

AKUT BÖBREK YETMEZLİĞİ DENEY HAYVAN MODELLERİ

10 BÖLÜM

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GİRİŞ:

Akut böbrek yetmezliği (ABY), metabolik denge, sıvı dengesi ve elektrolit homeostazı saatler veya günler içerisinde bozan, böbrek fonksiyonlarının ani bozulmasıyla karakterize akut gelişen ve genellikle geçici bir süreçtir. %25-70 mortal seyrederek. Travma, komplike cerrahiler, yoğun bakım hastalarında, kemik iliği transplantasyonu, karaciğer yetmezliği, kardiyak cerrahi geçirecek hastalarda ABY geliştiğinde mortalite riski daha da artmaktadır.¹ Hemodinamik instabilite, hipovolemi, ateroskleroz, diüretik tedavisi, beslenme-sıvı alım bozuklukları, sarılık, diabetes mellitus(DM), hipoksi, iskemi ve reperfüzyon, eklampsi/preeklampsi, sepsis, majör yanıklar ve pankreatit ABY'ye yol açabilen hastalıklardır.² Patofizyolojisine göre 3 tipte sınıflandırılır: prerenal, intrinsek ve postrenal. Prerenal ABY, hipovolemi, şok veya iskemiye bağlı renal perfüzyonun bozulmasına bağlı glomerüler renal filtrasyondaki (GFR) azalmaya bağlı olarak gelişir. İntrinsek renal yetmezlik, glomerül, tübül, böbreği besleyen damarlar, veya interstisyuma meydana gelen hasar sonucu oluşur. İntrinsek yetmezliğin ana nedenleri genellikle iskemi veya nefrotoksik hasara bağlı akut tübül nekrozudur(ATN). Prerenal ABY ve ATN tüm ABY nedenlerinin neredeyse %75'ini oluş-

turur. Post renal akut böbrek yetmezliği, renal toplayıcı sistemde basınç artışına bağlı GFR'yi düşüren ve böbrek yetmezliğine yol açan üreter toplayıcı sistemdeki obstrüksiyon gelişmesi nedeniyle meydana gelir. Rabdomyoliz, çizgili kas yıkımına bağlı olarak ekstrasellüler sıvıya masif myoglobin salınımına bağlı oluşan bir sendromdur. Myoglobinin tübül yapıları tıkaması, nitrik oksit salınımına bağlı intrarenal vazokonstrüksiyonun artması ve hipovolemi meydana gelen ATN'yi daha da şiddetlendirir.¹ Gentamisin gibi antibiyotikler, sisplatin gibi antikanser ilaçları, ifosfamid, radyokontrast madde, non-steroid antiinflamatuvar ilaçlar (NSAİİ), ozmotik değişiklikler, folik asit gibi diette bulunan veya endojen olan ajanlar ABY'ye yol açan faktörlerdir.³⁻⁶ Deneysel ABY hayvan modelleri hipoksik, toksik veya sepsise bağlı olarak gelişen olarak sınıflandırılabilir. Fakat bu durumlar bazen aynı anda görülebileceğinden birbirlerini etkilerler. Mesela dehidratasyon, sisplatin gibi nefrotoksinlerin birikimini arttırdığından renal mikrosirkülasyonun azalmasına yol açar veya hipoksi tübül toksiktir fakat hipoksiye bağlı sekonder gelişen enflamasyon da tübül toksisiteyi artırır. Hipertansiyon, DM, yaşlılık, anemi yine renal medüller hasar yapar, oksijen tüketimini artırır ve renal mikrosirkülasyonu bozar.⁷⁻⁸ Bu

