2 of monoHER as a 10 min i.v. infusion. Hb, Ht, platelets, WBC and its differential count were determined before the infusion and 24 h and 7 days after the end of the infusion.

Pharmacokinetics

The pharmacokinetics of monoHER was measured at each dose level with the aim to obtain at least the same peak plasma concentration (C_{max} of 131 μM) and a comparable concentration–time profile (AUC$^{\infty}$ of 6.3 μM min) in healthy volunteers as obtained in mice [3]. At the same time linearity of the pharmacokinetics was checked.

Venous blood samples (2 ml) were collected from all volunteers (including those receiving placebo) just before infusion, just before the end of the infusion, 15, 30, 60 and 90 min and 2, 4, 6, 8, 21 and 24 h after the end of the infusion. Blood was collected in a cooled sodium heparin–containing glass tube (3 ml), which was kept on ice until processed shortly thereafter. Blood cells were spun down in a cooled centrifuge (4°C) at 4,000 rpm for 3 min. Aliquots of the plasma (supernatant) were transferred into polypropylene micro-test tubes (> 150 μl/tube). Each sample was frozen immediately at −80°C until analysis.

Urine was collected in three portions during 2 h since the start of the infusion. Before infusion a blank urine sample was collected. Urine samples were collected in wide-mouthed polyethylene bottles. Each 2-h urine portion was gently shaken and the total volume was measured. Four aliquots of 2 ml were transferred into polypropylene micro-test tubes and frozen at −80°C until analysis.

HPLC analysis

Concentrations of monoHER in plasma and urine were analyzed by HPLC with electrochemical detection as previously described by Abou El Hassan et al. [1]. In short, monoHER was extracted from plasma and urine with methanol. After centrifugation (9,000 rpm, 3 min, 1°C), two portions of supernatant were transferred into a polypropylene micro-test tube (1.5 ml) and diluted with 25 mM phosphate buffer (pH 3.33). After centrifugation (9,000 rpm, 3 min, 1°C), the supernatant was transferred into a new polypropylene micro test tube (1.5 ml) and placed in the autosampler (Basic Marathon with cooled tray, 4°C, Spark Holland, The Netherlands). The level of monoHER was measured in duplicate. Calibration standards and quality control samples were freshly prepared on each day of analysis.

Results

Side effects

The side effects were expressed using the NCI's Common Toxicity Criteria, Version 2. No serious side effects were observed at the different dose levels. After a dose of 100 mg/m^2 monoHER, one volunteer complained about a burning sensation at the injection site during less than 1 min. She also complained about light-headedness during the whole day, but it did not interfere with her daily pursuits. The day after the infusion of 200 mg/m^2 monoHER, one volunteer

complained about paresthesia in all her fingertips at the site of the infusion. This was reversible and disappeared the day thereafter. One volunteer in the placebo group at the 400 mg/m^2 dose level experienced a vasovagal episode without loss of consciousness during the infusion. One volunteer reported a slight tension headache 2 h after monoHER infusion at a dose of 400 mg/m^2. This headache disappeared 5 h later. He was still able to work. One volunteer mentioned a slight feeling of nausea during and after infusion of monoHER at a dose of 400 mg/m^2 and 1,500 mg/m^2 but did not mention this during or after receiving placebo at the 800 mg/m^2 dose level.

Pulse frequency and blood pressure showed intra-subject variation within the normal range. No relation could be found with the administration of monoHER or placebo. Liver function (bilirubin, γGT, ASAT, ALAT) and kidney function (creatinine) also showed intra-subject variability, but could not be related to the administration of monoHER or placebo.

Two volunteers were discovered with abnormalities on their initial ECG. One volunteer, a 19-year-old female, was diagnosed with a Wolff-Parkinson-White syndrome. This volunteer received placebo without any change in the ECG. She was excluded from further participation in the study. In another volunteer, a 42-year-old female, the initial ECG showed ischemic changes. This volunteer did not receive any treatment and she was excluded from the study. Administration of monoHER or placebo did not show any change in the ECGs of the participating volunteers.

Hematological parameters (Hb, Ht, platelets, WBC and differential count) were analyzed at the earlier described time points. The administration of monoHER had no influence on these hematological parameters.

