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ORIGINAL ARTICLE

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The effects of food on the pharmacokinetic profile of oral vinorelbine

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Abstract The effects of food on the pharmacokinetics and safety profile of a soft-gel capsule formulation of vinorelbine (Navelbine Oral) were evaluated in fed and fasted patients with solid tumours or lymphomas. A group of 18 patients (12 planned) were entered into a multicentre phase I pharmacokinetic study following a crossover design with a 1-week wash-out period. Patients received the first dose of 80 mg/m^2 oral vinorelbine either after fasting or after ingestion of a standard continental breakfast. The second dose of 80 mg/m^2 was administered 1 week later in the alternate feeding condition to the first dose. Of the 18 patients, 13 were eligible for pharmacokinetic evaluation. The mean time to maximum concentration (T_{max}) was shorter in fasted patients (1.63 ± 0.98 h in blood, 1.67 ± 0.96 h in plasma) than in fed patients (2.48 ± 1.40 h in blood, 2.56 ± 1.65 h in plasma) but these differences are not likely to modify the safety and/or efficacy of oral vinorelbine. Values for C_{max} and AUC were similar in fed and fasted patients and no significant differences were observed. The safety profile of oral vinorelbine observed in this limited number of patients appears to be comparable to that usually reported for vinorelbine, the main toxicity being neutropenia. Only one episode of febrile neutropenia was reported. The main nonhaematological toxicities encountered were gastrointestinal, consisting of nausea, vomiting, diarrhoea and constipation. A tendency for a lower incidence of vomiting was suggested when oral vinorelbine was administered after a standard breakfast. Based on this study, the administration of oral vinorelbine to fasted patients is not mandatory since administration after a standard breakfast does not lead to differences in body exposure to the drug. As the comfort of patients may be improved when the treatment is administered after a light meal, this procedure can be recommended in clinical practice.

Keywords Vinorelbine · Oral · Food · Pharmacokinetics

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Introduction

Vinca alkaloids are cytotoxic drugs extensively used in the treatment of certain neoplastic diseases. Vinorelbine is a semisynthetic drug which differs chemically from other vinca alkaloids by an important substitution on the catharanthine ring, rather than on the vindoline ring of the molecule as in the first generation of vincas [5]. These structural modifications make vinorelbine more lipophilic than other vinca alkaloids. An injectable formulation of vinorelbine (Navelbine IV) is currently being marketed for the treatment of non-small-cell lung cancer and advanced breast cancer in most countries of the world. Intravenous Navelbine has a proven activity in these two diseases and possesses a good safety profile, particularly when compared with the other drugs of the same category. The usual therapeutic dose of Navelbine is 25–30 mg/m^2 per week.

An oral soft-gel capsule formulation has been developed and marketed in several European countries under the trade name Navelbine Oral. In a phase I study, the recommended dose for oral vinorelbine has been determined to be 80 mg/m^2 [1]. The bioavailability of the oral formulation compared with Navelbine IV is $43 \pm 14\%$ with an equivalent interpatient variability between

routes [4] and equivalence in exposure between 80 mg/m^2 oral and 30 mg/m^2 IV vinorelbine has been established.

In these studies, oral vinorelbine was tested in fasted patients. However, in the clinical setting, administering an oral formulation of vinorelbine together with a light meal could be interesting, given that some side effects such as nausea are frequently increased in fasted patients. Moreover, it is always difficult in clinical practice to ensure that the required fasting period has actually been observed.

Food can have marked effects on drug absorption, including increasing, decreasing and simply delaying it [7]. Food can also influence drug metabolism. For an oral formulation it is therefore essential to investigate the effect of food coadministration on the pharmacokinetics [8]. The objective of the present study was to compare the pharmacokinetic profiles in fed and fasted patients after oral administration of the soft-gel capsule formulation of vinorelbine.

Materials and methods

Study design

The study was an open, randomized pharmacokinetic study following a crossover design with a 1-week wash-out period. It was conducted in adults with solid tumours or lymphomas at three centres in France: (1) Institut Claudius Regaud, Toulouse, (2) Centre René Gauducheau, Saint-Herblain and (3) Centre Hospitalier Universitaire Morvan, Brest. Patients were randomized to receive their first dose of 80 mg/m^2 oral vinorelbine either in a fasted state or after a standard breakfast. A second oral dose of 80 mg/m^2 was given 1 week later in the alternate state relative to the first dose. Blood sampling was performed after each administration of the dose to assess the effects of food on the pharmacokinetic profile of the orally administered vinorelbine.

