EFFECT OF NICORANDIL ON SERUM POTASSIUM LEVELS IN PATIENTS WITH CORONARY ARTERY DISEASE.

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ABSTRACT: ***Nicorandil is an antinational drug, which has both nitrate-like and ATP-sensitive potassium (K-ATP) channel activator properties. Activation of potassium channels by nicorandil causes expulsion of potassium ions into the extracellular space leading to membrane hyperpolarization, closure of voltage-gated calcium channels and finally vasodilation. However, on the other hand, being an activator of K-ATP channel, it can expel potassium ions out of the cells and it can cause hyperkalemia. This review is to investigate the effect of nicorandil on serum potassium levels and to determine the beneficial effects of nicorandil in coronary artery disease patients.***

KEYWORDS: ***Nicorandil, Coronary artery disease, Potassium, Hyperkalemia.***

I. INTRODUCTION

Nicorandil is an arterial vasodilator having cardio protective properties via action of ATP sensitive potassium (K+ATP) channels. It is used as an antinational agent and coronary vasodilator due to its nitrate- like and K+ATP channel activator properties. In humans, the nitrate action of nicorandil dilates the large coronary arteries at low plasma concentrations. At high plasma concentrations, nicorandil reduces coronary vascular resistance, which is associated with increased K+ATP channel opening.

Potassium is a mineral as well as an electrolyte, which means it has an electrical charge. The normal serum potassium level ranges from 3.5-5mmol/L. If the potassium level in the blood is high, the electrical signal it carries can lead to changes in the heartbeat called arrhythmias. If arrhythmias become severe, they can change the heart's pumping action to such an extent that normal blood flow is interrupted, which can lead to sudden cardiac arrest.

Activation of potassium channels by nicorandil causes expulsion of potassium ions into the extracellular space leading to membrane hyperpolarization, closure of voltage gated calcium channels and finally vasodilation. However, excessive activation of K+ATP channel, it can expel potassium ions out of the cells and cause Hyperkalemia. In ATP depleted patients with simultaneous use of potassium channel openers can cause channel dysfunction for a prolonged period leading to intractable hyperkalemia.

Coronary Artery Disease can be classified into two : Acute Coronary Syndrome and Stable Angina. Coronary Artery Disease (CAD) can occur due to the deposition of plaques in the innerwall of arteries that supply blood to heart muscles (Atherosclerosis). Thus blood flow gets restricted and can lead to ischemia followed by angina, heart attack and heart failure. The elevated levels of serum potassium are closely associated with the severity of coronary artery lesions.

Since nicorandil is a potassium channel agonist, it should be taken into consideration that there can be changes in serum potassium levels.

II. REVIEW OF LITERATURE

[1] Shigeo Horinaka, MD et al; (2010) conducted a study about effects of nicorandil on cardiovascular events in japanese patients with coronary artery disease. It was multicenter collaborative prospective observational study of a large cohort of coronary artery disease patients. The effect of nicorandil on outcome was examined. In total, 2,558 patients with nicorandil treatment and controls subjected to propensity score matching were eligible among 13,812 patients registered in the JCAD study. The mean follow-up interval was 2.7 years. The primary endpoint, death from all causes, was significantly lower, by 35% (hazard ratio 0.65,P=0.0008), in the nicorandil group than in the control group. There were also significant reductions in secondary endpoints, including cardiac death (56%), fatal myocardial infarction (56%), cerebral or vascular death (71%), and congestive heart failure (33%) in the nicorandil group, with no excess of deaths from other non-cardiovascular causes. Treatment with nicorandil reduced the number of deaths from all causes to a similar extent with or without treatment with sulfonylureas. The reduction in cardiovascular death with nicorandil was large in patients with IHD.

[2] Vivek Chowdhry et al; (2014) conducted a case study on intractable hyperkalemia due to nicorandil induced potassium channel syndrome. This case report was based on a 68 year old male patient with unstable angina, diabetic nephropathy with serum creatinine of 1.6mg/dl was admitted with coronary artery disease. Coronary angiography revealed distal left main 70% stenosis and diffused triple vessel disease with bad target vessels. The patient underwent off-pump coronary artery bypass surgery, and three vein grafts were anastomosed. The surgery was uneventful, and the patient was shifted to the ICU for post-operative recovery with stable hemodynamic and minimal inotropic support. In the ICU, Nicorandil infusion was started to prevent spasm of the small caliber and diffusely diseased native coronary arteries, and low dose aspirin was administered. Despite no sign of low cardiac output, the serum potassium was high around 5.2-5.5 mEq/L. Serial serum potassium estimation had a rising trend and remained persistently high. In order to lower down the serum potassium level, dextrose insulin solution, intermittent furosemide and potassium binding resins were repeatedly tried. Despite all the efforts, serum potassium was persistently high and gradually rose to 6.4mEq/L. Finally, trying to find out the cause of this intractable hyperkalemia we reviewed the patient's drug chart and after thorough discussion, the Nicorandil infusion was stopped. After stopping the nicorandil infusion, the serum potassium started decreasing. After 2

hours of stopping nicorandil infusion, serum potassium decreased to 5.3mEq/L and after 24 hours it became 4.8mEq/L and remained at the safer level thereafter. Rest of the course was uneventful. The case study concluded that hyperkalemia should be recognized as one of the rare but potential side effects of Nicorandil.

