[6]

Use of sympathomimetic drugs leads to increased risk of hospitalisation for arrhythmias in patients with congestive heart failure

Marcel L Bouvy PharmD[1, 2], Eibert R Heerdink PhD[1],
Marie L De Bruin PharmD[1], Ron MC Herings PharmD PhD[1,3],
Hubert GM Leufkens PharmD PhD[1], Arno W. Hoes MD PhD[4]

1. Department of Pharmacoepidemiology & Pharmacotherapy, Utrecht Institute for Pharmaceutical Sciences (UIPS), The Netherlands
2. SIR Institute for Pharmacy Practice Research, Leiden, The Netherlands
3. PHARMO Institute, Utrecht, The Netherlands
4. Julius Centre for General Practice & Patient-Oriented Research, University Medical Centre, Utrecht, The Netherlands

Archives of Internal Medicine 2000;160:2477-80.

Abstract

Background Sympathomimetic agents have a direct positive chronotropic effect on heart rate and may cause hypokalaemia, even when administered by inhalation. In selected patients (e.g. patients with heart failure) this can lead to arrhythmias. Despite the potential adverse effects of these agents, they are used frequently in patients with heart failure, due to a high incidence of respiratory co-morbidity.

Objective To investigate the effects of sympathomimetics on the incidence of hospitalisations for arrhythmias in patients with heart failure.

Methods In a cohort of 1 208 patients with a validated hospital discharge diagnosis of heart failure, we identified 149 cases with a readmission for arrhythmias, and compared these in a nested matched case-control design with 149 controls from the remainder of the cohort with no hospital readmission for any cardiac cause. Conditional logistic regression was used to calculate the risk for hospitalisation for arrhythmias associated with exposure to sympathomimetic agents, expressed as odds ratios.

Results Of 149 case patients, a total of 33 (22.1%) were treated with any sympathomimetic agent, and 6 patients (4.0%) were treated with systemic sympathomimetics. The use of any sympathomimetic drug was associated with an increased risk of admission for arrhythmia (odds ratio, 4.0; CI 95% [1.0-15.1]). For systemic sympathomimetic drugs, the corresponding odds ratio was 15.7; CI 95% [1.1-228.0].

Conclusions The results of this study strongly suggest an increased risk of hospitalisation for arrhythmias in patients with heart failure treated with sympathomimetic drugs. Sympathomimetics should be given under close surveillance to patients with heart failure.

INTRODUCTION

Arrhythmias can be induced or aggravated by a variety of drugs, which include cardiotonic drugs (digoxin, sympathomimetics, and antiarrhythmics), and by drugs that lower plasma potassium levels, such as diuretics and corticosteroids. A special group comprises drugs that lengthen QT interval and can lead to induction of torsade de pointes (e.g. antihistamines, antidepressants, macrolide antibiotics, cisapride, and antipsychotics).[1]
Sympathomimetic drugs have a direct positive chronotropic effect that can promote arrhythmia. Moreover, sympathomimetics can induce hypokalaemia, further increasing the risk for arrhythmias.[2, 3] Studies on chronotropic and hypokalaemic effects of sympathomimetics have shown small but significant effects, which can even be induced by inhalation of sympathomimetics.[4, 5] At the introduction of selective β_2-sympathomimetics, a limited number of small-scale studies suggested that these drugs could be safely used in patients with chronic obstructive pulmonary disease (COPD).[6] Evidence, however, accumulates that arrhythmias due to systemic use of sympathomimetics do occur occasionally.[7, 8] Even the occurrence of arrhythmias after inhalation of sympathomimetics has incidentally been reported.
Elderly patients and patients with heart failure, renal or hepatic dysfunction, electrolyte disturbance (hypokalaemia, hypomagnesia), or a history of arrhythmias are probably more prone to the proarrhythmic effect of sympathomimetics.[10] Moreover, patients with heart failure often use diuretics. The hypokalaemic response to diuretics could be additive to that of sympathomimetics.[11, 12]
Cardiac arrest and arrhythmia are the major causes of death in patients with heart failure.[13] Despite the potential negative effects of sympathomimetics in patients with heart failure, they often receive such drugs, due to a high incidence of respiratory co-morbidity (in particular COPD). This study investigates the effects of sympathomimetics on the incidence of hospitalisations due to arrhythmias in patients with heart failure.