KAYNAKLAR

- Lameire N, Van Biesen W, Vanholder R. The changing epidemiology of acute renal failure. *Nat Clin Pract Nephrol*, 2006, 2, 364–377.
- Jacob R. Acute renal failure. *Indian J Anaesth*, 2003, 47,367–372.
- Muthuraman A, Singla SK, Rana A, Singh A, Sood S. Reno-protective role of flunarizine (mitochondrial permeability transition pore inactivator) against gentamicin induced nephrotoxicity in rats. *Yakugaku Zasshi*, 2011, 131, 437–443.
- Izuwa Y, Kusaba J, Horiuchi M. Comparative study of increased plasma quinidine concentration in rats with glycerol and cisplatin induced acute renal failure. *Drug Metab Pharmacokinet*, 2009, 24, 451–457.
- Mitazaki S, Kato N, Suto M. Interleukin-6 deficiency accelerates cisplatin-induced acute renal failure but not systemic injury. *Toxicology*, 2009, 265, 115–121.
- Muthuraman A, Sood S, Singla SK, Rana A. Ameliorative effect of flunarizine in cisplatin-induced acute renal failure via mitochondrial permeability transition pore inactivation in rats. *Naunyn Schmiedebergs Arch Pharmacol*, 2011, 383, 57–64.
- Efrati S, Berman S, Siman-Tov Y. N-acetylcysteine attenuates NSAID induced rat renal failure by restoring intrarenal prostaglandin synthesis. *Nephrol Dial Transplant*, 2007, 22, 1873–1881.
- Gamal el-din AM, Mostafa AM, Al-Shabanah OA. Protective effect of arabic gum against acetaminophen-induced hepatotoxicity in mice. *Pharmacol Res*, 2003, 48, 631–63
- Lee HT, Jan M, Bae SC. A1 adenosine receptor knockout mice are protected against acute radiocontrast nephropathy in vivo. *Am J Physiol Renal Physiol*, 2006, 290, F1367–F137
- Wan B, Hao L, Qiu Y. Blocking tumor necrosis factor- α inhibits folic acid-induced acute renal failure. *Exp Mol Pathol*, 2006, 81, 211–216.
- Nielsen JB, Andersen HR, Andersen O, et al. Mercuric chloride-induced kidney damage in mice: time course and effect of dose. *J Toxicol Environ Health* 1991;34:469-83
- Cheng CW, Rifai A, Ka SM, et al. Calcium-binding proteins annexin A2 and S100A6 are sensors of tubular injury and recovery in acute renal failure. *Kidney Int* 2005;68:2694-703
- Zager RA, Johnson AC, Naito M, et al. K. Maleate nephrotoxicity: mechanisms of injury and correlates with ischemic/hypoxic tubular cell death. *Am J Physiol* 2008;294:F187-97
- Porter GA, Bennett WM, Gilbert DN. Unrevealing aminoglycoside nephrotoxicity using animal models. *J Clin Pharmacol* 1983;23:445-52
- Morin NJ, Laurent G, Nonclercq D, et al. Epidermal growth factor accelerates renal tissue repair in a model of gentamicin nephrotoxicity in rats. *Am J Physiol* 1992;263:F806-11
- Mathew TH: Drug-induced renal disease. *Med J Aust*, 1992, 156, 724–728.
- Selby NM, Shaw S, Woodier N. Gentamicin-associated acute kidney injury. *Q J Med*, 2009, 102, 873–880.
- Susser Z, Raveh D, Yinnon AM. Safety of once daily aminoglycosides in the elderly. *J Am Geriatr Soc*, 2000, 48, 857–859.
- Erdem A, Gundogan NU, Usubutun A. The protective effect of taurine against gentamicin-induced acute tubular necrosis in rats. *Nephrol Dial Transplant*, 2000, 15, 1175–1182.
- Xie Y, Nishi S, Iguchi S et al. Expression of osteopontin in gentamicin-induced acute tubular necrosis and its recovery process. *Kidney Int*, 2001, 59, 959–974.
- Volpini RA, Balbi APC, Costa RS. Increased expression of p38 mitogen activated protein kinase is related to the acute renal lesions induced by gentamicin. *Braz J Med Biol Res*, 2006, 39, 817–823.
- Singh A, Muthuraman A, Jaggi S. A. Animal models of acute renal failure. *Pharmacological Reports*, 2012, 64, 31–44.
- Gülmez A, Çeliker H, Biçim S. Gentamisin ile Oluşturulan Deneysel Nefropati Modelinde Adropinin Terapotik Etkisi *Türk Neph Dial Transpl* 2018; 27 (3): 240-248
- Willox JC, McAllister EJ, Sangster G. Effects of magnesium supplementation in testicular cancer patients receiving cisplatin: a randomised trial. *Br J Cancer*, 1986, 54, 19–23.
- Arany I, Safirstein RL. Cisplatin nephrotoxicity. *Semin Nephrol*, 2003, 23, 460–464.
- Buzzi FC, Fracasso M, Filho VC. New antinociceptive agents related to dihydrosphingosine. *Pharmacol Rep*, 2010, 62, 849–857.
- Kawai Y, Nakao T, Kunimura N. Relationship of intracellular calcium and oxygen radicals to cisplatin-related renal cell injury. *J Pharmacol Sci*, 2006, 100, 65–72.
- Roncal CS, Mu W, Croker B. Effect of elevated serum uric acid on cisplatin induced acute renal failure. *Am J Physiol Renal Physiol*, 2007, 292, 116–122.
- Lee S, Ahn D. Expression of endothelin-1 and its receptors in cisplatin-induced acute renal failure in mice. *Korean J Physiol Pharmacol*, 2008, 12, 149–153.
- Lu LH, Oh DJ, Dursun B. Increased macrophage infiltration and fractalkine expression in cisplatin induced acute renal failure in mice. *J Pharmacol Exp Ther*, 2008, 324, 111–117.
- Ajith TA, Abhishek G, Roshny D. Co-supplementation of single and multi doses of vitamins C and E ameliorates cisplatin-induced acute renal failure in mice. *Exp Toxicol Pathol*, 2009, 61, 565–571.
- Aleksunes LM, Augustine LM, Scheffer GL. Renal xenobiotic transporters are differentially expressed in mice following cisplatin treatment. *Toxicology*, 2008, 250, 82–88.
- Liu M, Chien CC, Burne-Taney M. A pathophysiologic role for T lymphocytes in murine acute cisplatin nephrotoxicity. *J Am Soc Nephrol*, 2006, 17, 765–774.
- Brown JR, Thompson CA. Contrast-induced acute kidney injury: The at-risk patient and protective measures. *Curr Cardiol Rep*, 2010, 12, 440–445.
- Erley CM, Heyne N, Burgert K. Prevention of radiocontrast-induced nephropathy by adenosine antagonists in rats with chronic nitric oxide deficiency. *J Am*

