PHARMACOLOGY AND TOXICOLOGY

Survival of Rats with Experimental Chronic Heart Failure Depending on Pharmacodynamic and Pharmacokinetic Parameters of Angiotensin-Converting Enzyme Inhibitors and β-Adrenoceptor Blockers

V. N. Fedorov, E. V. Sal'nikov, A. V. Sidorov, A. V. Bogatushin, and M. M. Fateev

Translated from *Byulleten' Eksperimental'noi Biologii i Meditsiny*, Vol. 141, No. 1, pp. 45-48, January, 2006
Original article submitted June 21, 2005

Lipophilic inhibitors of angiotensin-converting enzyme increased 6-month survival and/or lifetime of rats with experimental chronic heart failure. These drugs had no effect on the mortality rate of animals with acute decompensation of the disease. β-Adrenoceptor blockers without intrinsic sympathomimetic activity not only prolonged 6-month survival and lifetime, but also decreased the mortality rate of rats with decompensation of chronic heart failure.

Key Words: *experimental chronic heart failure; survival; lifetime; angiotensin-converting enzyme inhibitors; β-adrenoceptor blockers*

Neurohormonal modulators, including inhibitors of angiotensin-converting enzyme (ACE) and β-adrenoceptor blockers, are extensively used in the therapy of chronic heart failure (CHF). These drugs differ in pharmacodynamic and pharmacokinetic parameters. The effects of ACE inhibitors and β-adrenoceptor blockers on survival of patients with CHF were not compared in fundamental clinical trials. Otherwise, these trials produced contradictory results (for example, study of carvedilol *vs*. metoprolol tartrate [1,9]). Moreover, CHF patients usually receive combination pharmacotherapy. Therefore, it is difficult to evaluate the effects of each drug on symptoms of this disease. The effects of the test drugs should be evaluated in experimental studies on animals with CHF.

Department of Pharmacology, Department of Biology, Department of Normal Physiology, Yaroslavl State Medical Academy. ***Address for correspondence:*** fateev52@mail.ru. M. M. Fateev

Here we compared the effects of some ACE inhibitors and β-adrenoceptor blockers on survival of rats with CHF.

MATERIALS AND METHODS

CHF in hexenal-anesthetized rats (100 mg/kg intraperitoneally) was modeled by bilateral intrapleural injection of 1.5 ml silicon oil per 100 g body weight (model of N. N. Pyatnitskii and Yu. A. Blinkov with modifications [7]). The left and right sides of the chest wall were punctured at the midpoint between the lower angle of the scapula and spine. Threefold intrapleural injections of oil in a dose of 1 ml per 100 g body weight were made at 90-day intervals. The test drugs were administered intragastrically starting from day 31. We used captopril (Capoten, Bristol-Myers Squibb, 10 mg/kg), quinapril (Accupril, Pfizer, 2.5 mg/kg), lisinopril (Diro-

0007-4888/06/1411-0040

ton, Richter Gedeon, 0.8 mg/kg), enalapril (Renitec, Merck Sharp&Dohme, 2.5 mg/kg), atenolol (Atenolol, Pliva, 5 mg/kg), nebivolol (Nebilet, Berlin Chemie, 0.5 mg/kg), metoprolol (Metocard, Polpharma, 10 mg/kg), pindolol (Visken, Novartis Pharma, 2.5 mg/kg), propranolol (Anaprilin, Medisorb, 10 mg/kg), and celiprolol (Celiprol, Leciva, 15 mg/kg). The doses of the test drugs were calculated with a conversion factor of 5.9 [4]. The rats received monotherapy with ACE inhibitors (4 groups) or β-adrenoceptor blockers (6 groups). Some rats received combination therapy with enalapril and metoprolol. The control group included untreated rats with CHF.

The test drugs belong to major classes of ACE inhibitors (hydrophilic and lipophilic drugs and prodrugs [6]) and β-adrenoceptor blockers differing in selectivity for cardiac β_1-adrenoceptors, intrinsic sympathomimetic activity (ISA), physicochemical properties, and additional vasodilatory effect [2].

