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Idebenone: An emerging therapy for Friedreich ataxia

Abstract This paper reviews the history and pre-clinical development of idebenone and summarises the results of clinical studies, published from 1999 to 2008, on the use of idebenone in the treatment of patients with Friedreich ataxia (FRDA). As a benzoquinone that can undergo reversible redox reactions, idebenone influences the electron balance in mitochondria. *In vitro* studies have shown that it acts both as an anti-oxidant, preventing damage to the mitochondrial membrane, and, more importantly, as an electron carrier, supporting mitochondrial function and adenosine triphosphate (ATP) production. In clinical studies, idebenone has been well tolerated by patients with various pathological conditions. The most common adverse events have been gastrointestinal effects of mild to moderate severity. No neurotoxic or adverse cardiac reactions have been reported in pre-clinical or clinical studies. The good safety profile of idebenone is supported by large clinical trials in Alzheimer's disease and by post-marketing surveillance. Phase 1 studies demonstrated the safety and tolerability of idebenone at relatively high doses (up to 60 mg/kg/day). Results from 11 clinical studies (randomised, controlled, and open-label trials), involving a total of about 200 patients, provide evidence of improvement in both cardiac hypertrophy and neurological symptoms among patients with FRDA treated with idebenone.

Key words Friedreich ataxia · idebenone · hypertrophic cardiomyopathy · ataxia rating scale · clinical trials

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The History of Idebenone

Idebenone was initially developed by Takeda Pharmaceuticals Company Ltd. (Takeda) for the treatment of patients with cognitive disorders and Alzheimer's disease and was approved in Japan in 1986 for the treatment of those with decreased volition and emotional disturbances associated with cerebrovascular disease.

Since 1999, idebenone has been studied as a possible therapy for Friedreich ataxia (FRDA) in investigator-initiated clinical trials, with the involvement of several academic institutions, the U.S. National Institutes of Health (NIH), and industry.

In the past, idebenone was referred to as a natural compound, vitamin, or dietary supplement. However, the U.S. Food and Drug Administration (FDA) has classified idebenone as a prescription drug under the Federal Food, Drug, and Cosmetic Act. Therefore, idebenone will require formal approval for use in humans and is subject to regulations governing the use of prescription drugs in the United States [1], the EU, and other countries.

Idebenone – An Improved Benzoquinone

The benzoquinone ring of idebenone (Fig. 1) can undergo reversible reduction/oxidation (redox) reactions and, similar to co-enzyme Q10, can influence the electron balance within mitochondria. It is interesting to note that the 10-carbon atom hydroxydecyl side chain of idebenone appears to be of the ideal length for balancing the partition co-efficient and the effects on mito-

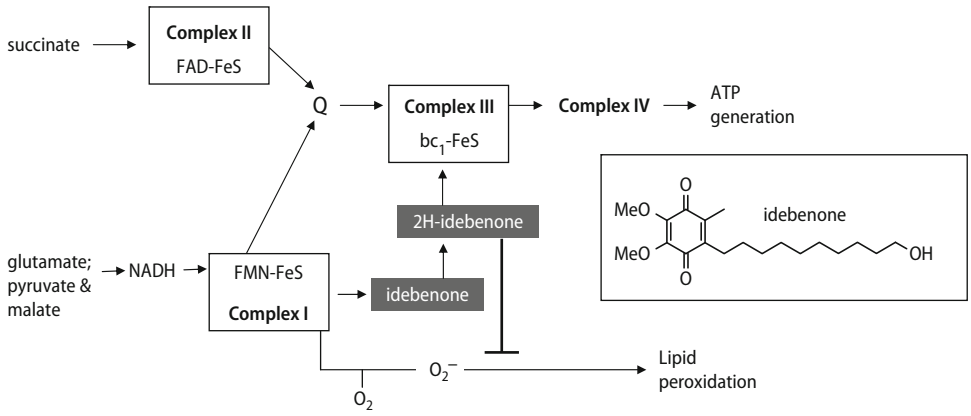

Fig. 1 Schematic representation of idebenone's proposed mode of action as an electron carrier in the mitochondrial respiratory chain. Idebenone can be reduced by complex I to reduced idebenone (2H-idebenone), which can return electrons to complex III, thereby facilitating the generation of ATP. Furthermore, cell-damaging lipid peroxidation is inhibited by reduced idebenone. FeS, iron-sulphur cluster centers; Q, co-enzyme Q; arrows, electron flux. (Adapted from Sugiyama et al. 1985, with permission [7].)

chondrial respiration. When compared with a series of structural analogues, idebenone appears to have an optimal chemical structure for the restoration of mitochondrial function [2].

