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MDL 17,043 Therapy in Severe Congestive Heart Failure: Characterization of the Early and Late Hemodynamic, Pharmacokinetic, Hormonal and Clinical Response

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MDL 17,043, an agent with both inotropic and vasodilator properties, was evaluated in the treatment of chronic severe heart failure. The early and late hemodynamic, hormonal, pharmacokinetic and clinical responses to oral MDL 17,043 were studied in 20 patients. MDL 17,043 acutely increased cardiac output from 3.6 ± 0.9 to 4.6 ± 1.0 liters/min (+28%, $p < 0.001$) and decreased mean pulmonary artery wedge pressure from 24 ± 8 to 13 ± 8 mm Hg (−46%, $p < 0.001$), mean right atrial pressure from 10 ± 5 to 4 ± 4 mm Hg (−60%, $p < 0.001$) and mean arterial pressure from 78 ± 9 to 70 ± 11 mm Hg (−10%, $p < 0.001$). Hemodynamic improvement was sustained for 8 hours. Plasma renin activity tended to increase ($0.10 < p > 0.05$), plasma norepinephrine tended to decrease ($0.10 < p > 0.05$) and arginine vasopressin did not show any directional change. Elimination half-life for MDL 17,043 was approximately 20 hours.

Hemodynamic responsiveness was maintained in six patients undergoing restudy at 4 weeks. Initial subjective improvement in the 20 patients occurred in 90%, was present at 4 weeks in 50% and continued longer than 3 months in 25%. Side effects occurred in 75% and required cessation of treatment in 10%. Thirteen (93%) of 14 patients on long-term therapy died (median time after start of MDL 17,043 therapy 39 days). Deaths were sudden in 69%.

It is concluded that oral MDL 17,043 produces early and late hemodynamic improvement in patients with severe heart failure. The clinical response suggests caution in its use and controlled trials to ascertain whether MDL 17,043 is safe and efficacious in chronic severe heart failure.

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Inotropic therapy attempts to counteract directly the contractile deficit in myocardial failure. Such theoretic appeal has led to the development of several potential agents for the treatment of heart failure (1–3). One such compound is MDL 17,043 (4). This drug possesses vasodilating as well as inotropic properties (5). The exact mechanism for these actions has not been defined, although this agent is known to be a potent phosphodiesterase inhibitor (6). In previous studies from our laboratory (4,7), we have shown intravenous and oral MDL 17,043 to produce a dramatic short-term improvement in hemodynamic status. The long-term hemodynamic effects of this agent, however, have not been clarified and the short- and long-term hormonal response and pharmacokinetics have not been described. To evaluate the utility of MDL 17,043 in the treatment of chronic heart failure, we investigated the early and late hemodynamic, hormonal, pharmacokinetic and clinical responses to this agent in patients with severe heart failure.

Methods

Patients. Twenty patients with severe heart failure were studied, after giving informed consent, using a protocol approved by our institution's Human Use Committee. The origin of the heart failure was ischemic in 11, idiopathic in 7 and hypertensive in 1; 1 patient with long-standing mitral regurgitation and severe myocardial dysfunction despite a well functioning valve prosthesis was studied. There were 16 men and 4 women. Fifteen were in New York Heart

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Association functional class IV and 5 were in class III. The average age was 61 ± 12 years. The average ejection fraction by radionuclide or contrast angiography was 16 ± 5%, blood urea nitrogen was 35 ± 24 mg/100 ml and creatinine was 1.7 ± 0.8 mg/100 ml.

The following vasodilators had previously been used by the referring physician and considered by the referring physician to be not totally satisfactory: a nitrate preparation in 13, captopril in 11, hydralazine in 5 and prazosin in 4. All vasodilator drugs were withheld for at least 18 hours before invasive study. Short-term intravenous dobutamine in two patients and dopamine in one patient had previously been infused. All patients were receiving diuretic and digitalis therapy. These agents were withheld the day of the invasive study.

