Epidemiological and Pharmacological Profile of Congestive Heart Failure at Turkish Academic Hospitals

Türk Eğitim Hastanelerinde Konjestif Kalp Yetersizliğinin Epidemiyolojik ve Farmakolojik Profili

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Abstract

Objective: We aimed to investigate the status of the treatment of congestive heart failure (CHF) in academic hospitals in Turkey.

Methods: Overall 661 successive patients from 16 academic hospitals were included in this retrospective study. In addition to treatments given to the patients before admission to hospital, during their hospital stay, and at hospital discharge, data regarding their functional classifications, causes of CHF, and laboratory findings were also recorded.

Results: In our study the mean age of patients was 61±12 years and the mean hospital stay 10±6 days. Ischemic CHF was observed more frequently in men (72%, 46%, p<0.001), while hypertension and rheumatic CHF were more frequent in women (27% vs 19%, p<0.001 and 24% vs 9%, p<0.001 respectively). While 90% patients' were in NYHA III-IV class at admission to hospital, only 2% of patients were in class IV at hospital discharge. The proportion of smokers was greater in men than in women (68% vs. 12%). Atrial fibrillation was present in 35% of patients. During hospitalization, angiotensin converting enzyme (ACE) inhibitors were used by 77%, diuretics by 95%, digitalis by 76%, nitrate by 85%, beta-blockers by 3 %, aspirin by 86%, anticoagulants by 44%, Ca antagonist by 10%, positive inotropic agents by 42%; and antiarrhythmic agents by 15% of patients.

Conclusion: The use of ACE inhibitors, the major milestone of CHF treatment, is not on an adequate level yet. The use of beta blockers should also be encouraged.*(Anadolu Kardiyol Derg 2004; 4: 32-8)*

Key Words: Epidemiology, heart failure, Turkish academic hospitals

Özet

Amaç: Konjestif kalp yetersizliği (KKY) tedavisinde Türkiyede üniversite hastanelerinde uygulanan tedavi yöntemlerini araştırmaktır.

Yöntem: Çalışmaya 16 üniversite hastanesinde retrospektif olarak incelenen 661 hasta alındı. Hastaların hastaneye kabulden önceki, hastanede kaldıkları süre içindeki tedavileri, fonksiyonel durumu, KKY'nin etyolojisi ve laboratuar bulguları incelenerek kaydedildi.

Bulgular: Çalışma hastalarımızın yaş ortalamaları 61±12 yıl, hastanede ortalama kalış süreleri 10±6 gündü. İskemiye bağlı KKY erkeklerde daha sık (%72 karşı %46, p<0.001), hipertansiyon ve romatizmal KKY kadınlarda daha sıktı (sırasıyla kadın-erkek %27 karşı %19 p<0.001 ve %24 karşı 9%, p<0.001). Hastaneye kabulde hastaların %90'nı NYHA'ya göre III-IV. grupta, taburcu edildiklerinde %2'si IV. gruptaydı. Erkeklerde sigara içme oranı kadınlardan fazlaydı (%68 karşı %12). Elektrokardiyografileri incelenen (%81) hastaların %35'inde atriyal fibrilasyon mevcuttu. Hastanede yattıkları süre içerisinde hastaların %77'sinde anjiyotensin konverting enzim (ACE) inhibitörü, %95'inde diüretik, %76'ında dijitalis, %85'inde nitrat, %3'ünde beta bloker, %86'sında aspirin, %44'ünde antikoagülan, %10'unda kalsiyum antagonisti, %42'sinde pozitif inotropik ajanlar ve %15'inde antiaritmik ajanlar kullanıldı.

Sonuç: Konjestif kalp yetersizliğinin tedavisinde önemli bir dönüm noktası olan ACE inhibitörleri henüz yeterli düzeyde kullanılmamaktadır. Konjestif kalp yetersizliğinde beta bloker tedavisi özendirilmelidir.*(Anadolu Kardiyol Derg 2004; 4: 32-8)*

Anahtar Kelimeler: Epidemiyoloji, kalp yetersizliği, Türkiye'de üniversite hastaneleri

