REVIEW

Cardiovascular Therapeutics

When Should We Use Nitrates in Congestive Heart Failure?

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SUMMARY

Organic nitrates remain among the oldest and most commonly employed drugs in cardiology. Although, in most cases, their use in acute and chronic heart failure is based on clinical practice, only a few clinical trials have been conducted to evaluate their use in acute and chronic heart failure, most of which compare them with other drugs to evaluate differing endpoints. The purpose of this review is to examine the various trials that have evaluated the use of nitrates in acute and chronic heart failure.

Introduction

Intravenous vasodilators are often used in the treatment of patients hospitalized with heart failure (HF). Among the vasodilators, nitrovasodilators are widely used in clinical practice. They make up a chemically heterogeneous class of molecules with a similar mechanism of action because of their capacity to release nitric oxide (NO) that includes organic nitrates (ON) such as nitroglycerin (NTG) and inorganic nitrates, such as sodium nitroprusside (SNP). Recent American and European guidelines on the management of acute and chronic HF have recommended consideration for use of NTG, SPN, or nesiritide (a preparation of human B-type natriuretic peptide [BNP]) in addiction to diuretics to achieve hemodynamic and symptomatic improvement [1–3]. The purpose of this review is to examine clinical studies about using ON in acute and chronic HF.

Mechanism of Actions of ON

ON are prodrugs that undergo a metabolic biotransformation predominantly in smooth muscle intracellular space [4]. This biotransformation leads to the formation of NO or a related S-nitrosothiol, which stimulates the enzyme, guanylate cyclase, and leads to the formation of cyclic guanosine monophosphate in the vascular wall. Cyclic guanosine monophosphate reduces intracellular calcium levels by decreasing the calcium's exit from the cytoplasmic reticulum and reducing its influx from the extracellular space. The decrease in intracellular calcium leads to venous and arterial vasodilation, which is the main effect of these cardiovascular drugs; production and release of endothelial prostacyclin may contribute to this effect [5]. ON are removed by extraction in the vascular beds, hydrolysis in blood, and glutathione reductase activity of nitrate in the liver [6]. Specific preparations of ON are summarized in Table 1.

In view of their mechanism of action, they are effectively used in angina pectoris and acute coronary syndromes. They are also used in HF on the rational basis of a unique combination of vascular effects that favorably influence the conditions of preload and afterload of the failing heart and the imbalance between consumption and myocardial oxygen supply in patients with ischemic HF [7–9]. Indeed, they induce a substantial reduction in right and left ventricular filling pressures, systemic and pulmonary vascular resistance, and systemic blood pressure [10]. These conditions lead to a downward shift of the pressure/volume relationship, hence the same volume has lower filling pressures [11]. ON can also modestly increase cardiac output leading to lower systemic vascular resistance because of an impairment of ventricular–aortic compliance [12].

There are some differences between ON and inorganic nitrates such as SNP (Table 2).

Table 1 Main organic nitrates and their pharmacokinetic parameters

Main organic nitrates	Half life (min)	Venous plasma clearance (L/min)	Apparent volume of distribution (L/kg)	Oral bioavailability (%)
Isosorbide dinitrate	10	4	4	20
Isosorbide 5 mononitrate	280	0.1	0.6	100
Nitroglycerin	3	50	3	0

Table 2 Differences between the two main class of nitrovasodilators

Variables	Nitroglycerin	Nitroprusside
Clinical studies in heart failure	+	−
Tolerance	++	−
Effect on coronary blood flow	↑↑	↓
Myocardial ischemia	↓	↑
Effect on neurohormones	+/−	↑

Despite the known hemodynamic effects of ON, it is unclear whether their use may influence the neurohumoral activation induced by HF [13–15].

ON in Acute HF

ON, which have been used as vasodilators in acute HF for many years, have never been evaluated in a prospective randomized study. Data from the EuroHeart Failure Survey showed the use of ON varies from 6% to 70% in different European regions [16]. The ADHERE registry documented similar findings in the United States [17].

The underuse of ON contrasts with the fact that these drugs associated to noninvasive ventilation are the only treatments in acute HF based on positive randomized controlled trials.

Two small, not blinded randomized trials performed in intensive care units regarding patients with acute HF beginning with acute pulmonary edema found that high-dose intravenous NTG therapy showed a significantly improvement inhospital outcome [18,19].

One of these trials included 104 patients randomized to high-dose isosorbide dinitrate (ISDN) therapy (3 mg bolus administered intravenously every 5 min) and low dose of furosemide (40 mg) versus high-dose furosemide (80 mg bolus administered intravenously every 15 min) and low dose of ISDN (1 mg/h, increased every 10 min by 1 mg/h) [18].

The other study included 40 patients randomly allocated to receive repeated boluses of ISDN 4 mg intra venous (i.v.) every 4 min or bilevel positive airway ventilation plus standard dose ISDN therapy (started with 10 μmol/min and increased every 5 to 10 min by 10 μmol/min) [19].

