Saterinone, a Phosphodiesterase (PDE) III Inhibitor and $\alpha_1$-Adrenergic Antagonist

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INTRODUCTION

Phosphodiesterase III (PDE III) inhibitors are well established in the acute intravenous treatment of patients with decompensated chronic congestive heart failure. They act by a catecholamine-independent positive inotropic mechanism. Since ACE inhibitors became the gold standard in the therapy of chronic congestive heart failure, the focus in the pharmacological management of heart failure patients shifted from positive inotropic drugs to vasodilators. Saterinone, a PDE III inhibitor chemically related to milrinone, has pronounced vasodilator properties. This article reviews the chemistry, pharmacology, pharmacokinetics, and pharmacodynamics of saterinone.

CHEMISTRY

(±)-1,2-Dihydro-5-[4-[2-hydroxy-3-[4-2-(methoxyphenyl)-1-piperazinyl]propoxy]-phenyl]-6-methyl-2-oxo-3-pyridine-carbonitrile (BDF 8634; saterinone) was synthesized at Beiersdorf AG (Hamburg, Germany). Saterinone is a PDE III inhibitor of the bipyridine type with an $\alpha_1$-adrenoceptor antagonistic moiety. Chemically it resembles milrinone and urapidil. The chemical structures of these three drugs are shown in Fig. 1.

PHARMACOLOGY

Saterinone has a positive inotropic effect on the isolated guinea pig papillary muscle and a potent antagonistic effect at vascular $\alpha_1$-adrenoceptors. The $EC_{50}$ for its positive inotropic effect was $3.2 \times 10^{-6}$ mol/L. Its positive inotropic activity was associated with an elevation of myocardial cAMP content and was not mediated by either $\beta$-adrenoceptors or $H_2$-histaminergic receptors. In homogenates of guinea pig right ventricles, saterinone inhibited cAMP phosphodiesterase (PDE) with an $IC_{50}$ of $2.3 \times 10^{-5}$ mol/L (2).
The effects of saterinone have been compared with those of 3-isobutyl-1-methylxanthine (IBMX) and milrinone. In guinea pig papillary muscles, saterinone caused a concentration-dependent (1 to $30 \times 10^{-6}$ mol/L) inotropic effect. As a positive inotropic agent, saterinone ($EC_{50} = 9.1 \times 10^{-6}$ mol/L) was more potent than milrinone ($EC_{50} = 6.95 \times 10^{-4}$ mol/L). The efficacy (maximal obtainable effect) of saterinone was, however, only half that of milrinone. The positive inotropic effect of saterinone is at least partially due to a cAMP-dependent mechanism. At $1 \times 10^{-5}$ mol/L, carbachol, which inhibits adenylate cyclase and thereby cAMP formation, abolished the positive inotropic effect of saterinone ($3 \times 10^{-5}$ mol/L) without decreasing the force of contraction below control values. Saterinone selectively and potently inhibited the isoenzyme III of PDE ($IC_{50} = 6 \times 10^{-8}$ mol/L). The saterinone-induced increase in the rate of contractions of spontaneously beating right guinea pig atria was only half as pronounced as that caused by isoproterenol at concentrations producing a similar positive inotropic effect. Even though the maximal inotropic activity of saterinone coincided with the maximal inhibition of PDE III, there was no convincing correlation between its mechanical ($EC_{50} = 9.1 \times 10^{-6}$ mol/L) and PDE III-inhibitory ($IC_{50} = 6 \times 10^{-8}$ mol/L) effects (7).

The mechanisms of action of saterinone were studied also in vivo in small animals. In pithed guinea pigs, saterinone had a positive inotropic effect. At the maximal inotropic dose of 3 mg/kg, saterinone increased left ventricular (LV) dP/dt max by about 180% without affecting heart rate; it also antagonized the pressor effect of phenylephrine.

In conscious rabbits, saterinone dose dependently increased LV dP/dt max (at 1 mg/kg i.v. by about 80%) and heart rate, lowered arterial blood pressure and antagonized the pressor effects of phenylephrine (by about 35% at a dose of 0.03 mg/kg and by 80% at 3.0 mg/kg i.v.). The duration of saterinone-induced $\alpha_1$-adrenoceptor blockade was longer than that of its positive inotropic effect.

FIG. 1. Chemical structures of saterinone, milrinone, and urapidil.
In anesthetized cats, saterinone by slow infusion into the femoral vein produced simultaneous positive inotropic and vasodilator effects. After pretreatment with phenoxybenzamine, saterinone (unlike prazosin) further decreased arterial pressure. This finding indicated that saterinone, in addition to \( \alpha_1 \)-adrenoceptor blockade, has another mechanism of vasodilator action.