Patient selection

At least 12 evaluable patients were required, presenting histologically confirmed metastatic and/or advanced cancer. They had failed standard therapy for their disease and were not eligible for further standard treatment. All solid tumours or lymphomas were acceptable for inclusion. Other criteria for inclusion were: (1) age ≥18 years; (2) performance status (PS) ≤ 2 (WHO scale); (3) life expectancy > 6 weeks; (4) off previous anticancer therapy, including hormonal and radiation therapy, for at least 3 weeks (6 weeks with prior nitrosourea or mitomycin C) and recovered from the toxic effects of that treatment; (5) adequate haematopoietic (neutrophil count > 2000/mm^3, platelets > 100,000/mm^3, haemoglobin > 9 g/dl), renal (creatinine < 220 μmol/l) and hepatic (total bilirubin not more than 1.5 times upper normal limit, gamma glutamyl transferase and glutamate pyruvate transferase less than three times upper normal limit) functions; (6) no unstable, pre-existing major medical condition; (7) in women of childbearing age, the use of adequate contraception and not pregnant or lactating; (8) no pre-existing clinically significant peripheral neuropathy; (9) no evidence of malabsorption syndrome or disease significantly affecting gastrointestinal tract function; (10) no previous significant surgical resection of the stomach or small bowel; (11) psychological, familial, sociological or geographical compliance which permitted weekly medical follow-up and adherence to the study protocol; (12) adequate venous access for blood sampling; and (13) the ability to eat a standard meal. All patients were required to give informed written consent prior to registration.

Drug administration and dosage

Oral vinorelbine was supplied as gelatine capsules (Navelbine Oral; Pierre Fabre Médicament) in two dose strengths (30 or 40 mg). The unit dosages consisted of soft gelatine capsules containing vinorelbine tartrate diluted in an ethanol/water/glycerol/macrogol 400 solution. The oral dose was calculated using the patient's body surface area on the day of treatment to achieve a constant dose of 80 mg/m^2. The total administered dose was rounded to the nearest 10 mg. The same amount was given to the same patient during the two periods to allow direct comparison between nutritional status. At the time of inclusion, the patients were randomized to receive oral vinorelbine swallowed with water after fasting (i.e. 8 h after and 3 h before eating) or within 15 min of finishing a standard breakfast (i.e. 45 min after starting the breakfast). The standardized breakfast provided 12 g protein, 8.4 g lipids, 102 g carbohydrates and 542 kcal, and consisted of four sorts of breakfast to be chosen by the patient. The breakfast content was derived from the FDA standard breakfast, adapted to French eating habits. The composition of these four breakfasts including, for example, milk, sugar, bread, marmalade and orange juice was defined by the dietician of the Institut Claudius Regaud. The second administration (day 8) of 80 mg/m^2 was given in the opposite feeding condition.

Pretreatment with an antiemetic was instigated after the treatment of five patients because of poor gastrointestinal tolerance. Intravenous granisetron was administered at a dose of 3 mg as a 5-min infusion, 15 min before each administration of oral vinorelbine to the 13 other patients. Intravenous granisetron was preferred to the oral form in order to avoid any source of variation in oral absorption of vinorelbine. This preventive treatment was equivalent for both administrations and was not considered to interfere with the aims of the study. Each patient received two administrations of the drug. No dose reduction was allowed but delay in the second administration (up to 3 weeks) was possible in cases of haematological, neurological or hepatic toxicity. The study was completed after the safety evaluation on day 8 following the second administration.

Pretreatment and follow-up assessments

A complete medical history was taken and the tumour evaluated, with special focus on previous treatments for the disease, before the study. Within 1 week prior to the first day of treatment and on days 1, 8 and 15 the following examinations were carried out: physical examination, WHO performance status, vital signs (including body weight), symptoms and toxicities. Complete blood counts, including differential and platelet counts were assessed on days 1 and 8 immediately prior to treatment and on day 15.

