



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

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Authors' contributions

This work was carried out in collaboration between all authors. All authors read and approved the final manuscript.

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ABSTRACT

N^G – Nitro- L- arginine methyl ester (L-NAME) is a synthetic drug in which a guanidino is substituted for L-arginine analogues. It is a competitive enzyme inhibitor which inhibits nitric oxide synthase, hence, decreasing nitric oxide production [1].

Keywords: L-NAME; pharmacodynamics; pharmacokinetic; NG- L- arginine; Nitric Oxide (NO); hypertension.

1. INTRODUCTION

Nitric oxide contributes to the pathogenicity of septic shock [2,3]; human septic shock is often characterized by considerable systemic vasodilation with low vascular resistance and hypotension resistant to treatment with vasopressors [4]. Inhibition of NO production by competitive enzyme inhibitors like NG-Nitro-L-arginine methyl ester (L-NAME) can be used therapeutically to reverse hypotension in patients with severe septic shock [2,3]. Since L-NAME is a synthetic drug for clinical trials, and can be used in the clinical practice. It is crucially important to know the basic pharmacology of this drug.

2. NITRIC OXIDE

Nitric oxide (NO) is an endogenous vasodilator which is responsible for the natural properties of the endothelial – derived relaxing factor (EDRF). It is the endogenous stimulator of the soluble guanylate cyclases. NO is an effector molecule excreted by neurons, endothelial cells and macrophage plus other cells after immunological activation [5]. It is synthesized in vivo from the amino acid L-arginine as precursor by the effect of enzyme called nitric oxide synthase (NOS). There are three different isoforms of the NOS which produced by different genes with quite distinct localization, regulation, catalytic properties and inhibitor sensitivity. These isoforms are neuronal NOS & vascular endothelial NOS which are called the constitutive NOS isoforms (cNOS), and inducible NOS [6,7]. The constitutive NOS isoforms (cNOS) are calcium dependence, and they can be inhibited by the administration of L-NAME [6,7], while the inducible form of the NOSs is calcium independence, and its induction can be inhibited by treatment with glucocorticoids [5].

3. PHARMACOKINETICS OF THE NG - NITRO - L - ARGININE METHYL ESTER

L- NAME is high water soluble compound [8], and it can be administrated by two routs of administration, enteral (drinking) rout or parenteral (Intraperitoneal or Intravascular) rout [9,10,11].

In vitro, Krejcy et al. [12] 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. [13], 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 [13].

4. 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 [11] 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 [10]. When L-NAME is administered 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 [10]. Recently L-NAME can be considered as a therapeutic agent for some of gastrointestinal disorder like pancreatitis. Sugiyama et al. [14] 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 [14].

The effect of L-NAME on the reproductive system has been examined by Rueda et al. [9]. 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 [9].

Nitric oxide synthase inhibitors L-NAME and NG-monomethyl-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 uremia to normal [15].

Research has been done on the effects of L-NAME on the CVS showed that 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 [8]. 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 [2]. However the cardiac output data were unchanged during the study period. Also L-NAME treatment increases the pulmonary arterial pressure & the pulmonary vascular resistance [16]. Also L-NAME treatment produces hypertension [17] 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 [18], augmentation the effect of alpha adrenoceptor agonist in endotoxin-treated rats [19] and increase the activity of the angiotensin converting enzyme in the aorta due to L-NAME treatment [20].

5. 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. [21], L-NAME produce cardiac remodeling, 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 [22]. Also L-NAME considerably inhibits DNA synthesis in various myocardial zones and the proliferative activity decreased in all myocardial zones [23].

Yoshikawa K et al. demonstrates that: In vivo administration of L-NAME to pregnant mice reduces fetal and placental weight [24]. Recently, Guo YX et al. proved that, in vitro administration of L-NAME on goat luteinized granulosa cells; inhibit synthesis of steroid hormone from the luteinized granulosa cells [25]. Furthermore, inhibition of the NO production by L-NAME treatment reduces the expression of mitochondria biogenesis related genes, and increase apoptosis of the luteinized granulosa cells [25].

6. CONCLUSION

This mini review sheds some light on the basic pharmacology of L-NAME, the clinical trials of which are still ongoing. The documented spectrum of L-NAME actions is wide, ranging from effects on various systems to effects on genes of biogenesis.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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