Patients and methods

Setting

Data were used from the PHARMO record linkage system, a database containing drug dispensing records from community pharmacies and linked hospital discharge records of a defined population of 300 000 residents of 6 medium-sized cities in The Netherlands.[14]
Medication histories and hospital data were collected from 1986 to 1992. Drugs were coded according to the Anatomical Therapeutic Chemical (ATC) classification. Hospital discharge records were coded according to the International Classification of Diseases, Ninth Revision (ICD-9). Clinical modification codes were used.[15]

Patients

A total of 1 208 patients with a validated hospital discharge diagnosis for heart failure were included in the study.[16] These patients were followed up for a total of 5 038 person-years (mean follow-up, 4.2 years per patient). In this cohort we identified a total of 454 readmissions for cardiac causes, including myocardial infarction, angina pectoris, arrhythmias, and heart failure. We found 149 patients with a re-hospitalisation for arrhythmias (cases). For each case, a control was sampled randomly from the remainder of the cohort who were not readmitted for any cardiac cause and matched according to follow-up time. An index date was assigned to each control matching the hospitalisation date of the case.

exposure definition

A patient was defined as exposed when there was at least 1 prescription filled for a given drug in the 3 months before hospital admission for the cases or the corresponding index date for the controls.

DATA ANALYSIS

We performed a nested case-control analysis comparing exposure in cases vs. controls. Odds ratios (ORs) were calculated for exposure to sympathomimetic agents, at the time of the hospitalisation due to arrhythmias (cases) or matched index date (controls). Conditional logistic regression techniques were applied to adjust for potential confounders. All statistical analyses were performed with Egret software (Egret for Windows, version 2.0, Cytel Software Corporation).

COVARIATES

This study was done in a group of patients with a high frequency of co-morbidity. Arrhythmia is a common complication in patients with heart failure. Left ventricular hypertrophy and local ischaemia of heart tissue may contribute to arrhythmogenic effects.

Arrhythmias frequently occur in patients with COPD. An important risk factor is the occurrence of hypoxemia in patients with COPD. An increased risk for hospital admissions for arrhythmias could therefore be related to the underlying disease instead of the use of sympathomimetics. On the other hand, sympathomimetics can also aggravate the effects of hypoxemia.[17]

In addition, a broad range of drugs could affect the occurrence of arrhythmias by direct effect on heart rate (e.g. Angiotensin Converting Enzyme (ACE) inhibitors, beta-blockers, calcium channel blockers, digoxin, antiarrhythmics, and ibopamin), blood potassium levels (e.g. ACE inhibitors, corticosteroids, diuretics, and laxatives), or QT interval (e.g. antihistaminic drugs, antidepressants, antipsychotics, macrolides, and cisapride).

We corrected for potential confounders by including the number of hospital admissions for arrhythmias, myocardial infarction, angina pectoris, asthma, and COPD in the year preceding the hospitalisation for heart failure and the use of aforementioned drugs in the 3 months prior to the hospital admission in a multiple regression model.

*Table 1. Age, gender, preceding hospitalisations and type of arrhythmias according to the use of sympathomimetic agents**

	NO SYMPATHOMIMETICS (N=248)	USE OF SYMPATHOMIMETICS (N=50)
AGE		
<-64	32 (12.9)	5 (10)
65-74	89 (35.9)	14 (28)
75->	127 (51.2)	31 (62)
MALE	109 (44.0)	37 (74)
HOSPITAL ADMISSIONS IN PRECEDING YEAR		
GENERAL	85 (34.3)	16 (32)
WITH ARRHYTHMIA	22 (8.9)	4 (8)
WITH COPD, ASTHMA OR EMPHYSEMA	3 (1.2)	8 (16)
WITH MYOCARDIAL INFARCTION	12 (4.8)	3 (6)
WITH ANGINA PECTORIS	7 (2.8)	1 (2)
TYPE OF ARRHYTHMIA DURING FOLLOW-UP†		
PAROXYSMAL SUPRAVENTRICULAR TACHYCARDIA	2 (0.8)	1 (2)
PAROXYSMAL VENTRICULAR TACHYCARDIA	15 (6.0)	0
PAROXYSMAL TACHYCARDIA	1 (0.4)	0
ATRIAL FIBRILLATION	73 (29)	25 (50)
ATRIAL FLUTTER	6 (2.4)	1 (2)
VENTRICULAR FIBRILLATION	14 (5.6)	2 (4)
CARDIAC ARREST	7 (2.8)	0
PREMATURE HEARTBEATS	2 (0.8)	3 (6)
SINO-ATRIAL KNOT DYSFUNCTION	1 (0.4)	1 (2)
CARDIAC DYSRYTHMIA	6 (2.4)	2 (4)
CARDIAC DYSRYTHMIA, NOS.	2 (0.8)	0