Pharmacokinetics in plasma

The mean plasma concentration–time curve of monoHER after 1,500 mg/m^2 in six healthy volunteers is shown in Fig. 2. At this dose the mean peak plasma concentration was 360 ± 69.3 μM; the mean AUC$^{\infty}$ was 6.8 ± 2.1 μmol min/ml. Because these values were comparable or higher than the targeted values, no further dose escalation was applied.

At the highest dose (1,500 mg/m^2), monoHER disappeared triphasically from the plasma compartment with a $t_{1/2}\alpha$ of 5.0 ± 1.6 min, a $t_{1/2}\beta$ of 27.0 ± 11.2 min and a $t_{1/2}\gamma$ of 168 ± 148 min, respectively. The MRT, body clearance (Cl) and volume of distribution at steady state (V_d^{ss}) were 33.4 ± 8.8 min, 0.70 ± 0.22 l/min and 22.9 ± 8.7 l, respectively. The pharmacokinetics of monoHER seemed to be nonlinear as shown by the plots of C_{max} and AUC$^{\infty}$ versus the dose (Figs. 3, 4, respectively).

Pharmacokinetics in urine

Mean amounts of monoHER excreted in the urine (expressed as percentage of the dose) after administrations of monoHER at the different dose levels are shown in Fig. 5. Urinary excretion of monoHER principally took place during the first 2 h since the start of the infusion. Thereafter only small amounts of monoHER were excreted in the urine. At the highest dose of 1,500 mg/m^2, the mean ($\pm$SD) amount excreted within the first 2 h since the start of the infusion was 11.5 ± 8.4% of the total dose (D) of monoHER administered. The urinary excretion from 2–4 h and 4–6 h were 0.7 ± 0.6% and 0.1 ± 0.0% D, respectively. A large inter-individual

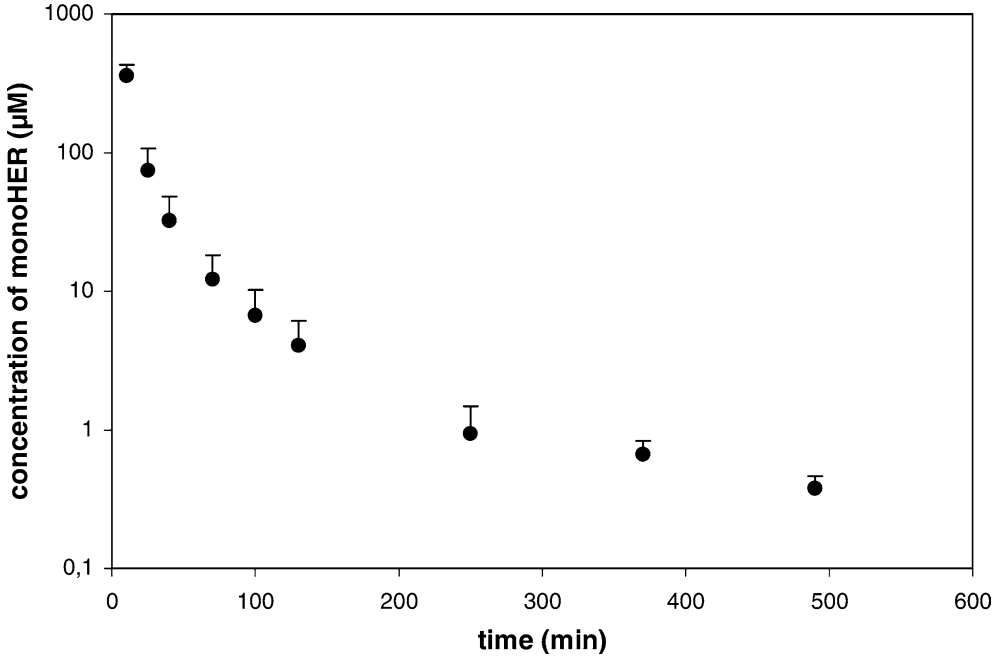

Fig. 2 Mean concentration ($\pm$SD) versus time curve at a dose of 1,500 mg/m^2 monoHER in six volunteers

