Manipulation with colours has not brought any significant effect onto the M-VEPs latencies. Nevertheless, the yellow colour increased significantly the M-VEPs amplitude in both groups of dyslexics. It is in agreement with a finding of Solman et al. (12), however, it does not support the former theory that blue filters reduce light and contrast can improve reading – likely via a better function of the magnocellular pathway (e.g. 16,11). Comparison of M-VEPs parameters (including the latencies of the later part in case of the split N160 peaks) in grey and colour stimuli provides the scatter diagram in Fig. 1 (data from 25 younger dyslexics). It is evident that distribution of the N160 latencies, both of normal and pathological values, is independent on the stimulus colour.

Abnormal EEG frequency spectra parameters were found in only two (out of 25) dyslexics who displayed prevailing theta activity and the dominant frequency below 8 Hz. Thus, we cannot confirm existing findings of significant EEG frequency spectra abnormalities in dyslexics (e.g. 6). No correlation between the EEG, VEPs parameters and reading quotients was proved. However, a positive correlation between IQ and EEG dominant frequency (r = 0.53) in the group of younger dyslexics supports our above-specified speculation that the relatively low rate of the pathological M-VEPs in this group can be caused by subjects with the low IQ who are incorrectly censored as dyslexics. Thus, in our continuing research much more attention must be paid to correct classification of dyslexic subjects.

Conclusions

1. M-VEPs examination enables to detect magnocellular pathway and/or temporal association cortex disorder in a subgroup of dyslexics.

2. This disorder might represent a delayed maturation of the visual system or of the association and cognitive brain areas as one of the etiological factors contributing to the reading disability.

3. The gained M-VEPs data do not support the theory about the influence of light wavelength onto the magnocellular pathway function.

Acknowledgments

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Summary: The aim of this randomised, double-blind, placebo controlled, parallel group study was to assess the effect of trimetazidine (TMZ), a potent antiischaemic drug, on plasma C-reactive protein (CRP), cytokine and adhesion molecule levels. The study population consists of 18 patients (16 males, 2 females, average age 56.4 ± 10.9 years) with acute myocardial infarction admitted within 6 hours after onset of symptoms and treated with streptokinase. Blood samples were taken at 3-hour intervals during the time of treatment. All patients were randomised blindly using a centralised randomisation process, between trimetazidine (40 mg bolus iv + 60 mg per day for 48 hours intravenously in glucose infusion) or placebo group. Plasma CRP level was significantly lower in TMZ group (39.5 mg/ml ± 9.7 mg/ml) as compared to placebo (75.7 ± 29.4 mg/ml ±0.001) and peaked 28 hours later in TMZ group. Plasma interleukin 6 (IL 6) level showed a sharp peak 9 hours after the onset of the symptoms in TMZ group (116.9 ± 180.2 pg/ml vs. 45.4 ± 37.9 pg/ml) and was increased up to 30 hours after the onset of the symptoms. Plasma interleukin 1 beta (IL 1) was also higher in TMZ group notably 21 hours after the onset of symptoms (26.4 ± 9.3 pg/ml vs. 16.2 ± 2.4 pg/ml). TMZ group showed lower plasma E-selectin levels. Plasma IL 8, TNF α and ICAM 1 levels were without statistical significant differences. The present study demonstrates a significant reduction of plasma C-reactive protein level in the course of acute myocardial infarction treated with streptokinase and intravenous trimetazidine infusion compared with the group of patients without trimetazidine treatment.

Key words: Trimetazidine, Acute myocardial infarction, C-reactive protein, Interleukins, Adhesion molecules

Introduction

The association of inflammation with acute myocardial infarction (AMI) has been known for over a half of the century. Inflammatory lesions seen in tissue specimens many hours to days after the onset of infarct, in part, a healing process. In recent years many investigators have studied the potential pathogenic role of inflammation in the myocardial ischaemia-reperfusion (MI/R) process (11).