In conscious, spontaneously hypertensive rats, saterinone (10 or 30 mg/kg p.o.) significantly decreased arterial blood pressure. In conscious cats, saterinone (10 to 60 mg p.o.) increased LV dP/dt max by approximately 35% at 10 mg and 95% at 60 mg (1). In another study, the positive inotropic effects of the PDE III inhibitors (pimobendan, adibendan, and saterinone) were compared with those of isoproterenol, dihydrouoabain, and calcium. The experiments were performed on electrically driven ventricular trabeculae isolated from explanted failing (endstage myocardial failure) and nonfailing (prospective organ donors) human hearts. On the trabeculae from nonfailing hearts, the maximal positive inotropic effect of saterinone reached 45% of the maximal effect of calcium. The positive inotropic effects of dihydrouoabain and calcium were almost identical on the failing and nonfailing heart muscle, while PDE III inhibitors had only marginal inotropic effects on the trabeculae from failing hearts. The EC\(_{50}\) for saterinone was 4.5 (2.4 to 8.6) \( \times 10^{-6} \) mol/L. The positive inotropic effect of isoproterenol on the failing heart muscle was markedly reduced. These results may have been due to a decreased formation of cAMP in the failing hearts. It is noteworthy that the diminished effects of isoproterenol were restored by concomitant administration of the PDE III inhibitors (21). This observation was confirmed in a clinical study with pimobendan (5).

In another series of experiments the electrophysiological effects of saterinone and milrinone were compared using left guinea pig atria. A 90-min exposure to saterinone \( (10^{-4} \) mol/L) produced a sustained increase in the functional refractory period (FRP), while its positive inotropic effect gradually diminished during the same period. This effect may have been due to a decreased potassium conductance in the cell membrane. Milrinone did not change the functional refractory period.

On isolated guinea pig papillary muscles, saterinone, but not milrinone, increased the functional refractory period and action potential duration \( (8.3 \pm 2.79 \text{ ms at a concentration of } 10^{-4} \text{ mol/L}) \). In potassium-depolarized muscle preparations, both saterinone and milrinone decreased the amplitude, depolarization velocity, and duration of slow action potentials (8).

At \( \Lambda_1 \) adenosine receptors of myocardial membrane preparations from the left ventricles of patients with cardiomyopathy, saterinone inhibited binding of the adenosine agonist, \([^3H]DPCPX\). In this respect, saterinone was more potent than sulmazole, UD-CG 212.CI, or milrinone. At muscarinic cholinceptors, saterinone inhibited binding of the agonist, \([^3H]QNB\). Its inhibition constant was 3.5 \( (1.9 \text{ to } 4.0) \times 10^{-6} \) mol/L, and saterinone was much more potent than either sulmazole or UD-CG 212 CI. Milrinone had no relevant inhibitory effect, and its inhibition constant was \( >1 \times 10^{-2} \) mol/L. (19).

Saterinone’s plasma levels were determined by high-performance liquid chromatography (HPLC) (14). HPLC was also used for separation of saterinone’s enantiomers. This separation was achieved with excellent enantiomeric purity of more than 99%(15). Both enantiomers are detectable at low plasma levels of 0.5 ng/ml (17). In vitro receptor binding and in vivo animal studies demonstrated a slight enantioselectivity of (S)-saterinone at \( \alpha_1 \)-adrenoceptors. In functional studies, this enantioselectivity was reduced.
to an irrelevant magnitude. The positive inotropic and phosphodiesterase inhibitory effects of saterinone enantiomers lacked enantioselectivity either in vitro or in vivo (3).

It should be mentioned that the hypotensive effect of urapidil is not only due to postsynaptic $\alpha_1$-adrenoceptor blockade but also involves a central mechanism, possibly antagonism at the central 5-HT$_{1A}$ receptors (20). To our knowledge, the possibility that saterinone may have a similar additional central mechanism of hypotensive action has not yet been explored. Other pharmacological studies indicated that in vitro saterinone inhibits aggregation of human platelets and is in this respect more effective than acetylsalicylic acid (2).

