Medical Hypotheses 85 (2015) 874–877

Contents lists available at ScienceDirect

Medical Hypotheses

journal homepage: www.elsevier.com/locate/mehy

A hypothesis on the conflicting results of angiotensin converting enzyme inhibitor in the prevention of contrast-induced nephropathy

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ARTICLE INFO

Article history:
Received 17 June 2015
Accepted 20 September 2015

ABSTRACT

Contrast-induced nephropathy (CIN) is regarded as acute tubular necrosis resulting from the cytotoxicity of contrast media and the medullary hypoxia linking to the interplay of vasoconstriction and vasodilatation. Saline infusion may prevent CIN by inhibiting renin release and thus production of angiotensin II (ANG II), a vasoconstrictor, from angiotensin I (ANG I). Yet the use of angiotensin converting enzyme inhibitor (ACEI) yields conflicting results in the prevention of CIN. We hypothesise that ACEI will be useful for CIN prevention when the saline infusion is insufficient, useless when the saline infusion is sufficient, and counterproductive when the saline infusion is excessive, respectively. When the production of ANG I and thus ANG II is insufficiently inhibited by insufficient saline infusion, ACEI may help prevent CIN by conferring extra inhibition on the production of ANG II from ANG I. The counterproductive effect may result from ACEI blocking the generation of angiotensin 1–7, a potent vasodilator, from angiotensin 1–9 whose precursor, ANG I, is excessively diminished by excessive saline infusion. Clinical data suggest that normal saline infusion at a rate of 1 ml/kg/h for 12 h, 1 ml/kg/h for 6 h, and 2 ml/kg/h for 6 h before and after contrast injection provide sufficient, insufficient, and excessive hydration in the prevention of CIN, respectively. The mainstream guideline is to stop ACEI and provide sufficient hydration for CIN prevention. Alternatively one may continue to have ACEI but the use of normal saline infusion must be limited to 1 ml/kg/h for 6 h before and after contrast injection.

Introduction

Defined as an increase in serum creatinine concentration greater than 25% or 44.2 umol/L (>0.5 mg/dL) within 3 days of intravascular contrast administration in the absence of an alternative aetiology, contrast-induced nephropathy (CIN) is the third leading cause of hospital-acquired renal failure [1,2]. The incidences of CIN are significantly higher in patients with chronic renal insufficiency and diabetes mellitus, e.g. 10% for non-azotaemic patients vs 30% for azotaemic ones; 2% for non-diabetics vs 16% for diabetics, and 38% for those with both diabetes and azotaemia in a centre studying 394 patients in a period of less than 1 year [3,4]. Other risk factors include high osmolar contrast media and a contrast volume of more than 150 ml [5,6].

CIN is regarded as acute tubular necrosis resulting from the cytotoxicity of contrast media and the medullary hypoxia linking to the interplay of vasoconstriction and vasodilatation in the kidney [7–12]. After contrast injection there is a brief period of renal vasodilatation followed by vasoconstriction, which is presumably related to angiotensin II (ANG II), endothelin, adenosine, and reactive oxygen species (ROS) [7,13]. In female Wistar rats there were a significant increase of plasma renin activity and an abrupt rise of renal ROS for at least one hour after injection of ioxitalamate but not ioxaglate, iohexol, or iodixanol [14]. In male Sprague–Dawley rats the levels of plasma atrial natriuretic peptide (ANP) rose abruptly after injection of sodium iothalamate, peaked at 5 min later, and returned to just above the baseline at one hour, meanwhile the plasma endothelin levels peaked at 10–15 min and sustained at 30 min. These were associated with an initial fall in arterial blood pressure that returned to the baseline as plasma ANP levels declined and endothelin levels peaked [15].

In 1981 Eisenberg et al. reported a zero incidence of acute renal failure in 537 patients receiving about 550 ml of normal saline intravenously before angiography and 250 ml of heparinized saline as flush solution during each hour of procedure time [16]. This was very different from the 12% incidence of renal failure in 109 patients receiving 5% dextrose in water at a rate of 80 ml/h during angiography in the other centre where "data seldom indicated volume depletion before or after administration of the contrast

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http://dx.doi.org/10.1016/j.mehy.2015.09.020
0306-9877/

Table 1
Conflicting results of using saline, ACEI, and ARB for CIN prevention.

