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Pharmacokinetic properties and metabolism of idebenone

Abstract Four phase 1 studies were conducted to assess the pharmacokinetics and metabolism of idebenone (including parent drug and inactive metabolites QS10, QS6, and QS4) and to evaluate the safety of a wide range of idebenone doses and regimens in healthy adult men. After a single oral dose of idebenone 150 mg, 750 mg, or 1050 mg in fasted or fed subjects, blood samples were taken for up to 72 hours. In one study, after a single oral dose and a 7-day washout period, subjects received repeated doses of idebenone 150 mg or 750 mg every 8 hours for 14 days. In the repeated-dose study, urine samples also were taken. Plasma and urine samples were analysed with the use of liquid chromatography with tandem mass spectrometry. Non-compartmental standard pharmacokinetic methods were used. In these studies, a total of 69 subjects ranging in age from 19 to 41 years (body weight, 57–94.6 kg) were included. Plasma concentrations of parent idebenone were low but increased in proportion to dose and increased approximately five-fold in the presence of food. Total QS4 was the main metabolite in plasma and urine. The most common adverse events were loose stool, fatigue, headache, and disturbances in attention. Idebenone was well tolerated in single oral doses up to 1050 mg and in repeated daily doses up to 2250 mg. Idebenone showed linear pharmacokinetics after single and repeated oral dosing. Administration after a meal resulted in the highest exposure to parent idebenone.

Key words idebenone · Friedreich ataxia · pharmacokinetics · healthy subjects

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Introduction

Idebenone (2,3-dimethoxy-5-methyl-6-(10-hydroxydecyl)-1,4-benzoquinone) is a synthetic analogue of ubiquinone, an essential constituent of the electron transport chain and a vital cell membrane anti-oxidant. It has been shown that patients with Friedreich ataxia (FRDA) have a deficiency in biosynthesis of adenosine triphosphate (ATP) [1]. Idebenone is theorised to improve deficiencies in electron flow and to reduce oxidative stress in patients with FRDA. Several open-label studies found that 5 mg/kg/day of idebenone reduced cardiac hypertrophy in FRDA [2–4]. These studies also suggested that higher doses of idebenone may be necessary for patients to experience the full clinical benefit of idebenone treatment, particularly as it relates to improvements in neurological function [3, 5–7]. This hypothesis was confirmed in a placebo-controlled trial in paediatric patients with FRDA [8].

Information on the pharmacokinetics of the pharmacologically active parent idebenone has been limited. Parent idebenone is rapidly metabolised through oxidation and side chain shortening to the inactive metabolites QS10, QS8, QS6, and QS4 (Fig. 1) [9]. Both parent idebenone and its metabolites exist free or conjugated to sulfates and glucuronides. The analytical methods published to date were not sensitive enough to reliably mea-

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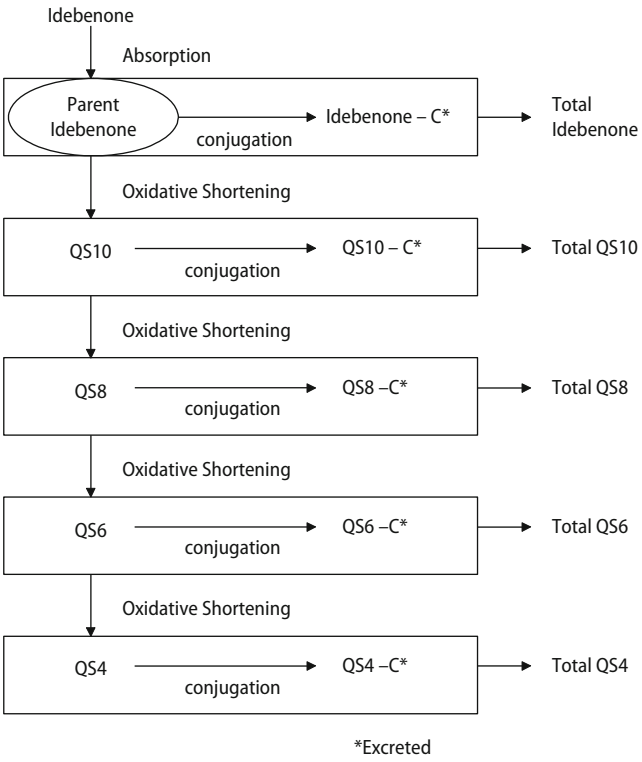

Fig. 1 Schematic presentation of the metabolism of idebenone. From Bodmer 2009 [10]

sure parent idebenone; therefore, it was possible to determine only the total amount of idebenone (parent drug plus conjugated idebenone) in plasma.

