Minireview Paper

Basic pharmacology of N^G -Nitro – L – Arginine Methyl Ester

Abstract

N^G – Nitro- L- arginine methyl ester (L-NAME) is a synthetic drug in which is a quanidino substituted L-arginine analoques. It is a competitive enzyme inhibitor which inhibits nitric oxide production by inhibiting nitric oxide synthase [1].

Key words: L-NAME, Pharmacodynamic, pharmacokinetic, NG- L- arginine, Nitric oxide (NO), Hpertention.

Pharmacokinetics of the NG -Nitro – L – arginine methyl ester

L- NAME is high water soluble compound [2], and it can be administrated by two routs of administration enteral (drinking) rout or parenteral (Intraperitoneal or Intravascular) rout [3, 4 & 5].

In vitro, Krejcy et al 1993 [6] demonstrated that when L-NAME is incubated with blood or plasma, it is metabolized to N^G- L- arginine (L-NOARG or L- NA) in blood and plasma. But when plasma incubated with L-NOARG, the L- NOARG level remains stable over the whole period of the observation. This shows that L- NAME but nearly no L-NOARG enters the cellular blood compartments and therefore in vitro the L- NAME has a wide volume of distribution compared to its metabolite. This observation led researchers to assume that L- NOARG is the active metabolite of L-NAME and nitric oxide synthase may be differently inhibited by L-NA or L-NAME due to their different distribution characteristics. This is proved by the investigation of Avontuur et al 1998 [7], who reported that incubation of L-NAME with plasma & blood in vitro hydrolyzed it to L-NOARG, which is the active inhibitor of nitric oxide synthase enzyme. While in vivo the L-NOARG did not undergo further degradation and it has a half life longer than the L-NAME. The half life of the L-NOARG is about 22.9 hours while the half life of the L-NAME is only 19.2 minutes. The calculated volume of distribution for L-NAME was 0.45 L\ Kg body weight and 1.96 L\Kg body weight for L-NOARG. The renal clearance for L-NOARG was 3.5% of the total body clearance for LNOARG, while L-NAME could not be detected in urine [7].

Pharmacodynamics of L-NAME:-

The effect of L-NAME on some body systems like Gastro-intestinal tract (GIT), reproductive, blood & cardiovascular (CVS) systems have been studied by many investigators. Takeuchi et al 1995 [5] showed that L-NAME has a protective effect against peptic ulcer disease. L-NAME increases bicarbonate ion secretion from the duodenum and this effect can protect duodenal mucosa against acid injury [4]. When L-NAME is administrated in the longitudinal myoenteric plexus of guinea pig ileum, it either completely blocks slow relaxation showing a late contraction, or increases the amplitude of late contraction [4] . Recently L-NAME can be considered as a therapeutic agent for some of gastrointestinal disorder like pancreatitis. Sugiyama et al 2005 [8] showed that both dexamethasone and L-NAME suppress the severity of pancreatitis induced by Caerulein administration and the effect of L-NAME compared with dexamethasone is more potent against mild pancreatitis but less potent against severe pancreatitis [8].

The effect of L-NAME on the reproductive system has been examined by Rueda et al 2004 [3]. They observed in 62 pregnant rat slaughtered on day 6 of gestation, there were significantly lower number of implantation sites observed in the L-NAME group compared to control and spontaneous hypertensive rat groups. Also there was a significant retardation of fetal growth in the L-NAME group when compared with control group. The intrauterine growth retardation was associated with small placental weight in the L-NAME treated groups [3].

Nitric oxide synthase inhibitors L-NAME and N^G momomethyl L- arginine (L-NMMA) increase platelet adhesion and aggregation. Also in an experimental model of uremia , inhibition of nitric oxide synthase by L-NAME restores the increased bleeding time caused by uraemia to normal [9] .

Many researches done on the effects of L-NAME on the CVS They showed that it the L-NAME has great effects on the CVS. Treatment with L-NAME causes a decrease in the heart rate, cardiac output, stroke volume, peak thoracic aortic blood flow, and the total peripheral conductance but the mean arterial pressure increases while there is no change in the central venous pressure [2]. In leukocytopenic patients with severe septic shock, the L-NAME causes an increase in the mean arterial pressure, systemic vascular resistance, and left ventricular stroke work index compared to baseline values [10] . However the cardiac output data were unchanged during the study period. Also L-NAME treatment increases the pulmonary arterial pressure & the pulmonary vascular resistance [11]. Also L-NAME treatment produces hypertension [12] and this effect could be explained by other ways rather than to be through NO deprivation. These ways occur simultaneously with the effects of L-NAME on

the physiological parameter of the heart via NO deprivation like; an inhibition of acetylcholine vasodilatation effect [13], augmentation the effect of alpha adrenoceptor agonist in endotoxin – treated rats [14] and increase the activity of the angiotensin converting enzyme in the aorta due to L-NAME treatment [15].

Adverse effect of L-NAME on the CVS:-

Some of the adverse effects of L-NAME on the CVS are presented by Zibadi et al 2007 [16], L-NAME produce cardiac remolding, dilated cardiomyopathy at compensated state, marked decrease in pro- collagen III alpha one gene expression and a subsequent reduction in cardiac total and cross-linked collagen content. Also recently it has been shown that L-NAME treatment can cause mild focal myocardial degradation [17]. Also L-NAME considerably inhibits DNA synthesis in various myocardial zones and the proliferative activity decreased in all myocardial zones [18].

