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A nested case–control study on mortality in users of ibopamine

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Abstract

Background: A recent interim analysis of the PRIME II placebo-controlled study showed a significantly higher mortality in the group treated with ibopamine than in the control group. The objective was to study mortality in patients on ibopamine, and to assess risk factors for death.

Methods: All 2147 drug-dispensing outlets (DDO) in the Netherlands were asked to provide a printout of the complete medication history of users of ibopamine. A reaction was received from 92% of the DDO. From the 14 024 identified former or current users of ibopamine, a sample of 3148 patients (22%) was enrolled in the follow-up study. All general practitioners (GP) of these patients received an enquiry pertaining to the vital status of their patient, cause of death, primary cause and NYHA classification of heart failure, echo- and electrocardiographic data, serum creatinine, admissions and the effects of ibopamine. Cases were defined as patients who died during the follow-up period which ended on the day of return of the questionnaire or the day of decease (index date). Two random controls were obtained for each case from the non-deceased patients at the index date. The design was a follow-up study with risk factor assessment in a nested case–control design.

Results: Questionnaires were returned regarding almost 70% of the sample. Mortality in this group was 25%. A case–control analysis was performed with the first 104 cases and 208 random controls. Patients with NYHA class IV had a 3-times increased risk of dying. In patients with a serum-creatinine level in the highest quartile the risk of dying was increased threefold. Higher doses of ibopamine seemed to have a protective effect. Significantly more cases than controls used amiodarone. Also, opioids were used more often, which may be related to their use in terminal cardiac failure.

Conclusion: NYHA classification and serum-creatinine levels were independent risk factors for death in patients with heart failure on ibopamine. Although there were increased risk estimates for current use of ibopamine and amiodarone, these did not reach statistical significance. This may be related, however, to the fact that this analysis was restricted to the first 20% of cases. © 1997 Elsevier Science B.V.

Keywords: Ibopamine; Case–control study; Amiodarone; Mortality; Pharmaco-epidemiology

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1. Introduction

Ibopamine is an oral dopamine agonist which was registered in the Netherlands in 1991 for the treatment of mild heart failure in combination with diuretics, and for moderate to severe heart failure in combination with diuretics, angiotensin converting enzyme (ACE) inhibitors and/or digoxin. Ibopamine is rapidly converted into the active metabolite *N*-methyldopamine (epinine) by plasma and tissue esterases. Epinine is excreted in the urine, after hepatic sulphate or glucuronic conjugation. In addition, epinine is metabolised by monoamine oxidase and catechol-*o*-methyltransferase and 75% is recovered in the urine as epinine metabolites. Epinine stimulates dopaminergic as well as β-adrenergic receptors in the cardiovascular system. This results in vasodilatation in the renal, cardiac, cerebral and mesenteric vasculature. Ibopamine has a mild positive inotropic activity, decreases sympathetic activity, inhibits the renine-angiotensin-aldosterone system and has natriuretic properties [1,2].

In 1992, in several European countries a randomized placebo-controlled clinical trial (PRIME II) was started to study the effect of ibopamine on mortality in patients with moderate to severe heart failure. Patients were enrolled with New York Heart Association (NYHA) classification III, III/IV and IV. In an interim analysis in 1840 patients with an average follow-up of 18 months, the mortality in the group treated with ibopamine was significantly higher than in the control group. Based on these results, the indication for use of ibopamine was restricted in the Netherlands to mild forms of heart failure (NYHA class I/II) on 31st August, 1995 [3]. At the same time, the Inspectorate for Health Care started a study on the mortality in patients on ibopamine, and risk factors for death.

2. Methods

2.1. Setting

On 1 September 1995, the Inspectorate for Health Care in the Netherlands issued a warning regarding the restricted indication of ibopamine (Inopamil). An earlier study on the adverse effects to acitretin demonstrated that such warnings are well taken but that the large majority of medical practitioners are unable to ascertain to which patients they have prescribed a specific drug [4]. Especially, drugs prescribed by medical specialists are difficult to trace by their prescribers. Hence, on 6th September, the Inspectorate for Health Care sent a request to all drug-dispensing outlets (DDO) to make a computer printout of all current users of ibopamine and inform the prescribers, and to send an anonymized copy of a printout of all current users, and of those treated with ibopamine in the preceding year to the Inspectorate for Health Care. This request was sent to all 2147 DDO in the Netherlands, comprising all 1516 community pharmacies and 631 drug-dispensing general practitioners. The request was not sent to hospital pharmacies. A reminder was sent on 3 November 1995.