- Soc Nephrol, 1997, 8, 1125–1132.
36. Yen HW, Lee HC, Lai WT. Effects of acetylcysteine and probucol on contrast medium-induced depression of intrinsic renal glutathione peroxidase activity in diabetic rats. *Arch Med Res*, 2007, 38, 291–296.
 37. Colbay M, Yuksel S, Uslan I. Novel approach for the prevention of contrast nephropathy. *Exp Toxicol Pathol*, 2010, 62, 81–89.
 38. Lee HT, Jan M, Bae SC. A1 adenosine receptor knockout mice are protected against acute radiocontrast nephropathy in vivo. *Am J Physiol Renal Physiol*, 2006, 290, F1367–F1375.
 39. Agmon Y, Peleg H, Greenfeld Z. Nitric oxide and prostanoids protect the renal outer medulla from radiocontrast toxicity in the rat. *J Clin Invest*, 1994, 94, 1069–1075.
 40. Chen N, Aleksa K, Woodland C.N-Acetylcysteine prevents ifosfamide induced nephrotoxicity in rats. *Br J Pharmacol*, 2008, 153, 1364–1372.
 41. Badary OA: L-Histidinol attenuates Fanconi syndrome induced by ifosfamide in rats. *Exp Nephrol*, 1999, 7, 323–327.
 42. Zhang J, Lu H: Ifosfamide induces acute renal failure via inhibition of the thioredoxin reductase activity. *Free Radic Biol Med*, 2007, 43, 1574–1583.
 43. Thun MJ, Baker DB, Steenland K. Renal toxicity in uranium mill workers. *Scand J Work Environ Health*, 1985, 311, 83–90.
 44. Avasthi PS, Evan AP, Hay D: Glomerular endothelial cells in uranyl nitrate induced acute renal failure in rats. *J Clin Invest*, 1980, 65, 121–127.
 45. Fleck C, Scholle T, Schwertfeger M. Determination of renal porphyrin handling in rats suffering from different kinds of chronic renal failure (CRF): Uranyl nitrate (UN) induced fibrosis or 5/6-nephrectomy (5/6NX). *Exp Toxic Pathol*, 2003, 54, 393–399.
 46. Choi YH, Lee I, Lee MG: Slower clearance of intravenous metformin in rats with acute renal failure induced by uranyl nitrate: contribution of slower renal and nonrenal clearances. *Eur J Pharm Sci*, 2010, 39, 1–7.
 47. Zimmermann HD, Schmidt E, Weller E. Intra- and extra renal vascular changes in the acute renal failure of the rat caused by mercury chloride. *Virchows Arch A Pathol Anat Histol*, 1977, 372, 259–285.
 48. Yoneya R, Ozasa H, Nagashima Y. Hemin pretreatment ameliorates aspects of the nephropathy induced by mercuric chloride in the rat. *Toxicol Lett*, 2000, 116, 223–229.
 49. Ewald KA, Calabrese EJ: Lead reduces the nephrotoxicity of mercuric chloride. *Ecotoxicol Environ Saf*, 2001, 48, 215–218.
 50. Sheehan PJ, Meyer DM, Sauer MM. Assessment of the human health risks posed by exposure to chromium-contaminated soils. *J Toxicol Environ Health*, 1991, 32, 161–201.
 51. Khan MR, Siddiqui S, Parveen K. Nephroprotective action of tocotrienol-rich fraction (TRF) from palm oil against potassium dichromate (K₂Cr₂O₇)-induced acute renal injury in rats. *Chem Biol Interact*, 2010, 186, 228–238.
