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B-type Natriuretic Peptide plasma concentration in acutely poisoned patients

Stężenie peptydu natriuretycznego typu (BNP) u pacjentów ostro zatrutych

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B-type natriuretic peptide (BNP) is synthesized in the cardiac ventricles upon ventricular myocyte stretch. BNP plasma concentration is useful in cardiology especially for identifying patients with congestive heart failure (CHF), as a prognostic marker of acute coronary syndromes and independent predictor of sudden cardiac death. Its value in clinical toxicology is unclear. As toxins frequently produce deleterious effects on the cardiovascular system we have decided to carry out the pilot study on BNP plasma levels in acutely poisoned patients. The 117 patients (65 males and 52 females) treated at the Department of Clinical Toxicology Jagiellonian University Medical College in Kraków in 2004 were included. 42 of them were intoxicated with ethanol, 35 with pharmaceuticals (mostly tricyclic antidepressants), 13 with CO. The mean age of examined group was 34.07 ± 12.08 year. The control group consisted of 54 healthy volunteers and employees of the Department (mean age; 32.7 ± 11.74). A significantly higher BNP concentration was found in poisoned patients than in the control group. The highest BNP plasma concentration was noted in pharmaceutical poisoned patients. Mean BNP concentration in poisonings of minor severity (grade 1) was significantly lower then in moderate (grade 2) or severe (grade 3) poisonings. BNP plasma measurement as an additional marker of cardiac disturbances in clinical toxicology practice may be suggested.

Peptyd natriuretyczny typu B (BNP) jest syntetyzowany w komorach serca na skutek zwiększonego napięcia miocytów. Oznaczanie stężenia BNP w osoczu krwi znalazła zastosowanie w kardiologii, szczególnie dla identyfikacji pacjentów z zastoinową niewydolnością krążenia, jako wskaźnik prognostyczny w ostrych zespołach wieńcowych, jak również jako niezależny predyktor nagłego zgonu sercowego. Znaczenie BNP w toksykologii jak do tej pory nie jest określone. Ponieważ substancje toksyczne często zaburzają funkcję układu sercowo-naczyniowego, zdecydowaliśmy przeprowadzić pilotażowe badanie stężenia BNP wśród osób ostro zatrutych. Do badania zostało włączonych 117 pacjentów (65 mężczyzn i 52 kobiet) leczonych w Klinice Toksykologii Collegium Medicum Uniwersytetu Jagiellońskiego w Krakowie w 2004 r. 42 osoby były zatrute etanolem, 35 lekami (w przeważającej mierze tricyklicznymi lekami przeciwdepresyjnymi) i 40 osób tlenkiem węgla. Średni wiek badanej grupy wyniósł 34.07 ± 12.08. Grupę kontrolną stanowiło 54 młodych ochotników oraz pracowników Kliniki (średni wiek 32.7 ± 11.74). Stwierdzono znamiennie wyższe stężenia BNP w grupie badanej w porównaniu z kontrolną. Najwyższe stężenia BNP odnotowano w grupie pacjentów ostro zatrutych lekami. Średnie stężenie BNP w grupie pacjentów lekko zatrutych (1 stopień) było znamiennie niższe, niż w grupie średnio (2 stopień) i ciężko (3 stopień) zatrutych. Wyniki wskazują na przydatność oznaczenia BNP w surowicy jako dodatkowy wskaźnik zaburzeń pracy serca w toksykologii klinicznej.

Introduction

There are three major natriuretic peptides: A-type, atrial natriuretic peptide (ANP), B-type (BNP) and C-type natriuretic peptide. ANP main storage sites include both the atria and ventricles whereas the major BNP plasma source is the cardiac ventricles. It is synthesized as preproBNP. C-type natriuretic peptide is of endothelial origin [3,13]. BNP levels accurately reflect the decompensated state of circulatory congestion [5]. It is an objective independent predictor of high left ventricular end-diastolic pressure and correlates well with the New York Heart Association (NYHA) functional system of classification in heart insufficiency [7]. In literature BNP is a recognized marker of heart dysfunction. BNP cutoff value of 100 pg/ml had a high sensitivity and a specificity for differentiating congestive heart failure (CHF)

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from other causes of dyspnoe. CHF is possible at BNP levels between 100 and 500 pg/ml and probable at levels greater than 500 pg/ml [6,12]. For screening asymptomatic populations for the detection of left ventricle dysfunction a much lower BNP cut-off is recommended (below 20 pg/ml). Berger et al. shown that cut-off BNP level of 130 pg/ml in patients with mild and moderate CHF (LVEF below 35%) differentiated well between patients with high and low survival rates from sudden death. BNP is a prognostic marker in Acute Coronary Syndromes (ACS) too. It has predictive value of recurrent ischemic events when BNP level is higher than 80 pg/ml [4].

