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# Preventing or attenuating amphotericin B nephrotoxicity with dopamine receptor agonists: a literature review

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## Abstract

Nephrotoxicity is generally considered as the most clinically significant and dose-limiting adverse reaction of amphotericin B. Currently, only the clinical effectiveness of salt loading and administering lipid formulations of amphotericin B have been clearly demonstrated to prevent its nephrotoxicity. In this review, we collected the published data related to dopamine receptor agonists in preventing amphotericin B nephrotoxicity. A literature search was conducted by the relevant keywords like ‘‘amphotericin B”, “nephrotoxicity’’, and ‘‘dopamine’’ in databases such as Scopus, Medline, Embase and ISI Web of Knowledge. Four relevant articles were considered. Results of all the 3 experimental studies demonstrated that co-administration of dopamine (0.5-10 µg/kg/min) as continuous intravenous infusion, SK&F R-105058, a prodrug of fenoldopam (10 mg/kg twice daily), orally or fenoldopam, a relatively selective dopamine receptor type 1 agonist, (0.5 or 1 µg/kg/min) as continuous intravenous infusion can at least significantly mitigate the decrease in creatinine clearance caused by amphotericin B. Furthermore, fenoldopam and SK&F R-105058 can also protect against or delay amphotericin B-induced tubular damage. In contrast, the only clinical trial published until now found that simultaneous continuous intravenous infusion of low dose dopamine (3 µg/kg/min) had no beneficial effect on the incidence, severity and time onset of developing amphotericin B-induced nephrotoxicity in autologous bone marrow transplant and leukemia patients. Considering the lack of beneficial effects in different settings such as acute kidney injury of any cause, negative results of the only clinical trial, and risk of significant adverse reactions, continuous intravenous infusion of low dose dopamine (1-3 µg/kg/min) or selective dopamine receptor type 1 agonists (e.g., fenoldopam) currently appears to have no promising clinical role in preventing or attenuating amphotericin B nephrotoxicity.

*Keywords*: Amphotericin B, Nephrotoxicity, Dopamine receptor agonists, Prevention.

## 1.Introduction

Amphotericin B (AmB) was first isolated and introduced for clinical use in 1955 (1). Despite more than 50 years of clinical use of AmB and introduction of newer antifungal agents, it has been considered as one of the main options of antifungal therapy for disseminated, serious and life-threatening mycotic infections. Its broad spectrum of antifungal activity, low rates of resistance, availability, and low cost can be taken into account for AmB persistence in the pharmaceutical market (2). AmB exerts its fungicidal actions through binding to ergosterol, the predominant sterol in the cell membrane of fungi, and altering

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the permeability of the cell by forming pores in the cell membrane. The pore formation results in the leakage of intracellular ions and macromolecules, eventually leading to cell death (1,3). AmB is active against a wide range of yeasts and molds such as *Candida albicans*, *Cryptococcus neoformans*, *Histoplasma capsulatum*, *Blastomyces dermatitidis*, *Aspergillus fumigates*, and mucormycosis. It also has limited activity against the protozoa *Leishmania braziliensis* and *Naegleria fowleri* (3).

Despite its antifungal efficacy, AmB can cause many acute and chronic adverse reactions such as infusion-related reactions (e.g., fever, chills, muscle spasms, vomiting, headache and hypotension), phlebitis, normocytic-normochromic anemia which is mostly mild and reversible, cardiac toxicity (e.g., ventricular tachycardia, hypertension and rare cases of dilated cardiomyopathy), hepatic toxicity (e.g., reversible increase in liver enzymes and bilirubin), neurologic toxicity (e.g., confusion, delirium, tremor, blurred vision and seizure), and nephrotoxicity (1,3).

