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Review Article

Role of methylxanthines in preventing acute renal failure in hypoxic newborns

Kiran P. Sathe [a,*], Anjali Kulkarni [b]

[a] Pediatric Nephrologist, Dept of Pediatrics, Sir HN Reliance Foundation Hospital, Mumbai, India
[b] Head of Dept, Neonatology and Pediatrics, Sir HN Reliance Foundation Hospital, Mumbai, India

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ABSTRACT

Background: Acute renal failure secondary to perinatal asphyxia is a serious & common problem in developing countries due to lack of appropriate delivery facilities. Under hypoxic conditions, there is an excess of adenosine production, which by its virtue of renal vasoconstriction serves to reduce the glomerular filtration rate. Studies have reported beneficial role of adenosine blockade by methylxanthines in preventing acute oliguric renal failure in hypoxic neonates.

Methods: We reviewed the available literature on pathophysiology of acute renal failure in hypoxic newborns and the therapeutic usefulness of methylxanthines in managing such patients. Well-designed randomized controlled trials evaluating the efficacy of methylxanthines in preventing acute oliguric renal failure were specifically reviewed for the methodology and outcome.

Results: Methylxanthines when used in hypoxic neonates seem to prevent oliguric renal failure. Their use has been associated with increased natriuresis and diuresis in initial hours of life in at risk patients and better outcome. Drug related side effects may be prevented by careful patient selection and drug level monitoring.

1. Introduction

Asphyxia and prematurity are the chief etiologies of acute renal failure in initial days of life.[1] Additional hypoxic insult to the physiologically immature neonatal kidneys endowed with a lower GFR, critically affects the renal function. Infact, kidney is primarily affected in a hypoxic insult and results in oliguria, volume overload and increased risk of mortality. Adenosine plays a central role in mediating the pathophysiology of oliguric renal failure in asphyxiated newborns.[2] Although studies report 3–5% risk of perinatal asphyxia in routine newborn deliveries, this percentage may be even higher in developing resource limited countries with poor maternal delivery facilities in most places. About 30–60% neonates who suffer from perinatal asphyxia develop acute renal failure.[1,3,4] This is a serious problem, as acute renal failure is frequently a part of multi-organ failure in critically ill neonates and can be a deciding factor in the successful management of such patients. Although non oliguric renal failure is more common complication of perinatal asphyxia, oliguric presentation especially carries a bad prognosis in such cases. As a result, till we are successful in reducing the load of unattended

* *Corresponding author*. Block no 8, Bldg. C-3, Suman Nagar, V.N Purav Marg, Chembur, Mumbai 400071, India.
E-mail addresses: kiranpsathe@yahoo.co.in, Kiran.sathe@hnhospital.com (K.P. Sathe).

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neonatal deliveries and perinatal asphyxia, we need to explore methods of avoiding renal failure arising out of perinatal asphyxia. There has been an interest in using methylxanthines as adenosine blocking agents in preventing acute renal failure in such situations. We highlight the mechanisms operating in acute renal failure and review the therapeutic usefulness of methylxanthines published till date.

2. Normal renal physiology and role of adenosine as mediator of tubulo-glomerular feedback

The enormous amount of glomerular filtrate (180 L/day) that is produced daily by the glomerulus is modified by the tubules by the process of tubular reabsorption and secretion so that only a fraction (1%) is ultimately lost as urine. This complex but highly efficient mechanism of concentrating and modifying the composition of urine is facilitated by certain intrarenal anatomical and physiological adjustments. Compared to the highly vascular superficial renal cortex, the deeper cortex and renal medulla physiologically receives lesser blood flow in a counter current fashion. Majority of the salts (Na^+, Cl^-) in the glomerular filtrate are reabsorbed along the proximal tubule and thick ascending limb of loop of Henle (TAL) such that only a small amount reaches the distal tubules. This mechanism helps to conserve the salts in our body and avoids salt wasting and vascular collapse. It also avoids overloading on the distal tubular segments located in deeper layers of cortex and medulla which is endowed with lesser energy reserves as compared to the proximal segments and are physiologically less efficient in this energy dependent salt reabsorption process. The macula densa located at the end of the TAL constantly senses the salinity of the tubular fluid and activates feedback mechanism if excess salt is present in the distal tubular fluid. This feedback mechanism also known as tubule-glomerular feedback (TGF) results in afferent vasoconstriction in superficial cortex thereby decreasing GFR and in effect controlling the salt content in glomerular filtrate. Renin is also simultaneously produced which serves to increase the proximal tubular salt reabsorption and reduce work load on distal tubules.[5]