Inappropriate inflammatory response can cause severe tissue destruction. During ischaemia-reperfusion, such as in acute myocardial infarction, the tissue damage may result not only from direct anoxic and hypoxic injury but also from other deleterious events occurring after the blood flow reestablishment to the occluded vascular bed. Reper- fusion injury is partly caused by oxygen radicals, proteolytic enzymes and cytokines released by adhered and activated leukocytes that infiltrate into the affected area, because neutrophil depletion or prevention of neutrophil accumula- tion significantly diminishes tissue damage and enhances the recovery of cardiac function (5).

Recent studies have focused on the possible role of the soluble early mediators of acute phase response during MI/R process. Particular emphasis has been given to the study of acute response proteins (C-reactive protein, α1 antitrypsin, serum amyloid) and cytokines.

Key role of interleukin 1beta (IL 1β), interleukin 6 (IL 6), interleukin 8 (IL 8), and tumor necrosis factor alpha (TNF α) in the process of lymphocyte, neutrophil, and pla- telet activation has been shown in previous studies (8,9,12,14). IL 6, IL 8, TNF α, and soluble adhesion molecule levels (ICAM 1, E-selectin et al.) in the course of ischaemic event have been studied ex- tensively. Based on these observations, new medicines should have protective effect on leukocytes, preserve myo- cellular function by decreasing ischaemic and reperfu- sion effect, and limit the area of necrosis.
Trimetazidine [TMZ, (1-(2,3,4-trimetoxybenzyl)] pipe-razine dichloride has cytoprotective properties and pre-vents metabolic disturbances that result from myocardial ischaemia. Its mechanism of action is, at least partially, di-rectly related to the mitochondrial enzymatic systems. TMZ stimulates glucose oxidation by primarily reducing ra-tes of β-oxidation (6), decreasing mitochondrial oxygen de-mand. TMZ has also been reported to have a protective effect in myocardial ischaemia-reperfusion process by in-creasing phospholipid turnover of the membrane (13). After periods of ischaemia it is able to improve cardiac function and reduce both the decrease in intracellular pH and ATP content (3,7). TMZ has been reported to reduce the pro-tein accumulation in myocardium during the is-chaemia-reperfusion process (15).

The objective of our study was to assess the effect of TMZ on inflammatory response to acute myocardial in-farction and to elucidate if TMZ can reduce interleukin and adhesion molecule production. Therefore, plasma C-reactive protein, IL6, IL, 6, IL 8, TNFα and soluble adhesion molecule levels were measured in the course of 96 hours AMI.

Material and methods

1. Study population

The study subjects consisted of eighteen patients with AMI (16 men and 2 women; mean age 56.45 years, ranging from 39 to 71 years) who were admitted within 6 h after the onset of the symptoms. They were treated by thrombolytic (streptokinase) therapy and randomised blindly, through a centralized randomisation process, to a trimetazidine or placebo group. The TMZ group consisted of 5 men and 1 woman (mean age 55.06 years ± 11.11 years) the placebo group had 11 patients (10 men, 1 woman, mean age 57.18 years ± 11.57 years). There were no significant differences between the two groups. Table No.1 shows the characteristics of study population. In the second week some of them underwent coronary arteriography.

Inclusion criteria

The diagnosis of suspected myocardial infarction was based on the following two criteria:

- A typical thoracic pain occurring within the previous 6 hours, prolonged (more than 30 minutes) or for less than 30 minutes, but still present and resistant to sublingual nitrates

- A typical ECG tracing with 2 mm or greater ST segment ele-vation in at least two leads or atypical but with highly pro-bable previous history of coronary disease.

All patients had a confirmed diagnosis of AMI by bio-chemical changes (elevation of the serum creatine kinase and MB isoenzyme level more than twice the normal upper limit).

Exclusion criteria were serious renal or liver failure, pregnancy, patients having taken TMZ within the last 48 hours, patients treated with established or experimental anti-oxidants, patients treated with fibrinolytic therapy within the last 24 hours, successful revascularisation, serious systemic connective tissue diseases, acute and inflammatory disor-ders, refusal of the informed consent.