Nephrotoxicity is generally considered as the most clinically significant and dose-limiting adverse reaction of AmB (4). Major features of AmB-induced nephrotoxicity include increased serum creatinine level, decreased glomerular filtration rate (GFR), urinary potassium wasting and hypokalemia, urinary magnesium wasting and hypomagnesemia, type 1 (distal) tubular acidosis, and nephrogenic diabetes insipidus (2,5,6). Some degree of increase in serum creatinine (Scr) as well as blood urea nitrogen (BUN) have been detected in up to 80% of the patients within the first 2 weeks of AmB administration (7,8). Both events are predominantly dose-dependent and reversible (2). However, about 15% of the affected individuals may require renal replacement therapy such as dialysis (6). Two prospective, observational studies conducted at 2 referral hematology-oncology and stem cell transplantation wards in Tehran, demonstrated that 25.71% and 27.8% of the patients, respectively developed an increase in Scr during their course of AmB treatment (9,10). Another investigation in an adult infectious diseases ward in Tehran reported that 10 out of 13 (76.92%) individuals receiving AmB alone, developed acute kidney injury (AKI). Interestingly, the incidence of AKI in patients given AmB along with another antibiotic including ceftriaxone and/or vancomycin was 86.68%. Ceftriaxone-induced AKI, crystalluria, and frank nephrolithiasis have been reported in the literature (11).

Electrolyte imbalances such as hypokalemia and hypomagnesemia can also occur respectively in 75-90% and 15.3-48.9% of AmB recipients (12,13). Similar to increase in Scr, electrolyte imbalances have been mostly reported to be dose-dependent and reversible. These imbalances can potentially cause life threatening complications such as rhabdomyolysis and arrhythmias especially in patients with underlying cirrhosis, congestive heart failure, diabetes and myocardial infarction (2,12)

Although the pathophysiology of AmB-induced nephrotoxicity has not been completely elucidated yet, but several mechanisms have been described in this regard. These mechanism include: (1) direct vasoconstriction of systemic vessels as well as afferent arteriole; (2) inducing tubule-glomerular feedback (TGF) that causes afferent arteriolar vasoconstriction most likely due to local adenosine release; (3) increasing the permeability of the distal tubule that promotes passive distal potassium as well as magnesium secretion; (4) back-diffusion of secreted hydrogen ions; and (5) reducing the concentrating ability of the kidney secondary to hypokalemia and decrease in the frequency of aquaporin 2 water channels in the collecting duct (2,14-16).

Male gender, high daily dose of AmB (>35 mg/day), high cumulative dose of AmB (>2-5 g), hypovolemia, co-administration of diuretics or corticosteroids, concomitant use of nephrotoxic agents (e.g., aminoglycosides, cyclosporine, foscarnet, acyclovir, cisplatin, ifosfamide), and underlying kidney diseases are identified as probable risk factors of AmB nephrotoxicity (2,15). Some literatures have suggested that patients with 2 or more of the aforementioned risk factors of AmB nephrotoxicity, should not preferably receive AmB (8,17).

Many modalities have been investigated in clinical studies during the past 4 decades to prevent or attenuate AmB nephrotoxicity. These include salt loading (150 mEq/day) before and/or during infusion of AmB, prolonging its duration of infusion (e.g., over 24 hours), co-administration

of osmotic (e.g., mannitol) or potassium-sparing diuretics (e.g., amiloride, spironolactone), co-administration of n-acetyl cysteine, concurrent infusion of renal dose of dopamine, adding AmB to intravenous lipid emulsion, and administration of lipid-based formulations of AmB (e.g., colloidal dispersion, lipid complex, liposomal) (18,20). Among these approaches studied so far, only the clinical effectiveness and safety of salt loading and administering lipid formulations of AmB have been clearly demonstrated (18,19). Using alternative antifungal agents such as the azoles (e.g., voriconazole, posaconazole) and echinocandins (e.g. caspofungin), with proven less nephrotoxicity than conventional AmB, may not be clinically feasible. This may be due to the ineffectiveness of azoles and echinocandins against certain pathogenic fungi (e.g., *Candida krusei* and *Candida parapsilosis*, respectively) (21), their high cost, and limited availability especially in developing countries such as Iran. Most of the above approaches for preventing AmB nephrotoxicity have been critically reviewed in our previous studies (18,19). In the current literature review, we collect and discuss the published and available experimental as well as clinical data pertained to the administration of dopamine receptor agonists, as potential nephroprotective agents, in preventing or mitigating AmB nephrotoxicity.