Early *in vitro* findings showed that idebenone had anti-oxidant and cell-protective properties [3–5]. Different sets of biochemical experiments were used to demonstrate that idebenone could protect respiratory function and ameliorate energy metabolism in mitochondria [6, 7]. Using mitochondrial assays, researchers also showed that idebenone was rapidly oxidised by mitochondrial complex III and was readily reduced by the ubiquinone reductase function of complex I, as well as by complex II and glyceraldehyde-3-phosphate dehydrogenase [8, 9].

Taken together, these data suggest that idebenone interacts with the mitochondrial respiratory chain as an electron carrier from complexes I and II to complex III, providing support for mitochondrial function and ATP production. In addition, idebenone acts as an antioxidant, protecting membranes from damage by inhibiting lipid peroxidation in mitochondria (Fig. 1).

The Safety Profile of Idebenone

For more than 20 years, the clinical safety and tolerability of idebenone have been studied in phase 1 to phase 3 clinical trials for various therapeutic applications, and additional data have been collected from post-marketing reports. It is estimated that more than 8 million patients have been exposed to idebenone. According to the original product label for cognitive disorders, the recommended dose of idebenone was 90 mg/day. In the Takeda phase 3 clinical program for Alzheimer's disease, approximately 1100 patients received daily idebenone doses up to 1080 mg; more than 100 of these patients received idebenone for longer than 1 year. In the recently completed phase 1 and 2 trials in FRDA, 92 patients received a dose of 900 mg/day or more for periods of up to 6 months. This number includes patients with body weight less than 45 kg, who received a weight-adjusted daily dose of 450 mg.

Idebenone generally is well tolerated. The most commonly reported adverse events are gastrointestinal effects, such as diarrhoea, nausea, and dyspepsia of mild to moderate severity. Ongoing and future studies will help investigators ascertain whether the uncommon instances of increased liver function test results and reduction in blood cell counts were caused by idebenone. Of particular relevance in FRDA is that no concerns regarding neurotoxic or adverse cardiac reactions have emerged in pre-clinical or clinical studies.

Evidence for Clinical Efficacy of Idebenone in FRDA

Until very recently, most clinical trials that investigated the efficacy of idebenone in FRDA were conducted with low, body weight-adjusted doses of idebenone (generally 5 mg/kg/day). On the basis of encouraging results from phase 1 trials in FRDA showing the safety and tolerability of higher doses of idebenone (up to 60 mg/kg/day for 1 month) [10], more recent clinical trials have studied the efficacy of idebenone at doses up to ~50 mg/kg/day.

Early clinical studies of idebenone at a dose of 5 mg/kg/day mainly demonstrated the efficacy of idebenone in FRDA-associated cardiomyopathy. More recent trials have shown improved neurological function, particularly with higher doses of idebenone. To date, efficacy data have been reported from 11 clinical studies of idebenone in the treatment of FRDA. Table 1 provides an overview of clinical trials published from 1999 to 2008 [11–22]. Most of these studies were open label, but three were randomised, double-blind, placebo-controlled trials. An open-label study investigated the effects of idebenone on a urinary biomarker for oxidative stress [11], while all remaining studies assessed the efficacy of idebenone on cardiac hypertrophy and/or neurological function. Until August 2008, the number of patients with FRDA included in published prospective intervention

