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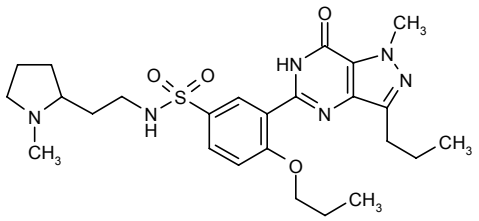
DA-8159

Erectogenic

Udenafil (Prop INN)

3-(1-Methyl-7-oxo-3-propyl-6,7-dihydro-1*H*-pyrazolo[4,3-*d*]pyrimidin-5-yl)-*N*-[2-methyl-pyrrolidin-2-yl)ethyl]-4-propoxy-benzenesulfonamide



$C_{24}H_{35}N_6O_4S$
Mol. wt: 516.66
CAS: 268203-93-6
EN: 290189

Abstract

Phosphodiesterase type 5 (PDE5) is an important target for the treatment of erectile dysfunction (ED). A novel, orally available selective inhibitor of PDE5, DA-8159, is under development for the treatment of ED by Dong-A. This agent is an appealing new alternative therapeutic for ED, as, unlike other available therapies, it does not inhibit PDE11, which may be related to testicular toxicity and myalgia. Various *in vitro* and *in vivo* studies have characterized the erectogenic efficacy of DA-8159 via elevated cyclic guanosine monophosphate (cGMP) levels. Moreover, DA-8159 displays favorable safety and pharmacokinetic profiles, with fast absorption and a relatively long terminal half-life, which would confer unique clinical properties of both a rapid onset and a long duration of action. DA-8159 is currently being evaluated in phase III clinical trials in Korea for the treatment of male ED.

Synthesis

A synthetic method for DA-8159 consists of a 13-step total synthesis starting from 2-pentanone, diethyloxalate, salicylic acid methyl ester and 2-(2-aminoethyl)-1-methylpyrrolidine.

Introduction

Erectile dysfunction (ED) is defined as the inability to achieve and maintain an erection adequate for sexual performance. It is a common problem that increases with age, with one study reporting that 52% of men between the ages of 40 and 70 years had experienced some degree of ED (1). ED has a strong relationship with overall quality of life. Therefore, the treatment of ED is now considered important for the maintenance of male health and well-being.

The most significant development in the treatment of ED in recent years has been the discovery of drugs that enable men to achieve and maintain erections by inhibiting the enzyme phosphodiesterase type 5 (PDE5). PDE5, which is the predominant isozyme in the penile corpus cavernosum, is the primary cyclic guanosine monophosphate (cGMP)-hydrolyzing enzyme and its inhibition results in penile erection by increasing the level of cGMP (2). The first pharmacotherapy with a PDE5 inhibitor for treating ED, sildenafil (Viagra®), was introduced in 1998 (3). With the successful introduction of sildenafil, the inhibition of PDE5 became the main target for new ED drug development and PDE5 inhibitors are being actively pursued by several pharmaceutical companies. Indeed, two other PDE5 inhibitors, vardenafil (Levitra®) and tadalafil (Cialis®), are now available as potent and effective treatments for ED, with a response rate of approximately 60-80%.

DA-8159 (udenafil) is an oral therapeutic agent under development for the treatment of ED by Dong-A. It is a selective inhibitor of cGMP-PDE5, with similar PDE isozyme selectivity to sildenafil; unlike tadalafil, however, it does not inhibit PDE11, which may be related to testicular toxicity and myalgia. Various *in vitro* and *in vivo* studies have supported the erectogenic efficacy of DA-8159. It increased endogenous cGMP concentrations in the rabbit corpus cavernosal smooth muscle and induced concentration-dependent relaxation of corpus cavernosal

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smooth muscle from normal and diabetic rabbits (4-6). The efficacy of DA-8159 in inducing penile erection was also established in animal models, including anesthetized dogs and conscious, diabetic and spinal cord-injured rabbits (5-8). Moreover, DA-8159 shows a favorable safety and pharmacokinetic profile, with fast absorption (C_{max} reached at 1.0-1.5 h) and a relatively long terminal half-life (11-13 h), which would confer unique clinical properties of both a rapid onset and a long duration of action (9-11). DA-8159 is now being evaluated in phase III clinical trials in Korea for the treatment of male ED.