Blood chemistry analysis of serum collected on days 1, 8 and 15 included bilirubin, glucose, alkaline phosphatase, glutamate oxaloacetate transferase (SGOT), glutamate pyruvate transferase (SGPT), electrolytes (sodium, potassium, calcium) and creatinine.

Pharmacokinetic studies

Since the first aim of this study was to determine the possible effects of food intake on the absorption of oral vinorelbine, it was decided to collect a high number of samples in the absorption phase. Given that the area under the curve after the first day represents only 33% of the total body exposure [4], it was considered that sampling up to 24 h was informative enough for comparison between fasted and fed patients.

Venous blood samples (5 ml) were drawn into heparinized glass tubes immediately prior to and then 15, 30 and 45 min and 1, 1.5, 2, 3, 5, 8, 12 and 24 h after oral dosing. From each sample of total blood, 1 ml was stored at –20°C, and the remainder was

immediately centrifuged for 10 min (3000 rpm at 10°C) and the plasma samples stored at –20°C.

In addition to the usual plasma profile and given the fact that vinorelbine is highly bound to blood components such as platelets [9], it was also decided to determine the whole-blood vinorelbine concentrations. Vinorelbine blood concentrations were quantified by high-performance liquid chromatography (HPLC). Briefly, vinorelbine was extracted the from biological fluid (1 ml) with diethyl ether at an alkaline pH together with vinblastine as internal standard, and purified using an aqueous solution buffered at pH 3. This extract was injected onto a reverse-phase cyano HPLC column and quantified by UV detection. The same method allowed the simultaneous determination of 4-*O*-deacetyl-vinorelbine, a metabolite of vinorelbine. This assay allowed the determination of these compounds at concentrations down to 2.5 $ng \cdot ml^{-1}$ with a maximal bias lower than 10%. Within- and between-day reproducibilities were below 12%.

Pharmacokinetic analysis

Blood and plasma parameters of vinorelbine and 4-*O*-deacetyl-vinorelbine were calculated using a model-independent approach with PHARM-NCA software (SIMED, France). The observed area under the curve (AUC_{last}) was calculated using the linear trapezoidal rule. AUC_{last} was preferred to AUC_{inf} in this analysis since sampling times up to 24 h do not allow a correct estimate of vinorelbine elimination half-life which is usually close to 40 h, but are convenient to investigate the absorption phase of oral vinorelbine. The peak blood concentration (C_{max}) and time to maximum concentration (T_{max}) were also calculated. Confidence intervals ($CI_{90\%}$) were determined from log-transformed data.

Statistical analysis

Differences in vinorelbine AUC_{last} and C_{max} between administrations in fasted and fed patients were analysed by analysis of variance [cross-over analysis by the GLM procedure in SAS software with patient (sequence) and treatment*sequence]. $CI_{90\%}$ values for the ratios of the means of test (after breakfast) and reference (fasted) status were calculated based upon the residual error of the analysis of variance. For T_{max}, a nonparametric Wilcoxon's test was used.

Adverse events were assessed in terms of haematological, biochemical and clinical tolerability. Toxicity was assessed using the CALGB expanded common toxicity criteria (CALGB/expanded CTC). Owing to the limited number of patients and courses evaluated, only descriptive statistics were carried out to allow a comparison between fed and fasted patients.

Pharmacokinetic/pharmacodynamic relationships

An exploratory analysis of the pharmacokinetic/pharmacodynamic relationships between drug exposure and both nonhaematological and haematological toxicity after the first administration was undertaken. Results for blood and plasma T_{max}, C_{max} and AUC_{last} were analysed according to toxicity grade (CALGB/expanded CTC scale) for each variable. Nonhaematological variables of vomiting, nausea, diarrhoea and constipation were analysed using Student's *t*-test or Wilcoxon's test.

For haematological parameters, polymorphonuclear leukocyte (PMN), white blood cell (WBC) and red blood cell (RBC) counts, and platelet and haemoglobin values on day 8 were compared with those on day 0 (before dosing) and the relationships between percent nadir and T_{max}, C_{max} and AUC_{last} were investigated by linear regression analysis using the PHARM-STAT program.