Study Protocol

Early study. In the initial hemodynamic study right heart pressures and cardiac output were measured through a triple lumen Swan-Ganz thermodilution catheter. Femoral artery pressure was measured directly. Cardiac output was determined in triplicate (with less than 10% variation) using iced 5% dextrose solution. Oxygen saturation and hemoglobin were measured from the systemic and pulmonary artery blood to determine systemic arteriovenous oxygen difference.

Supine baseline measurements at rest of pressures, cardiac output and systemic arteriovenous oxygen difference were obtained in duplicate 15 minutes apart. Baseline data represent an average of these values. Patients were then given a single dose of oral MDL 17,043 (the first 10 patients received 3 mg/kg and the second 10 patients 6 mg/kg). Hemodynamic measurements were made at 30 minutes and 1 to 8 hours after drug administration. The initial dose of 3 mg/kg was chosen on the basis of an intravenous study from our laboratory (4) suggesting that 3 mg/kg is in the middle of the dose-response curve.

Blood samples for plasma norepinephrine, renin activity and arginine vasopressin were obtained after the second set of baseline hemodynamic measurements, which were at least 1 hour after the patient was in the supine position. Blood for hormone levels were obtained at 1 and 4 hours after MDL 17,043 administration. Plasma norepinephrine was measured using high performance liquid chromatography (8). Plasma renin activity and arginine vasopressin were measured using previously described radioimmunoassay techniques (9,10). Hormone levels were obtained during early and late invasive studies in all patients.

Blood was obtained at baseline, coincident with each hemodynamic measurement, and at 24 hours after drug administration (18 patients) to measure plasma levels of MDL 17,043 and a major hemodynamically active metabolite MDL 19,438 (1,3-dihydro-4-methyl-5-[4-methylsulfinyl]-benzoyl-2H-imidazol-2-one) (7) using a high performance liquid chromatography method (11). The elimination half-life ($T\frac{1}{2}$) was estimated by fitting a simple linear regression to the terminal decay phase of the $\log_{10}$ plasma concentrations. The elimination rate (h^{-1}) is then: $k_e = 2.303\ b$, where b is the estimated slope of the linear regression. The elimination half-life (h) is $T\frac{1}{2} = 0.693/k_e$. Fourteen of the 20 patients had both relatively normal renal function (creatinine < 2.0 mg/100 ml) and sufficient data to calculate $T\frac{1}{2}$ for the early study.

An electrocardiogram and the following laboratory data were obtained before and on the day after invasive testing: complete blood count with differential, platelet count, urinalysis and determinations of alkaline phosphatase, serum glutamic oxaloacetic transaminase, serum glutamic pyruvate transaminase, bilirubin, blood urea nitrogen, creatinine, glucose, cholesterol, sodium, potassium, chloride, bicarbonate, calcium, phosphorus, uric acid, albumin and total protein.

Derived hemodynamic variables including systemic vascular and pulmonary arteriolar resistance and stroke work index were calculated using standard formulas (4).

Late study. After completion of the initial hemodynamic study, patients were offered long-term use of the agent. All agreed to continue taking the agent and to be seen weekly as an outpatient for the first 4 weeks and monthly thereafter or daily in the hospital. At these visits, the patient was questioned specifically regarding cardiovascular symptoms and signs, overall status and side effects. An electrocardiogram and blood studies as listed were measured. Responses were entered on standardized data forms. For analytical purposes, patients were given an overall score of "improved," "unchanged" or "worsened" in relation to baseline at each evaluation point. Death was considered sudden if it was witnessed and occurred within 1 hour of the onset of symptoms, usually with an abrupt loss of consciousness, or if it was unwitnessed and occurred within 24 hours of the time the patient was last seen in his usual state of health. Patients were allowed to continue on all medications, including vasodilators, if it was believed that clinical improvement, albeit incomplete, had occurred as a result of these medications.