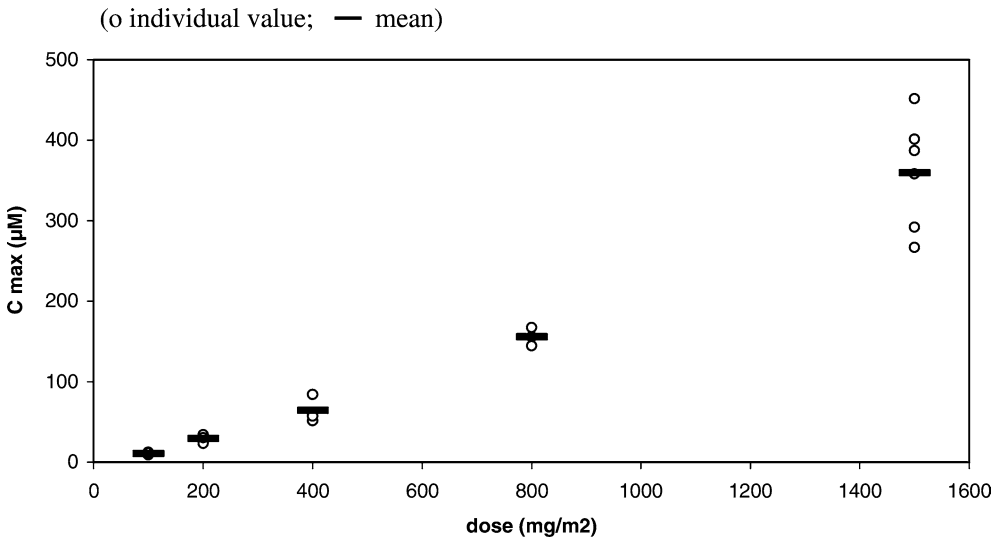

Fig. 3 Peak plasma concentration (C_{max}) versus the dose of monoHER (*circle* individual value; *thick line* mean)

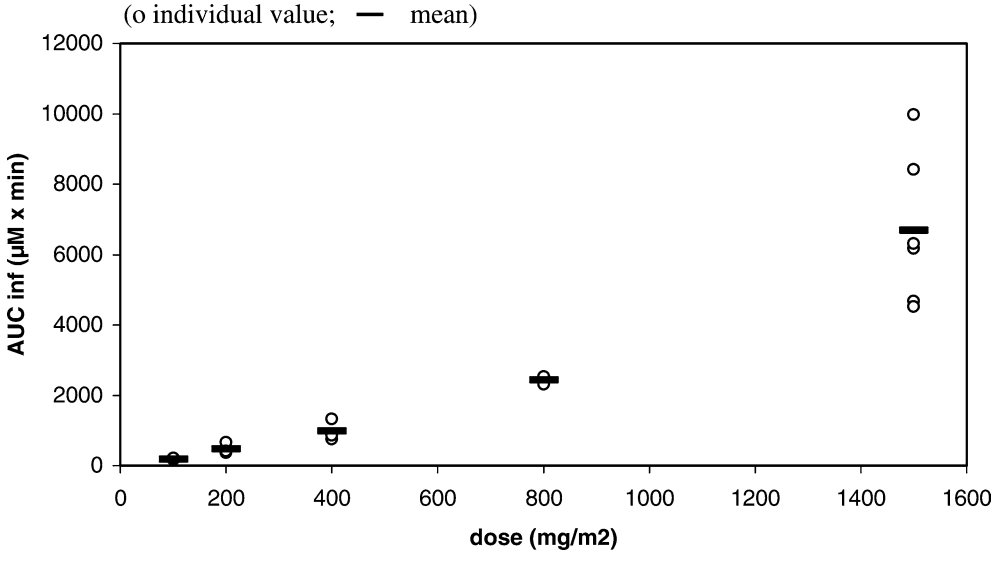

Fig. 4 Area under the curve extrapolated to infinity (AUC^{∞}) versus the dose of monoHER (*circle* individual value; *thick line* mean)