As toxins frequently produce deleterious effects on the cardiovascular system we have decided to carry out the pilot study on BNP plasma levels in acutely poisoned patients.

Material and methods

The 117 patients (65 males and 52 females) treated at the Department of Clinical Toxicology Jagiellonian University Medical College in Kraków in 2004 were included. 42 of them were intoxicated with ethanol, 35 with pharmaceuticals (mostly tricyclic antidepressants), 40 with CO. The mean age of examined group was 34.07 ± 12.08 year. Severity of poisoning was graded according to Poisoning Severity Score (PSS), a standardized and generally applicable scheme for grading the severity of poisoning. Patients with heart congestion or ischemic heart disease were excluded. The control group consisted of 54 healthy volunteers and employees of the Department. The mean age was 32.7 ± 11.74.

Toxicovigilance was performed and BNP plasma concentration was measured on admission. The quantitative determination of human B-type natriuretic peptide (BNP) in human EDTA plasma is based on Microparticle Enzyme Immunoassay (MEIA) technology and performed using the Abbott AxSYM System. In the procedure human BNP antigen in the sample competes with the alkaline phosphatase-labelled anti-BNP on the binding sites on the anti-BNP monoclonal antibody on the microparticles. The substrate, 4-methylumbelliferyl phosphate added to the reaction mixture is converted by the alkaline phosphatase-labeled conjugate to the fluorescence product measured by the MEIA optical assembly. EDTA plasma sample was collected in plastic tubes, because the BNP molecule has been shown to be unstable in glass containers. All samples were separated by centrifugation and frozen for up to 3 mouths at (-) 20°C. An analytical sensitivity of the AxSYM BNP assay was defined below 15 pg/ml. A nonparametric U-*Man Whitney* test and ANOVA *Kruskall-Wallis* and median test were used to statistical analysis using STATISTICA PL compuler program.

Results

No significant difference (z=0.754; p=0.4506) was noted between the age of examined and control group (figure 1).

BNP concentration in poisoned patients was significantly higher than in control group (figure 2).

BNP plasma concentration concerning the toxic agent involved is presented in figure 3. The highest BNP concentration in pharmaceutical poisoned patients (126.11 pg/ml) was followed in concentration by CO poisoned group (74.61 pg/ml). BNP plasma concentration in the pharmaceutical poisoned patients was significantly higher than in CO, ethanol poisoned (33.2 pg/ml) and the control group (30.5 pg/ml). No statistically significant difference in BNP plasma concentration was only found between ethanol poisoned patients and the control group.

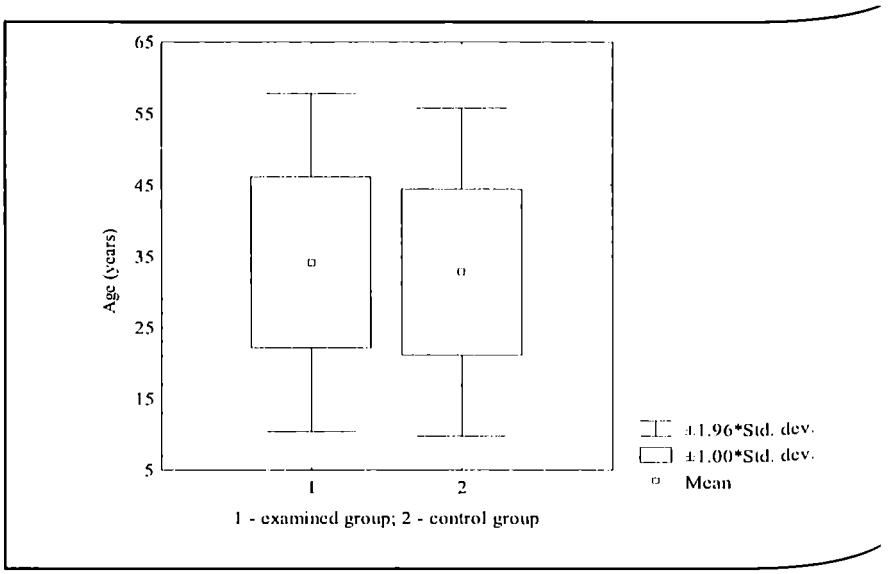

Figure 1
Age of examined and the control group.
Wiek grupy badanej i kontrolnej.