 52. Wan B, Hao L, Qiu Y et al. Blocking tumor necrosis factor- α inhibits folic acid-induced acute renal failure. *Exp Mol Pathol*, 2006, 81, 211–216.
 53. Hamazaki S, Okada S, Ebina Y. Acute renal failure and glucosuria induced by ferric nitrilotriacetate in rats. *Toxicol Appl Pharmacol*, 1985, 77, 267–274.
 54. De-Rosa CT, Johnson BL, Fay M. Public health implications of hazardous waste sites: findings, assessment and research. *Food Chem Toxicol*, 1996, 34, 1131–1138.
 55. Reddy RN, Latendresse JR, Mehendale HM. Colchicine antimetabolism causes progression of S-(1,2-dichlorovinyl)-L-cysteine-induced injury leading to acute renal failure and death in mice. *Toxicology*, 2006, 220, 147–159.
 56. Curry SC, Chang D, Connor D: Drug-and toxin-induced rhabdomyolysis. *Ann Emerg Med*, 1989, 18, 1068–1084.
 57. Savic V, Vlahovic P, Djordjevic V. Nephroprotective effects of pentoxifylline in experimental myoglobinuric acute renal failure. *Pathologie Biologie*, 2002, 50, 599–607.
 58. Ghosh J, Das J, Manna P, Sil PC. Acetaminophen induced renal injury via oxidative stress and TNF- α production: therapeutic potential of arjunolic acid. *Toxicology*, 2010, 268, 8–18.
 59. Palani S, Kumar RP, Kumar BS. Effect of the ethanolic extract of *Indigofera barberi* (L.) in acute acetaminophen induced nephrotoxic rats. *New Biotechnol*, 2009, 25, S14–S14.
 60. Cekmen M, Ilbey YO, Ozbek E. Curcumin prevents oxidative renal damage induced by acetaminophen in rats. *Food Chem Toxicol*, 2009, 47, 1480–1484.
 61. Kheradpezhoh E, Panjehshahin MR, Miri R. Curcumin protects rats against acetaminophen-induced hepatorenal damages and shows synergistic activity with N-acetylcysteine. *Eur J Pharmacol*, 2010, 628, 274–281.
 62. Li C, Liu J, Saavedra JE. The nitric oxide donor, V-PYRRO/NO, protects against acetaminophen induced nephrotoxicity in mice. *Toxicology*, 2003, 189, 173–180.
 63. Spalding DJ, Mitchell JR. Diquat hepatotoxicity in the Fischer-344 rat: the role of covalent binding to tissue proteins and lipids. *Toxicol Appl Pharmacol*, 1989, 101, 319–327.
 64. Lock EA, Ishmael J. The acute toxic effects of paraquat and diquat on the rat kidney. *Toxicol Appl Pharmacol*, 1979, 50, 67–76.
 65. Evans RG, Gardiner BS, Smith BW. Intrarenal oxygenation: unique challenges and the biophysical basis of homeostasis. *Am J Physiol* 2008;295:F1259-70
 66. Yatsu T, Arai Y, Takizawa K. Effect of YM435, a Dopamine DA1 receptor agonist, in a canine model of ischemic acute renal failure. *Gen Pharmacol*, 1998, 31, 803–807.
 67. Damianovich M, Ziv I, Heyman SN. ApoSense: a novel technology for functional molecular imaging of cell death in models of acute renal tubular necrosis. *Eur J Nucl Med Mol Imaging*, 2006, 33, 281–291.
 68. Muthuraman A, Sood S, Gill NS, Arora R. Therapeutic potential of *Emblica officinalis* L. fruit extract on ischemia reperfusion injury induced acute renal failure