Table 1 Overview of clinical studies (1999–2008) with idebenone in FRDA

Reference	No. of pts (age in y)[a]	Treatment duration	Idebenone dose[b]	Type	Clinical end point	Effects
Rustin 1999 [12]	3 (11, 19, 21)	4–9 mo	5 mg/kg/d	OL	Cardiac: SWT, PWT, LVMI	↓ SWT 31–36 %, ↓ PWT 8–20 %, ↓ LVMI 21–32 %
Rustin 2004 [16]	1	5 y				↓ Cardiac hypertrophy after 5 y
Schulz 2000 [11]	8	2 mo	5 mg/kg/d	OL	Biomarker: Urinary 8OH2′dG[c]	↓ 20 % ($P < 0.05$)
Schöls 2001 [17]	9 (19–54)	1.5 mo	360 mg/d (not weight adjusted)	RCT	Cardiac: SWT, PWT, LVMI, SF Biomarker: PCr recovery by ^{31}P-MRS	No improvement compared with P; treatment duration likely too short to allow conclusion Overall little change in PCr, ↑ ATP in aerobic exercise in 3 of 9 pts
Artuch 2002 [20]	9 (11–19)	12 mo	5 mg/kg/d	OL	Cardiac: SWT, PWT Neurological: ICARS	No change from baseline[d] ↓ 49 % from baseline ($P = 0.007$)
Hausse 2002 [13]	38 (4–22)	6 mo	5 mg/kg/d 1 pt: 10 mg/kg/d	OL	Cardiac: SWT, LVMI, SF	↓ LVMI > 20 % in half of pts ($P < 0.001$), stabilisation in rest of pts SF improvement in 5 of 6 pts with abnormal SF at BL
Mariotti 2003 [14]	29 (21–32)	12 mo	5 mg/kg/d (max: 450 mg/d)	RCT	Cardiac: LVM, SWT, PWT Neurological: ICARS	LVM: Ide: ↓ 5.6 %; P: ↑ 10.7 %, ($P = 0.01$) SWT: Ide: ↓ 4.6 %; P: ↑ 5.5 %, ($P = 0.004$) PWT: Ide: ↓ 8.6 %; P: ↓ 2.4 % , ($P = 0.18$) ICARS: No difference Ide vs P
Buyse 2003 [15]	8 (9–27)	12 mo	5 mg/kg/d (max: 300 mg/d)	OL	Cardiac: LVMI, SWT, PWT, strain and strain rate (longitudinal and radial dimensions) Neurological: CAGRS	LVMI: ↓ 16.2 %; $P = 0.03$ EOT vs BL SWT and PWT: Non-significant ↓ during study period. Strain/strain rate: Significant improvement in regional myocardial function CAGRS: No improvement
Arnold 2006 [21]	20 (adults)	Several mo (up to 3.5 y)	5–10 mg/kg/d	OL	Neurological: ICARS Biomarker: Blood MDA	ICARS: Improvement in dysarthria (63 % of pts), hand dexterity (58 %), fatigue (47 %) Total ICARS: No change during treatment for 2.9 y (10 pts) ↑ MDA levels after Ide treatment (5 pts)
Di Prospero 2007 [22]	48 (9–17)	6 mo	For body wt ≤ 45 kg/> 45 kg: L: 180/360 mg/d M: 450/900 mg/d H: 1350/2250 mg/d[e]	RCT	Neurological: ICARS, FARS, ADL Biomarker: urinary 8OH2′dG[c]	ICARS: ITT population, DD ↓ ($P = 0.03$)[f]; ambulatory pts[g], ↓ on mid-dose and high-dose Ide (difference mid-dose vs P: 6.24, $P = 0.03$; high dose vs P: 7.76, $P = 0.01$)[h] FARS: DD ↓ ($P = 0.14$[f], ITT; $P = 0.04$[f] ambulatory pts) ADL: DD ↓ ($P = 0.16$[f], ITT; $P = 0.05$[f] ambulatory pts) 8OH2′dG: Values normal at BL; no change on Ide
Ribaï 2007[i] [19]	104 pts (88 on Ide) (13–74)	6 mo–7 y	5 mg/kg/d	OL	Neurological: ICARS Cardiac: LVMI, SWT, PWT, EF	Ide: ↑ 1.93 ± 0.25 p. a.[j]; P: ↑ 4.43 ± 1.56 p. a. LVMI: ↓ Ide: 4.1 ± 1.5 g/m^2 p. a. SWT: ↓ Ide: 0.11 ± 0.07 mm p. a. PWT: ↓ Ide: 0.40 ± 0.08 mm p. a. EF (%): ↓ 1.32 ± 0.29 p. a.
Pineda 2008 [18]	10 children (8–18) 14 adults (18–46)	Up to 5 y	Children: 5–10 mg/kg/d (max: 650 mg/d) Adults: 5–20 mg/kg/d (max: 1400 mg/d)	OL	Neurological: ICARS Cardiac: LVMI, PWT, SWT, FS, EF	Children: Initial improvement on ICARS, stabilised for prolonged period, and returned to baseline ICARS after 5 y Adults: Worsening on ICARS Stabilisation on measures of cardiomyopathy in children and adults