2.2. Source population

A reaction was received from 1983 (92%) DDO, which had dispensed ibopamine to 14 024 patients. The mean age of these patients was 75 years, of which 51.4% were male and 48.2% female patients. Corrected for non-response, the total number of patients treated with ibopamine in the Netherlands in the preceding year was estimated at approximately 15 000. In view of the total population in the Netherlands of 15 000 000 inhabitants, the estimated 1-year-period population exposure prevalence was approximately 0.1%. The average number of patients per community pharmacy was 8.9 (median:6; range:0–145), and per GP with a DDO 2.8 (median:1; range:0–20).

2.3. Study population

All 1566 patients of general practitioners with a DDO, and a random sample of 1582 patients obtained through community pharmacies were enrolled in a follow-up study. All general practitioners of these patients received a questionnaire with questions pertaining to the vital status of the patient, cause of death, primary cause of heart failure, New York Heart Association (NYHA) classification, echo- and electrocardiographic data, serum creatinine, admissions, and the effect of ibopamine on cardiac

status. Patients were followed from the first day of their first prescription in the medication history until the day of their death or the day of return of the questionnaire.

2.4. Cases and controls

Cases were patients who died during the follow-up period. The day of death of the case was defined as the index date. Two random controls were obtained for each case from the patients in the study population who were still alive on the index date. For the analysis of exposure status, the controls were assigned the same index date as the case.

2.5. Exposure status

The use of ibopamine and all other drugs was obtained from the computer printouts. A drug-exposure window was defined as the period between 1 month before the index date and the index date. Hereto, for every prescription the legend duration was calculated on the basis of the ratio of the total number of tablets or capsules and the prescribed daily number of tablets or capsules. A case or control was considered exposed to every drug for which the legend duration of the prescription overlapped the exposure window.

2.6. Statistical analysis

The risk of death according to various risk factors was estimated by calculation of odds ratios with a 95% confidence interval [5]. Variables for which the distribution was significantly different between cases and controls in the univariate analysis, were included in a multivariate analysis according to an unconditional logistic regression model. In the logistic regression analysis, the following variables were included in a forward stepwise fashion: NYHA classification, serum creatinine level, angina pectoris, current use of ibopamine according to the general practitioner, use of digoxin, use of amiodarone and use of opioids. All analyses were done on a microcomputer with SPSSPC (version 5.0.2) and EGRET as statistical packages. One-tailed chi-square trend analyses were performed with EpiInfo (version 5).

3. Results

Computerized prescription histories and questionnaires have been obtained from almost 70% of the 3148 patients. In this group, there were 493 deaths (25%). For logistic reasons, we had to restrict this analysis to the first 20% of cases.

Hence, the study population in this report consisted of 104 cases and 208 controls. In Table 1, the general characteristics are given of cases and controls. Of the cases, 55% were male as against 45% of the controls. The average age of cases and controls was 77 and 76 years respectively. According to the general practitioners, almost 50% of patients died due to cardiac failure, 23% due to sudden cardiac death and 26% due to some other cause.

Most patients were NYHA class III or IV. Patients in the latter group had a 3-times increased risk of dying. The fact that the proportion of patients admitted to hospital was twice as high as in the group of controls was in accordance with the higher prevalence of NYHA class IV among the cases. Several cardiovascular diseases were similarly prevalent in cases and controls (Table 1), with the exception of angina pectoris which was more prevalent in cases. In cases, the average serum-creatinine level was significantly higher than in controls. In patients with a serum-creatinine level in the highest quartile (> 163 μmol/l) the risk of dying was 3-times greater than in the lowest quartile. According to the data from the general practitioners' questionnaire, the improvement of the cardiac status in controls was significantly higher than that in cases. Higher doses seemed to have a protective effect, which could be compatible with a beneficial effect of ibopamine. According to the general practitioners, 54 of the cases (52%) were using ibopamine up to the moment of their death whereas 70 controls (34%) were still using ibopamine at the moment of the enquiry. Based on the computerized pharmacy data, however, 66% of cases and 57% of controls were still using ibopamine in the exposure window, 30 days before the index date. Of the 40 cases (39%) who stopped ibopamine, the cardiac condition remained stable in 18 (45%), improved in 1 (2%), and worsened in 13 (33%) patients (6 patients with NYHA class IV, 6 patients with NYHA class III, and 1 with unknown cardiac status). In 8 patients (20%), the effect of