Investigators	Baseline serum creatinine (mg/dL)	Hydration	Before/after contrast (h)	Hydration and drugs	CIN prevention
Saudan [22]	<1.22	"No specific hydration protocol"	0/–	ACEI, ARB	Better preserved GFR
Li [23]	<2	Normal saline 1 ml/kg/h	6/6	ACEI	Useful
Cirit [24]	1.34 ± 0.20	Normal saline 2 ml/kg/h	6/6	ACEI	Counter-productive
Hashemi [25]	0.98 ± 0.43	Normal saline 60 ml/h	12/12	ACEI	No use, no harm
Shemirani [26]	<1.5	Normal saline 1 ml/kg/h	12/24	ACEI	No use, no harm
Gupta [27]	1.38 ± 0.27	Dextrose saline 1 ml/kg/h	>3/6	ACEI	Useful
Kini [28]	2.08 ± 0.71	Half saline 1 ml/kg/h	6–12/10–12	ACEI	Counter-productive
Dangas [29]	eGFR = 42.1 ± 12.4 (ml/min/1.73 m^2)	Half saline 1 ml/kg/h	12–24/18	ACEI	Counter-productive
Dangas [29]	eGFR = 88.0 ± 21.7 (ml/min/1.73 m^2)	Half saline 1 ml/kg/h	12–24/18	ACEI	Counter-productive

ACEI, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; GFR, glomerular filtration rate; eGFR, estimated GFR.

agent" [17]. Drugs like N-acetylcysteine, diuretics, mannitol, dopamine, antagonists of endothelin and adenosine, theophylline, and other agents have been used to prevent CIN and controversies abound [1]. "Only the administration of peri-procedural isotonic intravenous fluids has shown consistent renoprotection" [18]. This view is widely shared [19,20].

The beneficial effect of saline in the prevention of CIN is attributed to the sodium load on inhibiting the renin–angiotensin–aldosterone system (RAAS) that has been implicated as a potential mediator of vasoconstriction [13,21]. This has been supported by the favourable results from the use of angiotensin converting enzyme inhibitor (ACEI) in some centres but challenged by the counterproductive results elsewhere [18,22–30].

The mainstream guideline for the prevention of CIN is to provide adequate hydration and stop the use of ACEI before contrast injection because of the counterproductive results [24,28,29], although such a guideline may not be applicable to the patients with congestive heart failure or the emergent patients whose ACEI are still in effect.

Table 1 summarizes the conflicting results of using ACEI and various regimens of saline infusion for CIN prevention. We are interested in finding out why there are reports that ACEI is useful for CIN prevention (Table 1) [22,23,27]. Having reviewed the literature, we suggest the following hypothesis in order to explain the controversies.

Hypothesis

ACEI will be useful for CIN prevention when the saline infusion is insufficient, useless when the saline infusion is sufficient, and counterproductive when the saline infusion is excessive, respectively.

Physiological background of the hypothesis

The RAAS tends to induce vasoconstriction and raise blood pressure

Renin is synthesized in the juxtaglomerular granular cells and released in response to decreased salt intake and extracellular fluid volume as well as trauma and stress that increase sympathetic activities. A decrease in arterial blood pressure activates the baroreceptors in the juxtaglomerular cells of the afferent arteriole, which results in decreased stretch, *decreased* intracellular calcium concentration, and *increased* renin release from the granular cells. Angiotensinogen is secreted into the bloodstream by the liver. Renin, a proteolytic enzyme, splits angiotensinogen to form ANG I which is cleaved by the angiotensin converting enzyme (ACE) to produce ANG II [31,32].

Mediated by angiotensin type 1 receptors coupling with G protein, the actions of ANG II include elevating blood pressure by vasoconstriction of systemic arterioles as well as the renal afferent and efferent ones, reducing glomerular filtration rate (GFR) through a decrease in renal medullary blood flow, enhancing sodium and fluid reabsorption, and stimulating aldosterone release from the adrenal cortex to increase sodium chloride and fluid reabsorption in the distal nephron. Activation of ANG II receptors in the brain increases sympathetic outputs, which increases cardiac output and total peripheral resistance, thus contributing to the elevation of blood pressure [31]. ANG II also boosts release of vasopressin from the posterior pituitary gland, which is inhibited by ANP [31,33].

The different effects of ACEI on the RAAS

ACEI induces vasodilatation by curbing the vasoconstriction effect of ANG II through inhibition of its generation from ANG I. Preventing the rapid degradation of bradykinin by ACE, ACEI allows more bradykinin to stimulate the release of endothelium-derived vasodilator mediators such as nitric oxide (NO), endothelium-derived hyperpolarizing factor, and prostacyclin [34].

ACE-related carboxypeptidase (ACE2) is a human homolog of ACE resistant to the action of ACEI [35,36]. With optimal catalytic activity at pH 6.5 and in the presence of 1.0 M sodium chloride, ACE2 converts ANG I to angiotensin 1–9 (ANG 1–9) that can be further hydrolyzed by ACE to form angiotensin 1–7 (ANG 1–7) [35–38]. ANG 1–7 binds to the G protein-coupled receptor Mas, which causes vasodilatation by releasing prostaglandins and activating endothelial NO synthase to help generate NO [39]. ACEI prevents ACE from hydrolyzing ANG 1–9 to ANG 1–7, thus decreasing the levels of ANG 1–7 and the effects of vasodilatation [35,38].

ANP acts against the effects of the RAAS

ANP, a 28-amino acid peptide hormone, is released from the cardiac atrium in response to increased atrial wall tension as in the case of congestive heart failure. Secretion of ANP can also be affected by age, gender, hypoxia, renal function, stimuli of endothelin-A, ANG II and catecholamines, changes of heart rate, and contrast media [15,40–42].