Results

A total of 18 patients (11 men and 7 women) were included in the study. The median age of the patients was 52 years (range 22 to 73 years) and 67% of the patients had a WHO PS of 1 or less at inclusion. One of the 18 patients was considered ineligible due to a reduced life expectancy and a PS of 3 at the time of inclusion. The primary tumours were ovarian (five patients), lung (three patients), gastrointestinal (three patients), cutaneous (two patients), head and neck (two patients), sarcoma, penis and unknown primary (one patient each). Nine patients were included in each arm (i.e. those fed first versus those fasted first) of the study and there was no difference between the two arms as regards their demographic, clinical or biological characteristics.

Pharmacokinetic analysis

Of the 18 patients, 13 were evaluable for pharmacokinetics. Following administration of 80 mg/m^2 oral vinorelbine, vinorelbine concentrations showed large interindividual variability but this appeared equivalent for both fasted and fed states. Concentrations of 4-*O*-deacetyl-vinorelbine showed similar variability but concentrations were much lower than for vinorelbine and close to the limit of quantification (Fig. 1).

Mean values for vinorelbine T_{max} were shorter in fasted patients (1.63 ± 0.98 h in blood, 1.67 ± 0.96 h in plasma) than in fed patients (2.48 ± 1.40 h in blood, 2.56 ± 1.65 h in plasma; Table 1), but these differences were not significant by ANOVA, and no period or carry-over effects were detected. For C_{max} and AUC_{last}, blood vinorelbine values were comparable in fasted and fed patients, with respective mean C_{max} of 121.4 ± 54.9 and 120.4 ± 57.4 $ng \cdot ml^{-1}$ and respective AUC_{last} of 711.5 ± 279.6 and 685.4 ± 225.7 $ng \cdot h \cdot ml^{-1}$. The regulatory accepted range for bioequivalence in drug interaction studies ($CI_{90\%}$ 0.8–1.25) was not strictly achieved for these parameters, although the ranges were centred around 1 with values of 0.77–1.31 and 0.78–1.29 for C_{max} and AUC_{last}, respectively. A similar pattern was seen in the plasma parameters, with $CI_{90\%}$ 0.67–1.28 for C_{max} and 0.69–1.14 for AUC_{last}. Samples were collected over 24 h only so the part of the curve extrapolated to infinity was large and difficult to accurately estimate. As a consequence, $T_{1/2}$ values were lower than previously reported and were not used for comparison.

The peak concentrations of the metabolite 4-*O*-deacetyl-vinorelbine were slightly higher in fasted patients (C_{max} 7.9 ± 4.1 $ng \cdot ml^{-1}$ in blood, 7.2 ± 5.6 $ng \cdot ml^{-1}$ in plasma) than in fed patients (C_{max} 5.5 ± 1.3 $ng \cdot ml^{-1}$ in blood, 4.6 ± 1.9 $ng \cdot ml^{-1}$ in plasma). The estimated 4-*O*-deacetyl-vinorelbine AUC_{last} values were also higher in fasted patients (124.2 $ng \cdot h \cdot ml^{-1}$ in blood, 93.3 $ng \cdot h \cdot ml^{-1}$ in plasma) than in fed patients (87.1 $ng \cdot h \cdot ml^{-1}$ in blood, 45.8 $ng \cdot h \cdot ml^{-1}$ in plasma). However, large coefficients of variation were observed in AUC_{last} for the metabolite in both fasted (CV 57.1% in blood, 94.5% in plasma) and fed patients (CV 38.3% in blood, 69.9% in plasma). As the concentrations of the metabolite were close to the