Pharmacological Actions

The mechanism of action and erectogenic effects of DA-8159 have been evaluated in a number of animal studies (4-7, 12, 13). DA-8159 is a potent, selective and competitive inhibitor of human PDE5. *In vitro* experiments using a series of PDE isozymes (PDE1, 2, 3, 5 and 6) indicated that DA-8159 was a highly selective and potent antagonist of PDE5 from human and rabbit platelets, giving IC_{50} values of 8.25 and 5.84 nM, respectively.

In an *in vitro* assay using phenylephrine-precontracted corpus cavernosal smooth muscle, DA-8159 significantly and concentration-dependently enhanced the relaxant response to sodium nitroprusside (SNP), a nitric oxide (NO) donor (5, 6). In addition, DA-8159 enhanced the increase in intracavernosal pressure (ICP) elicited by SNP injection into the corpus cavernosum in anesthetized dogs. Intravenous administration of DA-8159 at doses of 1-300 μg/kg increased the magnitude and duration of the tumescent response to SNP in a dose-dependent manner (5).

The efficacy of DA-8159 in inducing penile erections was established in diabetic rabbits, spinal cord-injured rabbits, antidepressant-treated rats and diabetic rats, as well as normal animals, via selective inhibition of PDE5 (4, 6, 7, 12, 13). In diabetic rabbits, DA-8159 was given orally at doses of 1-10 mg/kg and the length of the uncovered penile shaft was measured in the presence or absence of intravenous SNP. The results showed that DA-8159 induced a dose-dependent penile erection, which was potentiated by intravenous SNP (6). DA-8159 was given orally at doses of 0.3-10 mg/kg to acute spinal cord-injured (ASCI) rabbits with surgical transection of the spinal cord at the L2-L4 lumbar vertebra or ischemia-reperfusion. The erection was evaluated in the same way as described above in diabetic rabbits. DA-8159 also induced a dose-dependent penile erection in both models of ASCI rabbits. The efficacy of DA-8159 was potentiated and the effective doses could be significantly reduced by intravenous SNP. In normal conscious rabbits, DA-8159 also induced a significant increase in penile erection (7). A frequently observed side effect of antidepressants is sexual dysfunction. Therefore, the efficacy of DA-8159 was evaluated by measuring ICP to determine whether it could improve antidepressant-induced erectile dysfunction. Acute treatment with paroxetine or fluoxetine, the most commonly prescribed selective serotonin reuptake inhibitors (SSRIs), significantly reduced ICP responses in rats, and a significant and frequency-dependent increase in the ICP response to electrical pelvic ganglion stimulation was seen after DA-8159 administration. The ratio of ICP/arterial blood pressure (BP) and the corresponding area under the curve (AUC) values were significantly different from the SSRI-treated controls. In addition, the maximum ICP/BP ratio was significantly increased after DA-8159 administration compared to controls (7). In a diabetic rat model, the ICP and BP were simultaneously recorded after electrical pelvic ganglion stimulation (2-10 Hz) and oral administration of DA-8159 at doses of 3 and 10 mg/kg. DA-8159 induced a frequency- and dose-dependent increase in the ICP. The ICP/BP ratio and the corresponding AUC values were also significantly and dose-dependently increased after DA-8159 administration. In addition, the detumescence time significantly increased after DA-8159 administration compared with controls (12).