All 20 patients agreed to return for a second hemodynamic study at 4 weeks; 6 patients actually underwent this study. The reasons for not undergoing a second hemodynamic evaluation included the following: death before 4 weeks of oral MDL 17,043 treatment (six), hospitalization at an outside institution and subsequent death (one), worsened state requiring changes in medication including use of dobutamine (two), side effects from MDL 17,043 resulting in cessation of drug use before 4 weeks (one), patient refusal (one), patient dropped from study by investigator because of poor compliance (one) and patient dropped from study by referring physician (one). One patient was admitted for restudy feeling subjectively improved over baseline but de-

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veloped a supraventricular tachycardia at a rate of greater than 200 beats/min and the study was postponed. Shortly after discharge, the patient had symptoms of digitoxicity and the serum digoxin level was elevated. Hospitalization for this problem was advised, but the patient refused and died suddenly the same day.

The hemodynamic, pharmacokinetic and hormonal protocols of the late study were identical to those of the early study. Vasodilators, digoxin and diuretic drugs were withheld for at least 18 hours before restudy. MDL 17,043 was last given between 12 and 24 hours before hemodynamic restudy.

Patients were examined monthly for the next 6 months and bimonthly thereafter and as needed. All cardiovascular drugs could be adjusted according to the clinical status of the patient. Follow-up data are complete up to May 1, 1984.

Statistical analysis. Data are presented as mean values ± SD unless otherwise specified. Baseline hemodynamic measurements were compared with those at each time period after drug administration using a mixed model single factor repeated measures analysis of variance (12). Baseline hormone levels after drug administration were compared using the Student's *t* test.

Results

Hemodynamic response. Improvement in most measured and calculated hemodynamic variables was apparent by 30 minutes after administration of MDL 17,043, and by 2 hours improvement was evident in all variables (Table 1). The hemodynamic measurements for the group of patients given 3 mg/kg and those given 6 mg/kg were not significantly different either at baseline or at any time after MDL 17,043 administration.

The six patients who underwent the 4 week study (Table 2) demonstrated baseline late hemodynamic measurements similar to those of the entire group in the early study, except for a small but significant increase in heart rate at rest in the late compared with the early study. These six patients felt subjectively improved. The peak early and late hemodynamic responses were nearly identical.

Hormonal response. Plasma norepinephrine and renin activity were not changed significantly at 1 hour after oral MDL 17,043 administration (Table 3). Plasma renin activity tended to increase at 4 hours ($0.1 < p > 0.05$, baseline versus 4 hours), whereas norepinephrine levels tended to decrease at 4 hours ($0.1 < p > 0.05$). Plasma arginine vasopressin did not show any significant directional changes.

Baseline plasma norepinephrine (763 ± 329 pg/ml), renin activity (14.2 ± 14.4 ng/ml per h) and arginine vasopressin (1.8 ± 0.9 pg/ml) levels were similar at restudy in the six patients as compared with the early study (early baseline plasma norepinephrine 968 ± 461 [pg/ml]; plasma renin activity 14.3 ± 14.4 [ng/ml per h] and arginine vasopressin

