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Clinical report

Phase Ia study of a hypoxic cell sensitizer doranidazole (PR-350) in combination with conventional radiotherapy

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A phase Ia study of a 2-nitroimidazole nucleoside analog radiosensitizer doranidazole was conducted to evaluate its toxicity and pharmacokinetics in patients undergoing conventional external beam radiotherapy. Twenty-nine patients, aged 40–74 years, with a WHO performance status of 0–2 and with adequate organ functions, were entered in the study. Single administration of doranidazole was investigated first with 13 patients and then a course of five consecutive daily administrations was tested in 16 patients. Doranidazole was given i.v. 25 min before irradiation. Doranidazole doses of 400, 800, 1300 and 2000 mg/m^2 were evaluated in the former study, and daily doses of 800, 1300 and 2000 mg/m^2 were investigated in the latter study. All patients tolerated doranidazole administration. Although a transient decrease in the 24-h creatinine clearance rate was observed in five patients (one in the single administration study and four in the repeat administration study), this was not considered to be the dose-limiting toxicity. Other toxicities (hematological and gastrointestinal), which may not be related to doranidazole administration, were also mild and were not dose limiting. No neurotoxicity was observed. The average maximum concentration, area under the time–concentration curve and half-life of doranidazole in serum were 172–194 μg/ml, 502–582 μg·h/l and 4.2–4.6 h, respectively, at 2000 mg/m^2. At the tested doses, administration of doranidaozle was tolerable and achieved serum concentrations at which reasonable radiosensitization could be expected. A phase Ib/II study to evaluate the feasibility and efficacy of up to 30 repeat administrations seems to be warranted. [© 2001 Lippincott Williams & Wilkins.]

Key words: Doranidazole, hypoxic cell sensitizer, phase I, radiosensitizer.

Introduction

Recent studies have shown that hypoxia in human tumors is associated with a poor prognosis.[1–5] Tumor hypoxia is not only a major problem for radiation therapy and chemotherapy but also appears to accelerate malignant progression and increase metastasis.[6,7] To overcome the problem of hypoxia, numerous new hypoxic cell radiosensitizers have been developed and screened since the introduction of misonidazole, and several of them have undergone clinical evaluation.[8–13] However, the clinical usefulness of the sensitizers remains controversial. Although misonidazole in combination with conventional external beam radiotherapy showed no effect in most of the trials,[13,14] it had effects against pharyngeal and laryngeal cancers in a Danish study.[15] Also, etanidazole and pimonidazole have not shown definite efficacy when combined with conventional radiotherapy,[8,9,11] whereas nimorazole has been proven to be effective in carcinomas of the supraglottic larynx and pharynx.[12] Therefore, more clinical studies are needed to conclude the clinical usefulness of hypoxic cell sensitizers.

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The new 2-nitroimidazole nucleoside analog doranidazole (code number: PR-350, (±)-(2*RS*,3*SR*)-3-[(2-nitro-imidazol-1-yl)-methoxy]butane-1,2,4-triol) is characterized by its very low toxicity, with a 50% lethal dose in mice exceeding 5 g/kg, while its efficiency is similar to that of etanidazole.[16–18] Since it had a lower toxicity in large animals than other 2-nitroimidazole nucleoside analogs such as RK-28 and RP-170,[19,20] it was decided to test the compound in phase I clinical studies. The purpose of this report is to describe the results of the phase Ia study in combination with conventional radiotherapy, in which a single or consecutive daily administration of doranidazole was investigated.

Materials and methods

Eligibility

The study consisted of two parts, i.e. the single administration study and the repeat administration study (five consecutive daily doses of doranidazole). The patient eligibility criteria were the same for both parts. To be eligible, patients had to be admitted to hospital and able to undergo external beam radiotherapy with 1.8–2 Gy daily fractions given 5 times per week over 4–7 weeks. They needed to be 20–74 years of age, and have a histologically or cytologically proven malignancy, WHO performance status (PS) score of 0–3, no influence of previous treatment, adequate cardiac, pulmonary, hepatic, renal and hematologic functions, and an expected survival time of at least 3 months. They had to have experienced no vomiting during radiotherapy with five or more fractions preceding doranidazole administration. Written informed consent was mandatory before entry.

Patients who were pregnant or nursing, who had a history of drug allergy or double cancer, who were irradiated to the abdomen, or who were taking antiemetics were excluded.