ADL activities of daily living scale (Note: a decrease in ADL score indicates improvement); *ANCOVA* analysis of co-variance; *BL* baseline; *CAGRS* Cooperative Ataxia Group Rating Scale; *DD* dose dependent; *EF* ejection fraction; *EOT* end of treatment; *FARS* Friedreich Ataxia Rating Scale (Note: a decrease in FARS score indicates improvement); *ICARS* International Cooperative Ataxia Rating Scale (Note: a decrease in ICARS score indicates improvement); *Ide* idebenone; *ITT* intent to treat group; *(L)VMI* (left) ventricular mass index; *MDA* malondiadehyde; *OL* open-label trial; *p. a.* per annum; *P* placebo; *PCr* phosphocreatine, *pt(s)* patient(s); *PWT* (left ventricular) posterior wall thickness; *^{31}P-MRS* ^{31}P magnetic resonance spectroscopy; *RCT* randomised, placebo-controlled trial; *SF* shortening fraction; *SWT* (inter ventricular) septal wall thickness; *8OH2′dG* 8-hydroxy-2′-deoxyguanosine
↑ Increase; ↓ Decrease; [a] Age at baseline of study (rounded numbers); [b] Where available, max. daily dose provided in brackets; [c] 8-hydroxy-2′-deoxyguanosine normalised to creatinine; [d] Most patients had no or only mild cardiac hypertrophy at start of study (average SWT: 9.96 mm; PWT: 10.6 mm); [e] Daily dose adapted to body weight. Low-dose group (L):180 mg/d for pts ≤ 45 kg; 360 mg/d for patients > 45 kg; mid-dose group (M): 450 mg/d for pts ≤ 45 kg, 900 mg/d for pts > 45 kg; high-dose group (H): 1350 mg/d for pts ≤ 45 kg; 2250 mg/d for pts > 45 kg; [f] Jonckheere trend test for dose-response; [g] Defined as ICARS score at baseline of 10 to 54 (pre-specified in statistical analysis plan); [h] ANCOVA with Bonferroni correction for multiple comparisons; [i] Natural history study, not focused on idebenone effects; [j] Data are means ± SD; evolution was determined with a linear mixed-effect model, taking into account several variables, including *GAA* repeat length and age of disease onset

trials ranged from 3 to 48 per trial, ~200 patients in total.

Evidence for Efficacy of Idebenone on Hypertrophic Cardiomyopathy in FRDA

Overall, in published studies, idebenone consistently improved cardiac hypertrophy in patients with FRDA, and this typically was expressed as reduction in interventricular septal wall thickness (SWT), left ventricular posterior wall thickness (PWT), or left ventricular mass index (LVMI). In patients with FRDA who received idebenone at a minimum dose of 5 mg/kg/day for at least 6 months, these anatomical cardiac parameters consistently improved [12–15], as did cardiac function, measured as changes in shortening fraction or cardiac strain [13, 15].

The first clinical trial with idebenone in patients with FRDA reported that idebenone at 5 mg/kg/day reduced SWT, PWT, and LVMI in three patients with FRDA after 4 to 9 months of therapy [12]. One patient from this original cohort showed reduced cardiac hypertrophy over a 5-year treatment period [16]. A subsequent series of trials largely confirmed the positive effect of idebenone on cardiac hypertrophy, with the exception of one placebo-controlled study [17]. It is important to note that this study analysed effects after only 1.5 months of idebenone treatment, which is probably too short a period for the drug's pharmacological action on cardiac hypertrophy to become clearly evident.

In a 6-month open-label study of 38 patients with FRDA (aged 4 to 22 years), M-mode echocardiography was used for cardiac assessment [13]. After 6 months of treatment with idebenone, the LVMI was reduced in 31 of 38 patients, with a reduction of 20 % or greater in 17 of 38 patients. Overall, the reduction in LVMI was highly significant (mean reduction, 27 % ± 6 %; $P < 0.001$ comparing before versus after treatment). Reduced shortening fraction at baseline was observed in 6 of 38 patients; after idebenone treatment, the shortening fraction improved in 5 of the 6 patients. In one patient, reduction in LVMI and improvement in shortening fraction were observed only after the idebenone dose was increased to 10 mg/kg/day. In this study, no significant correlation between patient age and the responsiveness of cardiac hypertrophy to idebenone was found, suggesting that the efficacy of idebenone in the amelioration of cardiomyopathy in FRDA is not limited to younger patients. In this study, a positive therapeutic response to idebenone was not correlated with either the genotype (number of *GAA* repeats of the shorter allele) or the stage of cardiac disease.