Table 1. Early Hemodynamic Response to Oral MDL 17,043 in 20 Patients

	Baseline	Hours After MDL 17,043 Ingestion							
		0.5	1	2	3	4	5	6	7	8
CO (liters/min)	3.6 ± 0.9	4.1 ± 1.1*	4.3 ± 1.0*	4.3 ± 0.9*	4.6 ± 1.0*	4.6 ± 1.0*	4.3 ± 1.0*	4.2 ± 0.9†	4.3 ± 0.9†	4.5 ± 1.1*
CI (liters/min per m^2)	1.9 ± 0.4	2.2 ± 0.5*	2.3 ± 0.4*	2.3 ± 0.4*	2.5 ± 0.5*	2.5 ± 0.5*	2.4 ± 0.5*	2.3 ± 0.5†	2.3 ± 0.4†	2.5 ± 0.5*
AVO_2 (vol %)	8.0 ± 1.6	6.9 ± 1.4*	6.3 ± 1.1*	6.0 ± 1.1*	5.9 ± 1.2*	6.0 ± 1.3*	6.4 ± 1.1*	6.5 ± 1.0*	6.4 ± 1.1*	6.5 ± 1.5*
HR (beats/min)	89 ± 17	93 ± 14‡	94 ± 15†	93 ± 15	94 ± 14‡	97 ± 15*	95 ± 12†	94 ± 11‡	96 ± 13†	95 ± 13
RA (mm Hg)	10 ± 5	8 ± 6*	6 ± 5*	5 ± 5*	4 ± 4*	6 ± 5*	6 ± 5*	6 ± 5*	5 ± 4*	6 ± 5*
PA (mm Hg)	38 ± 10	34 ± 12*	31 ± 12*	28 ± 12*	28 ± 11*	29 ± 11*	29 ± 12*	28 ± 12*	29 ± 12*	30 ± 11*
PAW (mm Hg)	24 ± 8	18 ± 9*	16 ± 9*	13 ± 8*	13 ± 8*	15 ± 9*	15 ± 8*	15 ± 9*	14 ± 7*	15 ± 6*
MAP (mm Hg)	78 ± 9	79 ± 13	75 ± 9†	71 ± 11*	70 ± 10*	72 ± 9*	71 ± 11*	70 ± 11*	70 ± 11*	71 ± 11*
PAR (dynes·s·cm^{-5})	347 ± 186	356 ± 229	312 ± 156	271 ± 132†	270 ± 120*	248 ± 109†	258 ± 113‡	257 ± 118‡	260 ± 120‡	252 ± 121†
SVR (dynes·s·cm^{-5})	1,641 ± 361	1,484 ± 423‡	1,353 ± 345*	1,258 ± 314*	1,183 ± 317*	1,184 ± 309†	1,269 ± 290*	1,302 ± 391‡	1,274 ± 359*	1,197 ± 312*
LVSWI (g-m per m^2)	18 ± 8	20 ± 8†	20 ± 6‡	20 ± 7‡	21 ± 7†	21 ± 6‡	19 ± 7	19 ± 7†	20 ± 8	20 ± 7

*$p < 0.001$; †$p < 0.01$; ‡$p < 0.05$. AVO_2 = systemic arteriovenous oxygen difference; CI = cardiac index; CO = cardiac output; HR = heart rate; MAP = mean systemic arterial pressure; PA = mean pulmonary artery pressure; PAR = pulmonary arteriolar pressure; PAW = mean pulmonary artery wedge pressure; RA = mean right atrial pressure.