Pharmacokinetics and Metabolism

In *in vitro* studies of the metabolism of DA-8159 in microsomes containing baculovirus-expressed rat hepatic microsomal cytochrome P-450 (CYP) isozymes (14), the compound was found to be metabolized to three metabolites: DA-8164 (*N*-dealkylated DA-8159; 5-[2-propyloxy-5-(amidosulfonyl)phenyl]-1-methyl-3-propyl-1,6-dihydro-7*H*-pyrazolo[4,3-*d*]pyrimidin-7-one), M1 (hydroxyl-DA-8159; 5-[2-propyloxy-5-(1-methyl-2-pyrrolidinylethylamidosulfonyl)phenyl]-1-methyl-3-hydroxypropyl-1,6-dihydro-7*H*-pyrazolo[4,3-*d*]pyrimidin-7-one) and M2 (*N*-demethyl-DA-8159; 5-[2-propyloxy-5-(1-methyl-2-pyrrolidinylethylamidosulfonyl)phenyl]-3-propyl-1,6-dihydro-7*H*-pyrazolo[4,3-*d*]pyrimidin-7-one). The formation of M1 was a major metabolic pathway for DA-8159 in rats; the intrinsic clearance (CL_{int}) values for the formation of M1, M2 and DA-8164 were 43.0, 0.08 and 16.6 ml/min/mg protein, respectively. Glucuronide and sulfate conjugation was not involved in the metabolism of DA-8159 (14). The urinary excretion of unchanged DA-8159 was < 4.30% and 0.423% of dose, respectively, in rats and rabbits administered 30 mg/kg i.v. (15, 16), suggesting that almost all of the drug is metabolized in animals. DA-8164 was formed via CYP3A4 in humans (17) and CYP3A23 in rats (18). DA-8164 was a major metabolite in humans; the DA-8164/DA-8159 ratio of total AUC was 299%, 192% and 78.6%, respectively, after oral administration of DA-8159 to mice at a dose of 30 mg/kg, to rats at a dose of 30 mg/kg and to humans at a dose of 100 mg (19). DA-8159 was mainly metabolized via CYP3A23 in rats (18).

In rats, after intravenous administration of DA-8159 at doses of 5, 10 and 30 mg/kg, the total AUC and time-averaged total body clearance (CL) values were dose-independent. However, the total AUC values for DA-8159 were dose-dependent after oral administration at doses of 20, 30, 50 and 100 mg/kg due to saturation of the first-

pass effect at high doses. At a dose of 30 mg/kg, the absolute oral bioavailability (F) was 38.0%, the intestinal first-pass effect was approximately 59% and approximately 23% of the drug absorbed into the portal vein was eliminated by the liver (hepatic first-pass effect; the value of 23% was equivalent to approximately 9.6% of the oral dose due to the intestinal first-pass effect) (16).

Following intravenous administration of DA-8159 at a dose of 30 mg/kg to PCM (protein-calorie malnutrition) rats, the clearance of DA-8159 was significantly slower (20) due to the decreased expression and mRNA level of CYP3A23 in these animals (21). In U-ARF (uranyl nitrate-induced acute renal failure) rats, the clearance of DA-8159 was also significantly slower compared to controls (22), but in DMIS (diabetes mellitus induced by streptozotocin) rats, the clearance of DA-8159 was comparable to in control rats (23). In 6-week-old spontaneously hypertensive rats (SHR), the clearance of DA-8159 was significantly faster than in controls, while in 16-week-old SHR and DOCA/salt-treated rats, DA-8159 clearance was similar to in controls (24). In rats pretreated with bacterial lipopolysaccharide (LPS), the clearance values were comparable to in control rats (25). The pharmacokinetics of orally administered DA-8159 were not changed when it was administered concurrently with intravenous nitroglycerin (26).

Circadian changes in the pharmacokinetics of DA-8159 were observed after intravenous administration to rats at 10:00 and 22:00 h. After intravenous administration at 22:00 h, the clearance of DA-8159 was significantly slower compared to when it was administered at 10:00 h (27). After intravenous administration of DA-8159 to mice, rats, rabbits and dogs, the clearance and apparent volume of distribution at steady state (V_{ss}) were well correlated to body weight and similar plasma concentration-time profiles were obtained (15).