The only randomized, placebocontrolled trial designed to compare effects of NTG, nesiritide, or placebo when added to standard care in acute heart failura (AHF) patients was the Vasodilatation in the Management of Acute CHF (VMAC) study [20]. Results of this study demonstrated that commonly used i.v. NTG doses (30–60 μg/min) were not effective in improving hemodynamics or symptoms.

The lack of clinical effects on VMAC study was probably related to a decrease in vasodilatory response to NTG (nitrate resistance) previously described in patients with HF [21], suggesting larger doses (>120 μg/min) employment to obtain a significant hemodynamic parameters improvement [21].

More recently, Breidthardt et al., have shown that using high doses of transdermal or sublingual NTG (82.4 mg) resulted in a greater decrease in BNP values in patients with acute HF than in patients treated with standard dosages (20 mg) within the first 48 h of treatment [22].

It must be noted that previous studies found similar hemodynamic effects using both transdermal NTG and intravenous nitrate formulations [23,24] (Table 3).

ON in Chronic HF

Differently to limited data about use of ON in acute HF, several trials demonstrate widespread use of ON in patients with chronic HF [25–27].

Main clinical trials evaluating the effects of ON in chronic HF was tested with an association of ISDN and hydralazine (H). The rationale for use that combination of molecules was in part because of their complementary "nitroprusside-like" hemodynamic effect caused by the predominant venodilatory action of ISDN and the arterial-dilatory effect of H. Therefore, it has been postulated that combining the NO donor (ISDN) with the antioxidant (H) may provide an alternative or supplemental approach to slow or reverse progressive HF [28].

The first placebo-controlled trial testing the effects of H-ISDN on mortality in patients with chronic HF was the Vasodilator-Heart Failure Trial (V-HeFT) I, which enrolled 642 men randomized to placebo, prazosin (20 mg/day), or H-ISDN (300/160 mg/day) added to a diuretic and digoxin. All the patients were not treated with antineurohormonal therapy such as beta blockers, ace inhibitors (ACEI), and angiotensin II receptor blockers (ARB) [29]. In V-HeFT I, the combination of H-ISDN provided a beneficial effect on prognosis in HF.

The V-HeFT II trial was designed to tested effects of H-ISDN in comparison to antineurohormonal therapy. This study enrolled 804 men, mainly in NYHA class II and III, randomized to enalapril (20 mg/day) or H-ISDN, added to a diuretic and digoxin without a beta blocker [30].

V-HeFT II demonstrated that enalapril had a more favorable effect on 2-year survival than a combination of H-ISDN. However, the H-ISDN combination exerted a positive short-term impact on exercise performance and left ventricular ejection fraction.

Subgroups analysis of each study showed a better prognosis in black populations. To confirm these data, the African-American Heart Failure Trial (A-HeFT) was designed. It enrolled 1050 African-American men and women in NYHA class III or IV, randomized to placebo or H-ISDN, added to a diuretic (in 90%), digoxin (60%), ACEI (70%), ARB (17%), beta blocker (74%), and spironolactone (39%) [31]. The trial was discontinued prematurely, after a median follow-up of 10 months, because of a significant reduction in mortality in the H-ISDN group. H-ISDN

Table 3 Principal studies regarding use of organic nitrates in acute heart failure

Study	Population	Treatment	Primary endpoint	Results
Cotter et al. [18]	Patients admitted to emergency unit with signs of congestive heart failure (n = 110)	ISDN (3 mg bolus administered intravenously every 5 min; n = 56) versus furosemide (80 mg bolus administered intravenously every 15 min, as well as ISDN 1 mg/h, increased every 10 min by 1 mg/h; n = 54)	Death Required mechanical ventilation Myocardial infarction	2% versus 6% ($P = 0.61$) 13% versus 40% ($P = 0.0041$) 17% versus 37% ($P = 0.047$)
Sharon et al. [19]	Consecutive patients with severe pulmonary edema (n = 40)	repeated boluses of IV ISDN 4 mg every 4 min (n = 20) versus BiPAP ventilation and standard dose nitrate therapy (n = 20).	Death Required mechanical ventilation Myocardial infarction Combined endpoint	0% versus 10% ($P = 0.49$) 20% versus 80% ($P = 0.0004$) 10% versus 55% ($P = 0.006$) 5% versus 85% ($P = 0.0003$)
VMAC Trial [20]	Inpatients with dyspnea at rest from decompensated HF (n = 489)	Intravenous nesiritide (n = 204), intravenous NTG (n = 143), or placebo (n = 142) added to standard medications for 3 hours, followed by nesiritide (n = 278) or NTG (n = 216) added to standard medication for 24 hours	Change in PCWP at 1 h Change in PCWP at 3 h Dyspnea at 3 h	$-5.5^{*/**}$ versus −2.8 versus −1.5 $-5.8^{*/**}$ versus −3.8 versus −2 ↓* versus ↓* versus = /↑ (*$P < 0.05$ niseritide versus Placebo) (**$P < 0.05$ niseritide versus NTG)
Breidthardt et al. [22]	Consecutive patients with acute heart failure (n = 128)	Higher doses of NTG sublingual and transdermal (82.4 mg [46.2–120.6]) versus standard therapy group (20 mg [10–30]) during the first 48 h versus	Decrease of BNP during the first 24 h Decrease of BNP during the first 48 h	33 ± 3.5% versus 16 ± 3.4% ($P = 0.005$) 29 ± 4.9% versus 15 ± 5.4% ($P = 0.06$)