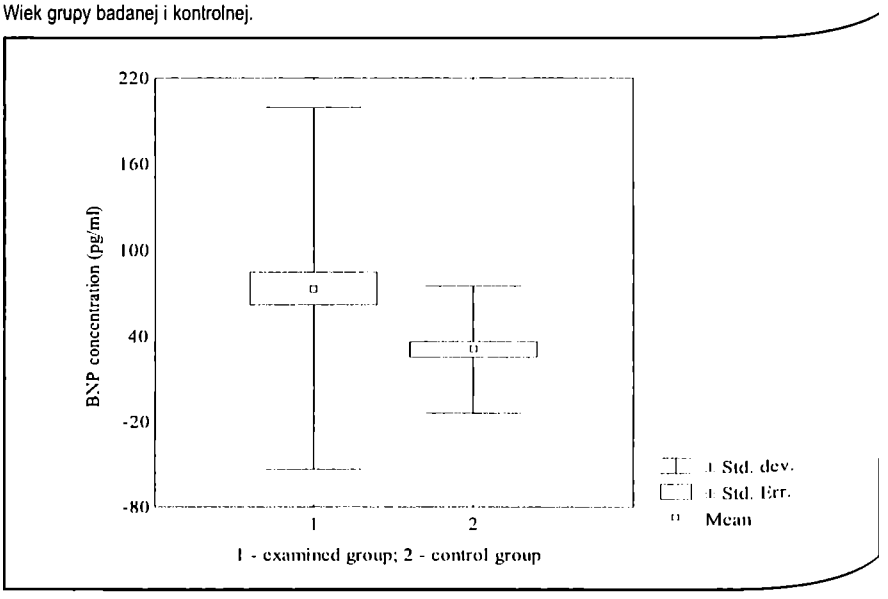

Figure 2
Plasma BNP concentration in examined and control group.
Stężenie BNP w grupie badanej i kontrolnej.

Mean BNP concentration in poisonings of minor severity (grade 1) was significantly lower then in moderate (grade 2) and severe (grade 3) poisonings. No significant difference in BNP concentration between moderate and severe poisoning grade was noted (figure 4). No significant difference in BNP concentration was noted between moderate and severe poisoning.

Discussion and conclusions

Many studies have shown BNP as an important and valuable marker in CHF as well as in ACS [3,4,5,8]. Results of our pilot study revealed higher BNP plasma concentrations in pharmaceuticals (among them tricyclic antidepressants) and carbon monoxide acutely poisoned patients. No significant difference in BNP plasma concentration was found between ethanol poisoned patients and the control group.

Carbon monoxide is well known cardiotoxic agent [2,9]. Poor tissue oxygen supply caused by impaired blood oxygen transportation due to the presence of carboxyhemoglobin (COHb) and a leftward shifting in the oxyhemoglobin dissociation curve, as well cytotoxic cellular effect due to binding of CO to myoglobin, reduced cytochromes, guanylate cyclase and nitric oxide synthase lead to myocardial ischaemia. The cardiac arrhythmia and the heart pump malfunction reflects these disturbances. The mean COHb concentration in our CO poisoned group was 21.3%, the mean BNP concentration was 56 pg/ml, and was significant higher then in the control group (30 pg/ml).

Tricyclic antidepressants (mostly represented in our group of pharmaceutical poisoned patients) directly affect the heart muscle. Anticholinergic effects and inhibition of neuronal reuptake of catecholamines result in tachycardia and mild hypertension. Peripheral alpha – adrenergic blockade induces vasodilation. Membrane – depressant effects cause myocardial depression and

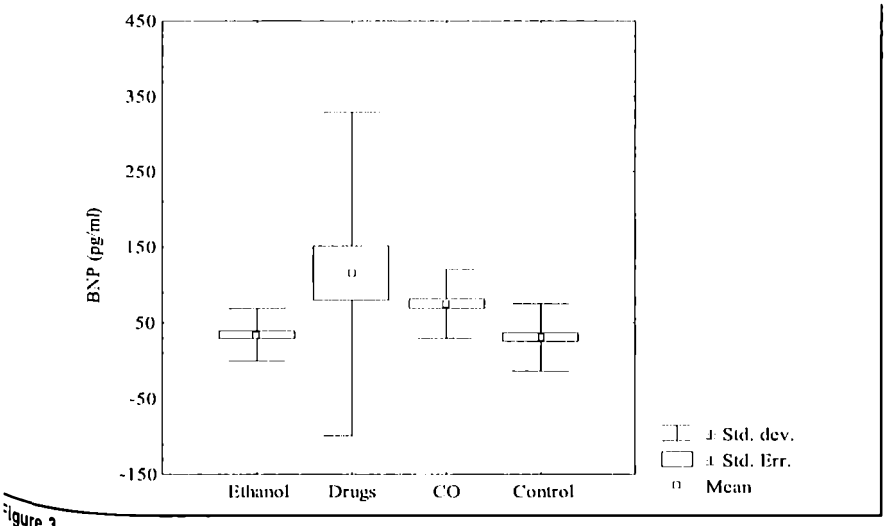

Figure 3
BNP plasma concentration concerning toxic agent involved.
Stężenie BNP w zależności od czynnika toksycznego.

