Diuretics, plasma brain natriuretic peptide and chronic obstructive pulmonary disease

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ABSTRACT

Background: Brain natriuretic peptide (BNP) is associated with increased myocardial stretching. This study aims to assess the effect of mild diuretics on plasma BNP levels in patients with an acute exacerbation of chronic obstructive pulmonary disease (COPD) who have high plasma concentrations of BNP.

Methods: Thirty consecutive patients with an acute exacerbation of COPD without any clinical evidence of cor pulmonale who had elevated plasma BNP concentrations (group 1) and 15 patients with stable COPD as controls (group 2) participated in this study. A mild diuretic treatment in addition to the standard treatment for an acute attack of COPD was randomised to 15 patients in group 1 (group 1A). The remaining patients in group 1 only took standard treatment for acute COPD exacerbation (group 1B). Plasma BNP concentrations were measured on admission and repeated on the 5th and 10th days.

Results: There was a significant decrease in plasma BNP concentrations, more striking in group 1A than 1B. Both in group 1A and 1B, the fall in plasma BNP concentrations was independent of either presence or absence of right ventricular dysfunction on echo evaluation.

Conclusion: Adding mild diuretics to the standard treatment for an acute attack of COPD may rapidly reduce plasma BNP levels in COPD patients with acute exacerbations who have high plasma BNP levels without any clinical evidence of cor pulmonale.

KEYWORDS

Brain natriuretic peptide, chronic obstructive pulmonary disease, cor pulmonale, diuretics

INTRODUCTION

Brain natriuretic peptide (BNP) originates from the ventricular myocardium and is secreted as a response to increased ventricular pressures and/or volume overload. It plays a role in the control of sodium excretion and blood pressure, and has a compensatory role in cardiorenal homeostasis. A high plasma level of BNP is an important criterion for cardiac failure. BNP has also been shown to increase in hypoxaemic patients with chronic obstructive pulmonary disease (COPD) and it is significantly increased, particularly in patients with cor pulmonale when compared with patients with COPD alone. It is especially increased in proportion to the degree of right ventricular (RV) dysfunction. Elevated plasma BNP concentrations in COPD patients could be a useful early indicator of RV systolic dysfunction and monitoring changes in plasma BNP may provide a quantitative method for assessing RV function during follow-up. Since high plasma concentration of BNP is associated with increased strain on the ventricles, patients with COPD who have elevated plasma BNP levels should have some degree of RV strain, contributing to raised BNP levels even in the absence of clinical findings of RV dysfunction. Therefore, patients suffering an acute attack of COPD with high plasma levels of BNP might benefit from mild diuretics to decrease the volumetric strain on the right ventricle. Based on this hypothesis we planned a study that aims to evaluate the effect of mild diuretic treatment on the plasma BNP level in patients with an acute exacerbation of COPD who have high concentrations of BNP.

MATERIALS AND METHODS

Subjects

Thirty-seven consecutive patients with acute exacerbation of COPD, according to the criteria of the Global Initiative
was randomised to 15 patients who were categorised as
day) in addition to the standard acute attack treatment
triamterene 50 mg and hydrochlorothiazide 25 mg/
A mild diuretic treatment (a combined preparation of
defined below.

The study included a total of 45 COPD patients, 30
were prefered as bronchodilators initially. Later the
treatment was maintained by formoterol fumarate
dehydrate (9 μg/twice daily) and tiotropium bromide
(18 μg/day) dry powder inhalations according to the
patient’s condition.

Methylxanthenes (theophylline, 5-6 mg/kg as loading
dose; 0.5 mg/kg/hour infusion as maintenance),
corticosteroids (methyl-prednisolone 1 mg/kg/day intravenously; then
decreasing doses of oral methyl-prednisolone for 15 days) and
antibiotics (when signs of bacterial infection were
present) were given to all patients.

A mild diuretic treatment (a combined preparation of
triaterene 50 mg and hydrochlorothiazide 25 mg/
day) in addition to the standard acute attack treatment
was randomised to 15 patients who were categorised as
group 1A. The remaining 15 patients in group 1, who
were not on mild diuretic treatment, were categorised as
group 1B. Group 2 served as a control group and consisted
of 15 patients who presented with stable COPD. Patients
in group 2 received only formoterol fumarate dehydrate
(9 μg/twice daily), budesonide (200 μg/twice daily) and
tiotropium (18 μg/day) dry powder inhalations. All patients
on mild diuretic treatment were also followed for any
electrolyte disturbance.