The positive effects of idebenone on cardiomyopathy were confirmed in a double-blind, randomised, placebo-controlled study of 29 adults with FRDA diagnosed with cardiac hypertrophy (defined as SWT or PWT ≥ 12 mm) [14]. Patients were stratified according to their septal thickness at baseline (group 1, 12 to 14 mm; group 2, > 14 mm), were assessed with the use of echocardiography, and were randomly assigned to receive idebenone 5 mg/kg/day (n = 14) or placebo (n = 15) for 12 months; the mean daily dose of idebenone was 324 mg/day (range, 240 to 450 mg). At 6 and 12 months, significant improvements were observed in SWT and left ventricular mass (LVM). At 12 months, SWT showed a 4.6 % reduction in the idebenone group versus a 5.5 % increase in the placebo group ($P = 0.004$), and LVM showed a 5.6 % reduction versus a 10.7 % increase in the placebo group ($P = 0.01$). No significant changes in ejection fraction (EF) were reported, because none of the enrolled patients had pathological functional indices at baseline (EF > 50 % for all patients during the 12-month period).

In a prospective, open-label study, eight patients with FRDA (aged 9 to 27 years) with concentric left ventricular hypertrophy at baseline were investigated [15]. After 12 months of idebenone therapy (5 mg/kg/day), mean LVMI was reduced from 130 ± 27 g/m^2 to 109 ± 28 g/m^2 ($P = 0.03$), and this reduction was accompanied by a non-significant reduction in the thickness of the interventricular septum and of the posterior wall. Fractional shortening and EF were normal at baseline in all patients and did not change significantly during treatment. In contrast, at the start of treatment, myocardial deformation properties (assessed by tissue Doppler imaging) were reduced for left ventricular longitudinal and radial function. During idebenone treatment, both properties showed early and significant improvement. This study suggested that the reduction in cardiac hypertrophy is preceded by an early and linear improvement in myocardial function. Indeed, improvements in regional deformation indices occurred as early as 4 months after treatment was initiated, and these indices continued to change over the 12 months of the study. During further prospective treatment of this patient cohort, cardiac hypertrophy and systolic function indices remained stable for a period of 5 years (GB, unpublished data).

An open-label study investigated 10 children and 14 adults with FRDA treated with idebenone for up to 5 years, with doses starting at 5 mg/kg/day and increasing to 10 mg/kg/day (children) or 20 mg/kg/day (adults) [18]. Among paediatric patients, measures of cardiac hypertrophy (SWT and PWT) remained stable over the entire study period, and after therapy, only 2 of 10 patients showed impaired heart function. In adult patients, hypertrophic cardiomyopathy (SWT, PWT, and LVMI) did not change during the study period; fractional shortening and EF slightly declined initially but stabilised later in the trial when the daily idebenone dose was increased. Results of this study suggest that idebenone treatment prevents progression of cardiomyopathy, which would be expected in the natural course of FRDA. However, the

uncontrolled design of the study does not allow a definitive conclusion.

A long-term, prospective, follow-up study provided data from 61 adult patients with FRDA who were treated with idebenone at a dose of 5 mg/kg/day [19]. LVMI decreased by 4.1 ± 1.5 g/m^2 per year, and PWT decreased by 0.4 ± 0.08 mm per year, while EF decreased slightly. Control patients in this study were too few to allow determination of whether the evolution of cardiomyopathy would have been different in untreated patients.

In conclusion, considerable clinical data demonstrate that idebenone can ameliorate hypertrophic cardiomyopathy in patients with FRDA who have increased SWT, PWT, or LVMI, and that this effect is maintained over the long term. As a consequence, idebenone already is widely used in the treatment of patients with FRDA.

Efficacy of Idebenone on Neurological Symptoms of FRDA

Initially, clinical data on the effects of idebenone on neurological aspects of FRDA were limited and primarily negative. Anecdotal observations suggested that idebenone treatment was associated with reduced general weakness, improvement in fine movement (e.g., handwriting) and speech, and decreased difficulty in swallowing [13]. However, other studies in which neurological assessment scales such as the International Cooperative Ataxia Rating Scale (ICARS) were used did not confirm an effect of low-dose (5 mg/kg/day) idebenone on neurological function in patients with FRDA [14, 15].

