

Letter to the Editor

How Really Selective, Renoprotective and Risk-Free is “Low Dose Dopamine”, for the Routine Clinical Use among Oliguric Critically Ill Patients?

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Dear Sir,

The extensive global use of Dopamine as a “renal protective” agent in critically ill patients for the prevention and treatment of acute renal failure (ARF) is based on the selective renal vasodilatation in animal models and human subjects when it is infused at low-dose, the “renal-dose”^[1-3]. Oliguria is generally viewed by many, as a worrying development for acute renal failure (ARF) with adverse outcome, especially in the critically ill patients admitted to Intensive Care Unit (ICU). The perceived useful effects of low-dose dopamine as described in early reports, ranged from increased cardiac output to natriuresis through enhanced renal perfusion, reduced tubular metabolic activity and diuresis, thus preventing and/or treating ARF under conditions of low renal perfusion in ICU settings^[1,2].

The expression ARF vaguely describes a sudden loss of glomerular filtration rate (GFR) with resultant rise in plasma urea and creatinine concentrations mainly manifesting as oliguria. The diagnosis of pre-renal ARF signifies that sufficient restoration of renal circulation will quickly reverse the renal failure. The ARF attributable to poor renal perfusion, not rapidly reversed by re-establishment of circulation, leads to acute tubular necrosis frequently coupled with characteristic histological changes. On the other hand, consistent histological acute tubular necrosis (ATN) is not obligatory, signifying the value of haemodynamic factors in the development and progression of ARF^[3, 4].

Dopamine exerts a composite action on the cardiovascular and renal systems that have wide-ranging actions, making the effects of dopamine infusion very complicated and difficult to interpret. According to current concept of mechanism of action, dopamine stimulates beta₁ adrenoreceptors and increases cardiac index^[5]. High-dose dopamine

interacts with peripheral alpha₁-adrenoreceptors that lead to systemic vasoconstriction^[6,7]. In addition, peripheral dopamine receptors consist of two novel main sub-groups, DA₁ receptors and DA₂ receptors, classified on the basis of synaptic localization^[6-8]. DA₁ receptor related vasodilatation and inhibition of electrolyte transport is mediated by cAMP. DA₂ receptors inhibit aldosterone production in the adrenal gland^[9]. In the inner medulla DA₂ receptor is linked to stimulation of prostaglandin E₂ production, apparently due to stimulation of phospholipase A₂^[10]. The overall function of DA₂ receptors may be actually the opposite of those noted for DA₁ receptor^[10]. Dopamine inhibits proximal tubular Na⁺-K⁺-ATPase via phospholipase C and protein kinase C coupled pathway by stimulation of DA₁ and DA₂ receptors. It also stimulates the proximal tubular Na⁺/H⁺ exchanger thus increasing natriuresis^[11,12]. Dopamine directly stimulates sodium uptake in proximal tubular cells; this suggests that the natriuretic effect of dopamine is due to changes in hemodynamics and distal tubular effects. Dopamine has been postulated to act as an intrarenal natriuretic hormone^[11]. However, De Werra *et al*^[13] suggested that natriuresis requires additional ATP consumption by renal tubular cells, thus enhancing the undesirable tubular metabolic activity and consequent medullary ischemia through altered renal tubular hemodynamics.

In view of the complexity of dopamine's actions it is not surprising that there is an overlap of doses at which a range of effects of dopamine are observed and no dose could in fact be exclusively renal in action. Low-dose dopamine (0.5-3.0 µg/kg/min) infusion in normal human subjects has been reported to enhance renal blood flow (RBF) and GFR by stimulation of DA₁ receptors^[13]. Nonetheless, Vargo *et al*^[14] found no significant

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change in GFR in their recent randomized, controlled, cross-over trials. Hence, the substantiating evidence of low-dose dopamine-induced variation of GFR in man is conflicting. In 1996, Denton et al concluded that renal-dose of dopamine "should not be used for its selective renal vasodilatory effect in patients with ARF until its efficacy is established conclusively"^[15].

Auriculic Anaritide Acute Renal Failure Study^[16] (AAARFS) Group USA, in 1997, conducted a randomized placebo controlled multi-center trial that included 250 patients with ARF to examine the relationship between low-dose dopamine (< 3 µg/kg/min) administration and outcomes of ARF. There were 93 (36%) deaths documented; 52 (20%) required dialysis during 60 days study period despite being on renal dose dopamine. The relative risk (RR) of death associated with dopamine administration was 1.11 [95% confidence interval (95% CI), 0.66 to 1.89] raising uncertainties pertaining to its safety and efficacy. Likewise, NORASEPT II Study^[17] USA (1999), in their controlled, randomized multicenter trial concluded that dopamine 'renal-dose' does not prevent ARF in patients with septic shock and oliguria. More recently, Kellum *et al*^[18] performed a meta-analysis of 58 studies (n = 1019) from 1966 to 2000 including 17 randomized clinical trials (n = 854) and reported that renal-dose dopamine did not prevent mortality (RR, 0.90[0.44-1.83]; p = 0.92), the onset of renal failure (RR, 0.81[0.55-1.19]; p = 0.34) the need for dialysis (RR, 0.83[0.55-1.24]; p = 0.42), and therefore should be eliminated from routine clinical use. Another recent report of a randomized, double blind, placebo controlled, multi-center study carried out, by Australian and New Zealand Intensive Care Society (ANZICS) clinical trial group^[19], in 328 patients admitted to 23 participating ICUs, randomly assigned continuous intravenous infusion of dopamine (2 µg/kg/min) or placebo administered through a central venous catheter (CVC) while in ICU. The patients assigned dopamine (n = 161) and those assigned placebo (n = 163), were similar in terms of baseline characteristics, renal function and duration of trial infusion. No difference between the dopamine and placebo group was found, in peak serum creatinine concentration during the treatment, in the increase from base line to highest value during treatment, in the numbers of patients whose serum creatinine concentration exceeded 300 µmol/L or who required renal replacement therapy. Sixty-nine patients in dopamine group died as well as 66 in the placebo group. The authors concluded that administration of low-dose dopamine by continuous infusion does not confer any protection from renal dysfunction in ICU.

In ICU patients even "low-dose" dopamine infusions have been reported to produce an immediate and intense fall in serum prolactin concentrations in both males and females. An abrupt transitory decrease in T-cell response to concanavalin A stimulation was also reported in patients receiving dopamine^[20]. Van den Berghe *et al*^[20] noted that dopamine's hypophysiotropic property suppresses the circulating concentrations of all anterior pituitary dependent hormones with the exception of cortisol. The different pituitary axes are vital determinants of a normal anabolism and immune function. Constantly augmented serum cortisol concentrations, insulin resistance, blunted prolactin release and attenuated pulsations of growth hormone and leutinizing hormone secretory patterns as well as multiple abnormalities of thyroid axis, represent the endocrine profile of prolong critical illness that is reminiscent of hormone profiles obtained following dopamine administration. For this reason, use of dopamine in critically ill patients with already compromised metabolic and immunologic homeostasis is unlikely to have favorable outcome.

Besides, dopamine accumulates in critically ill patients leading to inappropriately higher plasma levels which could have both, alpha and beta agonist effects, as well as dopamine receptor agonist effect, thus losing its so called 'renal protective' effect^[21]. Tolerance to vasodilatory effect of low dose dopamine in critically ill patients for prevention or treatment of ARF has been demonstrated within 2-3 days of initiating infusion, that further adds to the unpredictability of its pharmacological action^[21].

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