[3] The Iona Study Group (2002) conducted a study on effect of nicorandil on coronary events in patients with stable angina and the impact of nicorandil in angina randomised trials. In this study 5126 patients were randomly assigned 20mg nicorandil twice daily (n=2565) or identical placebo (n=2561) in addition to standard antianginal therapy. The primary composite endpoint was coronary heart disease death, non-fatal myocardial infarction, or unplanned hospital admission for cardiac chest pain. The secondary endpoint was the combined outcome of coronary heart disease death or nonfatal myocardial infarction. Other outcomes reported include all-cause mortality, all cardiovascular events, and acute coronary syndromes. Mean follow-up was 1·6 years (SD 0·5). Analysis was by intention to treat. There were 398 (15·5%) primary endpoint events in the placebo group and 337 (13·1%) in the nicorandil group (hazard ratio 0·83, 95% Cl 0·72–0·97; p=0·014). The frequency of the secondary endpoint was not significantly different between the groups (134 events [5·2%] vs 107 events [4·2%]; 0·79, 0·61–1·02; p=0·068). The rate of acute coronary syndromes was 195 (7·6%) in the placebo group and 156 (6·1%) in the nicorandil group (0·79, 0·64–0·98; p=0·028), and the corresponding rates for all cardiovascular events were 436 (17·0%) and 378 (14·7%; 0·86, 0·75–0·98; p=0·027). The study showed a significant improvement in outcome due to a reduction in major coronary events by antianginal therapy with nicorandil in patients with stable angina.

[4] Guang Xian Zhao et al; (2016) conducted a study on topic "serum potassium levels are associated with coronary artery lesion severity in coronary artery disease". The above study is to investigate the relation between serum potassium levels and the severity of coronary artery lesions in coronary artery disease (CAD). In this study 799 patients who underwent coronary angiography were selected. Serum potassium levels were measured, and Gensini scores were calculated to evaluate the severity of coronary artery lesions in CAD. The correlation between serum potassium level and Gensini scores was examined by Pearson Correlation analysis. Serum potassium levels were significantly increased in patients with lower ($\leq$ 39 points; 3.90 $\pm$ 0.02 mmol/l, n = 453) and higher ($>$ 39 points; 3.97 $\pm$ 0.02, n = 194) Gensini scores compared with normal controls (3.82 $\pm$ 0.03 mmol/l; $p < 0.05$). Furthermore, serum potassium level of the high-score group was also significantly higher than that of the low-score group ($P < 0.05$). Positive correlation between serum potassium level and Gensini scores in patients with CAD was observed ($r = 0.093$, $P < 0.05$). In addition, the levels of serum potassium in the single-vessel (3.95 $\pm$ 0.03 mmol/L, n = 214), dual-vessel (3.95 $\pm$ 0.03 mmol/L, n = 202), and multiple-vessel (3.94 $\pm$ 0.03 mmol/L, n = 231) groups were significantly higher than that in the normal control group (3.82 $\pm$ 0.03 mmol/L, n = 152; $P < 0.05$). The study demonstrates that elevated levels of serum potassium are closely associated with the severity of coronary artery lesions and the number of disease vessels in CAD patients.

[5] Hung-Hao Lee et al; (2012) conducted a case study on nicorandil induced hyperkalemia in a uremic patient. A uremic case suffering from repeated junctional bradycardia, especially before hemodialysis was selected. After detailed evaluation, nicorandil was suspected to be the cause of hyperkalemia which induced bradycardia. In this study, all other possible etiologies of hyperkalemia such as acidosis, high potassium diet, and other medications were excluded. The hyperkalemia was managed initially by hemodialysis, but extreme elevation of serum potassium level was found soon. After cessation of nicorandil, the serum potassium level did not elevate significantly even before hemodialysis. The study was concluded that, in addition to the anti ischemic benefit, we should be aware of the potential complication in patients receiving potassium channel activator, nicorandil.

[6] Tomohiro Sakamoto MD et al; (2004) conducted a study on effects of nicorandil on endogeneous fibrinolytic capacity in patients with coronary artery disease. In this study the effect of nicorandil on endogeneous fibrinolysis was examined by measuring plasma concentrations of tissue-type plasminogen activator(t-PA) antigen, type-1 plasminogen activator inhibitor(PAI-1) antigen and PAI activity in concecutive 11 patients(7 men and 4 women, mean age 63 years, ranges 41-84 years) with coronary artery disease. Nicorandil (15mg/day) was administered orally to each patient for 2 weeks. Venous blood samples were obtained from each patient before and after the administration of the drug in the early morning before eating. There were no significant changes in the plasma concentration of t-PA(12.4±1.9- 9.8±1.5) or PA-1(26.3±3.9-21.5±4.9) antigens (ng/ml, mean ± SEM) before and after nicorandil administration. On the other hand the plasma activity of PAI (IU/ml, mean ± SEM) decreased significantly after the treatment (12.9 ± 3.2-5.6±1.9, p=0.039). The study was concluded that the whole fibrinolytic capacity and oral administration of nicorandil decreased PAI activity in patients with coronary artery disease. The findings suggest that nicorandil improves the fibrinolytic capacity and may reduce the risk of coronary thrombus formation in such patients.

III. CONCLUSION

Coronary Artery Disease is one of the most common cardiovascular disease in our society. Nicorandil is the drug of choice for coronary artery disease (CAD). This review concluded that, since nicorandil is a potassium channel opener, there will be changes in the serum potassium levels (elevation in potassium levels). So while using nicorandil we should monitor and prevent all potential complications related to elevated serum potassium levels such as arrythmia, metabolic acidosis, AV node block etc.

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