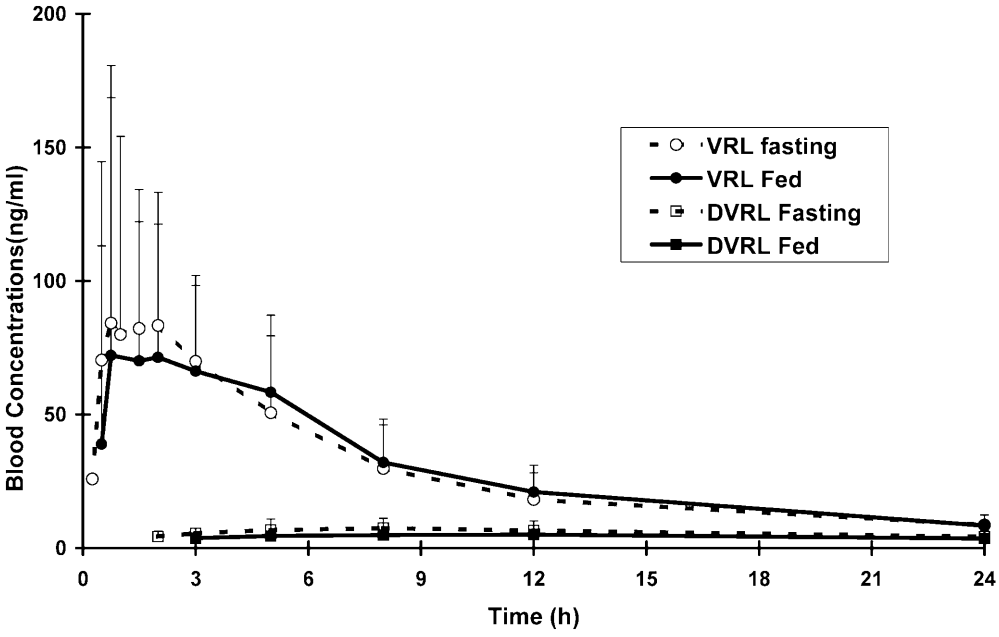

Fig. 1. Mean blood concentrations of vinorelbine and 4-*O*-deacetyl vinorelbine observed in both fed and fasted patients receiving 80 mg/m^2 oral vinorelbine

Table 1. Blood and plasma pharmacokinetic parameters after administration of 80 mg/m^2 vinorelbine to fed and fasted patients. The data are presented as means ± SD (range) (*CI* confidence interval, *n.c.* not calculated, *NS* not significant)

		Fasted	After breakfast	ANOVA food effect	$CI_{90\%}$
T_{max} (h)	Blood	1.63 ± 0.98 (0.50–3.00)	2.48 ± 1.40 (0.75–5.23)	NS	n.c.
	Plasma	1.67 ± 0.96 (0.50–3.00)	2.56 ± 1.65 (0.50–5.23)	NS	n.c.
C_{max} (ng·ml^{-1})	Blood	121.4 ± 54.9 (52.8–230.8)	120.4 ± 57.4 (65.6–273.0)	NS	0.77–1.31
	Plasma	88.4 ± 52.4 (29.0–223.7)	83.8 ± 64.8 (37.6–276.4)	NS	0.67–1.28
AUC_{last} (ng·h·ml^{-1})	Blood	711.5 ± 279.6 (192.5–1119.7)	685.4 ± 225.7 (380.3–1035.4)	NS	0.78–1.29
	Plasma	444.2 ± 183.5 (124.1–721.3)	373.3 ± 125.8 (216.8–630.0)	NS	0.69–1.14

limit of quantification its pharmacokinetic parameters were not well estimated and statistical analysis could not be achieved.

Safety analysis

A total of 17 fasted patients and 15 fed patients were eligible for the safety analysis of oral vinorelbine.

Haematological toxicity

Oral vinorelbine induced leucopenia, neutropenia and anaemia (Table 2). Thrombocytopenia was rare. Only one episode of febrile neutropenia was reported following the two administrations of oral vinorelbine. Blood chemistry was not altered following administration of oral vinorelbine.

Nonhaematological toxicity

Nausea, vomiting, diarrhoea and constipation were observed (Table 3). The incidence of vomiting appeared to be lower in fed patients. Although the limited number of patients could only suggest a tendency, this observation is consistent with the usual gastrointestinal tolerability of oral therapies.

Pharmacokinetic/pharmacodynamic relationships

A limited analysis was performed of the relationship between drug exposure and both nonhaematological and haematological toxicities. Due to the low number of patients it was not possible to compare the toxicities between the fasted and fed state, so the analysis was undertaken on the combined data. For nonhaematological toxicities, no difference was found in T_{max}, C_{max} or AUC_{last} between patients having or not experiencing either nausea or vomiting (grades 0 and 1 versus grades 2–4), or diarrhoea or constipation (grade 0 versus grades 1–4).