*Values are number (percentage) of patients.

The observation period for the no sympathomimetics group was 414 days and for the sympathomimetics group was 535 days.

COPD indicates chronic obstructive pulmonary disease; NOS. indicates not otherwise specified

†The total number of arrhythmias exceeds 149, because of multiple types of arrhythmia during one hospital admission.

*Table 2. Co-medication according to the use of sympathomimetic agents**

	NO SYMPATHOMIMETICS (N=248)	USE OF SYMPATHOMIMETICS (N=50)
SYSTEMIC CORTICOSTEROID	7 (2.8)	6 (12)
INHALATION CORTICOSTEROID	5 (2.0)	18 (36)
DIGOXIN	109 (44.0)	33 (66)
ORAL ANTICOAGULANT	127 (51.2)	17 (34)
VERAPAMIL OR DILTIAZEM	44 (17.7)	13 (26)
DIHYDROPYRIDINE	29 (11.7)	6 (12)
ACE INHIBITOR	119 (48.0)	21 (42)
BETA-BLOCKER	30 (12.1)	5 (10)
IBOPAMIN	8 (3.2)	1 (2)
LAXATIVE	22 (8.9)	9 (18)
ANTIARRHYTHMIC	26 (10.5)	6 (12)
THIAZIDE DIURETIC	2 (0.8)	1 (2)
THIAZIDE + POTASSIUM SPARING DIURETIC	32 (12.9)	5 (10)
LOOP DIURETIC	171 (69.0)	35 (70)
POTASSIUM SPARING DIURETIC	53 (21.4)	11 (22)
NITRATE	118 (47.6)	18 (36)
ANY PROARRHYTHMIC DRUG‡	14 (5.6)	3 (6)
ANTIDIABETIC DRUG	51 (20.6)	5 (10)

*Values are number (percentage) of patients. The observation period for the no sympathomimetics group was 414 days and for the sympathomimetics group was 535 days. ACE indicates angiotensin converting enzyme. ‡antipsychotic, antidepressant, antihistaminic, macrolide or cisapride)

RESULTS

Tables 1 and 2 detail the general characteristics of the study population. The majority of arrhythmias were classified as atrial fibrillation (n=98, 60%). The other frequently seen arrhythmias were ventricular tachycardia (n=15, 9%) and fibrillation (n=16, 10%). The characteristics of users of sympathomimetics differed in some aspects from patients not using these drugs (e.g. sex, use of corticosteroids, and prior hospital admissions for COPD). The following inhalation sympathomimetics were used: albuterol, 94% of all prescriptions;

and terbutaline sulfate, 6% of all prescriptions. Systemic sympathomimetics used were albuterol in 74% and terbutaline in 26%. There was only 1 nasal sympathomimetic used, which was xylometazoline hydrochloride.

Table 3. Association between use of sympathomimetic agents and risk of hospitalisation for arrhythmias

	no (%)		odds ratio (confidence interval 95%)	
	cases (n=149)	controls (n=149)	Crude	Adjusted†
current use of any sympathomimetic	33 (22.1)	17 (11.4)	2.2 [1.2-4.3]	4.0 [1.0-15.1]
systemic sympathomimetic	6 (4.0)	1 (0.7)	6.0 [0.7-49.8]	15.7 [1.1-228]
inhalation sympathomimetic	21 (14.1)	12 (8.1)	1.8 [0.9-3.8]	2.4 [0.5-13.1]
nasal sympathomimetic	2 (1.3)	1 (0.7)	2.0 [0.2-22.1]	3.5 [0.2-70.5]
theophyllin	14 (9.4)	12 (8.1)	1.2 [0.5-2.6]	1.4 [0.3-5.7]