Table 2. Early and Late Hemodynamic Response to Oral MDL 17,043 in 6 Patients

Case	CI (liters/min per m^2)	AVO_2 (vol %)	HR (beats/min)	SVI (ml/beats per m^2)	RA (mm Hg)	PA (mm Hg)	PAW (mm Hg)	MAP (mm Hg)	PAR (dynes·s·cm $^{-5}$)	SVR (dynes·s·cm $^{-5}$)	LVSWI (g-m per m^2)
1											
EB	2.5	7.2	115	21	2	41	15	81	435	1,292	19
ER	3.1	5.7	108	29	0	24	7	61	138	803	23
LB	2.1	8.0	132	16	8	59	41	82	349	1,487	9
LR	2.9	5.9	115	25	3	46	20	68	195	906	17
2											
EB	2.0	7.4	90	22	7	30	20	68	201	1,166	15
ER	2.6	5.4	104	27	0	14	5	56	90	899	21
LB	2.4	7.1	95	25	6	33	22	76	178	1,135	19
LR	2.6	6.3	102	27	0	20	9	56	154	869	19
3											
EB	1.4	8.0	93	15	12	30	17	73	483	2,250	12
ER	2.3	5.0	100	24	6	28	15	60	199	1,199	16
LB	1.8	6.2	106	17	16	32	23	63	253	1,417	9
LR	2.2	4.7	108	22	6	27	18	55	158	1,167	11
4											
EB	1.7	8.6	79	22	7	41	32	86	293	1,801	18
ER	2.6	6.0	96	30	−1	17	6	70	153	1,117	30
LB	2.0	8.1	96	21	3	31	25	90	111	1,776	19
LR	3.2	5.5	102	34	0	11	7	56	50	931	30
5											
EB	2.4	9.2	107	22	16	53	35	97	306	1,424	19
ER	3.0	6.4	116	29	9	40	24	87	214	1,040	24
LB	2.2	9.3	108	20	8	45	26	92	343	1,563	18
LR	2.6	6.8	112	25	3	29	15	83	185	1,143	22
6											
EB	2.9	5.5	67	44	4	15	10	87	164	1,358	48
ER	3.6	4.4	90	43	2	9	1	70	108	955	48
LB	3.0	4.7	72	41	7	23	14	97	138	1,374	46
LR	3.7	3.7	88	43	0	11	3	79	73	999	54
Mean											
EB	2.1 ± 0.5	7.6 ± 1.3	92 ± 18	25 ± 10	8 ± 5	35 ± 13	22 ± 10	82 ± 10	314 ± 126	1,549 ± 405	22 ± 13
ER	2.9 ± 0.5**	5.5 ± 0.7**	102 ± 9*	30 ± 6*	3 ± 4**	22 ± 11**	10 ± 8**	67 ± 11**	150 ± 19**	1,002 ± 146**	27 ± 11*
LB	2.2 ± 0.4	7.3 ± 1.6	102 ± 20†	23 ± 9	8 ± 4	30 ± 11	25 ± 9	83 ± 12	229 ± 103	1,459 ± 213	20 ± 14
LR	2.9 ± 0.5**	5.5 ± 1.1**	105 ± 10	29 ± 8*	2 ± 2**	24 ± 13**	12 ± 7**	66 ± 13**	139 ± 60**	1,002 ± 126**	25 ± 15*

The table reports baseline to peak hemodynamic change for each variable noted. EB = early baseline; ER = early response; LB = late baseline; LR = late response; Pt = patient number; SVI = stroke volume index; other abbreviations as in Table 1. †$p < 0.05$ early versus late baseline; *$p < 0.05$; **$p < 0.01$ baseline versus peak response (either early or late study).

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Table 3. Early Hormonal Response to Oral MDL 17,043 in 20 Patients

	Baseline	1 Hour After MDL 17,043	4 Hours After MDL 17,043
PRA (ng/ml per h)	7.7 ± 9.4	8.2 ± 7.4	13.6 ± 12.8*
NE (pg/ml)	869 ± 500	794 ± 419	748 ± 372*
AVP (pg/ml)	4.4 ± 4.4	5.8 ± 7.1	3.8 ± 4.2

*$0.1 < p > 0.05$. AVP = arginine vasopressin; NE = norepinephrine; PRA = plasma renin activity. Normal range: NE = 104 to 548 pg/ml; PRA = 1.1 to 5.4 ng/ml per h; AVP = 0.4 to 1.8 pg/ml.

3.4 ± 3.6 [pg/ml]). Late hormone responses were similar to early responses with a small nonsignificant decrease in plasma norepinephrine levels at 1 and 4 hours (1 hour 593 ± 411 pg/ml; 4 hours 622 ± 478), a moderate increase in plasma renin activity (1 hour 15.3 ± 15.9 ng/ml per h; 4 hours 22.3 ± 23.0) and no directional change in plasma arginine vasopressin (1 hour 1.70 ± 0.6 pg/ml; 4 hours 2.4 ± 1.2).