Compound

Doranidazole was supplied by Pola Chemical Industries (Yokohama, Japan). The vial for injection contained 1 g of doranidazole dissolved in 50 ml of physiological saline. Doranidazole was given i.v. over 25 min using an infusion pump. The infusion was ended 25 min before the start of radiation.

Study design

Approval for performing this study was obtained from the ethics committees at each participating institution. First, single doses of doranidazole were tested. The starting dose was determined to be 400 mg/m^2. This dose was derived from 60% of the non-toxic dose in dogs in a 4-week repeat administration study (650 mg/m^2). After evaluating at least three patients at each dose, dose escalation was performed based on a modified Fibonacci's scheme. Consequently, doses of 400, 800, 1300 and 2000 mg/m^2 were tested. This part of the study was carried out at three institutions.

In the next part of the study which was carried out at six institutions, five consecutive daily doses of doranidazole were given. In view of the results of the former part of the study, daily doses of 800, 1300 and 2000 mg/m^2 were tested. The planned patient number was three at the dose of 800 mg/m^2, and six each at 1300 and 2000 mg/m^2, when no serious toxicity was observed at each dose level.

In both parts of the study, chemotherapy, immunotherapy, hyperthermia, interstitial radiation and intraoperative radiotherapy were prohibited from 4 weeks before entry to 2 weeks after completion of radiotherapy.

Patient check-up and follow-up evaluation

Before doranidazole administration, electrocardiograms (ECG) and biochemical screening tests were performed in addition to an evaluation of the patients' background, symptoms, vital signs and performance status (PS). These evaluations were repeated at intervals up to 2 weeks after the last administration. In the latter part of the study, changes of tumor size were monitored using computed tomography, plain X-ray films and/or palpation.

Pharmacokinetics study

In the single administration study, venous whole blood of the patients was collected before, immediately after, and at 1, 3, 6 and 24 h after doranidazole infusion. In the repeat administration study, the blood samples were collected before, immediately after, and at 1, 3 and 6 h after infusion on the first day of administration, and before infusion on the second, third and fourth days (i.e. 24 h after the previous administration). On the fifth day, the blood samples were collected before, immediately after and 3 h after infusion. In both studies, urine was collected until 3 days after drug administration. Doranidazole levels in the blood and urine samples were analyzed by high-performance liquid chromatography (HPLC) at BML (Tokyo, Japan). HPLC was performed using a Hitachi L-7100 pump and a Hitachi L-7200 autosampler. The guard column was TSK guardgel ODS-80TM (5 μm,

3.2 mm i.d. × 15 mm) and the column was TSK gel ODS-80TM (5 μm, 4.6 mm i.d. × 250 mm). The elution peaks were detected at 320 nm wavelength. Phosphate buffer containing 1% methanol (pH 6) was used as the eluent. Metabolites of doranidazole in the urine were also investigated at BML using liquid chromatography–mass spectroscopy.

Results

Patient entry

Between July 1995 and October 1998, a total of 29 patients were entered into the study. The characteristics of the patients are summarized in Table 1.

Single administration study

Thirteen patients were evaluated in the single administration study. Three patients each received a dose of 400, 800 or 1300 mg/m^2, and four patients were given a dose of 2000 mg/m^2. After the administration, four patients developed mild symptoms or signs including fever, pain and decrease in blood pressure, none of which were considered to be attributable to the drug administration. No major changes were observed in PS, ECG, vital signs and biochemical tests of the patients, except for a temporary decrease in the 24-h creatinine clearance rate (CCR) in one patient who received 2000 mg/m^2 of doranidazole (Table 2). No change was found in blood urea nitrogen (BUN) or serum creatinine levels. Although the relation between the change in CCR and doranidazole administration could not be denied, all of these dosages were judged to be safe.

Table 1. Characteristics of patients entered into the study

Characteristic	Single administration study (n=13)	Repeat administration study (n=16)
Sex		
M	11	12
F	2	4
Age		
median	63	62
range	40–74	43–74
PS		
0	7	12
1	5	4
2	1	0
Distant metastasis		
+	7	12
−	6	4
Primary tumor		
lung	7	8
esophagus	4	1
head and neck	2	3
others	0	4

Figure 1 shows the serum concentration of doranidzole as a function of time after administration and Table 2 shows pharmacokinetic parameters in 12 patients in whom data were complete. The average maximum concentration was 117 μg/ml at the dose of 1300 mg/m^2 and 172 μg/ml at 2000 mg/m^2. The average half-life in serum was 4.2 h.

