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EDITORIAL

Pharmacotherapy: Drugs, the Kidney, and Hippocrates

Hippocrates first noted that the urinary output varied with exogenous intake of food and imbibition of liquids.[1] However, despite his insight, Hippocrates could exposit neither the role of normal kidneys in drug metabolism and disposition nor the consequent changes in pharmacokinetics and pharmacodynamics of medicinals that accrued in the face of kidney failure.[2] Certainly, he could not appreciate the fundamental concepts of renal drug elimination including (a) glomerular filtration, (b) active tubular secretion, and (c) passive reabsorption. Furthermore, this father of clinical nephrology neither possessed the investigative tools to elucidate the metabolic matrimony between the liver and kidney that was required of some drugs nor did he understand that drug elimination was more efficiently carried out by the active, organic anion/cation tubular-secretory components of the nephron than by its glomerular counterpart. In fact, the molecular tools required to elucidate the mechanisms of xenobiotic disposal lay centuries ahead and have been developed only recently.

The field of renal pharmacology has been defined by the careers of a relative few. These visionaries appreciated early on that high-level cognizance of pharmacology in chronic kidney disease was a prerequisite to the delivery of high quality medical care. They comprehended that one important consequence of increasing kidney failure was an attendant and escalating exposure to medications, *per se* constant drugging with continual exposure to nephrotoxic agents or drugs that required renal metabolism. The exacerbation of these potentially hazardous scenarios with the superimposition of acute kidney injury compounded matters further.

Early renal pharmacotherapeutic research and clinical practice was built upon the characterizations of renal elimination of an array of drugs. Now, it is eminently clear that the complex, aberrant biochemistry and inflammatory milieu of CKD and other states affect the disposition of drugs in a multitude of ways. Correspondingly, one key focus for research in pharmacotherapy of CKD will be to develop a deeper appreciation of the alterations of metabolism of therapeutic and/or potentially toxic agents. Such understanding will ultimately yield critical knowledge regarding how these changes influence therapeutic efficacy and/or toxicity profiles. Such insight will illuminate, at least in part, why some drugs that are highly efficacious in the general population are less effective, or not at all effective, in patients with CKD. The lack of efficacy of HMG-CoA reductase inhibitors in ESRD would be a point in this regard. Or, is this an example of using a drug in a trial wherein the drug would have not been anticipated to have an effect?

Problems with medication reconciliation and adherence are plentiful in CKD patients, particularly those with ESRD. This is hardly

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surprising given the pharmacopoeiac panoply prescribed, which generally amounts to about 7 to 10 medications per individual.[3] This number is easily achievable when one considers CKD as a complex of disease domains including: (a) hypertension (2 or 3 drugs), (b) CKD-mineral and bone disorder (1 or 2 drugs), (c) metabolic acidosis (1 drug), (d) edema formation (1 or 2 drugs), (e) cardiovascular disease prevention and treatment (1-5 drugs), (f) anemia of CKD (1-2 drugs), (g) diabetes (1-4 drugs), and (h) others. Moreover, the spectrum and number of agents sharply increase in kidney allograft recipients and those suffering from HIV or AIDS, thus compounding the problems of adherence, complications, and drug−drug interactions. In the course of a visit to the clinic, it is highly improbable that even the best patient could recall all that was required of him or her regarding medication changes and potential interactions.

Multiple risk factors, the most common of which is a depressed GFR, predispose to drug-induced kidney injury and/or disease. These factors are under-appreciated and include patient-specific, kidney-related, and drug-related factors that may synergize in a pernicious promotion of damage to vulnerable kidneys.[4] In addition, surreptitious drug-induced kidney damage may accrue through nontraditional acquisition of nephrotoxins, for example, through the Internet. Contemporary and relevant examples of such damage include the use of complementary medicines or herbal remedies such as aristolochic acid and adulterants like melamine.

Preventable events that induce or cause inappropriate medication usage or harm the patient, while a medication(s) is within the control of the patient or the health care professional, constitute prescribing errors, according to the National Coordinating Council for Medication Error Reporting and Prevention.[5] To comply with the Institute of Medicine's recommendation to reduce medication errors and mitigate hazardous drug−drug interactions, while facilitating and maintaining medication adherence, fully automated pharmacy database systems with real-time medication reconciliation must become the reality.[6] Such systems can preclude hazardous drug prescribing and interdict inadvertent drug−drug interactions promptly, in a just-in-time 24/7/365 manner. In addition, pro-active warning systems must be incorporated and wholly integrated into health care systems (and reforms) to provide greater patient safety during the conduction of the multiple drug administration(s) that characterize the CKD patient population.

In this issue, Guest Editors, Drs. Carol Moore and Amy Barton Pai, provide to *Advances in Chronic Kidney Disease* its first ever review of pharmacotherapy. Timely and precise updates regarding relevant issues in renal pharmacotherapy have been judiciously selected to overview the state of the art involving drugs and the kidney. By the end of this issue, one will even more greatly appreciate the intelligence of the renal organs. Not simply confined to filtration function and master balancer, and alchemist of electrolytes, divalent cations and "the acid and the alchaly," the kidneys metabolize drugs in a most profound manner. Nephrologists must appreciate this. Thus, I concur with the charter of our co-captains of the readership for this next-to-last issue of 2010 and their informed heading. Together with them, I say: "All Read Ahead."

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Editor

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