Pharmacokinetic response. In the early study, the plasma MDL 17,043 concentration (540 ± 234 ng/ml) peaked at 1.6 ± 1.2 hours after administration, whereas the plasma level of MDL 19,438 (1,818 ± 651 ng/ml) peaked at 2.5 ± 1.6 hours after administration. The elimination half-life was estimated to be 20.0 ± 5.8 hours (range 7.5 to 54.6) for MDL 17,043 and 25.6 ± 25.0 hours (range 3.4 to 56.5) for MDL 19,438. No significant differences were found in MDL 17,043 or MDL 19,438 blood levels between patients receiving the 3 and 6 mg/kg doses at any time period.

At baseline of the late study (time from last MDL 17,043 dose 23.8 ± 9.1 hours), significant plasma levels of MDL 17,043 (169 ± 152 ng/ml, range 0 to 352) and MDL 19,438 (1,555 ± 2,000 ng/ml, range 0 to 5,415) were present. In the late study, the values for time to peak plasma level of MDL 17,043 (2.7 ± 3.2 hours) and MDL 19,438 (4.7 ± 2.7) were similar to those of the early study. The elimination half-life during long-term use tended to be less but was not significantly different from that of the early study for both MDL 17,043 (10.2 ± 3.5 hours, range 4.9 to 13.5) and MDL 19,438 (13.1 ± 3.1 hours, range 6.2 to 15.3), although large interindividual variation was noted in both the early and late values.

Clinical response. The median follow-up period was 39 days (range 3 to 260). There was initial symptomatic improvement in 18 patients (90%). At 4 weeks, 10 patients (50%) still showed improvement. Diuretic drugs were maintained at prestudy levels in five patients, increased in three and decreased in two. Of the responders on captopril prestudy, two had the agent discontinued and one continued at the prestudy dose. Three of six patients receiving a nitrate preparation before the study had the drug discontinued at 4 weeks; the other three continued the nitrate maintained at prestudy levels. Long-term (>3 months) improvement occurred in 5 patients (25%). Diuretic drug dosage was decreased over baseline in two patients, was unchanged in two and increased in one. One of the long-term responders who had been receiving captopril before the study had captopril withdrawal continued at 3 months; the other long-term responder remained on the prestudy captopril dose. Two of three patients were withdrawn from isosorbide dinitrate and the other patient was maintained on the prestudy dose. Prazosin was discontinued by 3 months in one patient who had also been withdrawn from isosorbide dinitrate by 4 weeks.

Adverse effects occurred in 16 (75%) of 20 patients. Gastrointestinal symptoms were most frequent, with diarrhea or frequent (3 to 6/day) episodes of loose stools, nausea, vomiting or abdominal cramping in 13 patients (65%). Headache developed in two patients. A single patient developed reversible agranulocytosis.

Side effects required cessation of drug administration in two patients (agranulocytosis in one and nausea and diarrhea in one). One patient was withdrawn from the study because he underwent heart transplantation. One patient was withdrawn by the referring physician because of the development of an asymptomatic sinus tachycardia (87 beats/min before treatment to 110 beats/min after the start of MDL 17,043 therapy), although the investigators believed that the remainder of the hemodynamic response warranted a therapeutic trial. One patient was withdrawn by the investigators because of poor compliance. Of the remaining 14 patients, 13 (93%) have died (median time of death after MDL 17,043 institution 39 days, range 3 to 235). Nine (69%) of these deaths were sudden, one in the setting of digitalis toxicity; seven of these nine patients were receiving an antiarrhythmic drug at the time of death. Three sudden deaths were witnessed by medical personnel. In all medically witnessed sudden deaths, ventricular tachycardia and fibrillation were noted.

With long-term use, there were no changes in any laboratory variables except in the single patient in whom agranulocytosis developed.