For this reason, the goals of the present clinical pharmacology program were to assess more accurately the pharmacokinetics and metabolism of idebenone (parent drug and metabolites) and to evaluate the safety of idebenone, administered as single oral doses of up to 1050 mg under fasted and fed conditions, and of up to 2250 mg daily for 2 weeks, in healthy male subjects [10].

Methods

Study design

Four different clinical phase 1 studies were performed (Table 1). Study SNT-I-002 and SNT-I-004 were single-group studies in which healthy male subjects received one dose of idebenone after intake of a continental breakfast; study SNT-I-001 was a parallel-group, cross-over study of two dose levels of idebenone (150 mg and 750 mg) in which subjects received a single dose of idebenone once after fasting and once after a meal; study SNT-I-003 was a parallel-group study in which subjects received first a single oral dose of idebenone, followed after a 7-day washout period by repeated doses three times daily (tid) at 8-hour intervals for 14 days. The repeated-dose study was recently published [10]. The morning dose was given after intake of a continental breakfast. All studies were carried out in accordance with the ethical standards established in the 1964 Declaration of Helsinki, and they followed current International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) and Good Clinical Practice (GCP) Guidelines. Informed consent was obtained from all subjects as a pre-condition for participation in any of these studies.

Sampling

Blood samples for pharmacokinetics were taken up to 72 hours after dosing. In study SNT-I-003, urine was quantitatively collected after the last drug intake. Plasma and urine samples were deep frozen (at −80 °C) pending analysis. Safety assessments, including adverse event (AE) monitoring, 12-lead electrocardiograms (ECGs), and evaluation of vital signs and laboratory values (haematology, serum chemistry, and urinalysis), were performed.

Analytics

For determination of parent idebenone in plasma, 10 µL of ethylenediaminetetraacetic acid (EDTA) was added to the samples after thawing to avoid enzymatic degradation of the conjugates. For determination of total metabolites, a glucuronidase/sulfatase enzyme solution was added to plasma and urine samples for de-conjugation. Idebenone and its metabolites QS10, QS6, and QS4 were analysed by liquid chromatography with tandem mass spectrometry (LCMS/MS).

Pharmacokinetics

The pharmacokinetic parameters in plasma of parent and total idebenone, and of the idebenone metabolites total QS10, total QS6, and

Table 1 Clinical pharmacology studies with idebenone

Study number	Dose	*N*	Meal condition	Study site
Single oral dose				
SNT-I-002	150 mg	8	After continental breakfast	Swiss Pharma Contract Basel, Switzerland
SNT-I-004	1050 mg	8	After continental breakfast	Swiss Pharma Contract Basel, Switzerland
SNT-I-001	150 mg	14	Once fasted and once fed	CEPHA
	750 mg	14	Once fasted and once fed	Pilsen, Czech Republic
Repeated dose*				
SNT-I-003	150 mg	13	After continental breakfast	University Hospital
	750 mg	12	After continental breakfast	Basel, Switzerland

* Single oral dose followed after a washout of 7 days by repeated tid dosing for 14 days
N number of patients

total QS4, were calculated according to non-compartmental standard pharmacokinetic methods. The following parameters were determined from the plasma concentration-time profile: area under the curve from time zero to the last sampling time at which the concentration was at or above the lower limit of quantification (AUC_{0-t}), maximum concentration (C_{max}), time to C_{max} (t_{max}), apparent terminal half-life ($t_{½}$), and urinary excretion within a dosing interval after the last administration of idebenone (Aeτ).

Results

Subjects

The ages of subjects ranged from 19 to 41 years, and body weight ranged from 57 to 94.6 kg.

Pharmacokinetics

Table 2 presents the main pharmacokinetic parameters C_{max}, t_{max}, and AUC_{0-t} of pharmacologically active parent idebenone when idebenone is given in single oral doses to subjects after fasting, after a continental breakfast, and after a fat-rich meal. The data showed very low plasma concentrations of the parent drug. Inter-subject and between-study variability was quite high. Data from study SNT-I-003 showed an approximate five-fold increase in C_{max} and AUC_{0-t} of parent idebenone when the dose was increased five times. Similarly, the C_{max} of parent idebenone increased approximately seven-fold when the dose was increased seven times (study SNT-I-004 vs SNT-I-002). Food increased the bioavailability of idebenone by approximately five times. During repeated dosing of both 150 mg tid and 750 mg tid, the pre-dose plasma concentrations of parent idebenone were below or were only slightly above the lower limit of quantification at both dose levels. The average C_{max} increased 1.2-fold and the average AUC_{0-t} 1.3-fold after repeated dosing of the 150-mg dose, and they increased 1.4-fold and 1.1-fold, respectively, after repeated dosing of the 750-mg dose, indicating that no relevant accumulation of the drug had occurred. A meaningful half-life could not be calculated for parent idebenone.