## 2. Methods

A literature search was performed in the following databases: Scopus, Medline, Embase, Google scholar, Cochrane Central Register of Controlled Trials, and Cochrane Database Systematic Reviews. The initial key words used were as follows: “amphotericin B”, “dopamine”, “dopamine agonists”. Early literature search using these terms yielded more than 30 abstracts. The search was limited by considering the key words including “nephrotoxicity”, “renal toxicity”, “acute kidney injury” “prevention”, and “prophylaxis”. All published English-language clinical trials, prospective or retrospective human investigations, case series, case reports, *in vitro* and experimental (*in vivo*) studies were considered eligible for inclusion. No exclusion criteria regarding publication date, age category of the cohort in clinical studies (e.g., pediatrics versus adults), and article type (e.g., original research article versus letter to the editor or short communication) were considered to select articles. The reference list of published articles was also examined to identify any additional relevant studies. Based on this search strategy, 4 relevant articles including 3 experimental and 1 clinical studies were finally recruited for the current review. According to the US Agency for Healthcare Research and Quality’s definition, the level of scientific evidence of the only recruited clinical study was Ib.

## 3. Results

### *3.1 Experimental studies*

Three studies have focused on the role of dopamine receptor type 1 agonists in preventing and/or ameliorating AmB-induced nephrotoxicity in animal models. The first one was published by Reiner and Thompson in 1979. They divided 45 dogs into four groups including group I: 2.5 mg/kg AmB was given as intravenous infusion at 0.1 mg/kg/min (n=16); group II: 0.5-10 µg/kg/min dopamine was administered as continuous intravenous infusion. At the nadir of renal blood flow, AmB was initiated at the same dosage used in the group I (n=14); group III: Angiotensin II was given at the rate of 1.5 µg/min. Following angiotensin II administration, saralasin, an antagonist of angiotensin II receptor, was injected intravenously at 6-48 µg/kg/min. Angiotensin II was re-administered at the rate of 12 µg/min when saralasin effects became stable. Finally, AmB was given as in group I (n=7); group IV: dopamine was administered at a rate of 7.2 ± 0.5 µg/kg/min. After achieving the maximum renal vasodilation, saralasin was added at a rate of 6 or 12 µg/kg/min. When response to both dopamine and saralasin became stable, AmB was given as in group I (n=8). Studied parameters before and during dopamine, saralasin, and AmB infusion were as follows: renal blood flow, glomerular filtration rate (GFR), urine flow, electrolyte (sodium and potassium) clearance, pulmonary vascular resistance, non-renal systemic vascular resistance, central vein pressure, and cardiac output. In comparison to group I, the effect of AmB in decreasing renal blood flow was significantly lower in group III receiving dopamine plus saralasin (p=0.0000007).

Interestingly, this was also the case when it was compared to groups II and III that received only dopamine (p=0.036) and saralasin (p=0.0072), respectively. The decrease in GFR caused by AmB was significantly lower in dogs concurrently receiving dopamine (p=0.047) or dopamine plus saralasin (p=0.0096) compared to those receiving AmB alone. Unlike groups II and III, the effects of AmB in decreasing urine flow and increasing fractional potassium clearance were significantly lower in group IV (p=0.0247 and p=0.03, respectively). Dopamine alone or dopamine plus saralasin have no significant effects on fractional sodium clearance, renal vascular resistance, non-renal systemic vascular resistance, and cardiac output. Results of this preliminary study demonstrated the role of angiotensin II as a mediator in the development of AmB nephrotoxicity. In this regards, concurrent administration of dopamine-saralasin combination can significantly attenuate some aspects of AmB nephrotoxicity including decrease in renal blood flow, GFR and urine flow and increase in fractional potassium clearance. However, co-administration of dopamine alone, can only ameliorate AmB-induced drop in GFR (22).