Each group consisted of 30 rats. The maximum duration of the study was 390 days. We estimated the 6- and 12-month survival (%), lifetime (days), and mortality of rats during aggravation of CHF (%). The animals dying over 1 day after oil injections were excluded from further study, because their death could be caused by surgery (narcosis, trauma, *etc*.). Calculation was conducted on a personal computer using Biostatistika software. Statistical treatment included Gehan and Kruskal—Wallis tests. The differences were significant at $p<0.05$ [3].

RESULTS

Lipophilic ACE inhibitors captopril and quinapril increased the 6-month survival of rats by 2.2 and 2.7 times, respectively (Table 1). The survival rate of quinapril-receiving rats was 47% higher compared to animals of the lisinopril group. Only 10% rats of the quinapril and enalapril group survived for more than 1 year. The lifetime of CHF rats receiving lipophilic drugs quinapril and enalapril increased by 62 and 41%, respectively, compared to the control. Quinapril was more potent than captopril in increasing the lifetime of animals (by 46 and 39%, respectively).

Only 3 of cardioselective β-adrenoceptor blockers without ISA (metoprolol, atenolol and nebivolol) increased the 6-month survival of rats by 60-64% compared to the control (Table 1). Celiprolol with ISA was least potent in this respect. The 1-year survival rate increased only after treatment with nebivolol (by 32% compared to the control, $p<0.05$). Propranolol, metoprolol, and atenolol contributed to the 1-year survival of 19-20% rats. The test drugs with ISA had no effect on the lifetime of CHF rats. None of the rats receiving pindolol and celiprolol survived for more than 1 year. However, β-adrenoceptor blockers without ISA increased the lifetime of rats by 39 (propranolol), 46 (atenolol), 48 (metoprolol), and 64% (nebivolol). The rats receiving β-adrenoceptor blockers without ISA sur-

TABLE 1. Survival and Lifetime of Rats with Experimental CHF Receiving ACE Inhibitors and b-Adrenoceptor Blockers of Different Classes (*M*±*m*)

Drug	*n*	Survival, %		Lifetime, days
		6 months	12 months	
ACE inhibitors				
Control	30	30	0	163±23
Lisinopril	24	33	0	182±26
Captopril	26	65*	0	191±21
Enalapril	28	50	10	230±18*
Quinapril	30	80*+	10	265±19*+o
β-Adrenoceptor blockers				
Control	30	30	0	163±23
Propranolol	26	50+	19	227±19*+
Pindolol	30	40	0	182±21
Metoprolol	30	60*+	20	242±24*+
Atenolol	27	59*+	19	238±23*+
Celiprolol	30	15	0	142±25
Nebivolol	28	64*+	32*+o	268±18*+o

Note. $p<0.05$: *compared to the control; +compared to celiprolol; °compared to pindolol. Here and in Tables 2 and 3: *n*, number of animals.

TABLE 2. Effect of ACE Inhibitors and β-Adrenoceptor Blockers of Different Classes on Mortality Rate in Rats during Aggravation of CHF (3 Repeated Injections of Silicon Oil)

Drug		*n*	Mortality rate of animals (on corresponding days after injection of silicon oil, %)		
			days 1-7	days 8-14	other days
Control		30	67		33
β-Adrenoceptor blockers					
without ISA	propranolol	26	19*		81*
	nebivolol	28	25*		75*
	metoprolol	30	20*		80*
	atenolol	27	22*		78*
	total	109	22*		78*
with ISA	celiprolol	30	87		13
	pindolol	30	50		50
	total	60	68		32
ACE inhibitors	lisinopril	24	71		29
	captopril	26	19*	38	43
	enalapril	28	100		
	quinapril	30	40	20	40
	total	108	48	15	37

Note. *$p<0.05$ compared to the control.

vived for a longer period than animals of the celiprolol group (by 85-126 days, $p<0.05$). The average lifetime of nebivolol-receiving rats was 86 days longer compared to animals of the pindolol group ($p<0.05$). Our results are consistent with published data that ISA improves the quality of life and alleviates the side effects of β-adrenoceptor blockers, but has no effect on the lifetime of patients [5,8].