Table 3 shows the main pharmacokinetic parameters C_{max}, t_{max}, AUC_{0-t}, and $t_{½}$ of the metabolites total idebenone and total QS4 when idebenone is given as single and repeated oral doses after a continental breakfast. Concentrations of total idebenone are between 420- and 650-fold higher in plasma than those of the parent drug, and plasma concentrations of total QS4 are between three and four times higher than those of total idebenone, indicating that total QS4 is the main metabolic fraction of idebenone in plasma. Plasma concentrations of total QS10 are two-fold lower and those of total QS6 are four-fold lower than those of total idebenone. The mean plasma concentrations of parent idebenone and its metabolites – total idebenone, total QS10, total QS6, and total QS4 – after the last administration of idebenone in healthy male subjects who received 750 mg idebenone tid for 14 days are shown on a semi-logarithmic scale in Fig. 2.

After repeated tid oral administration of 750 mg idebenone, total QS4 is the main urinary metabolite. It represents 54.3 % of the drug amount administered. The second highest metabolite fraction excreted in urine is QS6 (8.7 %), whereas urinary excretion of total QS10 is 1.4 % and of total idebenone is below 1 %. The total average percentage of drug-derived material analysed was 65.3 %. Similar percentages were found after repeated tid oral administration of 150 mg idebenone.

Safety

Idebenone given as a single oral dose up to 1050 mg and as repeated daily doses up to 2250 mg was well tolerated. The most frequently reported adverse events (AEs) were loose stools, fatigue, headache, and disturbance in attention. A dose-dependent brownish discolouration of urine was reported by most of the subjects who received daily doses of 2250 mg idebenone.

Table 2 Mean (±SD) pharmacokinetic parameters of parent idebenone after a single oral dose

Study number	Dose	*N*	C_{max}, ng/mL	t_{max}, h	AUC_{0-t}, h·ng/mL
SNT-I-002	150 mg*	8	1.64 ± 0.99	3.37 ± 2.50	Not determined
SNT-I-004	1050 mg*	8	10.23 ± 8.40	2.46 ± 1.11	25.1 ± 27.0
SNT-I-001	150 mg fasted	14	0–1.25**	0.33–0.67**	0–0.42**
	150 mg fed	14	3.01 ± 1.99	1.31 ± 0.60	3.98 ± 2.35
	750 mg fasted	14	3.74 ± 2.40	1.18 ± 1.55	6.62 ± 4.32
	750 mg fed	14	16.31 ± 9.76	1.54 ± 0.93	30.77 ± 13.36
SNT-I-003	150 mg*	13	5.8 ± 4.6	0.87 ± 0.55	5.5 ± 3.7
	750 mg*	12	23.6 ± 24.8	2.13 ± 1.99	37.9 ± 18.0

* Drug intake after continental breakfast; ** range of data

AUC_{0-t} area under the plasma drug concentration-time curve from time zero to the last sampling time at which the concentration was at or above the lower limit of quantification; *C_{max}* maximum plasma concentration; *N* number of patients; *t_{max}* time to reach C_{max}

Table 3 Pharmacokinetic parameters of pharmacologically total idebenone and total QS4 in plasma after single and multiple oral doses of idebenone

PK parameter	Total idebenone				Total QS4			
	C_{max}, ng/mL	t_{max}, h	AUC_{0-t}, h·ng/mL	$t_{½}$, h	C_{max}, ng/mL	t_{max}, h	AUC_{0-t}, h·ng/mL	$t_{½}$, h
150 mg single dose								
Mean	1631	1.33	6277	3.10	1459	1.59	5635	3.54
SD	516	0.68	2619	2.29	632	0.76	1046	1.35
150 mg tid for 2 weeks (450 mg total daily dose)								
Mean	2061	1.83	7322	8.14	1899	1.55	6653	4.28
SD	868	1.19	3282	4.64	666	0.76	1544	1.92
750 mg single dose								
Mean	5229	2.43	32,757	10.80	6884	2.77	30591	4.15
SD	1683	1.27	12,296	3.71	3526	1.45	7027	2.08
750 mg tid for 2 weeks (2250 mg total daily dose)								
Mean	8158	1.93	32,221	15.08	9653	1.90	32837	32.49
SD	1978	0.80	10,142	4.47	1582	0.79	5508	18.08