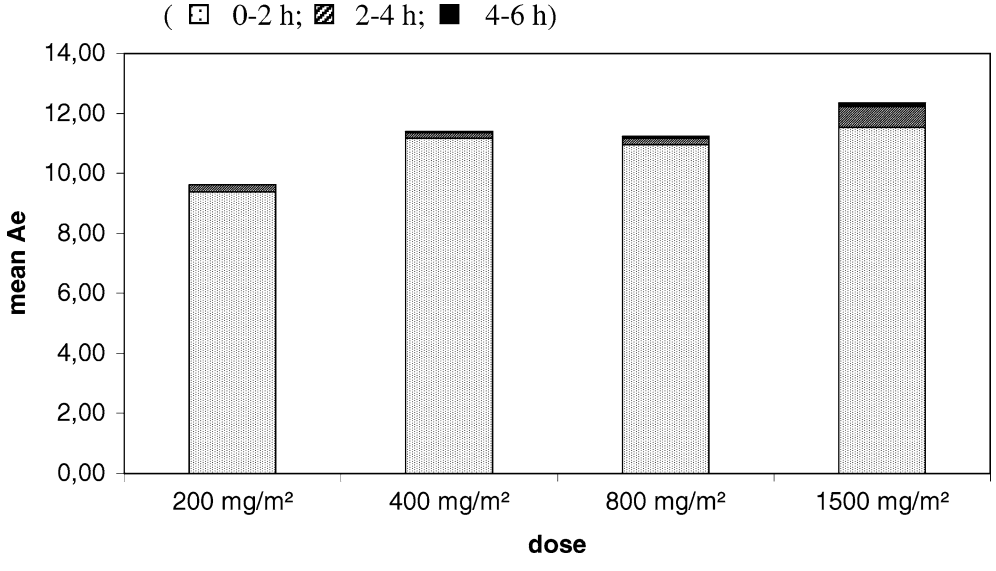

Fig. 5 The amount of monoHER excreted in the urine at each dose level expressed as percentage of the total dose ($n = 6$; *dotted area* 0–2 h; *stripped area* 2–4 h; *filled area* 4–6 h)

variability was observed. In total, about 12% of monoHER was eliminated by the kidneys within 6 h after the start of the infusion. No significant difference was measured between the mean amounts excreted at the various dose levels.

Discussion

In this study the pharmacokinetics and possible side effects of an i.v. infusion of monoHER, a very promising new agent in protecting the heart against anthracycline-induced toxicity [30, 33], were investigated in human.

Up to the highest dose of 1,500 mg/m^2, monoHER was well tolerated and no serious side effects were observed. The maximal tolerated dose (MTD) of monoHER was not investigated, because the pharmacokinetic end-points (C_{max}≥131 μM and AUC^{∞}≥6.3 μmol min/ml) were obtained and the solubility of monoHER at pH 8.4 (≅3,000 mg/100 ml) limited the administered dose to about 1,500 mg/m^2 when given in 100 ml as a 10 min i.v. infusion.

An important pharmacokinetic characteristic of monoHER was the rapid distribution and elimination of monoHER from the body plasma as indicated by the low values found for its half-lives and mean residence time (MRT). The rapid distribution and elimination of monoHER from the plasma compartment was also observed in various animal species [3, 16, 17]. The short distribution half-life of monoHER corresponded with the rapid uptake of monoHER in heart tissue as found in mice (C_{max} in heart tissue within 5 min after i.p. administration of monoHER) [3]. The volume of distribution at steady state ($V_d^{ss} = 22.9 \pm 8.7$ l) as found in the present phase I study indicates that monoHER is distributed at least in the extracellular fluid, and might be distributed in the intracellular fluid as well. This finding supports the idea that monoHER can intracellularly exert its effect against doxorubicin-induced cardiac damage. Our observations correspond with the previous findings of monoHER in mice studies [3, 14]. The V_d^{ss} of monoHER lies in the range of those observed in phase I studies of other flavonoids, e.g., 24–38 l/m^2, 161 l and 6.2–92.6 l for flavone acetic acid [11, 18], genistein [29] and quercetin [13], respectively; thus, indicating that these investigated flavonoids also seem to penetrate into the intra- and extracellular fluid.