Two-thirds of control rats with CHD died over 1 week after administration of silicon oil (Table 2). Treatment with lisinopril, enalapril, and quinapril did not decrease the mortality rate of animals with decompensated CHF. Only captopril significantly decreased the mortality rate of rats over 1 week after decompensation of CHF (by 3.5 times compared to the control, $p<0.05$). However, 38% rats of the captopril group died over the 2nd week. It should be emphasized that none of control animals died during this period. The average mortality rate of rats with decompensated CHF receiving ACE inhibitors did not differ from the control.

The number of rats receiving celiprolol and pindolol with ISA and dying from decompensation of CHF did not differ from the control. Propranolol,

TABLE 3. Survival and Lifetime of Rats with Experimental CHF Receiving Combination Therapy with Enalapril and Metoprolol (*M*±*m*)

Drug	*n*	Survival, %		Lifetime, days	Mortality rate of animals (on corresponding days after injection of silicon oil, %)	
		6 months	12 months		days 1-7	other days
Control	30	30	0	163±23		
Metoprolol	30	60*	20	242±24*	20+	80+
Enalapril	28	50	10	230±18*	100	
Metoprolol+ enalapril	30	60*	30*	261±23*	23+	78+

Note. $p<0.05$: *compared to the control; +compared to enalapril.

atenolol, nebivolol, and metoprolol decreased the mortality rate of animals over the 1st week after decompensation of CHF (by 2.7-3.5 times compared to the control). Mortality of these rats remained practically unchanged over study.

Modern methods for the therapy of CHF suggest combined treatment with ACE inhibitors and β-adrenoceptor blockers (when tolerated). We studied the effect of combination therapy with enalapril (100% mortality over the 1st week after oil administration) and metoprolol (minimum 7-day mortality) on rats with experimental CHF. These drugs are extensively used in the therapy of CHF. The 6-month survival rate of rats receiving combination therapy did not differ from that observed during monotherapy with metoprolol (Table 3). However, combination therapy with metoprolol and enalapril increased the 1-year survival of rats (compared to the control and monotherapy). Over the 1st week after decompensation of CHF the mortality rate of rats receiving combination therapy was similar to that in the metoprolol group, but 4 times lower than in the enalapril group ($p<0.05$).

Our results indicate that lipophilic ACE inhibitors quinapril, enalapril, and captopril increase the survival and lifetime of rats with experimental CHF (as differentiated from hydrophilic lisinopril). As regards treatment with β-adrenoceptor blockers, the absence of ISA or, to a lesser extent, existence of cardioselective properties is associated with a favorable prognosis of CHF animals. Combination therapy with an ACE inhibitor and β-adrenoceptor blocker without ISA should be used in the therapy of CHF. This treatment improves the survival rate of animals. As distinct from ACE inhibitors, β-adrenoceptor blockers prevent the development of life-threating complications during decompensation of the disease.

REFERENCES

1. G. P. Arutyunov, *Zh. Serdech. Nedostatoch*., **5**, No. 2, 64-65 (2004).
2. G. P. Arutyunov and A. K. Rylova, *Ibid*., **2**, No. 2, 92-94 (2001).
3. S. Glants, *Medical and Biological Statistics* [in Russian], Moscow (1999).
4. T. A. Gus'kova, *Khim.-Farm. Zh*., No. 7, 10-15 (1990).
5. A. G. Obrezan and I. V. Vologdina, *Chronic Heart Failure* [in Russian], St. Petersburg (2002).
6. D. V. Preobrazhenskii, B. A. Sidorenko, and T. A. Batyraliev, *ACE Inhibitors and AT_1 Receptor Antagonists in Clinical Practice* [in Russian], Moscow (2002).
7. V. N. Fedorov, A. L. Khokhlov, and O. V. Smirnova, *Ros. Kardiol. Zh*., **33**, No. 1, 56-58 (2002).
8. M. Bristow, *Circulation*, No. 101, 558-569 (2000).
9. P. A. Poole-Wilson, R. Swedberg, J. G. F. Cleland, *et al*., *Lancet*, No. 362, 7-14 (2003).