The average time from onset of the symptoms to ad-mission was 146.76 min.

The study protocol was approved by the Ethic Committee of our institution.

2. Treatment of the patients

The TMZ treatment comprised:

- TMZ group – intravenous bolus of 40 mg of TMZ fol-lowed by a continuous TMZ infusion 60 mg/24 hours for 48 hours. The bolus of a 40 mg TMZ was injected intra-venously over 2 minutes before thrombolysis. For the conti-nuous infusion, 6 ml (60 mg of TMZ) was diluted in 5% glucose solution and was administered over 24 hours. A control group received intravenously a placebo with the same regimen.

- Placebo group - received 25 mg of placebo intravenously.

3. Blood samples

The first blood sample was taken immediately after ad-ministration and then at 3 h intervals during the first 48 hours, and at 6 h intervals during the next 48 h. The blood was imme-diately centrifuged; aliquot parts of plasma were stored at -20°C overnight and stored at -70°C until the assessment of the immune parameters the plasma samples. Plasma levels of circulating IL1β, IL6, IL8, ICAM 1 and E-selectin were measured using commercial enzyme-linked immunosorbent assay (ELISA) developed by RD Quantikinine, Minnea-polis, MN, USA. TNFα was measured by using the com-mercial ELISA set purchased from Immunotech, Marseille, France.

4. Biochemical measurements

Serum creatine kinase was measured by Hitachi 704 autoanalyser using diagnostic kits of activated CK-NAC by the enzymatic assessment method developed by Boehrin-ger, Mannheim, Germany. The plasma CRP levels were me-asured by single radial immunodiffusion using antisera USOL Prague, Czech Republic and the Behring standard.

5. Statistical analysis

Data were expressed as mean and standard deviation (SD). Analysis of the differences between patients treated with TMZ and placebo was made by using the analysis of variance (ANOVA) design. The differences were consid-ered to be significant at p values less than 0.05 (p<0.05).

Results

7 patients received TMZ (intravenous bolus of 40mg in 2 minutes, then 60mg TMZ daily in glucose solution for 48 hours), and 11 were treated with placebo. In-hospital ma-nagement is shown in table No.2.

Tab. 2: In-hospital management.

| Variable | TMZ (n 7) | Placebo (n 11) | p |
|----------|----------|---------------|---|
| Coronary angiography (%) | 57.2 | 45.5 | ns |
| PTCA in hospital (%) | 28.6 | 27.3 | ns |
| Beta blockers (%) | 100 | 100 | ns |
| ACE inhibitors (%) | 57.2 | 55.5 | ns |
| Acetylsalicylic acid (%) | 100 | 100 | ns |
| Nitrates (%) | 100 | 100 | ns |
| Diuretics (%) | 42.9 | 45.5 | ns |
| Ca blockers (%) | 28.6 | 27.3 | ns |

Fig. 1: Mean plasma CRP levels (mg/ml) and SD in TMZ (– –) and placebo (– –) groups in the course of 96 hours AMI.

Plasma CRP level (fig. 1)

The plasma CRP level was elevated in both groups. Statistically significant differences were found in the inter-val from 18 to 60 hours after the onset of the symptoms. TMZ group showed a 52% significantly less elevation of the plasma C-RP level than the placebo group, (75.7 mg/ml vs. 39.5 mg/ml at p<0.001). The peak plasma CRP level (76.8 mg/ml ± 34.1mg/ml) of the placebo group occurred 54 hours after onset of the symp-toms as compared peak plasma CRP level of the TMZ group (52.6 mg/ml ± 23.3 mg/ml) which was measured 78 hours after the onset of the symptoms (i.e. 28 hours after the peak of the placebo group).

Plasma TNFα (fig. 2)

The plasma TNFα levels of both groups were elevated throughout the time of the observation, but neither group has shown significant differences. The peak plasma TNFα level of the TMZ group (40.56±6.28 pg/ml) was achieved 60 hours after the onset of the symptoms as compared to the peak of the placebo group (71.1pg/ml ± 60.1pg/ml), which was achieved 90 hours after the onset of the chest pain.

