Herbal Nephropathy

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INTRODUCTION

Herbal medicines and supplements have enjoyed thousands of years of popularity. In fact, their widespread use was confirmed by the Centers for Disease Control and Prevention in a 2002 report stating that roughly one-fifth of US adults use an herbal product as part of their health care.[1] The perceived safety of supplements and appeal for their "natural" ingredients may be some of the factors driving this use.[2] However, only a few such agents have had their efficacy and safety confirmed in rigorous clinical trials. The reality is that adverse effects do exist, including those related to renal toxicity.

There are multiple ways that herbal compound use can result in renal injury, including (A) a direct nephrotoxic effect of the compound or its metabolites, (B) toxicity of the additive compounds and adulterants used in manufacturing the product, (C) the interaction of herbal agents with concomitantly administered drugs, or (D) alterations in body homeostasis that result in nephrotoxic phenomena, such as excessive diuresis, rhabdomyolysis, and nephrolithiasis. Unfortunately, due to a lack of pharmacovigilance involving herbal compounds, the incidence and prevalence of herbal nephropathy is not known. In addition, since supplement doses are typically not adjusted according to a person's underlying renal function, those with altered baseline renal physiology (eg, children, the elderly) are at higher risk of toxicity. This column reviews the commonly used herbs implicated in renal injury and provides a broad overview of renal syndromes that have been reported with use of herbal supplements.

DIRECT NEPHROTOXIC EFFECT

Aristolochic acid (AA) nephropathy is a rapidly progressive renal interstitial fibrosis resulting from exposure to AA (perhaps as an adulterant) in Chinese herbal weight-loss medications. Initially reported from Belgium, AA nephropathy was referred to as the "Chinese herb nephropathy" and eventually attributed to AA exposure.[3] The histopathology is consistent with tubular apoptosis and necrosis with significant interstitial fibrosis. Clinical presentation includes unexplained rise in creatinine, profound anemia, minimal proteinuria, glycosuria, and sterile pyuria. Progression may occur in one of three ways: complete resolution, acute kidney injury (AKI) with subsequent slow progression (1-7 years) to end-stage renal disease (ESRD), or chronic kidney disease with relatively faster progression (< 2 years) to ESRD.[4]

Aristolochic acid nephropathy is also associated with urothelial malignancy,[5] and a cumulative dose of more than 200 grams of AA-containing compounds is thought to be a significant risk factor for its development. Management includes prompt recognition and cessation of AA exposure. Although there is no effective treatment, clinical studies have shown that glucocorticoids can slow, but not stop or reverse, the progression to ESRD. Lifelong surveillance for urothelial malignancies should be initiated in those with AA nephropathy and ESRD, with consideration to bilateral nephroureterectomy in patients undergoing dialysis or renal transplantation.[4]

Other natural substances associated with direct nephrotoxicity include chromium and germanium,[6,7] both trace elements present in plant-based foods, as well as plants such as mushroom, cape aloe, djenkol bean, and cat's claw.[8,9]

NEPHROTOXICITY FROM ADDITIVES AND ADULTERANTS

There have been reports of therapies branded as "herbal" or "natural" that were adulterated with undeclared compounds or heavy metals. There are also reports of Chinese herbal medicines

that have contained several undeclared pharmacological substances,[10] including nonsteroidal anti-inflammatory agents, which have a well-known nephrotoxic potential. Similarly, the presence of heavy metal in traditional Indian Ayurvedic as well as Chinese medicines has been well documented, with resultant nephrotoxicity from mercury, arsenic (AKI with rhabdomyolysis), and lead.[11-13]

TOXICITY FROM DRUG-HERB INTERACTIONS

Hypericum perforatum, a medicinal herb known as St. John's wort, is used as a supplement to help with symptoms of depression. However, it is a potent activator of the cytochrome p450 system of enzymes (cyp450) that accelerates the metabolism—and in turn lowers serum levels—of medications metabolized by this enzyme pathway.[14] Antirejection medications (eg, cyclosporine, tacrolimus) taken after organ transplantation fall in this category, and concomitant use of St. John's wort by kidney transplant patients has been reported to result in lower serum levels of these medications and thus a higher risk of rejection.[15,16] Conversely, grapefruit and chamomile tea inhibit cyp450 enzymes, thereby increasing cyclosporine blood levels and the potential for serious systemic and renal toxicity.[17]