Introduction

Congestive heart failure (CHF) continues to be a major clinical and public health problem although the management of heart failure has improved over the past decade. Prevalence of heart failure from all severity grades and in all ages varied from 2.3 to 3.9 % per annum (1-3). It is associated with decreased quality of life and increased morbidity and mortality risk. Mortality rate is approximately 25% within 1 year of initial diagnosis (1-4). Hospitalization for heart failure remains high; 19% of patients in the SOLVD Registry were hospitalized within 1 year of the initial diagnosis, and more than 40%

of patients with CHF require readmission within 3 to 6 months of hospital discharge (5). There was a shift in the etiology of heart failure in the last decade. The most common cause of CHF is no longer hypertension or valvular heart disease. In clinical trials, ischemia has been reported as the cause of heart failure in two thirds of patients in developed countries (6,7). Angiotensin-converting enzyme (ACE) inhibitors improve symptoms and reduce progressive worsening of heart failure, recurrent hospitalization and mortality (8). Despite this evidence, it has been seen that ACE inhibitors are prescribed to as few as one-third of the patients who might expect to benefit from them.

There are no sufficient documentation on management of CHF in Turkey. Therefore, to form such a documentation and to compare it with the relevant guideline will make our approaches more current. The aim of this study was to document pharmacological management profile of patients with CHF in Turkey.

Methods

Patients

Medical records of CHF were reviewed by investigators at 16 academic centers in Turkey (see Appendix A). Medical records of consecutive patients admitted for CHF between October 1997 and March 1998 were selected for review. Patients over the age of 18 years were eligible for enrollment if diagnosis of CHF was made by the clinical and/or echocardiographic criteria (9) and they were hospitalized and discharged after treatment. Patients were excluded if they died before discharge. In this retrospective study, the most recent, in average, 50 patients from each centre with sufficient data for CHF in their files were included. All the centers filled up the forms provided and sent them to the coordinating centre (Erciyes University).

Data collection

The main study variables collected were patient demographics, cause of CHF, New York Heart Association (NYHA) functional classification, presence or absence of concomitant condition, medical history, clinical features, result of laboratory investigations, use of cardiovascular medication before hospitalization, during the hospitalization and at hospital discharge. Those patients who had both ischemia and hypertension were grouped as ischemia, otherwise grouped as hypertension.

Statistical analysis

Continuous variables were expressed as mean values ± standard deviation (SD). Student-t test was used for comparison of the continuous variables. Dichotomic and polytomic variables were compared by Chi-square test. Cardiovascular medications before hospitalization, during the hospitalization and at hospital discharge were compared by Cochran' s Q test. For all tests, p>0.05 designated as non significant, and a value of p<0.05 was considered statistically significant. All analyses were performed with SPSS 10.0 software package.

Results

Overall 661 patients were enrolled in the study. The clinical characteristics of patients are shown in Table 1. Sixty three percent of patients were male and mean age was 61.4±12.3 years. About two thirds of patients were over 50 years of age. Women stayed in hospital longer than men (10.4±6.8 days vs. 9.3±5.9 days, p=0.05). While smoking, was higher in men than in women, hypertension, rheumatic fever and anemia were higher in women than in men. Determined etiologies of CHF were different between men and women. Ischemia and hypertension were the most common causes for CHF in men but ischemia, hypertension and rheumatic heart disease were the most common causes for CHF in women (Table 2). Effort capacity at admission was NYHA class III-IV in 90% of the patients and at hospital discharge NYHA class IV was seen only in 1.7% of the patients.

Laboratory findings

Ninety nine percent of the patients were subjected to teleradiography, 81% to echocardiography, and 24% to catheterization.

In biochemical parameters such as BUN, creatinin, total cholesterol, triglyceride, only creatinin was different between men and women. (Table 1).

In ECG's, 27% of the patients had sinus tachycardia and 35% atrial fibrillation. Ventricular tachycardia was observed in 1.5% of the patients, ventricular premature contractions in 7%, anterior myocardial infarction (MI) in 38% and inferior MI 16% of patients.

In echocardiographic assessment, mitral regurgitation was found in 68%, aortic regurgitation in 26%, aortic stenosis in 5% and tricuspid regurgitation in 45% of the patients. Mean left ventricular ejection fraction was 38%.