In 1991, Brooks *et al*. explored the probable effects of SK&F R-105058, an N-ethyl carbamate ester prodrug of fenoldopam as a selective dopamine receptor type 1 agonist on AmB-induced nephrotoxicity in dogs. Twenty four male mongrel dogs were allocated into 4 groups including vehicle-only (n=5), vehicle-SK&F R-105058 (n=5), vehicle-AmB (n=8), and SK&F R-105058-AmB (n=6). AmB (1 mg/kg/day) was administered intravenously for 3 consecutive days. SK&F R-105058 (10 mg/kg) was given orally twice a day, first dosing 30 min before and the second 6-8 hours after AmB administration. Serum as well as urine levels of creatinine, sodium, potassium and BUN were determined daily during the study. Histological examinations were done on the kidneys of sacrificed dogs at the end of the experiment. Two days after initiating AmB (days 2 & 3), 24-hr creatinine clearance and Scr values were significantly higher and lower, respectively in SK&F R-105058-AmB recipients than animals receiving AmB alone. However, BUN, urine flow, and fractional sodium excretion were comparable between SK&F R-105058-AmB and vehicle-AmB groups. In comparison to vehicle-only group, vehicle-SK&F R-105058 group did not show significant difference in Scr, creatinine clearance, and BUN. Histological findings were in favor of significantly lower tubular damage in SK&F R-105058-AmB than vehicle-AmB group. The authors attributed the protective effects of SK&F R-105058 on AmB nephrotoxicity to dopamine receptor 1-mediated renal vasodilation and the inhibition of TGF. Nevertheless, these nephroprotective effects appeared to be transient and were not sustained beyond 48 hours, probably due to the specific AmB regimen used in the study. Different mechanisms of renal, vascular and tubular dysfunction by AmB and/or aggressive models used in this study can be taken into account as the failure of SK&F R-105058 in providing protection against AmB-induced polyuria and urinary sodium excretion. Data of the current investigation demonstrated that administering fenoldopam prodrug orally can significantly delay and attenuate AmB-induced reduction in creatinine clearance and tubular damage, respectively without altering polyuria and increased fractional sodium excretion caused by AmB in dogs (23).

One year later, the same study group published the results of another investigation about the probable protective effects of fenoldopam on the acute and sub-acute nephrotoxicity of AmB in dogs. In acute AmB nephrotoxicity model, at first fenoldopam was infused at a rate of 1 μg/kg/min intravenously. After 20 minutes, intravenous infusion of 2 mg/kg AmB was initiated at the rate of 0.1 ml/kg/min and kept on for 20 min. The infusion of fenoldopam was continued for the duration of the experiment (over 40 min). Mean arterial pressure, renal blood flow, urine flow, creatinine clearance, and sodium excretion were measured every 40 min for 160 min after the end of AmB infusion. In the sub-acute AmB nephrotoxicity model, fenoldopam was given at 0.5 μg/kg/min as continuous intravenous infusion for 2 days. After 2 days, each dog received a bolus dose of 0.5 mg/kg AmB intravenously every other day over 8 days for a total of 4 doses. Scr and BUN were determined before and on alternate days during AmB administration. In the acute AmB nephrotoxicity model, only at 180 min, creatine clearance was significantly higher

in the fenoldopam than vehicle-treated animals ($p<0.05$). Similarly by 180 min, sodium excretion and urine flow rate significantly increased in fenoldopam recipients compared to the vehicle group. In sub-acute AmB nephrotoxicity model, fenoldopam significantly attenuated Scr and BUN increases caused by AmB over the treatment period ($p<0.05$). However, these protective effects of fenoldopam were only confined to the first two but not after the last two doses of AmB. The authors proposed that fenoldopam lacks direct inhibitory effects on AmB-mediated renal vasoconstriction secondary to TGF. Therefore, the effect of fenoldopam on attenuating AmB-induced decrease in creatine clearance may be related to its ability in activating dopamine receptor type 1 of mesangial cell and inhibiting mesangial cell contraction. Increasing urine flow rate and sodium excretion by fenoldopam can be justified through the dopamine receptor type 1-mediated proximal tubule Na+/K+-ATPase inhibition. In brief, fenoldopam infused intravenously at the rate of 1 and 0.5 µg/kg/min can provide protection against both acute and sub-acute effects of AmB on glomerular and tubular functions, independent of direct reversing renal vasoconstriction (24). Table 1 summarizes the characteristics of the 3 experimental studies assessed dopamine agonists in preventing and/or ameliorating AmB-induced nephrotoxicity in animal models.