SUPPLEMENT-RELATED NEPHROLITHIASIS

Cranberry supplements are very popular for prevention of recurrent urinary tract infections (UTI). A recent meta-analysis showed benefits of cranberry products in those with recurrent UTIs.[18] However, concerns have been raised that excessive ingestion of cranberry products may result in increased urinary excretion of calcium and oxalate, thus favoring formation of calcium oxalate renal stones.[19]

HERBAL SUPPLEMENTS AND ALTERED HOMEOSTASIS

Use of herbal medicines has been linked to alterations in body homeostasis, eventually leading to nephrotoxic phenomenon. Individual case reports have described patients experiencing rhabdomyolysis and AKI after using various herb-containing products, such as guarana (used in energy supplements because of its high caffeine content),[20] caffeine,[21] licorice,[22] brucine (used in traditional Chinese medicine for pain and inflammation),[23] and wormwood (used for digestive problems).[24]

In addition, many herbal medicinal plants may have diuretic properties.[25] To our knowledge, no direct association between diuresis-induced AKI and use of these herbs has been reported in human subjects; however, such an occurrence remains a distinct possibility. Indeed, a case of lithium toxicity associated with herbal diuretic use has been reported.[26] Although this case does not qualify as a nephropathy per se, it does underscore a very important implication of herbal agents for renal physiology.

Finally, case reports have emerged, mainly from the east, of massive intravascular hemolysis and acute renal failure after ingestion of herbal henna (*Lawsonia inermis*). The etiology of this has been attributed to G6PD enzyme deficiency.[27,28]

HERBAL SUPPLEMENTS AND RISK OF WORSENING RENAL DISEASE

Herbal dietary supplements can negatively affect renal function in patients with pre-existing renal disease. The National Kidney Foundation (NKF) has developed patient information resources, including a list of herbal medications that may be harmful in those with renal disease.[29]

A population-based study of patients from the National Health and Nutrition Examination Survey (NHANES) database indicated that 14% of the herbal supplements reportedly used by patients were potentially harmful; in fact, of the 37 herbs that the NKF identified as harmful in the setting of CKD, 18 were found among supplement ingredients.[30]

DRUGS OF ABUSE

The detrimental effects of commonly abused drugs (eg, nicotine, alcohol, heroin) have been described.[31] Of particular concern is the recent rise of synthetic cannabinoids, herbal blends with varying concentrations of synthetic cannabis analogues used for recreational purposes. Reports of renal toxicity associated with use of these agents have been described.[32]

In summary, the prevalence of herbal medicine-induced nephrotoxicity is likely to increase with the growth of the herbal medicine industry. Physicians should actively seek information from their patients—particularly those with underlying renal morbidity—about their use of herbal medicinal agents.

REFERENCES

1. Barnes PM, Powell-Griner E, McFann K, Nahin RL Complementary and alternative medicine use among adults: United States, 2002. Adv Data. 2004 May 27;(343):1-19.

2. Salamonsen A. Mind the gap! Lay and medical perceptions of risks associated with the use of alternative treatment and conventional medicine. Forsch Komplementmed. 2015;22(1):24-29.

3. Debelle FD, Vanherweghem JL, Nortier JL. Aristolochic acid nephropathy: a worldwide problem. Kidney Int. 2008 Jul;74(2):158-69.

4. Luciano RL, Perazella MA. Aristolochic acid nephropathy: epidemiology, clinical presentation, and treatment. Drug Saf. 2015 Jan;38(1):55-64.

5. Nortier JL, Martinez MC, Schmeiser HH, et al. Urothelial carcinoma associated with the use of a Chinese herb (Aristolochia fangchi). N Engl J Med. 2000 Jun 8;342(23):1686-92.

6. Wani S, Weskamp C, Marple J, Spry L. Acute tubular necrosis associated with chromium picolinate-containing dietary supplement. Ann Pharmacother. 2006 Mar;40(3):563-6.

7. Lück BE, Mann H, Melzer H, et al. Renal and other organ failure caused by germanium intoxication. Nephrol Dial Transplant. 1999 Oct;14(10):2464-8.

8. Nauffal M, Gabardi S. Nephrotoxicity of Natural Products. Blood Purif. 2016;41(1-3):123-9.

9. Jha V, Rathi M. Natural medicines causing acute kidney injury. Semin Nephrol. 2008 Jul;28(4):416-28.

10. Ernst E. Adulteration of Chinese herbal medicines with synthetic drugs: a systematic review. J Intern Med. 2002 Aug;252(2):107-13.

11. Sathe K, Ali U, Ohri A. Acute renal failure secondary to ingestion of ayurvedic medicine containing mercury. Indian J Nephrol. 2013 Jul;23(4):301-3.