Hospital treatments

Of 661 patients, 95% received diuretic treatment, among them 54%-loop diuretic, 53.8%-potassium-sparing diuretics and 19%-thiazide diuretic (Table 3). Angiotensin converting enzyme (ACE) inhibitors were administered to 77% of the patients: 35%-cilazapril, 34%-enalapril, 27%-captopril, 25%-fosinopril, 13%-lisinopril, 6%-perindopril, 2%-benazepril. When the patients were separated into two groups based on ACE inhibitor usage, there was no any relationship between ACE inhibitor use and systolic blood pressure (120±24 vs 125±26 mm Hg).

The use of ACE inhibitor did not vary according to NYHA classification of patients: 79% of class II, 81% of class III and 76% of class IV patients used ACE inhibitors. The combination of ACE inhibitors with diuretics was observed to be 71%, ACE inhibitors + digoxin 73%, ACE inhibitors + digoxin + diuretic use-54%. Digoxin was used by 60% in NYHA class II patients, by 75% in class III patients, and by 85% in class IV patients. Ca channel blockers were prescribed to 11% of our patients: amplodipine to 40%, diltizem to 40%, nifedipine to 12% , and nisoldipine to 8%. Only 3 % of our patients were given, β- bloc-

Table 1. Characteristics of the patients and their distribution among men and women

	Men (n=416)	Women (n=245)	P value
Age (years)	62±12	61±14	0.24
Smoking, (%)	68	11.8	0.001
Hypertension, (%)	36.3	53.4	0.001
Diabetes, (%)	21.8	30.2	0.22
ARF, (%)	7	13.4	0.011
Anemia, (%)	3.1	10.7	0.001
LVEF, (%)	37.1±9.2	39.4±10.4	0.018
SBP, (mmHg)	122±24	128±28	0.007
DBP, (mmHg)	76±14	78±15	0.1
Heart rate, (beats/min)	94±20	94±20	0.8
Total cholesterol, (mg/dl)	168±53	170±46	0.6
LDL cholesterol, (mg/dl)	109±53	109±35	0.9
HDL cholesterol, (mg/dl)	36±12	38±11	0.1
Triglycerides, (mg/dl)	126±56	137±53	0.067
Serum sodium, (mEq/lt)	138±9	139±6	0.2
Serum potassium, (mEq/lt)	4.3±0.6	4.4±0.6	0.1
Serum creatinine, (mg/dl)	1.3±0.6	1.2±0.5	0.02
BUN, (mg/dl)	35.5± 20.5	36.8±24.5	0.1
Serum hemoglobin, (g/dl)	13.2±2.1	12.3±1.8	0.001

ARF: acute rheumatic fever; LVEF: Left ventricular ejection fraction; SBP and DBP: systolic and diastolic blood pressures; LDL and HDL cholesterol: low- density and high density lipoprotein cholesterol

Table 2. Etiologies of CHF

	Men	Women	p
Ischemia	71.9	45.7	0.001
Hypertension	18.5	27	0.01
Rheumatic heart disease	8.9	24.1	0.001
Congenital heart disease	0	0.8	0.06
High-output state	0.7	2.4	0.06

Data in the table represent the percentage of patients

kers. As for the prescription of intravenous positive inotropic agent, it was 42%. It was used by 32% in NYHA class III patients, and by 63% of class IV patients. While aspirin was used by 86% of patients, warfarin sodium and heparin were used by 10% and 34% of patients, respectively. Antiarrhythmic therapy was applied to 15% of patients. Amiodarone and lidocaine were the most frequently used antiarrhythmic agents, (62% and 25%, respectively), while mexiletine was used by 8%, quinidine by 3% and, propafenone by 2% of patients.

Discussion

Despite the substantial progress in the therapy of CHF, it is still a disease with high morbidity and mortality. Nearly half of patients diagnosed CHF died within 5 years, and 29-47% of those discharged were re-hospitalized within 3-6 months (10). In this study, we reviewed the treatment protocols applied in CHF in academic hospitals in Turkey.

Digoxin

Digoxin supplementation in patients on ACE inhibitor and diuretic is known to reduce the number of hospitalizations and cases of mortality due to the worsening of CHF but not overall mortality (11-13). It is known that discontinuation of digitalis, in patients with CHF on digitalis, diuretic and ACE inhibitor combination, increases the number of hospitalizations, and shortens exercise duration (12,13). Seventy six percent of our patients had used digoxin during hospitalization. This proportion is greater than that in a centre in the USA which is known to be 50%

(14). The higher proportion in Turkey can be attributed to the greater number of the patients in NYHA class III and IV in our group (89%), unlike that in the USA. Although the proportion of the class III and IV patients reduced to 20%, the ratio of digoxin prescription rose up to 80.5% which was similar to that found in RADIANCE and PROVED studies (12,13).