**PHARMACOKINETICS**

The pharmacokinetic properties of saterinone were evaluated in a study involving 12 healthy male volunteers. Saterinone was infused intravenously at 2.5 $\mu$g/kg/min for 12 or 24 min. Half-lives of saterinone were estimated as 3.5 min for the $\alpha$-phase and as 5 h for the $\beta$-phase. The volume of distribution was 5 L/kg. Within 24 h, 7.4% of the infused dose was detected in the urine. The same individuals in the fasting state received 30 mg of saterinone p.o.; the maximal plasma concentration of the drug reached 22 ng/mL at 0.6 h, the bioavailability being 13%. After food ingestion, 30 mg of saterinone p.o. produced a maximal plasma concentration of 27 ng/mL at 0.8 h after treatment, and the bioavailability rose to 23% (9). When 60 mg of saterinone were taken p.o. by eight healthy male volunteers, the maximal plasma concentrations of saterinone (21 to 133 ng/mL) were reached at 1 to 2 h after treatment. After 120 mg p.o., the maximal plasma concentrations ranged from 44 to 166 ng/mL; and after 180 mg p.o., from 109 to 346 ng/mL (6).

In another study involving 12 healthy volunteers, plasma half-lives and maximal plasma saterinone concentrations were determined after oral administration of R-$(+)$ and S-$(−)$ enantiomers of saterinone. The two enantiomers were found to have similar half-lives and maximal plasma concentrations. Plasma half-lives of saterinone were approximately 8 h after 90, 150, or 180 mg of saterinone p.o. (Table 1). Maximal plasma concentrations were 63.6 ng/mL after 90 mg, 106.4 ng/mL after 150 mg, and 116.3 ng/mL after 180 mg of saterinone p.o. (Table 2) (17).

A study with 12 male patients with severe chronic heart failure (NYHA III; in eight patients of idiopathic and in four of ischemic origin) examined the effects of intravenous saterinone administration over 24 h. All patients received saterinone (1.5 $\mu$g/kg/min) throughout the study period. Relevant plasma levels of saterinone (ca.100 ng/mL) were

<table>
<thead>
<tr>
<th>Dose of saterinone (mg)</th>
<th>S-$(−)$ enantiomer ($t_{1/2}$, h) $^b$</th>
<th>R-$(+)$ enantiomer ($t_{1/2}$, h)</th>
</tr>
</thead>
<tbody>
<tr>
<td>90</td>
<td>7.5 ± 1.8 $^b$</td>
<td>9.2 ± 2.5 $^b$</td>
</tr>
<tr>
<td>150</td>
<td>7.8 ± 1.6</td>
<td>8.0 ± 1.7</td>
</tr>
<tr>
<td>180</td>
<td>7.1 ± 1.7</td>
<td>7.9 ± 1.7</td>
</tr>
</tbody>
</table>

$^a$ Adapted from ref. 17.

$^b$ Mean ± SD for 12 volunteers.
reached at 1 h after the start of infusion. The drug elimination curve after the end of saterinone infusion can best be described by a three-compartment model, with plasma half-lives of 4.2 min for the α-phase, 3 h for the β-phase, and 15.7 h for the terminal phase (4).

Analysis of [14C]saterinone and its metabolite levels in dog plasma, urine, and bile resulted in detection of six metabolites. The most important metabolites (saterinone sulfate and saterinone glucuronide) were found in bile as well as in urine (16).

**PHARMACODYNAMICS**

During infusion of saterinone at 2.5 μg/kg/min for 12 or 24 min to 12 healthy volunteers, the heart rate and mean arterial pressure did not change, while the left ventricular ejection fraction (LVEF), determined by M-mode echocardiography, increased significantly ($P < 0.05$) (9). In eight healthy male volunteers, saterinone (180 mg p.o.) reduced diastolic blood pressure by ca. 5 mmHg and systemic vascular resistance by up to 200 dyn s cm$^{-5}$; these effects lasted for more than 8 h. The heart rate increased by up to 14 beats/min (6).

In a study involving 11 patients (nine males, two females) with severe chronic heart failure (NYHA III; seven of ischemic and four of idiopathic origin) and pulmonary hypertension, hemodynamic measurements were performed after insertion of a Swan-Ganz catheter. The patients were given 60 mg of saterinone at 0 and 110 min, and the monitoring lasted for 4 h. A significant increase in cardiac output ($P < 0.05$) was paralleled by a significant decrease in systolic, diastolic, mean blood, and mean pulmonary arterial pressures. The heart rate did not change significantly (22).

In another study, 12 patients (eight males, four females) with severe congestive heart failure (six in NYHA Class III, six in NYHA Class IV failure; seven of ischemic and five of idiopathic origin) received increasing doses of saterinone (1, 2, 3 μg/kg/min) intravenously, for 15 min each. Hemodynamic measurements were performed every 5 min during infusion and at 15 min after the end of infusion. A marked, significant increase in cardiac index (from 1.4 to 2.3 L/min × m$^{-2}$, $P \leq 0.001$) was paralleled by a significant decrease in blood pressure ($P \leq 0.05$); right atrial, pulmonary arterial, and pulmonary capillary wedge pressures; and systemic vascular resistance ($P \leq 0.01$). Again, the heart rate did not change significantly (23).