Toxicity

The single-dose toxicity of DA-8159 was evaluated after oral administration to mice and rats and after intravenous administration to rats. The oral lethal dose was 1 g/kg in mice and 1.25 g/kg in rats and the intravenous lethal dose was 100 mg/kg in rats. Signs of toxicity included abdominal breathing, closed eyes, recumbency, decreased activity and soft stools.

Repeated-dose oral toxicity was also evaluated over 2 and 13 weeks in mice, 2, 4, 13 and 26 weeks in rats, and 1, 4 and 39 weeks in dogs. In a 2-week study in mice, dose-dependent increases in alanine aminotransferase (ALT) and total cholesterol levels in serum were observed at a dose above 500 mg/kg for both genders. Increases in absolute and relative liver weights were observed from the dose of 500 mg/kg/day. In a 13-week study in mice, hepatocelluar hypertrophy and increases in heart weight and alkaline phosphatase (ALP), ALT or total cholesterol levels were observed at doses above 500 mg/kg for both genders, indicating that the target organ is the liver. The no-observed-adverse-effect level (NOAEL) was estimated to be 350 mg/kg for both genders. DA-8159 was well tolerated in rats at doses up to 120 mg/kg for 2, 4, 13 and 26 weeks. Major side effects of DA-8159 in the 2-week study were decreases in body weight gain and food consumption, as well as an increase in DA-8159-related ALT and aspartate aminotransferase (AST) levels at a dose of 500 mg/kg/day. In the 4-, 13- and 26-week studies, the most prominent toxicological findings were effects on the liver and hematopoietic system (28). Absolute and relative liver and spleen weights increased in a dose-dependent manner at high doses (120 mg/kg/day for 13 weeks). In terms of histological findings, bone marrow myelostromal proliferation was observed. DA-8159 was considered to be less well tolerated in dogs. In the 1-week study, vomiting, conjunctival redness and diarrhea were observed at doses of 50 and 200 mg/kg/day. Increases in AST, ALT and heart rate and a decrease in the Q-T interval were also observed at high doses (200 mg/kg/day). Periangiocholitis of the liver was noted upon histopathological examination at high doses (200 mg/kg/day). In the 4-week studies in dogs, a decrease in body weight gain, vomiting, conjunctival redness and a decrease in activity were observed from the dose of 200 mg/kg/day (29). AST, ALT and cholesterol levels were elevated at the dose of 200 mg/kg/day. Decreases in serum levels of albumin, sodium, potassium and chloride were also noted at this dose. Electrocardiography revealed an increased heart rate at the dose of 200 mg/kg/day. In the 4-week study, atrophy of the prostate and thymus was observed in males at the dose of 200 mg/kg/day, and atrophy of the thymus was also seen in females at this dose. Adrenal weights were significantly greater in both males and females given this dose. Histopathological examination revealed atrophy of immune organs and tissues and lymphocyte depletion in both males and females treated at 200 mg/kg/day. Vacuolation of acinar cells in the pancreas was observed, as were inflammatory cell infiltration, vacuolar degeneration and hypertrophy of the adrenal gland, and inflammation, vacuolation and periangiocholitis in the liver. Also in females, vasculitis of the interventricular septum of the heart and interstitial nephritis of the kidneys were observed. The NOAEL value was therefore calculated to be 12.5 mg/kg in both genders. DA-8159 at a dose of 50 mg/kg/day for 39 weeks resulted in loose/liquid stools and an associated effect on body weight. In addition, conjunctivitis and transient increases in heart rate were detected. At doses of 3 or 12 mg/kg/day, transient increases in heart rate were noted in addition to loose and liquid stools, but these were not considered to be adverse effects at the higher dose, which was considered the NOAEL.

DA-8159 was not genotoxic or mutagenic based on the Ames test, the mammalian cell gene mutation assay and the *in vivo* mouse micronucleus test.