12. He H, An R, Hou J, Fu W. Arsenic trioxide induced rhabdomyolysis, a rare but severe side effect, in an APL patient: a case report. Front Med. 2017 Jun;11(2):284-286.

13. Prakash S, Hernandez GT, Dujaili I, Bhalla V. Lead poisoning from an Ayurvedic herbal medicine in a patient with chronic kidney disease. Nat Rev Nephrol. 2009 May;5(5):297-300.

14. Borrelli F, Izzo AA. Herb-drug interactions with St John's wort (Hypericum perforatum): an update on clinical observations. AAPS J. 2009 Dec;11(4):710-27.

15. Mai I, Störmer E, Bauer S, Krüger H, Budde K, Roots I. Impact of St John's wort treatment on the pharmacokinetics of tacrolimus and mycophenolic acid in renal transplant patients. Nephrol Dial Transplant. 2003 Apr;18(4):819-22.

16. Turton-Weeks SM, Barone GW, Gurley BJ, Ketel BL, Lightfoot ML, Abul-Ezz SR. St John's wort: a hidden risk for transplant patients. Prog Transplant. 2001 Jun;11(2):116-20.

17. Nowack R. Review article: cytochrome P450 enzyme, and transport protein mediated herb-drug interactions in renal transplant patients: grapefruit juice, St John's Wort - and beyond! Nephrology (Carlton). 2008 Jun;13(4):337-47.

18. Wang CH, Fang CC, Chen NC, et al. Cranberry-containing products for prevention of urinary tract infections in susceptible populations: a systematic review and meta-analysis of randomized controlled trials. Arch Intern Med. 2012 Jul 9;172(13):988-96.

19. Terris MK, Issa MM, Tacker JR. Dietary supplementation with cranberry concentrate tablets may increase the risk of nephrolithiasis. Urology. 2001 Jan;57(1):26-9.

20. Mansi IA, Huang J Rhabdomyolysis in response to weight-loss herbal medicine. Am J Med Sci. 2004 Jun;327(6):356-7.

21. Carol ML. Hydroxycut weight loss dietary supplements: a contributing factor in the development of exertional rhabdomyolysis in three U.S. Army soldiers. Mil Med. 2013 Sep;178(9):e1039-42.

22. Liew ZH, Lee KG. Liquorice-Induced Severe Hypokalaemic Rhabdomyolysis with Acute Kidney Injury. Ann Acad Med Singapore. 2017 Sep;46(9):354-355.

23. Naik BS, Chakrapani M. A rare case of brucine poisoning complicated by rhabdomyolysis and acute renal failure. Malays J Pathol. 2009 Jun;31(1):67-9.

24. Weisbord SD, Soule JB, Kimmel PL. Poison on line–acute renal failure caused by oil of wormwood purchased through the Internet. N Engl J Med. 1997 Sep 18;337(12):825-7.

25. Wright CI, Van-Buren L, Kroner CI, Koning MM. Herbal medicines as diuretics: a review of the scientific evidence. J Ethnopharmacol. 2007 Oct 8;114(1):1-31.

26. Pyevich D, Bogenschutz MP. Herbal diuretics and lithium toxicity. Am J Psychiatry. 2001 Aug;158(8):1329.

27. Khine YY. Acute Kidney Injury following Ingestion of Henna Leaf Extract: A Case Report from Myanmar. Blood Purif. 2017;44 Suppl 1:41-45.

28. Qurashi HE, Qumqumji AA, Zacharia Y. Acute renal failure and intravascular hemolysis following henna ingestion. Saudi J Kidney Dis Transpl. 2013 May;24(3):553-6.

29. National Kidney Foundation [Internet]. New York, NY: National Kidney Foundation, Inc.; 2019. A to Z Health Guide: Herbal Supplements and Kidney Disease; 2019 [cited 2019 Jul 15]. Available from: https://www.kidney.org/atoz/content/herbalsupp.

30. Grubbs V, Plantinga LC, Tuot DS, et al.; Centers for Disease Control and Prevention CKD Surveillance Team. Americans' use of dietary supplements that are potentially harmful in CKD. Am J Kidney Dis. 2013 May;61(5):739-47.

31. Singh VP, Singh N, Jaggi AS. A review on renal toxicity profile of common abusive drugs. Korean J Physiol Pharmacol. 2013 Aug;17(4):347-57.

32. Gudsoorkar VS, Perez JA Jr. A New Differential Diagnosis: Synthetic Cannabinoids-Associated Acute Renal Failure. Methodist Debakey Cardiovasc J. 2015 Jul-Sep;11(3):189-91.