The echocardiographer was blinded to both the medications
and the BNP levels of the patients. The echocardiographic
evidence of RV hypokinesia with or without dilatation
was used to define RV dysfunction. RV dysfunction and
pulmonary arterial pressures on echo examination and
evidence of RV strain on the electrocardiograms of all
patients were noted.

**Statistical analysis**

Data were expressed as mean ± SD and median (with 25th
and 75th percentages) where appropriate, and analysed
using SPSS 13.0 for Windows. The independent samples
t-test for continuous variables and χ² test for categorical
variables were used to analyse differences between groups.

For the comparison of 1st day measurements of BNP, the
Kruskal-Wallis variance analysis test was used among
groups and Mann-Whitney U test was used for binary
comparisons if a significant difference was observed
among groups. The latter was also used to compare the 5th
and 10th day measurements of BNP between groups 1A
and 1B. Friedman’s variance analysis test was applied to
compare three consecutive measurements of BNP in each
group. Wilcoxon’s test was used for binary comparisons if
a significant difference was observed among measurements.

Spearman’s correlation test was used where applicable.
A value of p<0.05 was considered significant.

**RESULTS**

The study included a total of 45 COPD patients, 30
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Spearman’s correlation test was used where applicable.
A value of p<0.05 was considered significant.
Although the fall in plasma BNP levels in group 1A was statistically significant among all three measurements, no significant drop was observed between the 5th and 10th day measurements in group 1B (Table 3).

Among all patients included in the study, 14 subjects (31.1%) had echo findings of RV dysfunction without any clinical evidence of right heart failure (6 patients in group 1A, 4 in group 1B and 4 in group 2). The groups did not differ for the presence of RV dysfunction on echo evaluation. Plasma BNP levels of the patients with acute exacerbation who had echo evidence of RV dysfunction were significantly different to those without evidence of RV dysfunction: 1459.5 pg/ml (IQR: 857.3-3017.5) vs 312.8 pg/ml (IQR: 222.6-737.5); p=0.01.

There was a positive correlation between 1st day BNP levels and the presence of echo evidence of RV dysfunction in patients with acute COPD exacerbations (p=0.008, r=0.474). However, both in group 1A and 1B, the fall in plasma BNP concentrations was independent of either presence or absence of RV dysfunction in echo evaluation.

**DISCUSSION**

We planned this study based on the fact that a likely RV strain in COPD patients may be responsible for high levels of plasma BNP concentrations and patients presenting with acute exacerbation of COPD who have high plasma BNP levels might benefit from a mild diuretic treatment to reduce plasma BNP concentrations. For this purpose we added a diuretic (a combined preparation of triamterene 50 mg and hydrochlorothiazide 25 mg/day) to the standard management of an acute attack of COPD in the studied population. We demonstrated that the fall in plasma BNP concentration was markedly higher in patients receiving additional diuretics than in patients receiving only standard acute attack treatment although significant decreases in plasma BNP levels were observed both in group 1A and 1B (p=0.0001 vs p=0.038). This finding indicates that adding diuretic treatment in patients with an acute exacerbation of COPD...
may have a role in reducing increased plasma BNP levels and thus the RV strain. It may be considered that plasma BNP concentrations may decrease more rapidly in those patients who have received diuretic treatment. Intravascular volume increases following RV insufficiency, polycythaemia, and sodium and water retention due to hypervolaemia. An increased RV afterload enhances RV contractility. Later RV failure develops and water leaks into the extravascular space. If the intravascular volume is decreased, pulmonary haemodynamics, RV performance and gas exchange may improve. Diuretics may act to reduce volume overload by enhancing salt and water excretion. Therefore, they may decrease the pulmonary arterial pressure and the workload of the right ventricle and thus the shift of interventricular septum into the left ventricle, which is caused by an increased volume load of the right ventricle.

Subjects in group 1B showed gradual decreases in plasma BNP levels, as well; however, a statistically significant decrease was not observed between the second and third measurements in contrast to that in group 1A (table 3). Theophylline, a drug that has a mild diuretic effect, which was used as part of the acute attack treatment in these patients, might contribute to the early fall of plasma BNP level in group 1B. The continuing statistical fall in plasma BNP levels between the second and third measurements in group 1A may justify the role of mild diuretics in patients with acute COPD exacerbations.