### *3.2. Clinical studies*

The first and only clinical trial that evaluated the efficacy of low-dose dopamine for prevention of AmB-induced nephrotoxicity was performed by Camp et al. They randomly assigned 71 autologous bone marrow transplant (BMT) and leukemia patients receiving AmB treatment following cytoreductive therapy either into a group receiving continuous infusion of 3 µg/kg/min dopamine (n=36) or those receiving no dopamine (n=35) in an un-blinded manner. AmB was dosed at 0.5 or 1.0 mg/kg/day based on computerized tomography scan results or positive blood cultures. Each dose of AmB was infused over 2 h and its

Table 1. Characteristics of experimental studies evaluating dopamine agonists in preventing and/or ameliorating amphotericin B-induced nephrotoxicity in animal models.

| Study | Subjects | Dopamine agonist dose, route, and duration of treatment | Studied parameters | Main results |
|---|---|---|---|---|
| Reiner and Thompson (22) | 45 dogs were given 2.5 mg/kg amphotericin B | 0.5-10 µg/kg/min dopamine as continuous intravenous infusion alone or in combination with saralasin before initiating amphotericin B | Renal blood flow, glomerular filtration rate, urine flow, electrolyte clearance | Co-administrating dopamine alonecan only ameliorated amphotericin B-induced decrease in glomerular filtration rate |
| Brooks *et al* (23) | - Fourteen dogs received 1 mg/kg/day amphotericin B alone or in combination with SK&F R-105058<br>- Eleven dogs received SK&F R-105058 alone or in combination with amphotericin B | 10 mg/kg SK&F R-105058, prodrug of fenoldopam, was given orally twice a day, 30 min before and 6-8 hours after amphotericin B administration | Serum as well as urine levels of creatinine, sodium, and potassium, blood urea nitrogen, histological examinations | SK&F R-105058 significantly delayed and attenuated amphotericin B-induced reduction in creatinine clearance and tubular damage without altering polyuria and increased fractional sodium excretion |
| Nichols et al (24) | - Acute nephrotoxicity model: 2 mg/kg amphotericin B for 20 min<br>- Subacute nephrotoxicity model: 0.5 mg/kg amphotericin B every other day over 8 days for a total of 4 doses | - Acute nephrotoxicity model: fenoldopam was infused at 1 µg/kg/min for 40 min<br>- Subacute nephrotoxicity model: 0.5 µg/kg/min as continuous intravenous infusion for 2 days | Renal blood flow, urine flow, creatinine clearance, sodium excretion, serum creatinine, blood urea nitrogen | Fenoldopam provided protection against both acute and subacute effects of amphotericin B on glomerular and tubular functions independent of direct reversal of renal vasoconstriction |

administration was continued daily until improvement seen in clinical status or if the patient was withdrawn from the study. Dopamine was given as a continuous infusion at 3 µg/kg/min beginning at the initiation of the AmB test dose. No patient was given saline boluses. Severity of AmB nephrotoxicity was graded on the basis of modified Southwest Oncology Group toxicity criteria including grade 0: baseline SCr level, grade I: 1.5- to 2.0-fold baseline SCr level, grade II: 2.1- to 2.5-fold baseline SCr level, grade III: 2.6- to 3.0-fold baseline SCr level, and grade IV: ≥3.0-fold baseline SCr level. AmB was given every other day and discontinued if patients developed grade III and IV nephrotoxicity, respectively. Although less patients developed nephrotoxicity (at least grade I) in the dopamine than no-dopamine group (66.7% versus 80%, respectively), this difference was not statistically significant (p=0.20). The rate of grade IV nephrotoxicity was also comparable between dopamine and no-dopamine groups (8.3% and 20%, respectively; p=0.19). In line with these results, the average time to develop each grade of nephrotoxicity did not differ significantly between the two groups. Twelve potential adverse drug reactions were reported including 11 in the dopamine and 1 in the no-dopamine group. These reactions included sinus tachycardia (n=3), hypotension (n=3), concurrent hypotension and sinus tachycardia (n=1), atrial fibrillation (n=1), ventricular tachycardia (n=1), paroxysmal nodal tachycardia (n=1), Raynaud's syndrome (n=1), and concurrent fever, chills, and hypotension (n=1). Results of this study suggested that low-dose (3 µg/kg/min) continuous infusion of dopamine appears to be ineffective in significant reduction of the incidence and severity as well as delaying time to development of AmB nephrotoxicity in BMT and leukemia patients. Furthermore, dopamine therapy was associated with cardiovascular complications (25).