Plasma IL1β (fig. 3)

The plasma IL1β levels were also elevated in both groups. Plasma IL1β levels of the TMZ group were higher almost all of the time during the observation course (except at 96 hour after the onset of the symptoms, when plasma IL1β level of placebo group was only slightly elev-ated). Plasma level elevation of the TMZ group was statistically significant 21 hours after the onset of the symptoms (26.4 pg/ml vs. 9.7 pg/ml, p<0.001).

Plasma IL6 (fig. 4)

Plasma IL6 levels of the TMZ group showed a sharp peak 9 hours after the onset of the symptoms (116.9 pg/ml ± 180.2 pg/ml vs. 45.4 pg/ml ± 37.9 pg/ml, p<0.01). The plasma IL6 level was increased from the beginning of the observation to 30 hours after the onset of the symp-toms.
Trimetazine [TMZ, (1-(2,3,4-trimetoxybenzyl)] pipe-razine dichloride has cytoprotective properties and prevents metabolic disturbances that result from myocardial ischaemia. Its mechanism of action is, at least partially, directly related to the mitochondrial enzymatic systems. TMZ stimulates glucose oxidation by primarily reducing rates of β-oxidation (6), decreasing mitochondrial oxygen demand. TMZ has also been reported to have a protective effect in myocardial ischaemia-reperfusion process by increasing phospholipids turnover of the membrane (13).

After periods of ischaemia it is able to improve cardiac function and reduce both the decrease in intracellular pH and ATP content (3,7). TMZ has been reported to reduce the neutrophil accumulation in myocardium during the ischaemia-reperfusion process (15).

The objective of our study was to assess the effect of TMZ on inflammatory response to acute myocardial in-farction and to elucidate if TMZ can reduce interleukin and adhesion molecule production. Therefore, plasma C-reactive protein, IL-6, IL-1 β, TNFα, and soluble adhesion molecule levels were measured in the course of 96 hours after AMI.

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5. Statistical analysis

Data were expressed as mean and standard deviation (SD). Analysis of the differences between patients treated with TMZ and placebo was made by using the analysis of variance (ANOVA) design. The differences were consid-ered to be significant at p values less than 0.05 (p<0.05).

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Plasma TNFα level (fig. 2)

The plasma TNFα levels of both groups were elevated throughout the time of the observation, but neither group has shown significant differences. The peak plasma TNFα level of the TMZ group (40.5 pg/ml ± 28.7 pg/ml) was achieved 60 hours after the onset of the symptoms as compared to the peak of the placebo group (71.1 pg/ml ± 60.1 pg/ml), which was achieved 90 hours after the onset of the chest pain.

Plasma IL-1β level (fig. 3)

The plasma IL-1β levels were also elevated in both groups. Plasma IL-1β levels of the TMZ group were hig-her almost all of the time during the observation course (except at 96 hour after the onset of the symptoms, when plasma IL-1β level of placebo group was only slightly ele-vated). Plasma level elevation of the TMZ group was statistically significant 21 hours after the onset of the symptoms (26.4 pg/ml ± 11.10 pg/ml vs. 9.7 pg/ml, p<0.001).

Plasma IL-6 level (fig. 4)

Plasma IL-6 levels of the TMZ group showed a sharp peak 9 hours after the onset of the symptoms (116.9 pg/ml ± 180.2 pg/ml vs. 45.4 pg/ml ± 37.9 pg/ml, p<0.01).
Trimetazidine Shifts Cardiac Energy Metabolism From Fatty Acid Oxidation to Intercellular Adhesion Molecule-1 and P-Selectin Mediate Leukocyte Binding to Ischemic Heart in Humans. J Am Coll Cardiol 2000; 36:122-9.

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Belcher PR, Drake-Holland AJ, Noble M. Trimetazidine in the treatment of acute myocardial infarction (AMI). Kardiol Pol 1996;45(suppl IV):15-20.