- in rat. *Lat Am J Pharm*, 2010, 29, 1208–1214
69. Baker RC, Armstrong MA, Young IS. Methyl prednisolone increases urinary nitrate concentrations and reduces subclinical renal injury during infrarenal aortic ischemia reperfusion. *Ann Surg*, 2006, 244,821–826.
 70. Susa D, Mitchell JR, Verweij M. Congenital DNAREpairdeficiency results in protection against renal ischemia reperfusion injury in mice. *Aging Cell*, 2009, 8, 192–200.
 71. Koch M, Broecker V, Heratizadeh. Induction of chronic renal allograft injury by injection of a monoclonal antibody against a donor MHC Ib molecule in a nude rat model. *Transpl Immunol* 2008;19:187-91
 72. Heyman S., Rosen S., Rosenberg C. Animal models of renal dysfunction: acute kidney injury. *Expert Opin. Drug Discov.* (2009) 4(6):629-641
 73. Yang Q, Liu D, Long Y. Acute renal failure during sepsis: Potential role of cell cycle regulation. *J Infect*, 2009, 58, 459–464
 74. Johannes T, Ince C, Klingel K. Iloprost preserves renal oxygenation and restores kidney function in endotoxemia-related acute renal failure in the rat. *Crit Care Med*, 2009, 37, 1423–1432.
 75. Nakamura A, Niimi R, Yanagawa Y. Protection from sepsis-induced acute renal failure by adenoviral-mediated gene transfer of β_2 -adrenoceptor. *Nephrol Dial Transplant*, 2010, 25, 730–73
 76. D, May CN, Bellomo R. Vital organ blood flow during hyperdynamic sepsis. *Chest* 2003;124:1053-9
 77. Zhang J, Duarte CG, Ellis S. Contrast medium and mannitol induced apoptosis in heart and kidney of SHR rats. *Toxicol Pathol*, 1999, 27, 427–435.