The average proportion of the unchanged form of doranidazole excreted into the urine was 37% within 3 h after administration, 52% within 6 h, 77% within 24 h and 79% within 48 h. Glucuronate and carbonate conjugates were detected in the urine as metabolites of doranidazole.

Repeat administration study

Sixteen patients were entered; three patients received a daily doranidazole dose of 800 mg/m^2, and six and seven patients received a dose of 1300 and 2000 mg/m^2, respectively. One patient discontinued doranidazole treatment and radiation therapy, because he developed signs of cardiac failure after the second administration at 2000 mg/m^2. He had had cardiomegaly before the start of doranidazole administration. The patient returned to the pretreatment condition 2 weeks later. The cause of this symptom was considered to be psychological stress due to radiotherapy and frequent blood sampling. All the other patients completed the five doses. Of the other patients, eight developed symptoms of chest pain, transient dyspnea, anorexia, nasal obstruction, tachyuria, headache or insomnia, but none of these symptoms was considered to be related to the doranidazole administration. Nausea and vomiting was observed in another patient receiving the daily dose of 2000 mg/m^2 on day 4 of administration, but the symptom was considered to be more closely related to radiation than doranidazole administration, although a relationship to the latter could not be excluded.

The PS temporarily declined in one patient with heart failure, and another with nausea and vomiting. Sporadic changes in the vital signs were not considered to be related to doranidazole administration. Changes on ECG were observed in six patients (two at 800 mg/m^2, three at 1300 mg/m^2, and one at 2000 mg/m^2). Observed abnormalities were ventricular premature beats, atrio-ventricular block, left axis deviation and complete right bundle branch block. All but one of these abnormalities had been observed sporadically prior to doranidazole administration; in

Table 2. Pharmacokinetic parameters (means ± SD)

Doranidazole dose (mg/m^2)	Study	No. of patients	C_{max} (μg/ml)	AUC (μgh/ml)	Half-life (h)
400	1	3	38 ± 1	101 ± 9	3.5 ± 0.4
800	1	3	89 ± 21	248 ± 21	4.4 ± 0.3
	2	3	74 ± 4	197 ± 27	4.2 ± 1.2
1300	1	3	117 ± 5	319 ± 40	4.9 ± 0.8
	2	6	123 ± 20	360 ± 27	4.9 ± 0.7
2000	1	3	172 ± 8	502 ± 27	4.2 ± 0.3
	2	7	194 ± 20	582 ± 165	4.6 ± 1.0

Study 1, single administration study; Study 2, repeat administration study.

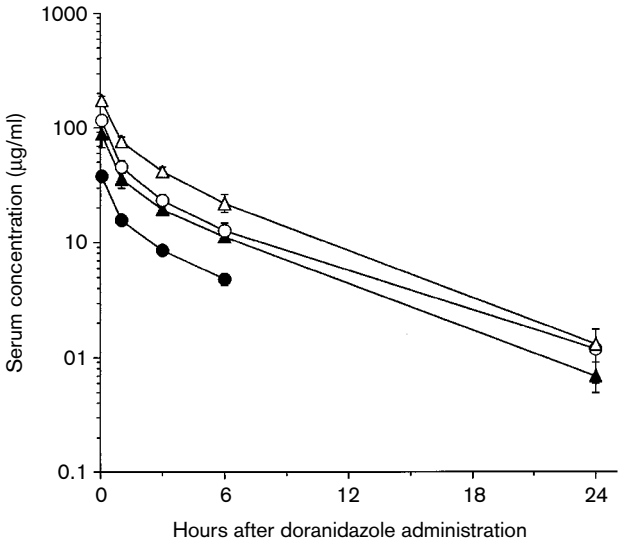

Figure 1. Concentration of doranidazole in the serum as a function of time after administration in the single administration study (error bars represent SD of three patients): ●, 400 mg/m^2; ▲, 800 mg/m^2; ○, 1300 mg/m^2; △, 2000 mg/m^2. Doranidazole concentrations at 24 h after administration at 400 mg/m^2 were lower than the detection limit (0.5 μg/ml).

one patient receiving the dose of 800 mg/m^2, ventricular premature beats were observed on day 5, 2 weeks later and on follow-up examinations, but this patient did not have such ECG findings before administration. Therefore, a relationship to doranidazole administration could not be denied.