Table 1
Characteristics of the study population

	Cases (n = 104)	Controls (n = 208)	Odds ratio/p-value
Gender			
Females	47 (45%)	113 (55%)	Reference
Males	57 (55%)	93 (45%)	1.5 (0.9–2.4)
Age (years)	77 (SE:0.9)	76 (SE:0.7)	$p = 0.25$
Cause of death			
Cardiac failure	49 (47%)		
Sudden death	24 (23%)		
Other	27 (26%)		
Unknown	4 (4%)		
NYHA Classification			
NYHA I/II	6 (6%)	28 (14%)	Reference
NYHA III	45 (43%)	108 (52%)	1.9 (0.7–6.1)
NYHA IV	43 (41%)	59 (28%)	**3.4 (1.2–10.9)**
Unknown	10 (10%)	13 (6%)	–
		Chi-square trend: p = **0.004**	
Coronary artery disease	62 (60%)	109 (52%)	1.3 (0.8–2.2)
Hypertension	12 (12%)	28 (14%)	0.8 (0.4–1.8)
Cardiomyopathy	36 (35%)	56 (27%)	1.4 (0.8–2.5)
History of MI	61 (59%)	102 (49%)	1.5 (0.9–2.4)
Angina pectoris	67 (64%)	106 (51%)	**1.7 (1.1–2.9)**
Syncope < 5 years	32 (31%)	42 (20%)	1.8 (0.9–3.1)
COPD	31 (30%)	60 (29%)	1.1 (0.6–1.8)
Atrial fibrillation	44 (42%)	67 (32%)	1.5 (0.9–2.6)
Diabetes mellitus	32 (31%)	59 (28%)	1.1 (0.7–1.9)
S-Creatinine	163 (SE:11.7)	126 (SE:3.9)	p = **0.0003**
< 96 μmol/l	15 (14%)	45 (22%)	Reference
96–119 μmol/l	17 (16%)	48 (23%)	1.1 (0.4–2.6)
120–163 μmol/l	24 (23%)	40 (19%)	1.8 (0.8–4.2)
> 163 μmol/l	32 (31%)	31 (15%)	**3.1 (1.4–7.2)**
Unknown	16 (15%)	44 (21%)	–
		Chi-square trend: p = **0.001**	
Ibopamine improved cardiac status (< 2 months)	39 (38%)	124 (60%)	**0.4 (0.2–0.7)**
Re-admitted because of cardiac failure	32 (31%)	38 (18%)	**2.0 (1.1–3.6)**
Current use ibopamine [a]			
According to GP	54 (52%)	70 (34%)	**2.1 (1.3–3.5)**
According to pharmacist	69 (66%)	119 (57%)	1.5 (0.9–2.5)
Average duration of use (days)	220 (SE:25)	240 (SE:16)	$p = 0.5$
Daily dose			
< 200 mg	24 (23%)	22 (11%)	Reference
201–400 mg	44 (42%)	129 (62%)	**0.3 (0.2–0.7)**
> 400 mg	11 (11%)	25 (12%)	0.4 (0.1–1.1)
Unknown	25 (24%)	32 (15%)	–

[a] Cases: still using ibopamine at time of death, controls: still using ibopamine at time of enquiry.
Odds ratios and p-values significantly different from the null hypothesis are printed in bold.

discontinuation was unknown. Of the 99 controls (48%) who discontinued ibopamine, the cardiac condition remained stable in 73 (74%), improved in 9 (9%) and worsened in 8 patients (8%). In 9 patients, the effect was unknown.

In Table 2, the use of other drugs in the exposure window is given. Most drugs were used by similar proportions of cases and controls. There were some exceptions as significantly more cases used the antiarrhythmic agent amiodarone. Also, opioids were

Table 2
Current use of drugs in cases and controls on index date

Drug	ATC-code	Cases(n = 104)	Controls(n = 208)	Odds ratio (95% CI)
Insulins	A10AA	9	25	0.7 (0.3 -1.5)
Biguanide hypogl.	A10BA	5	8	1.3 (0.4–4.0)
Sulfonylurea hypogl.	A10BB	14	26	1.1 (0.5–2.2)
Potassium salts	A12BA	6	9	1.4 (0.5–3.9)
Coumarines	B01AA	36	68	1.1 (0.7–1.8)
HMG-CoA reductase in.	B04AB	1	9	0.2 (0.0–1.7)
Digoxin	C01AA	47	84	1.2 (0.8–2.0)
Anti-arrhythmics (IA)	C01BA	1	1	2.0 (0.1–32.5)
Anti-arrhythmics (1C)	C01BC	2	5	0.8 (0.2- 4.2)
Anti-arrhythmics (III)	C01BD	12	11	2.3 (1.0–5.5) *
Nitrates	C01DA	36	85	0.8 (0.5–1.3)
Thiazide diuretics	C03AA	16	24	1.4 (0.7–2.9)
Furosemides	C03CA	85	155	1.5 (0.9–2.8)
Aldosterone antagon.	C03DA	14	30	0.9 (0.5–1.8)
Other diuretics	C03DB	10	17	1.2 (0.5–2.7)
Vasodilators	C04AX	2	2	2.0 (0.3–14.5)
β-Blockers	C07AA	10	35	0.5 (0.2–1.2)
Ca-antagonists I	C08CA	8	13	1.3 (0.5–3.1)
Ca-antagonists II	C08DA	10	18	1.1 (0.5–2.5)
ACE-inhibitors	C09AA	61	110	1.3 (0.8–2.0)
Corticosteroids	H02AB	6	17	0.7 (0.3–1.8)
NSAID	M01AB	11	14	1.6 (0.7–4.0)
Opioids	N02AA	17	1	40.4 (5.3–308.7) *
Salicylates	N02BA	23	56	0.8 (0.4–1.3)
β Mimetic agents	R03AB	10	13	1.6 (0.6–4.1)
Corticosteroids inhal.	R03BA	7	17	0.8 (0.3–2.0)
Parasympathicolytics	R03BB	11	13	1.8 (0.8–4.1)
Xanthine derivatives	R03DA	3	6	1.0 (0.2–4.1)