In contrast to findings in adult patients, another study reported neurological efficacy in a cohort of nine patients aged 11 to 19 years with FRDA treated with idebenone for 1 year at a dose of 5 mg/kg/day [20]. ICARS scores showed significant improvement from baseline after 3, 6, and 12 months of treatment ($P = 0.017$, $P = 0.012$, and $P = 0.007$, respectively), indicating the possibility of a rapid onset of efficacy in young patients. A recent study described 10 children (aged 8 to 18 years) and 14 adults (aged 18 to 46 years) with FRDA who were treated for up to 5 years with idebenone [18]. In children, dosing started at 5 mg/kg/day for 18 months with a subsequent increase to 10 mg/kg/day; in adults, the same starting dose was given for 1 year, with subsequent increases to 10 mg/kg/day and then to 20 mg/kg/day. ICARS scores in all 10 children improved during the first 12 months of treatment and were stable for ~3 to 4 years, but they declined thereafter, reaching values at the end of the 4- to 5-year treatment period that were similar to baseline values. In the cohort of adult patients, ICARS scores worsened throughout the entire observation period. Because this study lacked a placebo arm, no conclusions can be drawn regarding the possible influence of idebenone on the rate of decline in patients with FRDA.

Another open-label study reported neurological improvement, especially in dysarthria (speech), handwriting, manual dexterity, and fatigue, in patients with FRDA treated with idebenone 5 mg/kg/day and followed for up to 3.5 years while on therapy [21].

A rationale for high-dose idebenone treatment in FRDA was established in phase 1a and 1b trials conducted by the NIH [10]. These studies showed that idebenone, given at a single oral dose of up to 75 mg/kg or at a dose of 60 mg/kg daily over 1 month, was safe and generally well tolerated in patients of all age groups with FRDA. This work also defined the maximum dose of idebenone to be used in clinical efficacy trials as total plasma idebenone increased in proportion to the dose, up to, but not beyond, a dose of 55 mg/kg/day.

On the basis of this information, a double-blind, randomised, placebo-controlled trial of 48 paediatric patients with FRDA was conducted by the NIH in collaboration with Santhera Pharmaceuticals (NICOSIA trial). This 6-month study tested three dose levels of idebenone given as weight-adjusted, fixed doses up to a maximum daily dose of 1350 mg/day for patients of body weight ≤ 45 kg and 2250 mg/day for patients of body weight > 45 kg. Idebenone, particularly when given at higher doses and to ambulatory patients, improved neurological function (measured by ICARS) and activities of daily living, which were secondary end points in this study. (See the article in this supplement by Schulz, DiProspero, and Fischbeck for additional details.)

In summary, existing clinical data have provided encouraging evidence that idebenone can ameliorate hypertrophic cardiomyopathy in patients with FRDA. Recent clinical data indicate that idebenone, when given at higher doses, also improves neurological function in young patients with FRDA. Idebenone appears to be safe and well tolerated in patients with FRDA. Double-blind, randomised, placebo-controlled clinical trials are ongoing in Europe and the United States to confirm the safety and efficacy of idebenone in FRDA, particularly when given at higher doses.

Conflict of interest Dr. Meier is a regular employee of Santhera Pharmaceuticals.

Dr. Buyse has no conflicts to report.