Discussion

Hemodynamic response. Oral MDL 17,043 improved cardiac performance to a level similar to that reported by us with the intravenous form of the agent (4). Both the intravenous and oral preparations produced significant decreases in right atrial and pulmonary artery wedge pressures and an increase in cardiac output. There was a small but significant decrease in mean systemic and pulmonary artery pressures and a modest increase in heart rate. Both forms of administration produce a sustained hemodynamic effect. In the present study, all hemodynamic variables were still significantly altered 8 hours after drug ingestion. There also appear to be significant differences in response to the two dosing forms. In the doses employed in the intravenous and

oral studies, the peak decreases in mean right atrial, pulmonary artery, pulmonary artery wedge and systemic arterial pressures were comparable. In contrast, peak cardiac output averaged 76% improvement after intravenous administration, but only 28% in the present oral study.

In the intravenous study, cardiac output tended to peak with an MDL 17,043 dose of 5 to 6 mg/kg. In the present study, 3 mg/kg produced as great an improvement in cardiac output as did 6 mg/kg. Although the reason for the differences in cardiac output can only be speculated on, it is of interest that the plasma drug levels of MDL 17,043 and MDL 19,438 after oral administration at peak cardiac output for 3 and 6 mg/kg were similar. These data suggest a limitation of oral absorption of MDL 17,043 at a dose of 3 mg/kg or less. It may be, therefore, that at similar doses the plasma drug concentrations of both MDL 17,043 and MDL 19,438 are significantly higher with intravenous than with oral administration, accounting for the differences in cardiac output. Because preload and afterload changes were similar with the oral and intravenous preparations, it is suggested that the greater increase in cardiac output with the intravenous form may be related to an inotropic response apparent at higher MDL 17,043 plasma levels.

Hemodynamic responsiveness was maintained in the six patients studied at 4 weeks. This time period was chosen as a compromise between a longer restudy time and the expected patient attrition from the underlying condition. In studies utilizing beta-receptor agonists and arterial vasodilators, loss of hemodynamic effects including short-term tachyphylaxis and long-term attenuation or complete loss of response have been reported from 1 day to 4 weeks after drug institution (13–16). Thus, we believe that 4 weeks represent a reasonable, practical compromise to observe a chronic effect. It should be emphasized that of the six patients studied, all felt subjectively improved. Thus, it is concluded that in patients who have clinical improvement, hemodynamic responsiveness is maintained. It remains to be determined whether patients whose clinical condition worsens or does not improve also maintain hemodynamic responsivity.

Hormonal response. This study emphasizes the heterogeneity of hormonal responses to heart failure. In only 35% of patients were plasma norepinephrine, renin activity and arginine vasopressin levels all elevated at baseline. Plasma vasopressin was the most frequently elevated; all three hormones showed wide plasma level variation. Plasma renin activity tended to increase ($0.1 < p > 0.05$) after administration of oral MDL 17,043 (a response similar to that seen with the intravenous form of the agent [17]). The stimulus for this increase may only be speculated on from this study. It may be that the small but consistent decrease in mean arterial pressure decreased renal perfusion pressure, thus stimulating renin release. The improvement in cardiac performance did not translate to a suppression of either plasma norepinephrine or arginine vasopressin levels, which may be expected on the basis of cardiovascular factors known to stimulate or depress secretion of these hormones (18). At the 4 week restudy, hormone levels were similar to those determined at the early study. The long-term hormonal response in patients who have improved clinically on therapy has not been completely characterized (19,20). These data suggest that, at least with oral MDL 17,043, subjective improvement is not associated with suppression of the hormone systems studied.