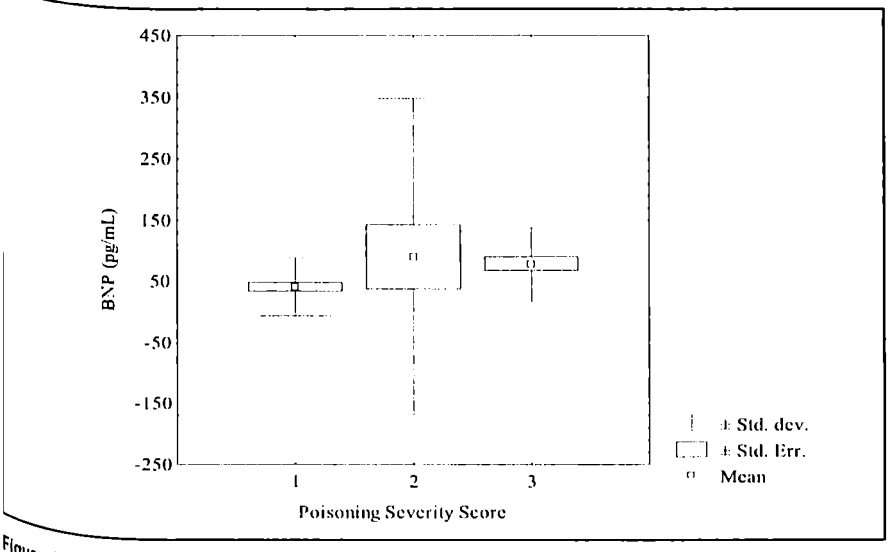

Figure 4
BNP plasma concentration concerning severity of poisoning.
Stężenie BNP w zależności od stopnia ciężkości zatrucia.

cardiac conduction disturbances by inhibition of the fast sodium channel that initiates the cardiac cell action potential [1]. Tricyclic antidepressants typically are associated with sedation, orthostatic hypotension and impairment of intracardiac conduction. Cardiovascular toxicity with intractable myocardial depression, ventricular tachycardia, and ventricular fibrillation are common mechanisms of death [1]. The mean BNP plasma concentration in the pharmaceuticals poisoned group was higher than 100 pg/ml – the level pointed to possibility of CHF. Radiographic evidence of pulmonary oedema is observed in about 10% of TCA overdose patients [1]. The highest mean BNP concentration in pharmaceutical group correlates positively with TCA cardiotoxic potential.

The mean BNP concentration in ethanol acutely poisoned patients did not differ from control group. The group consisted of alcohol dependent individuals. A relatively low BNP concentration in young alcoholics, despite high ethanol level (from 1.48 - 5.34; x= 3.16 mg/L) properly corresponded to our clinical experience. In acute alcohol intoxication heart insufficiency is not typically observed despite deep central nervous system depression.

BNP plasma level were dependent on poisoning severity graded according to the Poison Severity Score. This standardized and generally applicable scheme for grading the severity of poisoning takes into account only the observed clinical symptoms and signs. PSS allows qualitative evaluation of morbidity and facilitates comparability of data and is intended for all types of poisoning [10]. Mean BNP concentration in poisonings of minor severity (grade 1) was significantly lower then in moderate (grade 2) and severe (grade 3) poisonings. No significant difference in BNP concentration between moderate and severe poisoning grade was noted in our poisoned patients.

BNP is not stored in granules (different then ANP) but synthesized in bursts [8]. A minor stimulus, such exercise, can trigger release of significant amounts of ANP [11]. BNP half-life is relatively short (22 minutes) and it's releasing is in direct proportion to ventricular wall tension [5]. The short half-life allow to detect hemodynamic changes even every 2 hours [6]. These facts let to formulate the thesis that BNP concentration can accurately reflect functional status of the left ventricle of the heart. BNP has some advantages over its precursor, N-terminal proBNP (NT-proBNP), also used for reflecting heart failure severity. NT-proBNP's half-life is relatively long (120 min) what lets to reflect hemodynamic changes every 12 hours. It's level grows with normal aging and stronger, then BNP, correlates with glomerular filtration rate (GFR) [6]. These facts and results of our pilot study suggest BNP plasma concentration higher than 100 pg/ml to be an additional marker of cardiac disturbances in clinical toxicology practice. BNP plasma concentration above 100 pg/ml may be helpful in identifying a higher risk of cardiac disturbances in patients exposed to agent of known cardiotoxic potential or to unknown agent. It also may be helpful in selecting the patients with pre-existing heart failure, monitoring haemodynamic status and the treatment.

Study are continued. The cardiac enzymes activity, 24hours ECG and 24hours blood pressure monitoring with Holter method, echocardiography, and Tc99mMIBI SPECT (rest and stress) examinations are performed in those poisoned patients in whom the cut-off value (100 pg/ml) of BNP plasma concentration is exceeded.

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