Both the natriuretic peptides, atrial natriuretic peptide (ANP) and BNP, have a counter-regulatory role in cor pulmonale. They are released in response to atrial and ventricular stretching and attenuate increases in RV afterload in response to hypoxaemia and may therefore be important as a regulator. These peptides can produce significant pulmonary vasodilatation in cor pulmonale, as well. Both natriuretic peptides have beneficial effects on plasma aldosterone levels and these properties may be important in attenuating the overactivity of the renin-angiotensin-aldosterone system observed in cor pulmonale. By suppressing renin release and decreasing angiotensin II and aldosterone production, ANP and BNP may act to prevent excessive salt and water retention which may well be important in acute exacerbations of cor pulmonale. In the present study we did not include patients with a clinical picture of cor pulmonale. Our aim was to indicate increased RV afterload in patients with acute exacerbations of COPD without clinical evidence of cor pulmonale. BNP may also be a valuable marker of increased RV strain in patients with an acute COPD attack and diuretic treatment may help to reduce acute increases in RV strain. Thus BNP may be useful in the follow-up of such patients. Yap has also noted that assessment of the plasma BNP concentration may be a noninvasive means of diagnosing RV dysfunction and pulmonary hypertension and may be used in follow-up of these patients.

In the literature, studies enrolling patients with congestive heart failure have demonstrated that a low dose of spironolactone reduced plasma BNP levels, left ventricular diastolic volumes, and improved echocardiographic left ventricular ejection fraction. The BNP level also correlated well with the degree of ventricular overload. It has been demonstrated that long-term spironolactone treatment decreased plasma BNP levels in patients with congestive heart failure. Johnson, too, reported that neurohormonal activation in patients with class IV heart failure rapidly decreased after a short-term therapy with intravenous diuretics and vasodilators by decreasing elevated filling pressures. In our study we also found a correlation between plasma BNP levels and the echo evidence of RV dysfunction in patients with acute COPD exacerbations. However, the total number of patients with RV dysfunction in all groups was not statistically sufficient for any inference.

Plasma BNP concentrations may be found to be elevated in most patients with an acute exacerbation of COPD even if the patient has no clinical or echo evidence of cor pulmonale. Increased plasma BNP levels in these patients may be due to pulmonary hypertension during acute exacerbation. In the literature it has been reported that high BNP concentrations predicted moderate-severe pulmonary hypertension with 100% sensitivity and 73 to 89% specificity. Compared with the 69% sensitivity and 94% specificity of the echo, as established in the WHO Multicentre Study, the plasma BNP concentration appears to be a more sensitive but less specific means of predicting pulmonary hypertension and cor pulmonale. Leuchte especially emphasised that BNP could be regarded as a potentially helpful diagnostic tool to detect pulmonary hypertension in patients with pulmonary fibrosis. Ishii also showed that plasma BNP concentration closely correlated with the mean pulmonary arterial pressure and pulmonary vascular resistance in patients with chronic respiratory diseases.

Our study has some limitations, as it is the first in this respect. We did not use invasive cardiac imaging procedures, especially right heart catheterisation. Pulmonary arterial pressures of the subjects might have been measured via right heart catheterisation before and after treatment in this study. Instead, we only included subjects who were evaluated by echo. Doppler echo allows an estimation of the pulmonary arterial pressure and provides information about right and left ventricular function. However, it has limited accuracy. In this study we also used a small stable dose of a combination of triamterene and hydrochlorothiazide, which has a mild diuretic effect, so the dose-response effect of this combined preparation on the plasma BNP concentration must also be evaluated. BNP may act to prevent excessive salt and water retention by decreasing plasma aldosterone levels.
We did not quantitatively evaluate the plasma aldosterone level. Therefore, we were not able to show in what way the diuretics might have a lowering effect on plasma BNP levels in COPD patients. We suggest evaluating plasma BNP levels in all patients who have an acute COPD exacerbation without any clinical evidence of cor pulmonale, as a high plasma BNP level may be a noninvasive means of showing increased RV afterload as previous studies have documented. A more rapid decrease in plasma BNP levels in the group treated with diuretics compared with the non-treated group may aid in early clinical improvement in the COPD patients with high plasma BNP concentrations; however, this hypothesis should be tested by using a daily symptom scoring questionnaire, which could be the subject of another study.

As a conclusion, in patients with a high level of plasma BNP concentration, adding a mild diuretic to the standard treatment for an acute COPD attack may aid in rapidly reducing plasma BNP levels and may prevent the clinical findings of cor pulmonale from developing. However, before considering a mild diuretic therapy as a possible therapeutic strategy in COPD patients with acute exacerbation who have high plasma BNP levels, there is a need for additional data obtained from studies enrolling large numbers of COPD patients.

REFERENCES