For haematological toxicities, the regression analysis of percent variation from baseline to nadir of each blood parameter showed no significant correlations for platelets, haemoglobin or RBC with the pharmacokinetic parameters (Table 4). For percent nadir WBC and percent nadir PMN, significant relationships were found

Table 2. Analysis of haematological toxicities (CALGB/expanded CTC scale). Values are percentage grades 3/4

	Fasted	After breakfast
WBC	23.5	6.7
PMN	18.8	6.7
Haemoglobin	11.8	0.0
Platelets	0.0	0.0

Table 3. Analysis of nonhaematological toxicities (CALGB/expanded CTC grade). Values are percentage grades 2–4

	Fasted	After breakfast
Nausea	35.3	26.7
Vomiting	41.2	33.3
Diarrhoea	17.7	6.7
Constipation	18.7	6.7

with blood and plasma AUC_{last} and the concentration 24 h after dosing (C_{24h}). For blood C_{max}, a significant correlation with percent nadir PMN was found only when the data from both the first and second courses of treatment with oral vinorelbine were pooled.

Discussion

The effects of food on the pharmacokinetics and safety profile of oral formulations of cytotoxic drugs are not frequently reported since the number of available oral formulations is still relatively small. In a study including 18 patients, the lack of an effect of coadministration of a meal with oral topotecan on the pharmacokinetics [3] has been demonstrated.

In 1996, Rowinsky et al., using a previously developed oral formulation, found a significant reduction in vinorelbine body exposure when the oral formulation was administered together with a high-fat meal [6]. However, the power of the statistical analysis, restricted to a paired *t*-test, appeared to be low because of large interpatient variability (coefficient of variation in AUC 20–75%). In the present study, the crossover design and less-variable pharmacokinetic profiles (coefficient of variation in AUC_{last} 33–41%) allowed a more accurate statistical analysis [2].

After coadministration of a standardized continental breakfast, oral vinorelbine pharmacokinetics were comparable to those observed in fasted patients. No significant difference between fasted and fed patients was found and no period effect was observed. No effect of the first administration on the second one (carry-over effect) was detected.

Peak concentrations appeared to be delayed (T_{max} 1 h 40 min and 2 h 30 min for fasted and fed patients) but were neither decreased nor increased in fed patients. The delay in drug absorption in fed patients is generally attributed to a later delivery from the stomach to the small bowel [7]. In the previous study [6], a similar delay in time to peak plasma concentrations was found, T_{max} being 1.3 ± 1.6 h in the fasted state and 2.5 ± 1.6 h following a high-fat meal.

When the onset of action depends on the rapidity of absorption, a modification in T_{max} is likely to have therapeutic consequences (e.g. antiemetics, antalgics). However, for oral vinorelbine, which is administered on a weekly schedule, a delay of 1 h is unlikely to be clinically relevant. Fasting is therefore not required to improve absorption and oral vinorelbine can be administered to patients with a meal without affecting its pharmacokinetics.

The safety analysis was a limited secondary objective of the study. It suggested no major difference between the two modes of administration and therefore did not support initial recommendation to administer the drug to fasted patients. In conclusion, food did not affect the extent of vinorelbine blood exposure and might decrease the incidence of vomiting. Fasting is not justified when administering oral vinorelbine to patients.

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Table 4. Pharmacokinetic/pharmacodynamic regression analysis of percentage variation in haematological values (*n* number of courses, *r* correlation coefficient, *P* *P*-value, *NS* not significant)

Parameter		Percent nadir WBC		Percent nadir PMN		Percent nadir platelets	Percent nadir haemoglobin	Percent nadir RBC
		Course 1	Courses 1 + 2	Course 1	Courses 1 + 2	Course 1	Course 1	Course 1
AUC_{last}	*n*	18	33	18	31	18	18	18
	r	0.6550	0.4966	0.6283	0.6588	0.1517	0.0458	0.0714
	P	0.0032	0.0033	0.0052	0.0001	NS	NS	NS
C_{max}	*n*	18	33	18	31	18	18	18
	r	0.4287	0.0374	0.4469	0.4624	0.1323	0.1393	0.1694
	P	NS	NS	NS	0.0088	NS	NS	NS
C_{24h}	*n*	17	32	17	30	17	17	17
	r	0.6026	0.4671	0.5467	0.5048	0.0632	0.0566	0.0566
	P	0.0105	0.0070	0.0232	0.0044	NS	NS	NS

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