A double-blind, placebo-controlled trial involved 36 patients with moderate to severe heart failure. Twenty-four of these patients were randomized to saterinone, and twelve

### TABLE 2. Maximal plasma concentrations of saterinone enantiomers after oral administration of saterinone to human volunteers

<table>
<thead>
<tr>
<th>Dose of saterinone (mg)</th>
<th>$S$-(−) enantiomer ($C_{max}$, ng/mL)</th>
<th>$R$-(+) enantiomer ($C_{max}$, ng/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>90</td>
<td>65.9 ± 24.9$^b$</td>
<td>63.6 ± 24.7$^b$</td>
</tr>
<tr>
<td>150</td>
<td>107.2 ± 38.8</td>
<td>106.4 ± 43.3</td>
</tr>
<tr>
<td>180</td>
<td>115.8 ± 56.0</td>
<td>116.3 ± 54.8</td>
</tr>
</tbody>
</table>

$^a$ Adapted from ref. 17.

$^b$ Mean ± SD for 12 volunteers.
received placebo. Saterinone was infused intravenously at a rate of 2 µg/kg/min for a period of 180 min. In comparison with the placebo, the drug significantly decreased systemic vascular resistance, systolic and diastolic blood pressures \( (P \leq 0.01) \), and pulmonary capillary wedge pressure \( (P \leq 0.05) \). These effects were accompanied by a borderline increase in heart rate \( (P = 0.05) \). The cardiac index did not change significantly. Plasma norepinephrine and epinephrine levels as well as plasma renin activity remained unchanged \( (18) \).

In 12 patients with idiopathic congestive cardiomyopathy (NYHA III), the hemodynamic effects of saterinone were compared with those of dobutamine and sodium nitroprusside (NPN). After insertion of a Swan-Ganz catheter the day prior to the study, hemodynamic measurements were performed on all patients. At the dose corresponding to the peak of its dose-response curve, saterinone increased the cardiac index by 102%, stroke volume by 97%, and heart rate by 6%, and decreased the pulmonary capillary wedge pressure by 46% and the right atrial pressure by 51%. Saterinone decreased the mean pulmonary arterial pressure by 38%, mean systemic blood pressure by 9%, systemic vascular resistance by 54%, and pulmonary vascular resistance by 58%. Dobutamine led to a similar increase in cardiac output and stroke volume, but it lacked the marked vasodilatory characteristics of saterinone. NPN, in contrast, produced pronounced vasodilatory effects but less increase in cardiac output and stroke volume than did either saterinone or dobutamine. The hemodynamic characteristics of the three drugs are demonstrated by the Frank-Starling relation in Fig. 2. The “double product” \( (\text{heart rate} \times \text{systolic blood pressure}) \), which estimates myocardial oxygen consumption \( (11) \), rose by 28% with dobutamine, was unchanged with saterinone \( (+2\%) \), and decreased with NPN \( (-10\%) \) \( (10) \).

In 12 patients with severe chronic heart failure (NYHA III; four of ischemic and eight of idiopathic origin), saterinone was infused i.v. at the rate of 1.5 µg/kg/min for a period of 24 h. At this dose, saterinone increased the cardiac index by 56.6%, stroke volume by 48.9%, and heart rate by 28.4%. At the same time saterinone decreased the mean blood pressure by 13.7%, mean pulmonary arterial pressure by 38.4%, right atrial pressure by 74.2%, pulmonary capillary wedge pressure by 46.9%, systemic vascular resistance by 39.9%, and pulmonary vascular resistance by 71.8%. The logarithms of saterinone plasma concentrations and of hemodynamic effects showed a high correlation \( (4) \).

**DISCUSSION**

The data presented in this survey demonstrate the positive inotropic and marked vasodilator properties of saterinone. The chemical structures in Fig. 1 suggest that saterinone may not be a pure PDE III inhibitor but may combine PDE III-inhibitory and \( \alpha_1 \)-adrenoceptor antagonist properties.

The pharmacological studies demonstrated a positive inotropic effect of saterinone, which is at least partially due to PDE inhibition and partially due to a vasodilation caused mainly by \( \alpha_1 \)-adrenoceptor antagonism \( (2,7) \). Another possible mechanism responsible for vasodilation might be central 5-HT\(_{1A} \) receptor stimulation as it has been described for urapidil \( (20) \).