†adjusted for age, sex, prior hospital admissions (for arrhythmia, chronic obstructive pulmonary disease, asthma, emphysema, myocardial infarction or angina pectoris) in the preceding year and concomitant use of corticosteroids, digoxin, oral anticoagulants, calcium channel blocker, ACE inhibitors, beta-blockers, ibopamin, laxatives, antiarrhythmics, (potassium-sparing) diuretics, nitrates, any proarrhythmic drugs (antipsychotic, antidepressant, antihistaminic, macrolide or cisapride), antidiabetics

Of the 149 cases 33 (22%) and of the 147 controls 17 (11%) were treated with any sympathomimetic agent, yielding a crude OR of 2.2 (CI 95% [1.2-4.3]). We adjusted for a number of possible confounders, notably, sex, age, prior hospitalisations for arrhythmia, asthma, COPD, myocardial infarction, and angina pectoris. In addition, we adjusted for the use of a broad range of drugs that may have direct proarrhythmic effects, give rise to hyperkalemia or hypokalaemia, or are markers for a history of rhythm disturbances, such as digoxin, calcium channel blocker, beta-blockers, oral anticoagulants, antiarrhythmics, ACE inhibitors, corticosteroids, laxatives, diuretics, nitrates, neuroleptics, H_1-antihistamines, antidepressants, and ibopamin. Adjusted ORs were 4.0 (CI 95% [1.0-15.1]) for the use of any sympathomimetic drug and

15.7 (CI 95% [1.1-228]) for the use of systemic sympathomimetic drugs (Table 3). Separate ORs for inhalation and nasal sympathomimetics and theophyllin were not significantly associated with hospitalisation for arrhythmia.

Discussion

Our results strongly suggest an increased risk (OR 4.0; CI 95% [1.0-15.1]) for hospitalisation for arrhythmias in patients with heart failure using sympathomimetic drugs. This risk was much higher (OR 15.7; CI 95% [1.1-228]) in patients using systemic sympathomimetics than in patients using inhalation sympathomimetics (OR 2.4; CI 95% [0.5-13.1]). Possibly due to the relative small number of patients, the risk found for the inhalation group was not statistically significant, but data suggest that use of sympathomimetics by inhalation also leads to an increase in the risk of arrhythmia.

Surprisingly, we did not find an increased risk for arrhythmias in patients taking theophyllin. This is difficult to explain, since the hypokalaemic and heart rate effects of theophyllin are well known. Perhaps, physicians are familiar with these effects and only prescribe theophyllin for low-risk patients. Moreover, theophyllin is usually prescribed as a maintenance dose, while sympathomimetics are probably more often used 'on demand'. Patients with acute dyspnea due to heart failure could overuse these bronchodilators, while they are already more susceptible to develop arrhythmias.

In this study there were no patients using long-acting sympathomimetics. Studies suggest that these drugs have systemic effects comparable to those of short-acting sympathomimetics.[18] More research on their effects in patients with heart failure is warranted.

We did not have direct data on the severity of heart failure. However, we tried to compensate for this by correcting for a variety of co-medications and previous hospitalisations that we see as 'proxies' for the severity of heart failure. After adjustment for possible confounders such as sex, age, prior hospitalisations for arrhythmia, asthma, COPD, myocardial infarction, angina pectoris, and the use of a broad range of co-medications, the OR remained increased. These findings are suggestive of a causal relation between use of

sympathomimetics and arrhythmias. We were not able to control for caffeine use, which could also be a confounder.
This study was conducted in a selected group of seriously ill patients. Use of β_2-sympathomimetics is generally safe in patients with asthma or COPD.[19] However, patients with severe cardiac co-morbidity are probably more prone to their systemic effects.
Sudden death – often due to arrhythmias – is the major cause for mortality in patients with heart failure. This study was not designed to reveal the incidence of sudden death outside the hospital. The effects of sympathomimetics could therefore even be more deleterious. In this light, it seems important to avoid every possible factor that could lead to arrhythmias in these patients. Due to the high rate of co-morbidity, the complete avoidance of sympathomimetics is often not possible. However, the necessity of the use of sympathomimetics should be evaluated critically. The beneficial effects of bronchodilators in patients with heart failure and shortness of breath should be clearly documented by pulmonary function test before these drugs are prescribed. Oral sympathomimetics should be avoided in all patients. When patients have problems with inhalation, extra attention should be given to inhalation instruction. Potassium levels should be measured regularly and the clinician should be alert for the occurrence of arrhythmias.