Diuretics

One of the milestones of the treatment of symptomatic CHF, diuretics are not proposed as the primary agents in the treatment of mild and moderate CHF's (14). NYHA clinical classes in our group were high, and diuretics were used in 95% and 94% of patients in class IV and III, respectively. In class II patients they were used by 82%. At hospital discharge nearly 90% of patients in class I and II received diuretics. The reason for this may be lack of consideration of patients' functional capacities while prescribing their drugs at discharge. However, it must be remembered that intensive diuretic treatment in such patients could cause increase in frequency of hyponatremia, hypokalemia, rise in the levels of BUN and creatinine, as well as even more pronounced activation of neurohumoral system which has already been elevated in the early stage CHF's (15).

ACE inhibitors

CONSENSUS and SOLVD studies have demonstrated the effects of ACE inhibitors such as improvement in functional capacity, reduction in the frequency of hospitalizations and meaningful decrease in mortality (15). Despite the presence of numerous favorable studies regarding ACE inhibitors, these drugs are not used with adequate frequency and in appropriate do-

Table 3. Pharmacological profiles

	At admission	During hospitalization	At hospital discharge	p
ACE inhibitor	50.1*	77.3	84.5	0.001
Diuretic	68.3*	95.1	92.9	0.001
Digoxin	65.2*	75.5	80.5	0.001
Nitrate	55.1*	84.6	70.2	0.001
Beta-blocker	4.7	3.1	3.1	0.2
Calcium antagonist	14	10.7	11.6	0.1
Aspirin	64.1*	85.5	89.2	0.001
Anticoagulants	8.7&	44.2	11.4	0.001
Positive inotropic	-	41.6	-	
Antiarrhythmic	5	15.2	13.1	0.001

Data in the table represent the percentage of patients
 *, the comparison with during hospitalization and at hospital discharge is significant, p-0,05
&, the comparison with during hospitalization is significant, p-0,05

ses (16-22). The administration of an ACE inhibitor in therapeutic dose is more important than selection of which ACE inhibitor should be administered (18). While the frequency of ACE inhibitor use in our group was 50% before hospitalization, the proposed ACE inhibitor use frequency, at hospital discharge, was 85%. This ratio is fairly close to the USA ratio of 89% reported by Rich et al. (14). The usage ratios of ACE inhibitors in patients in our group did not change in patients with different functional capacity and different etiology of CRF. The frequency of ACE inhibitor use before admission to hospital is rather low. One reason for this may be of lack of awareness of our physicians on the benefits to ACE inhibitors. Another point may be that the clinicians keep broad the scope of the contraindications of ACE inhibitors. It was proposed that ACE inhibitors should be started in low doses to be titrated up to tolerable doses even when the patients' blood pressures are low (80-90 mmHg) (23,24). The most frequently prescribed ACE inhibitor was enalapril and captopril. The reasons for their wide use may be efficacy of these agents supported by many studies as well as their low cost.

Beta Blockers

Beta blockers reduce harmful effects of adrenergic stimulation, which has already been elevated in CHF, thereby they reduce the frequency of hospitalizations and mortality (25-27). The meta analyses of the 21 studies revealed that these drugs increased left ventricular ejection fraction by 25% (28). Additionally, the results of the studies where carvedilol has been used are favorable (29). Of the 661 patients included in our study, 4.7% had been on beta-blocker before admission to hospital, and this ratio dropped to 3% at hospitalization. These ratios are well below those in literature. This ratio in a centre in the USA was 2.1% in 1990 and rose to 15.7% in 1995 (14). The reason for the low ratio of prescribing beta blockers in our country may be the necessity of starting the drug in low doses and its titration up to targeted dose (longer hospital stay, higher cost, bed capacity), or low functional capacity in patients group. Furthermore, it seems that the classical knowledge that beta blocker administration in CHF is contraindicated will take a long time to change.