We examined the effect of trimetazidine on the cytokines, adhesion molecule levels and plasma C-RP levels in the course of AMI treated by streptokinase. We found a significant reduction of the inflammatory response, and intercellular interactions. This observation is compatible with the hypothesis that trimetazidine could reduce the inflammatory response to ischemia also by improving a glucose metabolism in the ischemic area. This process can reduce an inflammatory response, and intercellular interactions. This observation is compatible with the experiment of Williams (15), showing that TMZ inhibits the neutrophil accumulation in the infarcted area.

Extravascular neutrophil migration depends on generation or release of chemoattractants agents and on initial adhesion of leukocytes to vascular endothelium. The latter process is mediated by adhesion molecules expressed on the surface of both neutrophil and endothelial cells. To determine whether trimetazidine affects release of plasma chemoattractant substances and the expression of adhesion molecules, plasma interleukin (IL 6), IL 8, TNFα, IL 6) and adhesion molecules (E-selectin and ICAM 1) levels were examined. Although plasma levels of these cytokines have been elevated throughout the observation period, there was no significant difference in plasma levels of these intercellins and adhesion molecules of patients treated with TMZ compared with subjects on placebo.

In spite of the fact that plasma CK level can reflect the size of myocardial necrosis, we did not find a statistical difference in plasma CK level between the placebo and TMZ group. We also didn’t find strong positive correlation between the plasma C-RP and CK levels.

Furthermore, it is known, that neutrophil accumulation in the ischemic area depends on expression of CD11/CD18 adhesion molecule levels (10) and interleukin 1 beta elicits neutrophil accumulation not through a direct action on the leukocytes, but rather by induced expression of endothelial adhesion molecule 1 (E selectin) and intercellular adhesion molecule 1 (ICAM 1). At this time we have no sufficient explanation for the inhibition of neutrophil accumulation in the infarct site.

Despite the limitations (small number of the patients, and inability to compare the size of the infarcted area), our study has shown the significant effect of trimetazidine on plasma C-RP level, which was lower as compared with the placebo group. The study has also shown that TMZ suppressed neutrophil accumulation is not dependent on plasma chemoattractants such as interleukin 1 beta, interleukin 8 and adhesion molecules.

Acknowledgements

The study was supported by a grant from The Ministry of Health of the Czech Republic, No. 1944-2, and realised with the support of Laboratories Servier.

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Mean plasma CK levels in both groups was achieved 9 hours after the onset of symptoms and reached 31.5 ± 28.5 kat/l/ml in placebo group vs. 26.1 kat/l/ml ± 15.1 kat/l/ml in TMZ group, p non significant. There were no significant differences between the two groups.
Trimetazidine Shifts Cardiac Energy Metabolism From Fatty Acid Oxidation to Intercellular Adhesion Molecule-1 and P-Selectin Mediate Leukocyte Binding to Ischemic Heart in Humans. J Am Coll Cardiol 2000; 36:122-9.

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We examined the effect of trimetazidine on the cytokines, adhesion molecule levels and plasma C-RP levels in the course of AMI treated by streptokinase. We found a significant decrease of plasma C-RP levels and a significant elevation of adhesion molecule levels (E-selectin and ICAM 1) of patients treated with TMZ compared with subjects on placebo. Furthermore, it is known, that neutrophil accumulation in the infarcted area depends on expression of CD11/CD18 adhesion molecules levels (10) and interleukin 1 beta elicits neutrophil accumulation not through a direct action on the leukocyte, but rather by induced expression of endothelial adhesion molecule 1 (E-selectin) and intercellular adhesion molecule 1 (ICAM 1). At this time we have no sufficient explanation for the inhibition of neutrophil accumulation in the infarct site.

Despite the limitations (small number of the patients, and inability to compare the size of the infarcted area), our study has shown the significant effect of trimetazidine on plasma C-RP level, which was lower as compared with the placebo group. The study has also shown that TMZ suppressed neutrophil accumulation is not dependent on plasma chemotaxants such as interleukin 1 beta, interleukin 8 and adhesion molecules.