Table 4 Principal studies regarding use of organic nitrates in chronic heart failure

Study	Population	Treatment	Endpoint	Results
V-Heft I [29]	Patients with impaired cardiac function (average EF = 30%) and reduced exercise tolerance (n = 642)	Placebo (n = 263) versus 2.5 mg prazosin/daily (n = 183) versus 300–160 mg H-ISDN/daily (n = 186)	Cumulative mortality rate in 2.3 years of follow up	Similar in placebo and prazosin group. Risk reduction by 2 years: 34% H-ISDN versus Placebo ($P < 0.028$)
V-Heft II [30]	Patients with impaired cardiac function (average EF = 29%) and reduced exercise tolerance (n = 804)	Enalapril 20 mg/daily (n = 403) versus H-ISDN 300–160 mg/daily (n = 401)	Total mortality after 2 years Oxygen consumption (ml/Kg/min)	18% versus 25% ($P = 0.016$) Increased only by H-ISDN ($P < 0.05$)
A-Heft [31]	Black patients who had New York Heart Association class III or IV heart failure with average EF 30% (n = 1050)	H-ISDN 225–120 mg/daily (n = 518) versus placebo (n = 532)	Total mortality First hospitalization for heart failure	10.2% versus 6.2% ($P = 0.02$) 24.4% versus 16.4% ($P = 0.001$)
Mullens et al. [32]	Patient discharged with advance systolic congestive heart failure (NHYA III-IV; n = 239)	H-ISDN + ACE I/ARB (n = 142) versus ACEI/ARB (n = 97) titrated to hemodynamic response	All-cause mortality Cardiac transplant HF rehospitalization All-cause mortality + HF rehospitalization	34% versus 41% ($P = 0.04$) 22% versus 19% ($P = 0.5$) 59% versus 64% ($P = 0.4$) 70% versus 85% ($P = 0.03$)

also reduced the risk of HF hospitalization and improved quality of life.

These results taken together constitute a strong recommendation to the addition of the combination of H-ISDN to the standard medical regimen for HF in African-Americans.

Although white patients did not appear to have a mortality benefit in the retrospective analysis of V-HeFT, these data cannot exclude a benefit of the H-ISDN combination in non African-Americans when added to the standard optimal antineuhormonal HF therapy.

More recently Mullens et al. showed that a fixed dose of H-ISDN, in addition to neurohormonal blockade, is associated with a more favorable hemodynamic profile and long-term clinical outcomes in patients discharged with

low-output advanced decompensated HF, regardless of race [32] (Table 4).

Recommendations in Guidelines

In the early phase of acute HF, ESC guidelines recommend NTG as continuous infusion, at the initial dosage of 10–20 μg/min increase up to 200 μg/min, or ISDN at the initial dosage of 1 mg/h increase up to 10 mg/h (Class of recommendation I, level of evidence B) in patients with systolic blood pressure (SBP) >110 mmHg, and used with caution in patients with SBP between 90 and 110 mmHg [1]. Furthermore, more recently, AHA guidelines have recommended the use of vasodilators such as i.v. NTG in addition to diuretics and/or in patients who do not respond to diuretics alone, and in those with evidence of severely symptomatic fluid overload in the absence of systemic hypotension (Class of recommendation IIa, level of evidence C) [2].

Indeed, in chronic HF, ESC guidelines recommend H-ISDN use (Class of recommendation I, level of evidence B) in patients as an alternative to an ACEI/ARB therapy when both of the latter are not tolerated, as add-on therapy to an ACEI if an ARB or aldosterone antagonist is not tolerated and in patients of African-American descent [1]. AHA guidelines modified their recommendations including H-ISDN to improve outcomes for patients self-described as African-Americans, with moderate–severe symptoms on optimal therapy with ACEI, beta blockers, and diuretics (Level of Evidence: B) [2]. HFSA guidelines also recommend H-ISDN as a part of standard therapy in addition to beta blockers and ACEI for African-Americans with HF and reduced LVEF with moderate–severe symptoms (Level of Evidence A) or with mild symptoms (Level of Evidence B) and in non African-American patients with HF and impaired LVEF who remain symptomatic despite optimized standard therapy (Level of Evidence C) [3].

Conclusions

Although the use of ON represents the cornerstone of treatment of ischemic heart disease, well known for over 100 years, more recent evidence also suggests that this therapy could be used in the treatment of acute and chronic HF. The rational basis for their use in HF is a unique combination of vascular effects that favorably influence conditions of preload and afterload in acute and chronic settings. In the absence of arterial hypotension, nitrates are considered effective and economical, compared to other vasodilators and recommended in patients with congestive HF.

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