On laboratory tests, some changes were observed in erythrocyte, leukocyte or platelet counts in three patients, but these changes were considered unlikely to be related to doranidazole administration, although the possibility could not be completely excluded. Decrease in the 24 h CCR was observed in four patients (Table 3). Although the relationship of these changes to adminstration of doranidazole was undeniable, no changes were observed in BUN and creatinine levels or in PS in any of the patients.

Table 3. Patients who showed a decrease in the 24 h CCR

Age/sex	Doranidazole administration		24 h CCR (mg/ml)		
	Dose (mg/m^2)	No.	Before	Day after	2 weeks after
67/M	2000	1	136	57	62
70/M	1300	5	83	55	80
65/M	1300	5	80	30	65
43/M	1300	5	91	55	69
65/M	2000	5	105	61	81

Pharmacokinetic data following the first administration of doranidazole were similar to those observed in the single administration study (Table 2). Doranidazole concentrations on days 2–5 before administration were less than 1 μg/ml and no increase in the concentration was observed following repeated administration. The average percentage of unchanged doranidazole excreted into the urine was between 62 and 68% on days 1–5, 1.4% on day 6, and 0.4% on day 7. As metabolites, glucuronate and carbonate conjugates of doranidazole were detected, as in the single administration study.

Tumor response was evaluable in 14 patients; five achieved a complete response and three achieved a partial response (greater than 50% reduction in the maximum tumor area), while five had a minor or no response and one had progressive disease (greater than 25% increase). Seven patients died at 4–22 months, and nine were alive at 4–26 months.

Discussion

Doranidazole is characterized by very low toxicity. Its 50% lethal dose in mice was very high (greater than 5 g/kg)[16] and also its toxicities in large animals were much lower than those of the other 2-nitroimdazole

nucleoside analogs (unpublished data). Therefore, it is quite reasonable that a single dose of 2 g/m^2 was tolerable in humans. This daily dose is the same as that for etanidazole used in the phase III studies.[9,11] Administration of still higher single doses might be possible, considering the doses of misonidazole, etanidazole and KU-2285 used in combination with intraoperative radiotherapy,[21–23] but cumulative toxicity may be more important when the treatment is combined with fractionated radiotherapy. The pharmacokinetic study showed that the average C_{max} at the dose of 2000 mg/m^2 was approximately 185 μg/ml, which is 0.75 mM. At this concentration, the enhancement ratio would be 1.4–1.6 in murine tumor systems.[16,18] Higher concentrations would produce a more evident effect, so daily dose escalation should be considered when the maximum tolerated cumulative dose becomes clear in future studies.

No patients complained of major symptoms considered attributable to this compound and it was judged that there was no dose-limiting toxicity in this study. Although a decrease in the 24-h CCR was observed in five patients, there was no change in their serum BUN and creatinine levels, and no patients had any symptoms related to this change in CCR. One of the reasons for the decrease in CCR may be that CCR, which is liable to change daily, was measured only once prior to administration. Thus, the decrease in CCR was not considered to be the dose-limiting factor and it was judged that clinical studies could be continued. Neurotoxicity was not observed in the present study, probably because the total dose was 10 g/m^2. The next study should investigate whether doranidazole would produce neurotoxicity in humans.

Tumor responses were monitored in the repeat administration study to detect unusual occurrences, but they were within the limits of expected responses. It is too early to refer to the efficacy of doranidazole. A phase Ib/II study will soon be started to investigate the cumulative toxicity and in part efficacy in patients with non-small cell lung cancer. In the forthcoming study, a daily dose of 2 g/m^2 will be given 10, 20 or 30 times, if feasible. Since the same dose of etanidazole was given 17 times in the phase III studies[9,11] and 1.2 g/m^2 of nimorazole was given 30 times in the Danish study,[12] it seems that at least 20 doses of 2 g/m^2 doranidazole should be tolerable in order for this compound to enter a phase III study. At such a dosage, doranidazole may indeed prove effective, since the compound is not as hydrophilic as etanidazole and the problem of poor tissue penetration by a hydrophilic compound may not be so evident. It is hoped that doranidaozle will be tested in phase III studies and some insights will be obtained regarding the usefulness of hypoxic cell sensitizers when used in combination with conventional fractionated radiotherapy.

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