Ca Channel Blockers

It is known that in CHF diltiazem, nifedipine and nikardipine increase mortality while felodipine and amplodipine do not have negative effects (30-32). Ca antagonists were administered to 11% of our patients at hospitalization. The prescription frequency of these drugs, given with the intention of normalizing blood pressure in patients when it is high, or of bringing angina under control in those who suffer from this, is below the rate (21.3%) in the USA academic hospital (14)

Parenteral Inotropic Agents

It is known that dobutamine, which is used briefly and intermittently, provides symptomatic and hemodynamic improvement. Nevertheless, it should also be remembered that these drugs, let alone, increase mortality (33). In our study groups, positive inotropic agents were used in 42% of patients. This rate, which is rather high, may have resulted from our desire to increase positive clinical response in a short term.

Antiaggregants and Anticoagulants

It is known that aspirin reduces embolic and ischemic events in patients with CHF but not in patients with angina and acute myocardial infarction (34). However, aspirin is not recommended for patients with nonischemic cardiomyopathy. Although CHF due to ischemia was observed in 61% of our patients, aspirin was prescribed to 90% of our patients and this ratio remained unchanged at hospital discharge. When compared with the ratio of antiaggregants prescription (56%) in SOLVD study in which patients with CAD comprised 83% of the study group, this ratio appears to be high. In nonischemic CHF's, antiaggregants treatment is recommended only if there are ischemia or thrombus. Regarding this, we should say that aspirin is overused in our country. It is known that the probability of sudden death, myocardial infarction and stroke decreases in patients who have received warfarin sodium treatment (35). The ratio of anticoagulants prescription, which was 12% in SOLVD, was 44% in our country. The distribution of anticoagulants use was as following: 56% for heparin, 21%-warfarin sodium and 23%-low molecular weight heparin. The ratio of anticoagulant prescription (all was warfarin), which was rather high at hospitalization period, dropped to 11% at discharge.

Nitrates

Nitrates are used in CHF in order to reduce the incidence of ischemic events and angina due to CAD; to decrease venous return; and to produce favorable effects on hemodynamics and mortality in combination with warfarin it with hydralazine (36,37). Nitrate in combination with hydralazine is recommended only for patients who are intolerant to ACE inhibitors. In patients whose ventricular filling pressures

can not be lowered despite intensive diuretic treatment, nitrate can be added. The rates of nitrates prescription at hospitalization and at discharge in aor study were 85% and 70%, respectively. These ratios are higher than in literature, which may be related to differences in our patients group including probably higher amount of ischemic patients (5,14).

Antiarrhythmic treatment

Sudden death comprises 30-70% cases of mortality in CHF. While antiarrhythmic treatment regimens reduce number of ventricular extrasystoles and attacks of nonsustained ventricular tachycardia, they do not reduce mortality (38). Nowadays, amiodarone is the first choice of drug with this indication in CHF (39). The ratio of antiarrhythmic drug prescription, which was 15% in our patients group, did not different from that, in the SOLVD group (14.4 %).

Conclusion

Our study has revealed that while the use of diuretics, ACE inhibitors, Ca channel blockers and antiarrhythmic drugs in Turkey is not much different from those proposed in the relevant guideline, digitalis and antiaggregants drug prescription is more frequent and the use of beta blockers is less frequent in our country. Efforts should be made for widespread use of ACE inhibitors and beta blockers as suggested by the new guideline for CHF.

Appendix A

The following institutions and physicians participated in the study:

Akdeniz University Hospital, Necmi Değer, MD; Atatürk University Hospital, Necip Alp, MD; Cumhuriyet University Hospital, Süleyman Aslan, MD; Çukurova University Hospital, Mustafa Demirtaş, MD; Ege University Hospital, Mustafa Akın, MD; Erciyes University Hospital, Ali Ergin, MD; Fırat University Hospital, Nadi Aslan, MD; Gülhane Askeri Tıp Akedemisi Hospital, Ersoy Işık, MD; Haseki Kardiyoloji Enstitüsü, Rasim Enar; Karadeniz University Hospital, Ali Bayram, MD; Koşuyolu Kalp ve Araştırma Hospital, Nuri Çağlar, MD; Ondokuz Mayıs University Hospital, Olcay Sağkan, MD; Osmangazi University Hospital, Bilgin Timuralp, MD; Selçuk Üniversity Hospital, Hasan Gök, MD; Yüksek İhtisas Hospital, Emine Kütük, MD; Uludağ University Hospital, İbrahim Baran, MD.

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