## 4. Discussion

In the kidneys, dopamine is synthesized at the proximal tubule from circulating L-dopa. Furthermore, renal nerve endings also contain dopamine (26). In healthy individuals, dopamine at doses 1-3 µg/kg/min has been demonstrated to selectively dilate the renal vasculature at both afferent and efferent arterioles, increase renal blood flow, and to some extent, GFR and urine output (27,28). Furthermore, by inhibiting Na+-H+ exchanger in the luminal membrane of proximal convoluted tubule along with blocking Na+-K+-ATPase activity in the basolateral membrane of proximal convoluted tubule, medullary thick ascending limb of the Henle loop, and cortical collecting duct, dopamine can induce natriuresis (29). Decrease in the secretion of aldosterone can also contribute to natriuresis caused by dopamine (30).

The use of low-dose or renal-dose of dopamine (≤3 µg/kg/min) to prevent or treat renal dysfunction has been generally accepted by many physicians and surgeons in clinical practice (31). This concept is based on the effectof dopamine in increasing renal blood flow and inducing natriuresis observed in animals and healthy humans (32-34). However, these beneficial effects have not been reproduced in at least one large randomized, controlled, clinical trial (35). In addition, the results of several meta-analyses studies have demonstrated that low-dose dopamine has no clinically significant role in the prevention or treatment of AKI (36-38). It is noteworthy that dopamine can develop several undesirable adverse events. In this regard for example, dopamine even at low doses can cause tachycardia, cardiac arrhythmias, myocardial ischemia and infarction. It can also increase the pulmonary shunt fraction by depressing chemoreceptor responsiveness to carbon dioxide and oxygen in the carotid bodies. Other probable adverse events of low-dose dopamine include gut ischemia and subsequent multisystem organ dysfunction, soft tissue extravasation, inhibition of T-lymphocyte proliferation and immunoglobulin synthesis, promoting lymphocyte apoptosis, and decreasing growth hormone, prolactin, as well as thyrotropin release (31,37). Due to lack of clinical efficacy in large randomized, controlled, clinical trials, drawbacks of most relevant clinical studies with positive results such as small sample size or inadequate randomization, and numerous potentially harmful adverse events, several guidelines such as 2012 Kidney Disease: Improving Global Outcomes (KDIGO) recommends against the use of low-dose dopamine for prevention or treatment of AKI by any cause (1A) (21).

Fenoldopam is a relatively pure and selective dopamine receptor type 1 agonist that has similar hemodynamic renal effects as low dose dopamine including increase in sodium excretion and renal blood flow in healthy as well as hypertensive individuals (39). In contrast to dopamine, fenoldopam lacks systemic α- or β-adrenergic agonistic effects (40). Animal and human studies suggested that fenoldopam may prevent or attenuate the course of AKI in the settings of coronary artery bypass graft or cardiac surgery (41). However, most clinical studies suffer from inadequate statistical power and methodological drawbacks (21). A meta analysis of 16 randomized clinical trials in critically ill patients with or at risk for AKI published up to October 2005 demonstrated that fenoldopam significantly reduces the risk of AKI (odds ratio [OR], 0.43; 95% confidence interval [CI], 0.32 to 0.59; $p<0.001$), need for renal replacement therapy (OR, 0.54; 95% CI, 0.34 to 0.84; $p=0.007$), and in-hospital death (OR, 0.64; 95% CI, 0.45 to 0.91; $p=0.01$) (42). However, the results of this meta analysis should be interpreted cautiously because it has several limitations such as heterogeneity of included patients and lack of consistent criteria for initiating renal replacement therapy. In summary, despite promising findings of pilot studies, considering the fact that there is no data from adequately powered, multicenter, clinical trials along with safety concerns regarding significant hypotension especially in high risk perioperative and critically ill patients, the 2012 KDIGO guideline is not in favor of using fenoldopam to prevent or treat AKI (2C) (21). Furthermore, according to the results of at least two prospective randomized clinical trials (43,44), KDIGO recommends not to use fenoldopam to prevent contrast-induced AKI (1B) (21).