* Statistically significant.

used more often which is probably related to the use of these agents in the terminal phase of cardiac failure.

In the logistic regression analysis, the following variables were included in a forward stepwise fashion: NYHA classification, serum creatinine level, angina pectoris, current use of ibopamine according to the general practitioner, use of digoxin, use of amiodarone and use of opioids. Although the latter is usually given in the final stage of the disease, it might contribute to death. Hence, it was included in the model. The multivariate analysis showed that NYHA classification with an odds ratio of 1.7 (95%CI: 1.1–2.9) and serum-creatinine level with an odds ratio of 1.6 (95%CI: 1.2–2.2) were independent risk factors for death but that a history of angina pectoris, current use of ibopamine and amiodarone or digoxin were no longer significant. Re-analyses with current use of ibopamine according to pharmacy data, dosage in 3 levels, and without opioids gave similar results.

4. Discussion

In this case–control study nested in a cohort of ibopamine users, we found that NYHA classification and serum-creatinine levels were independent risk factors for death in patients with heart failure. In view of the known pathophysiology of this disease, this is not surprising. The strong association between opioids and the risk of death is a reflection of the use of these agents in the terminal phase of the illness. In the univariate analysis, improvement of cardiac function to ibopamine in the first 2 months of treatment was significantly less frequent in cases, according to

the general practitioner. Cases were significantly more frequently using ibopamine than controls on the index date. This may be explained in part by a liability of doctors to continue treatment in the more severe cases of heart failure (confounding by severity). After correction for severity on the basis of NYHA classification, however, this association was still present, albeit no longer significant. It should be emphasized, however, that a significantly higher rate of exposure in cases was no longer present when the exposure status was based on the filling data from pharmacies. Filling data tend to be more reliable than prescription data from general practitioners. On the other hand, general practitioners might be better aware of any recent discontinuation of a drug shortly before a patients dies. Therefore, we performed the multivariate analysis twice with the 2 exposure definitions but this had little effect on the results. Remarkably, the data are suggestive of a protective effect of higher doses of ibopamine or may be compatible with under-treatment in cases by using a daily dose which is too low. The association with use of amiodarone in the univariate analysis is interesting as the PRIME II study suggests that the combination of ibopamine and amiodarone may increase the risk of death. In our study, the association was no longer present in the multivariate analysis. The point estimate of the odds ratio of approximately 2, however, persisted which is in line with the results from the PRIME II trial.

There are some considerations which should be taken into account before drawing conclusions from our data. First, for logistic reasons we had to restrict this analysis to the first 104 cases. These came mostly from general practitioners with a drug-dispensing outlet, who have direct access to both drug dispensing and morbidity data and who have given excellent support to this kind of study in the past [6]. Although several of our findings are compatible with the results of the PRIME II study they may have been non-significant due to low numbers. Secondly, although we did distinguish between the different causes of death in our patients, overall mortality was used as the outcome despite the fact that sudden cardiac death or death by aggravating heart failure may have a different pathogenesis. Overall mortality was also the outcome in the PRIME II study, however, and as it may be difficult to distinguish mortality on the basis of data from general practitioners, we included all deaths in our analysis. Thirdly, our results are based on morbidity and mortality data from general practitioners. There is no reason to believe that general practitioners are not able to evaluate cardiovascular disease, and it is plausible that much of their data came from cardiologists. Even so, we were not able to check the consistency or validity of the data by reference to the original patient files, discharge summaries or medical records.

In conclusion, the current study confirms that NYHA classification and serum-creatinine levels are independent risk factors for death in patients with heart failure who were treated with ibopamine. Although the use of opioids was strongly associated with death, this may be the result of their use in terminal patients rather than being a direct cause of death. Although current use of ibopamine and amiodarone were associated with an increased risk, these did not reach statistical significance in the multivariate analysis, possibly due to the fact that this case–control analysis was confined to the first 104 cases.

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