Pharmacokinetic response. Pharmacokinetic data reveal that MDL 17,043 is relatively rapidly absorbed with a long elimination half-life in patients with heart failure. It undergoes a reversible conversion in the liver to MDL 19,438, a metabolite with approximately 20% of the hemodynamic activity, at least in dogs, as MDL 17,043 (4). Our study indicates that a plateau in plasma levels occurs after oral administration such that the plasma levels after a single 6 mg/kg dose were not significantly higher than those after a 3 mg/kg dose. A concomitant plateau in hemodynamic measurements was observed, which may be related to the comparable plasma drug levels. A limitation in absorption as seen with certain other drugs, including tetracycline, phenytoin, phenylbutazone and chlorthiazide, among others (21), may be the cause of the plasma level plateau. Although the long elimination half-life might recommend an infrequent dosing interval, for example, every 12 to 24 hours, the plasma drug level plateau after oral administration suggests that a rather more frequent dosing schedule would allow for higher drug levels and possibly a greater hemodynamic effect, particularly in cardiac output.

The late pharmacokinetic response resembled the early response. Thus, pharmacokinetic modification by hepatic enzyme induction or other mechanisms probably does not occur.

Clinical response. Because of the protocol employed in the clinical follow-up study, caution should be used in interpreting the clinical efficacy of this agent. The lack of a blinding procedure and a placebo control group prevents any conclusion as to how much of the clinical response was placebo effect. Vasodilators were reinstituted in many patients and diuretic drugs continued in all, which may have accounted for at least part of the clinical response. However, patients receiving vasodilators were referred for MDL 17,043 because of a response that was considered to be unsatisfactory by the referring physician, and in long-term responders vasodilator dosage was either maintained or reduced compared with prestudy levels. Many of the patients receiving MDL 17,043 were hospitalized for severe heart failure at the time of drug study. Although the drug was given at a time of "clinical stability," we consider that at least some of the immediate subjective improvement was due to a combination of supportive care and increased attention from the medical and nursing personnel involved in this study, as

well as a placebo effect. The clinical response should be interpreted with these caveats in mind.

Initial subjective improvement with MDL 17,043 in 90% of the patients is encouraging. However, only 25% were long-term (>3 month) responders. It is difficult to determine, in the absence of a control group, whether this percent is, in fact, acceptable, particularly in view of the extreme severity of these patients' status. Side effects were frequent and required drug termination in 10%.

The death rate of 93% (13 of 14 patients on long-term therapy) is higher than that in recent prospective studies of patients with "refractory" heart failure (22,23), most of whom were taking vasodilators, digoxin and diuretic drugs. Franciosa et al. (22) reported an overall mortality rate of 34% at 1 year; it was higher in patients with coronary artery disease (46%) than in those with idiopathic dilated cardiomyopathy (23%). Wilson et al. (23) demonstrated a 1 year mortality rate of 48% with a similar death rate in patients with ischemia and dilated cardiomyopathy. Similarly, the percent (69%) of sudden deaths in our series is higher than in other studies (22,23). The percent of sudden death in the series of Franciosa et al. (22), using a definition of "sudden" comparable with that in our series, was 45%. In the study by Wilson et al. (23), death occurred suddenly in 43% of cardiac deaths. Our study group and those reported by others may not, however, be comparable. Although the two studies cited utilized patients with "refractory" heart failure, the patients in our study may have been even more severely ill. The ejection fraction of the patients in the series of Wilson et al. was somewhat higher (27 ± 10%) than in our study (16 ± 5%). Franciosa et al. demonstrated hemodynamic differences in survivors versus nonsurvivors. The hemodynamic profile of patients in our series more closely resembles that of the nonsurvivors (except that it is slightly worse for most variables) than that of the survivors. Thus, the higher mortality in this series may actually reflect the extreme severity of the patients' cardiac status. Furthermore, the high percent of patients with sudden death may reflect a decrease in deaths from terminal heart failure without significant overall improvement in survival, thus producing a higher relative incidence of sudden deaths. On the other hand, if the survival rate actually decreases, this finding may represent a direct detrimental effect of MDL 17,043 on survival. A randomized, controlled trial using patients who have a reasonable expectation of at least 1 year's survival (functional classes II and III) will be required to resolve whether MDL 17,043 is efficacious and safe.

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