References

1. Rees DD, Palmer RM, Schulz R, Hodson HF, Moncada S. Characterization of three inhibitors of endothelial nitric oxide synthase in vitro and in vivo. Br J Pharmacol. 1990 ;101:746-52.

2. Gardiner SM, Compton AM, Kemp PA, Bennett T. Regional and cardiac haemodynamic effects of NG-nitro-L-arginine methyl ester in conscious, Long Evans rats. Br J Pharmacol. 1990 ;101:625-31.

3. Carbajo Rueda M, Muñoz Rodríguez M, Fernández Celadilla L. IGF-I, 17beta-estradiol and progesterone in SHR and in rats treated with L-NAME: fetal-placental development. Arch Gynecol Obstet. 2004 ;270:235-9

4. Oztürk H, Dokucu AI, Yağmur Y, Sari I. Effects of supplemental L-arginine on the intestinal adaptive response after massive small-bowel resection in rats. Pediatr Surg Int. 2002 ;18:332-6.

5. Takeuchi K, Ohuchi T, Okabe S. Effects of nitric oxide synthase inhibitor NG-nitro-L-arginine methyl ester on duodenal alkaline secretory and ulcerogenic responses induced by mepirizole in rats. Dig Dis Sci. 1995 ;40:670-7.

6. Krejcy K, Schwarzacher S, Raberger G. Distribution and metabolism of NG-nitro-L-arginine and NG-nitro-L-arginine methylester in canine blood in vitro. Naunyn Schmiedebergs Arch Pharmacol. 1993;347:342-5

7. Avontuur JA, Buijk SL, Bruining HA. Distribution and metabolism of N(G)-nitro-L-arginine methyl ester in patients with septic shock. Eur J Clin Pharmacol. 1998 ;54:627-31.

8. Sugiyama Y, Kato S, Abe M, Mitsufuji S, Takeuchi K. Different effects of dexamethasone and the nitric oxide synthase inhibitor L-NAME on caerulein-induced rat acute pancreatitis, depending on the severity. Inflammopharmacology. 2005;13:291-301.

9. Brunini TM, Yaqoob MM, Novaes Malagris LE, Ellory JC, Mann GE, Mendes Ribeiro AC. Increased nitric oxide synthesis in uraemic platelets is dependent on L-arginine transport via system y(+)L. Pflugers Arch – Eur J physiol. 2003 ;445:547-50.

10. Kiehl MG, Ostermann H, Meyer J, Kienast J. Nitric oxide synthase inhibition by L-NAME in leukocytopenic patients with severe septic shock. Intensive Care Med. 1997 ;23:561-6.

11. Meyer J, Traber LD, Nelson S, Lentz CW, Nakazawa H, Herndon DN, Noda H, Traber DL. Reversal of hyperdynamic response to continuous endotoxin administration by inhibition of NO synthesis. J Appl Physiol. 1992 ;73:324-8.

12. Gokcimen A, Kocak A, Kilbas S, Bayram D, Kilbas A, Cim A, Kockar C, Kutluhan S. Effect of lisinopril on rat liver tissues in L-NAME induced hypertension model. Mol Cell Biochem. 2007 ;296:159-64.

13. Moore PK, al-Swayeh OA, Chong NW, Evans RA, Gibson A. L-NG-nitro arginine (L-NOARG), a novel, L-arginine-reversible inhibitor of endothelium-dependent vasodilatation in vitro. Br J Pharmacol. 1990 ;99:408-12.

14. Guc MO, Furman BL, Paratt JR. Modification of alpha-adrenoceptor-mediated pressor responses by NG-nitro-L-arginine methyl ester and vasopressin in endotoxin-treated pithed rats. Eur J Pharmacol. 1992;224:63-9.

15. Korystova AF, Emel'yanov MO, Kublik LN, Levitman MK, Shaposhnikova VV, Kim YA,Korystov YN. Distribution of the activity of the angiotensin-converting enzyme in the rat aorta and changes in the activity with aging and by the action of L: -NAME. Age (Dordr). 2011. [Epub ahead of print]

16. Zibadi S, Yu Q, Rohdewald PJ, Larson DF, Watson RR. Impact of Pycnogenol on cardiac extracellular matrix remodeling induced by L-NAME administration to old mice. Cardiovasc Toxicol. 2007;7:10-8.

17. Tisljar M, Grabarević Z, Artuković B, Dzaja P, Cenan S, Zelenika TA, Cooper RG, Dinarina-Sablić M. The impact of L-NAME and L-arginine chronic toxicity induced lesions on ascites--pulmonary hypertension syndrome development in broiler chickens. Coll Antropol. 2011;35:547-56.

160 18. Sazonova EN, Pikalova VM, Timoshin SS. Effect of NO synthase
161 inhibitor L-NAME on DNA synthesis in the myocardium of albino rats during
162 early postnatal ontogeny. Bull Exp Biol Med. 2002 ;133:20-2.

163

164