The markedly diminished positive inotropic effect of saterinone on the trabeculae from failing human hearts has not been adequately explained. It has been speculated that
decreased cAMP formation in the myocardium of heart failure patients might explain the diminished inotropic activity in spite of the PDE III- inhibitory activity of saterinone (21). If this is true, one could further speculate that saterinone-induced restoration of the positive inotropic effects of β-adrenoceptor agonists can be achieved by pharmacological inhibition of PDE-III with only slight increases in cAMP. On the other hand, saterinone might, as already mentioned, have relevant positive inotropic effects due to A1 adenosine receptor and/or muscarinic cholinoreceptor antagonism (19).

It is of interest that, in spite of the similarities in the chemical structures of milrinone and saterinone, only saterinone increases the functional refractory period of the myocardium (8). It can be, therefore, expected that the arrhythmogenic potential of saterinone might well be different from that of other PDE III inhibitors.

The observed in vitro inhibition of platelet aggregation by saterinone (2) has not been studied in vivo. The majority of heart failure patients with a low left ventricular ejection fraction also have coronary heart disease. Inhibition of platelet aggregation is a desirable
property of a drug for such patients. The study with saterinone enantiomers (3) clearly demonstrated that both enantiomers are equally effective.

In the pharmacokinetic studies involving healthy volunteers and chronic heart failure patients, the plasma half-lives for intravenously administered saterinone were ca. 4 min for the α-phase and 4 h for the β-phase. When saterinone was administered orally, its half-life was ca. 8 h, so that oral therapy with saterinone is feasible.

Saterinone had only a marginal positive inotropic effect in muscle preparations from failing human hearts (21). This finding suggests that this drug should not be expected to have a relevant positive inotropic effect in heart failure patients. However, in healthy volunteers, saterinone significantly increased the left ventricular ejection fraction (6) and, in four studies with heart failure patients, saterinone produced an impressive increase in the cardiac index (4,10,22,23). Only in the fifth study did the cardiac index not change significantly after saterinone (18). Even though this is the only study with no relevant increase in the cardiac index, this finding is important because this was the only double-blind and placebo-controlled trial. On the other hand, the experimental protocol may have been responsible for the failure of investigators to detect the positive inotropic activity of saterinone. All baseline hemodynamic parameters were clearly better in the saterinone group. The Swan-Ganz and the intraarterial catheters were introduced on the day of the study. According to our own experience, hemodynamic parameters are often affected for hours after the introduction of catheters, probably because of the release of endogenous catecholamines during catheterization. For this reason, we did not start our studies on the day of instrumentation (4,10). If saterinone has no positive inotropic action in heart failure patients, it would not have produced a further increase in the cardiac index at dose levels that cause no further decrease in the pulmonary capillary wedge pressure (4).

The vasodilator effects of saterinone have been demonstrated in all the studies mentioned. Filling pressure, as well as systemic and pulmonary arterial pressures, was reduced by saterinone without any exception.

It is noteworthy that saterinone produced only a marginal increase in the heart rate in three of five studies with heart failure patients (10,22,23). It is conceivable that afterload reduction, induced by saterinone due to its α₁-adrenoceptor antagonist activity, and the subsequent increase in stroke volume are responsible for the unexpectedly low increase in heart rate. This mechanism could also explain the stable “double product” after saterinone but not dobutamine. NPN, a pure vasodilator, tends to decrease oxygen consumption while increasing the cardiac index (10).

The available data suggest that patients with chronic heart failure and an elevated systemic vascular resistance, who do not profit sufficiently from a pure vasodilator, should be treated with a PDE III inhibitor rather than with a catecholamine. Saterinone, with its pronounced vasodilator activity, offers an excellent hemodynamic profile.

It has been questioned whether we should focus on the hemodynamic abnormalities in heart failure patients (12), and it has been demonstrated that chronic treatment with milrinone tends to increase mortality in patients with heart failure. A clear difference in the survival rate was found after 8 months of treatment with milrinone (13).

At first glance there seems to be a contradiction, but there is none. It is important to distinguish between the acute treatment of decompensated patients with chronic heart failure and the chronic treatment of patients with the same disease. While hemodynamic parameters in the chronic situation might not reflect prognosis, hemodynamic improve-
ment seems to be essential in acutely decompensated patients (to our knowledge this has not yet been questioned in the literature). While chronic oral treatment with milrinone leads to an adverse outcome, a PDE III inhibitor such as saterinone might well stabilize the impaired circulation and metabolism of an acutely decompensated patient.

To summarize, saterinone, a phosphodiesterase III inhibitor of the bipyridine type with an $\alpha_1$-adrenoceptor antagonistic moiety, combines positive inotropic with marked vasodilator properties. According to the literature, saterinone appears to be a safe drug that could find a place in the acute intravenous treatment of decompensated patients with chronic congestive heart failure.

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