Of the various mediators proposed, adenosine is the most well studied mediator of this TGF. Levels of adenosine fluctuate in tandem with the salinity of the distal tubular fluid. Adenosine acts via its specialized receptors which are located throughout the body. It is generated intracellularly through hydrolysis of adenosine triphosphate (ATP) under stressful situations such as hypoxia and when the work load on the kidneys increase. Extracellular adenosine is derived from the diffusion of intracellular adenosine through cell membranes. Unlike in other organs where it mediates vasodilation and enhanced blood and oxygen supply in hypoxic-ischemic states; in kidneys it effects afferent vasoconstriction in superficial cortical nephrons, vasodilation in deeper nephrons and thereby destresses the precariously vascular renal medullae. While these effects are a part of normal physiological compensation; exaggerated response leads to renal injury. This is reflected as a drop in urine output and increased creatinine secondary to lowered GFR in pathological conditions. The underlying renal damage is typically acute tubular necrosis secondary to ischemic damage to deeper medullary nephron segments.[5]

2.1. *Adenosine receptors*

The actions of adenosine are mediated via specialized G protein receptors which are believed to be present in all body tissues. While A1 receptors are important in mediating renal afferent vasoconstriction; A2a receptors are involved in regulating coronary blood supply and controlling the neuronal hyperexcitability. A2b receptor agonists induce bronchospasm while A3 receptors mediate anti-inflammatory effects and regulation of coronary blood flow. The neuronal and cardiorespiratory adverse effects related to methylxanthine usage are believed to resulting from non-selective mode of action, thus blocking the adenosine receptors in non-renal tissues.[5,6]

3. Therapeutic rationale for using methylxanthines in hypoxic neonates & the golden hour of life

It is clear from the earlier discussion that adenosine is responsible for renal vasoconstriction induced fall in GFR in hypoxic conditions. Various studies have attempted adenosine blockade using methylxanthines in an effort to prevent renal failure in at risk newborns. Diuretic property of natural methylxanthines such as caffeine and theophylline is known since last century. In addition, these drugs also result in significant natriuresis by blocking proximal tubular NaCl reabsorption and without significantly altering the glomerular filtration and renal blood flow. This property is helpful in eliminating the excess sodium and water content in initial days of life in presence of physiologically low GFR.[5,7] During a hypoxic ischemic insult, initially there is a sharp drop in oxygen and blood flow to the affected organ. There is progressive depletion of cellular energy stores, ultimately resulting in irreversible damage to the cellular architecture. The reperfusion phase which follows the initial ischemic stage by few days, further aggravates the damage by inflammatory and free radical mediated necrosis and apoptosis. Studies have shown that prompt restoration of visceral blood flow by adenosine blockade in the first hour of life after hypoxic delivery will help in preventing the damage during the acute phase as well as the subsequent reperfusion phase. Thus various studies have studied the effects of therapeutic adenosine blockade in first hour of life in such neonates.[8] Theophylline and aminophylline are non-selective adenosine receptor antagonists and this fact has been experimentally exploited in mitigating renal failure in at risk patients. Chief renal indications where methylxanthines have been used include acute renal failure in asphyxiated newborns, preventing renal failure in preterm neonates with respiratory distress syndrome and prevention of contrast nephropathy.[7,9]

3.1. *Clinical studies on use of methylxanthines in hypoxic neonates*

Although there has been an interest in exploring the therapeutic benefit of adenosine blockade in hypoxic-ischemic