References

1. Doig JC. Drug-induced cardiac arrhythmias: incidence, prevention and management. *Drug Saf* 1997;17:265-75.
2. Haffner CA, Kendall MJ. Metabolic effects of ß-agonists. *J Clin Pharm Ther* 1992;17:155-64.
3. Lipworth BJ. Risks versus benefits of inhaled ß -agonists in the management of asthma. *Drug Saf* 1992;7:54-70.
4. Udezue E, D'Souza L, Mahajan M. Hypokalemia after normal doses of nebulized albuterol (salbutamol). *Am J Emerg Med* 1995;13:168-71.
5. Wong CS, Pavord ID, Williams J, Britton JR, Tattersfield AE. Bronchodilator, cardiovascular, and hypokalaemic effects of fenoterol, salbutamol, and terbutaline in asthma. *Lancet* 1990;336:1396-9.

6. Crawford SM, Miles DW. Salbutamol and cardiac arrhythmias. *Curr Med Res Opin* 1981;7:410-5.
7. Banner A, Sunderrajan E, Agarwal M, Addington W. Arrhythmogenic effects of orally administered bronchodilators. *Arch Intern Med* 1979;139:434-7.
8. Mettauer B, Rouleau JL, Burgess JH. Detrimental arrhythmogenic and sustained beneficial hemodynamic effects of oral salbutamol in patients with chronic congestive heart failure. *Am Heart J* 1985;109:840-7.
9. Breeden CC, Safirstein BH. Albuterol and spacer-induced atrial fibrillatio n. *Chest* 1990;98:762-3.
10. Cazzola M, Imperatore F, Salzillo A, et al. Cardiac effects of formoterol and salmeterol in patients suffering from COPD with preexisting cardiac arrhythmias and hypoxemia. *Chest* 1998;114:411-5.
11. Newnham DM, McDevitt DG, Lipworth BJ. The effects of frusemide and triamterene on the hypokalaemic and electrocardiographic responses to inhaled terbutaline. *Br J Clin Pharmacol* 1991;32:630-2.
12. Struthers AD, Whitesmith R, Reid JL. Prior thiazide diuretic treatment increases adrenaline-induced hypokalaemia. *Lancet* 1983;1:1358-61.
13. Goldberger JJ. Treatment and prevention of sudden cardiac death: effect of recent clinical trials. *Arch Intern Med* 1999;159:1281-7.
14. Herings RM, Bakker A, Stricker BH, Nap G. Pharmaco-morbidity linkage : a feasibility study comparing morbidity in two pharmacy based exposure cohorts. *J Epidemiol Community Health* 1992;46:136-40.
15. World Health Organisation. *International Classification of Diseases, Ninth Revision (ICD-9)* Geneva, Switzerland: World Health Organisation; 1977.
16. Heerdink ER, Leufkens HG, Herings RM, Ottervanger JP, Stricker BH, Bakker A. NSAIDS associated with increased risk of congestive heart failure in elderly patients taking diuretics. *Arch Intern Med* 1998;158:1108-12.
17. Crane J, Burgess CD, Graham AN, Maling TJ. Hypokalaemic and electrocardiographic effects of aminophylline and salbutamol in obstructive airways disease. *N Z Med J* 1987;100:309-11.
18. Bennett JA, Smyth ET, Pavord ID, Wilding PJ, Tatters field AE. Systemic effects of salbutamol and salmeterol in patients with asthma. *Thorax* 1994;49:771-4.
19. Martelli NA, Raimondi AC, Lazzari JO. Asthma, cardiac arrhythmias, and albuterol aerosol. *Chest* 1986;89:192-4.