The distribution and elimination half-lives of monoHER in plasma (5.0, 27.0 and 168 min) of our volunteers were comparable to those found in mice [16] and dogs [17]. It also corresponded with the final half-lives found for other flavonoids during phase I studies, e.g., 3.1, 0.7–2.4 and 3.2–7.1 h for flavone acetic acid [11], quercetin [12, 15] and genistein [10, 29], respectively. Thus, the investigated flavonoids, including monoHER, stay for a relatively short time in the plasma compartment. This is not a drawback, because doxorubicin-induced cardiotoxicity seems to be related to the peak serum level of doxorubicin, as the incidence of doxorubicin-induced heart failure decreased after a low-dose weekly schedule or a prolonged infusion period [7]. Because of the very short initial half-life of doxorubicin [25], high plasma levels of doxorubicin are only present during the first 2 h after the start of the infusion. At least during this time, high levels of monoHER are present to prevent radical formation and to scavenge radicals from doxorubicin, which seems to be enough to cause the observed cardioprotective effect.

In the present phase I study, a high dose (1,500 mg/m^2) of the semisynthetic flavonoid monoHER administered intravenously did not cause serious side effects. Only one volunteer complained about a slight feeling of nausea after 400 mg/m^2 and after 1,500 mg/m^2 monoHER, but not after the placebo, indicating that nausea could be a side effect related to monoHER infusion. The administration of monoHER did not influence the liver and kidney function. These favorable observations are in agreement with the toxicity studies in animals. At the highest single dose given orally to mice (16 g/kg), rats (16 g/kg) and dogs (32 g/kg), no side effects were observed related to the drug (Internal Report Zyma SA, 1973). Also, no teratogenic effects were observed in pregnant mice, rats and rabbits after an oral dose of 2,700 mg/kg given daily for 10 days during pregnancy (Internal Report Zyma SA, 1974). In contrast with ICRF-187, administration of monoHER did not influence the hematological parameters [19, 24]. Thus, monoHER at a dose of 1,500 mg/m^2 i.v. can be administered safely.

A few flavonoids have been investigated as a drug in a phase I study. For instance, quercetin, the main flavonol in our diet, caused a dose-limiting nephrotoxicity at 2,000 mg/m^2 intravenously [13]. Flavone acetic acid, a synthetic flavonoid, caused a dose-limiting hypotension at a dose of 10,000 mg/m^2 i.v. At doses less than or equal to 5,000 mg/m^2, side effects were minimal [11, 18]. It cannot be excluded that an MTD of monoHER would have been found at dose levels not too far from 1,500 mg/m^2. This may be promoted—and also warns for care if further dose escalation would be considered—by the possible nonlinear pharmacokinetic behaviour of monoHER. Nonlinear pharmacokinetics was also observed for tri- and tetra-HER after administration of Venoruton to healthy volunteers as a 6-h i.v. infusion [5]. In general, the liver is the main organ involved in the metabolism of polyphenols of which the flavonoids are a subgroup [8, 28]. In particular, monoHER was mainly excreted in bile as was found in several mice and rat experiments [6, 17]. This corresponds with the low excretion of monoHER by the kidneys (about 12% of the total dose) as found in the present study, which is in agreement with previous data from studies in mice, rats and dog [6, 16, 17]. This suggests that the nonlinear pharmacokinetics of monoHER might be caused by a rate-limiting step in the metabolism and/or excretion by the liver.

Side effects might also appear after cumulative dosages of monoHER, but this does not seem very likely. Seven volunteers received two or more dosages of monoHER, but no cumulative dose-related side effects were observed in those volunteers. These findings are in agreement with a chronic toxicity study on Beagle dogs receiving monoHER at a dose of 150 mg/kg/day for 160 days without showing any side effects of the drug (Internal Report Zyma SA, 1974). Also, flavone acetic acid when administered intravenously at dosages of 6.4 g/m^2 with an interval of 48 h did not result in severe toxicity nor showed evidence of drug accumulation [11]. Thus, monoHER at a dose of 1,500 mg/m^2 can be administered safely. This dose will be used in a phase II study in which the cardioprotection of monoHER will be investigated in cancer patients receiving doxorubicin.

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