AUC_{0-t} area under the plasma drug concentration-time curve from time zero to the last sampling time at which the concentration was at or above the lower limit of quantification; *C_{max}* maximum plasma concentration; *PK* pharmacokinetic; *SD* standard deviation; *$t_{½}$* elimination half-life; *tid* three times daily; *t_{max}* time to reach C_{max}
Adapted from Bodmer 2009 [10]

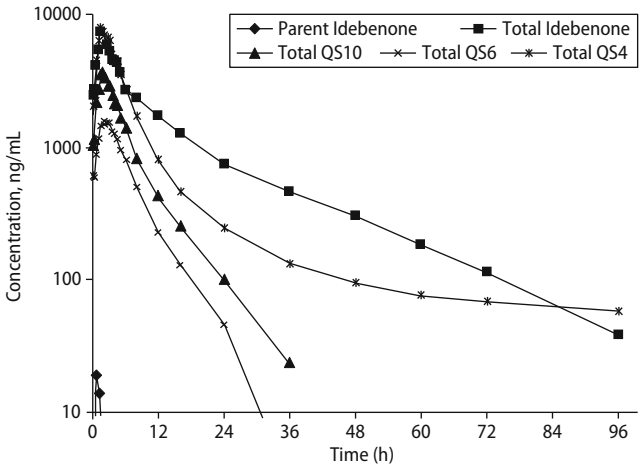

Fig. 2 Mean plasma concentrations of parent idebenone and its metabolites – total idebenone, total QS10, total QS6, and total QS4 – after the last administration of idebenone in healthy male subjects (n = 12) who received idebenone 750 mg tid for 14 days. Adapted from Bodmer 2009 [10]

Discussion

The pharmacokinetic characteristics of idebenone and its safety were investigated in four clinical pharmacology studies. Idebenone given as a single oral dose up to 1050 mg and as repeated daily doses up to 2250 mg was well tolerated. Dose-dependent discolouration of urine was due to the presence of inactive, coloured metabolites. Other AEs that were rare or were reported only once were non-specific and typical for this population of healthy male subjects.

Idebenone is quickly absorbed. Inter-subject variability was high for parent idebenone after single and repeated tid oral doses of idebenone 150 mg or 750 mg. Because of the low number of plasma concentrations that were above the lower limit of quantification, no meaningful calculations of $t_{½}$ and AUC of parent idebenone were possible.

The metabolites total idebenone, total QS10, total QS6, and total QS4 appeared moderately quickly and almost at the same time. Total idebenone reached plasma concentrations approximately 420- to 650-fold higher than those of parent idebenone after single and repeated tid oral doses of idebenone 150 mg or 5 × idebenone 150 mg. Plasma concentrations of total QS4 were in the same range but were slightly lower than those of total idebenone. Plasma concentrations of total QS10 and total QS6 were lower than those of QS4.

The ratios in C_{max} for most of the metabolites between the 5 × 150-mg dose and the 150-mg dose of idebenone under single and repeated tid administration were always close to 5, indicating linear pharmacokinetics in the dose range investigated with single and repeated oral dosing.

A moderate food effect was observed after a single administration of idebenone 750 mg, as was a two-fold increase in C_{max} of total idebenone and total QS10 and a slight increase in C_{max} of total QS6 and QS4 (64 % and 68 %, respectively). However, food intake had no relevant effects on t_{max}, $t_{½}$, and $AUC_{∞}$ of total idebenone, total QS10, total QS6, and total QS4.

Urine was the main route of elimination. Analysis of urinary data revealed that total QS4 was the predominant drug-derived material in urine, representing nearly

50 % of the drug administered. The second highest fraction in urine was QS6, whereas the amounts of total QS10 and total idebenone were about 1 % or below. Because these relationships did not change from single dose to repeated doses or between the two dose strengths, this analysis provides evidence of linear pharmacokinetics.

This evaluation indicated linear pharmacokinetics of idebenone after single and repeated oral administration. Because of the moderate increase in bioavailability when idebenone was given after administration of a fat-rich meal, it is recommended that idebenone always be administered after meal intake to guarantee the highest exposure to parent idebenone. The pharmacokinetic parameters assessed in healthy subjects were comparable with the data reported after idebenone administration in patients with FRDA [11].

Conflict of interest Dr. Kutz is an independent consultant to Santhera Pharmaceuticals.

Dr. Drewe has been the recipient of a research grant from Santhera Pharmaceuticals.

Dr. Vankan is an employee of Santhera Pharmaceuticals.

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