Reproductive toxicity studies were conducted in rats. Salivation, loss of fur and a slight decrease in body weight gain were noted at high doses (280 mg/kg/day). At necropsy, a decrease in prostate weight and increases in

liver, spleen and lung weights were seen at high doses. At the dose of 280 mg/kg/day, increases in the mean length of the estrous cycle and the incidence of irregular estrous cycles were observed. A decrease in the number of corpora lutea, implantations and litter size was observed at this dose and was associated with a decrease in the fertility and pregnancy indices. There were no treatment-related changes in sperm parameters and serum testosterone concentrations. Based on these data, the NOAEL for reproductive effects and general toxicity was estimated to be 70 mg/kg/day in rats.

To determine the toxicities of the metabolite DA-8164, single- and repeated-dose toxicity studies were conducted in rats. The acute lethal dose of DA-8164 was estimated to be > 2.5 g/kg and at a dose of 800 mg/kg/day for 2 weeks it was tolerated. DA-8164 also had no mutagenic potential in a battery of three genotoxicity assays.

The preclinical toxicology studies conducted with DA-8159 demonstrate that the drug is generally well tolerated in mice, rats and dogs. A NOAEL for any toxicity was considered to be 350 mg/kg in mice, 60 mg/kg in rats and 12 mg/kg in dogs, which produces exposure 105-, 18- and 3.6-fold greater, respectively, than the maximum recommended human exposure (at a dose of 200 mg of DA-8159). The preclinical data support the safety of the proposed dose of 200 mg in humans.

Clinical Studies

A double-blind, placebo-controlled phase I study was conducted in healthy male Korean subjects to assess the safety, tolerability and pharmacokinetics of DA-8159 following single and multiple oral doses (9, 11). In the single-dose study, 42 healthy male volunteers were administered doses of 12.5, 25, 50, 100, 200 and 300 mg of DA-8159 or placebo. DA-8159 was well tolerated over the dose range tested, drug-related adverse events being mainly headache, facial flushing and penile erection (all mild in severity). The number of adverse events related to DA-8159 and the number of subjects experiencing adverse events increased with dose. The results in terms of pharmacokinetics revealed that the drug is rapidly absorbed, mean peak plasma concentrations occurring at approximately 1-2 h postdose. The mean terminal half-life ranged between 7 and 12 h, and total AUC and C_{max} values increased more than dose proportionally.

Another double-blind, placebo-controlled phase I study was conducted in healthy male Caucasian subjects to assess the safety and tolerability of DA-8159 and the pharmacokinetics of DA-8159 and DA-8164 following single oral doses of 50, 100, 200 and 400 mg and multiple doses of 100 and 200 mg/day for 10 days (10). DA-8159 was safe and well tolerated. The drug was rapidly absorbed and systemic exposure (total AUC) increased in a dose-propotional manner after both single and multiple doses. The metabolite DA-8164 appeared rapidly in plasma, indicating rapid formation from DA-8159. There was little or no accumulation of DA-8159 upon multiple dosing.

A multicenter, randomized, double-blind, placebo-controlled, parallel-group, fixed-dose phase II trial was conducted in 319 ED patients. The primary efficacy endpoint was the change in the International Index of Erectile Function (IIEF) score measured from baseline to the final visit at 12 weeks. The EF scores in subjects receiving both 100 and 200 mg were significantly higher ($p < 0.001$) after 12 weeks of drug therapy compared to the placebo group. DA-8159 produced a highly significant improvement in erectile function after 12 weeks of drug therapy, with an up to 91% vaginal penetration success rate and up to 67% intercourse completion rate compared to 29% for the placebo group. Additionally, 40% of the patients in the 200-mg group returned to normal function after 12 weeks on the drug compared to only 9% on the placebo. The overall patient satisfaction measured by the standard global assessment question (GAQ) was up to 86% in the higher dose group compared to 26% in the placebo group. DA-8159 was well tolerated in humans at doses of 100 and 200 mg. The most frequently noted side effects were mild to moderate facial flushing and headache. The incidence of these side effects, as well as dyspepsia, was, however, relatively low. More importantly, there were no cases of myalgia in this study, nor were there any severe or serious adverse events related to DA-8159. Of the 282 patients who completed the study, no patient discontinued due to adverse events.

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Source

Dong-A Pharmaceutical Co., Ltd. (KR).

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