Regarding the major role of TGF in AmB nephrotoxicity, that is mainly related to vasoconstriction and decreased renal blood flow, GFR and consequently, ischemic injury to the kidney (2), increasing renal blood flow and GFR might be a potential intervention in preventing AmB-associated nephrotoxicity. In this regards, Schnermann *et al*. demonstrated that both intravenous and peritubular infusion of dopamine at the rates of 4, 15, 35, and 75 μg/kg/min significantly attenuated TGF in rats (45). Results of all the above 3 experimental studies implicated that co-administrating dopamine (0.5-10 μg/kg/min) as continuous intravenous infusion, prodrug of fenoldopam (10 mg/kg twice daily) orally, or fenoldopam (0.5 or 1 μg/kg/min) as continuous intravenous infusion can at least significantly attenuate AmB-induced decrease in GFR (22-24). Apart from this effect, fenoldopam or its oral prodrug (SK&F R-105058) can also protect against or delay tubular damages caused by AmB (23). The exact mechanisms by which dopamine or fenoldopam exert their nephroprotective effects were not determined in these studies. However, it appears that inhibiting dopamine receptor type 1-mediated proximal tubule $Na^+/K^+$-ATPase, activating mesangial cell dopamine receptor type 1, and inhibiting mesangial cell contraction, rather than direct inhibitory effects on TGF, can partially be taken into account as the protective effects of dopamine or fenoldopam against studied aspects of AmB nephrotoxicity. In contrast to experimental studies, findings of the only relevant clinical trial suggested that continuous intravenous infusion of low dose dopamine (3 μg/kg/min) has no beneficial effects on the incidence, severity, as well as time onset of developing AmB-induced nephrotoxicity (25). The authors of the only relevant clinical trial did not justify these findings. One probable explanation for these different results in experimental and clinical studies is that dopamine, fenoldopam, or fenoldopam oral prodrug were given first for a time period before starting AmB in experimental studies (22-24). While in the relevant clinical trial, dopamine infusion was initiated concurrent with AmB administration (25). Based on the results of the above clinical trial, it can be inferred that dopamine alone at the studied dosage regimen failed to block different pathways (e.g., activating angiotensin II receptor) by which AmB exerts its deleterious effects on the kidney. In this regard for example, administration of dopamine with saralasin, an antagonist of angiotensin II receptor, can significantly attenuate decreasing renal blood flow, GFR and urine flow and increasing fractional potassium clearance caused by AmB compared to dopamine alone that only mitigate AmB-induced GFR decrease (22). Interestingly, a number of studies in animal models of contrast-induced AKI suggested that angiotensin II accentuates both the magnitude

as well as duration of the vasoconstrictive phase and also enhances the generation of reactive oxygen species (46,47). A study by Gupta *et al*. in India, randomized diabetic patients undergoing cardiac catheterization received either captopril 25 mg three times daily for 3 days (starting 1 h prior to contrast administration) or no therapy. A 79% risk reduction of contrast-induced AKI in captopril recipients compared to controls that received no therapy was identified (48). These recent data along with Reiner and Thompson findings, highlight the importance of angiotensin II as a key mediator in the development or aggravation of nephrotoxicity by certain medications such as AmB. It can also be inferred that angiotensin-converting-enzyme inhibitors may have potential nephroprotective actions in the setting of AmB-induced AKI.

In conclusion, limited experimental studies demonstrated that co-administration of dopamine and fenoldopam as continuous intravenous infusion or fenoldopam prodrug orally can significantly ameliorate different aspects of AmB nephrotoxicity such as increase in Scr or decrease in GFR. However, these nephroprotective effects of dopamine have not been yet reproduced in the only clinical trial performed. Considering the lack of beneficial effects in different settings of AKI such as contrast-induced nephropathy, negative results of the only clinical trial, and the risk of significant adverse reactions (e.g., hypotension, ventricular arrhythmia), continuous intravenous infusion of low-dose dopamine (1-3 µg/kg/min) or selective dopamine receptor type 1 agonists (e.g., fenoldopam) currently appears to have no real clinical use and role in preventing or mitigating different aspects of AmB nephrotoxicity.

## Conflict of Interest

None declared.

## 5. References


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