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Introduction

Several diseases have been described as a cause of osteoporosis, such as diabetes mellitus but its results are uncertain in type 2 diabetes. Osteopenia is more severe when diabetes begins in the pubertal age and the reduction in the bone mineral density is more significant in the first 5 years after the onset of disease. It is reported that demineralization is also related with the level of HbA1c (1,2). Some authors have reported low bone mineral density (BMD) in patients with type 2 diabetes but other studies found normal or higher levels than normal (1).

Giacca et al. found no differences in radial BMD between control subjects and patients with type 2 diabetes (4). Buysschaert et al. reported low BMD values in male patients with type 2 diabetes but normal values in female patients with type 2 diabetes (2). Kraukauer et al. found lower BMD values in type 2 diabetic patients than non-diabetic patients (6).

The aim of this study is to examine the osteoporosis in type 2 diabetes and to ascertain whether it is a condition predisposing to reduced BMD.

Subjects and Methods

We studied 161 post-menopausal diabetic women with mean body mass index (BMI) of 30.17 ± 4.9 SD. The inclusion criteria for the survey were: Diabetes diagnosed at ≥30 years of age and patients who had type 2 diabetes for at least 2 years. We excluded subjects affected by diseases that can influence bone metabolism, history of any systemic diseases, hip and vertebral fracture and subjects treated with insulin and any drug that can interfere with bone turnover.

As a control group, we selected 90 healthy, non-diabetic women of similar age, menopausal age and BMI to diabetic patients. They had no history of any systemic disease, hip and vertebral fracture and drug administration that can interfere with bone metabolism.

In diabetic patients, no subjects had high creatine levels. We studied 161 post-menopausal women with type 2 diabetes and a control group. We examined bone mineral density (BMD) at the lumbar and femoral regions.

Bone mineral density was assessed using the DXA technique (hologic QDR 4500). Our results are expressed as BMD (g/cm²) and T score. The serum levels of calcium, phosphorus, total alkaline phosphatase (ALP) and osteocalcin, in the serum. We also evaluated calcium (mg) in the 24-h urine sample collected in the morning after an overnight fast.

The levels of the following markers of the bone remodeling were measured: Calcium, phosphorus, total alkaline phosphatase (ALP) and osteocalcin, in the serum. We also evaluated calcium (mg) in the 24-h urine sample collected in the morning after an overnight fast.

The two groups were similar for physical activity and no history of smoking and previous history of hormone therapy. Patients with clinically relevant scoliosis or ectopic calcification were excluded.

RESULTS

The comparison of bone mineral density between the diabetic and control groups, is shown in Table 1. Lumbar and femoral bone mineral density were significantly reduced in diabetic patients compared to controls (1.2).

The relationship between type 2 diabetes and osteoporosis has not been well established. We studied a population composed of 161 post-menopausal women with type 2 diabetes and a control group. We examined bone mineral density with the dual energy X-ray absorptiometry (DXA) technique at the lumbar and femoral regions and in a subgroup of patients, we also measured the levels of markers of bone remodeling. We found significantly higher levels of bone mineral density at the lumbar and femoral levels in the diabetic subjects compared with the control group. Moreover, we found higher level of urinary calcium in the controls. On the basis of these results, we suggest that osteoporosis cannot be considered a complication of type 2 diabetes.

Summary:
The relationship between type 2 diabetes and osteoporosis has not been well established. We studied a population composed of 161 post-menopausal women with type 2 diabetes and a control group. We examined bone mineral density with the dual energy X-ray absorptiometry (DXA) technique at the lumbar and femoral regions and in a subgroup of patients, we also measured the levels of markers of bone remodeling. We found significantly higher levels of bone mineral density at the lumbar and femoral levels in the diabetic subjects compared with the control group. Moreover, we found higher level of urinary calcium in the controls. On the basis of these results, we suggest that osteoporosis cannot be considered a complication of type 2 diabetes.

Key words: Type 2 diabetes; Denisitometry; Osteoporosis

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