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References

1. McGuffin M, Young AL (2004) Premarket notifications of new dietary ingredients – a ten year review. Food Drug Law J 59:233
2. Okamoto K, Matsumoto M, Watanabe M, Kawada M, Imamoto T, Imada I (1985) Effects of 6-(ω-substituted alkyl)-2,3-dimethoxy-5-methyl-1,4-benzoquinones and related compounds on mitochondrial succinate and reduced nicotinamide adenine dinucleotide oxidase systems. Chem Pharm Bull 33:3745–3755
3. Suno M, Nagaoka A (1984) Inhibition of lipid peroxidation by a novel compound, idebenone (CV-2619). Jpn J Pharmacol 35:196–198
4. Suno M, Nagaoka A (1984) Inhibition of lipid peroxidation by a novel compound (CV-2619) in brain mitochondria and mode of action of the inhibition. Biochem Biophys Res Comm 125: 1046–1052
5. Suno M, Nagaoka A (1985) Inhibition of mitochondrial swelling and lipid peroxidation by a novel compound, idebenone (CV-2619). Jpn Pharmacol Ther 13:673–678
6. Sugiyama Y, Fujita T (1985) Stimulation of the respiratory and phosphorylating activities in rat brain mitochondria by idebenone (CV-2619), a new agent improving cerebral metabolism. FEBS Lett 184:48–51
7. Sugiyama Y, Fujita T, Matsumoto M, Okamoto K, Imada I (1985) Effects of idebenone (CV-2619) and its metabolites on respiratory activity and lipid peroxidation in brain mitochondria from rats and dogs. J Pharmacobio-Dyn 8:1006–1017
8. Esposti MD, Ngo A, Ghelli A, Benelli B, Carelli V, McLennan H, Linnane AW (1996) The interaction of Q analogs, particularly hydroxydecyl benzoquinone (idebenone), with the respiratory complexes of heart mitochondria. Arch Biochem Biophys 330:395–400
9. James AM, Cocheme HM, Smith R, Murphy MP (2005) Interactions of mitochondria-targeted and untargeted ubiquinones with the mitochondrial respiratory chain and reactive oxygen species. J Biol Chem 280:21295–21312
10. Di Prospero NA, Sumner CJ, Penzak SR, Ravina B, Fischbeck KH, Taylor JP (2007) Safety, tolerability, and pharmacokinetics of high-dose idebenone in patients with Friedreich ataxia. Arch Neurol 64:803–808
11. Schulz JB, Dehmer T, Schöls L, Mende H, Hardt C, Vorgerd M, Bürk K, Matson W, Dichgans J, Beal MF, Bogdonav MB (2000) Oxidative stress in patients with Friedreich's ataxia. Neurology 55: 1719–1721
12. Rustin P, von Kleist-Retzow JC, Chantrel-Groussard K, Sidi D, Munnich A, Rotig A (1999) Effect of idebenone on cardiomyopathy in Friedreich's ataxia: a preliminary study. Lancet 354: 477–479
13. Hausse AO, Aggoun Y, Bonnet D, Sidi D, Munnich A, Rötig A, Rustin P (2002) Idebenone and reduced cardiac hypertrophy in Friedreich's ataxia. Heart 87: 346–349
14. Mariotti C, Solari A, Torta D, Marano L, Fiorentini C, Di Donato S (2003) Idebenone treatment in Friedreich patients: one-year-long randomised placebo-controlled trial. Neurology 60:1676–1679
15. Buyse G, Mertens L, Di Salvo G, Matthijs I, Wiedemann F, Eyskens B, Goossens W, Goemans N, Sutherland GR, Van Hove JL (2003) Idebenone treatment in Friedreich's ataxia: neurological, cardiac and biochemical monitoring. Neurology 60:1679–1681
16. Rustin P, Bonnet D, Roetig A, Munnich A, Sidi D (2004) Idebenone treatment in Friedreich patients. Neurology 62: 524–525
17. Schöls L, Vorgerd M, Schillings M, Skipka G, Zange J (2001) Idebenone in patients with Friedreich's ataxia. Neurosci Lett 306:169–172
18. Pineda M, Arpa J, Montero R, Aracil A, Domínguez F, Galván M, Mas A, Martorell L, Sierra C, Brandi N, García-Arumí E, Rissech M, Velasco D, Costa JA, Artuch R (2008) Idebenone treatment in paediatric and adult patients with Friedreich ataxia: long-term follow up. Eur J Paediat Neurol 12: 470–475
19. Ribaï P, Pousset F, Tanguy ML, Rivaud-Pechoux S, LeBer I, Gasparini F, Charles P, Béraud AS, Schmitt M, Koenig M, Mallet A, Brice A, Dürr A (2007) Neurological, cardiological, and oculomotor progression in 104 patients with Friedreich ataxia during long-term follow-up. Arch Neurol 64: 558–564
20. Artuch R, Aracil A, Mas A, Colomé C, Rissech M, Monrós E, Pineda M (2002) Friedreich's ataxia: idebenone treatment in early stage patients. Neuropediatrics 33:130–193
21. Arnold P, Boulat O, Maire R, Kuntzer T (2006) Expanding view of phenotype and oxidative stress in Friedreich ataxia patients with and without idebenone. Schweizer Archiv für Neurology und Psychiatry 157: 169–176
22. Di Prospero NA, Baker A, Jeffries N, Fischbeck KH (2007) Neurological effects of high-dose idebenone in patients with Friedreich's ataxia: a randomised, placebo-controlled trial. Lancet Neurol 6:878–886