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Early Research on Renal Function and Drug Action

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Abstract

Starting in the 1960's systematic studies of drug action in renal failure found many differences between patients with this condition and metabolically normal people. Impaired excretion of drugs was known much earlier and related to the glomerular filtration rate (GFR). Kunin first tabulated pharmacokinetics of antimicrobials and dosage recommendations for azotemic patients in 1967. Other effects of renal failure on drug action include increases in some pathways of drug metabolism with decreases in others and no change in the rest. Some changes in specific drug distribution, drug-protein binding, and drug sensitivity have also been demonstrated. This knowledge makes the response of an azotemic patient to a specific dose of a specific drug more predictable than before. This predictability makes drug therapy both safer and more effective for azotemic patients.

Following the thalidomide disaster of 1961–2¹, systematic study of adverse drug reactions began. Prior to this time, specific drug-induced diseases such as aplastic anemia and halothane hepatitis were studied but adverse drug reactions, as a topic, was not a subject for medical research. Thalidomide changed that, and epidemiologic techniques developed for infectious disease research were transferred to the study of drug effects.

In 1966, Smith, Seidl, and Cluff reported on adverse events in hospitalized patients and found that people with blood urea nitrogen (BUN) greater than 40 mg/dl (14.3mmol/L) had 2.5 times the number of adverse drug reactions as those whose BUN values were below 20 mg/dl (7.1mmol/L). Other investigators in the 1960's also found that patients with poor kidney function were predisposed to various adverse drug reactions (see the introduction in ref 3). Those observations stimulated research on why people with impaired renal function were predisposed to adverse drug reactions.

It was known at that time that drugs that were excreted unchanged were cleared more slowly in people with poor renal function than in those with normal renal function. Kunin was the first, in 1967, to publish a table of data of antibiotic kinetics in patients including dosage recommendations for patients with renal disease ⁴. Periodically, this table was updated with additional classes of drugs included and published in the *Annals of Internal Medicine* ^{5,6}. Now, dosage recommendations are considered in the official labeling of all new drugs.

In 1970, Dettli, Spring, and Habersang presented their rigorous paper on calculating drug doses in renal failure ⁷. Their contribution was that by knowing the drug elimination rate in normal subjects and uremic patients, one can extrapolate to find the elimination rates for patients with renal function between these extreme values. They used creatinine clearance as their valid measure of renal function and showed how the kinetics of the drug in normal subjects including the fraction eliminated by non-renal mechanisms, and the creatinine clearance of the patient, could be used to calculate the dose. This approach was a big advance over not knowing how to calculate a dose for a drug with both renal and non-renal clearance. Despite, or perhaps because of, the mathematical rigor of Dettli's analyses, his approach did not achieve wide spread use in clinical medicine. When the Cockcroft and

Gault method of calculating creatinine clearance was reported⁸, determining dosage for individual patients was further simplified.

A problem in understanding the information from the epidemiological studies of adverse reactions in the 1960's was that studies showing increased rates of adverse reactions in uremic patients were done in major university hospitals. One could assume that the doctors knew to give low doses of excreted drugs but conventional wisdom was to give full doses of metabolized drugs to azotemic patients if they did not have concurrent liver disease. At that time, little was known about drug metabolism in uremia or whether nonrenal clearance was altered in azotemic patients. To study drug metabolism systematically, one had to classify drugs by their pathways of metabolism and not by their therapeutic use. Then, one could select drugs to probe specific pathways of drug metabolism with the results potentially generalizable to all drugs metabolized by the pathway studied. My first study of drug metabolism in renal failure in 1968 used sulfisoxazole as the test drug since its pathways of elimination, several drug conjugations, were known and it was safe to give to volunteers. Its metabolism was slowed in azotemic patients⁹. Research in 1960's (reviewed in ref 3, chapter 3) found that people who metabolized some drugs slowly metabolized some other drugs slowly as well. I then classified drugs by their pathways of metabolism in 1971 and presented in a table what was known about how renal failure effects drug metabolic pathways in 1974^{3, 10}. At that time the metabolic pathways were classified as oxidation, reduction, syntheses, and hydrolyses. Subsequent research by many investigators expanded the list of drugs studied and subcategorized the metabolic pathways in each of these major groups.

Observations that azotemic patients developed toxicity from the usual loading dose of digoxin led to the finding by Aronson and Grahame-Smith that the volume of distribution of digoxin was reduced in renal failure¹¹. This study showed that pharmacokinetic processes in addition to drug elimination could be affected by renal failure.

An epileptic patient with cessation of seizures with phenytoin concentrations well below the therapeutic range (10–20 mg/L) had impaired drug plasma protein binding of phenytoin. This determination led to a systematic study of drug- protein binding in renal failure¹⁰ concluding that protein binding is impaired for drugs that are anionic in renal failure but not for cationic drugs¹¹. A nomogram showing the value for the appropriate therapeutic level of phenytoin for varying degrees of azotemia presented in 1973¹² remains in use today.

Studies of laboratory animals in the 1950's found that azotemia increased sensitivity to barbiturates and bromide, presumable due to an impaired blood-brain barrier. Altered sensitivity to some drugs in azotemia was first shown in humans in 1954 by Dundee and Richards who found in patients having prostatectomy that those with azotimia received less thiopental than those with normal kidney function to achieve the same level of sedation (chapter 4 of ref 3). A study of the dose-response to atropine found a diminished response to atropine in azotemic subjects¹³. Thus drug sensitivity as well as drug disposition is altered in renal failure.

Summary

Starting in the 1960's systematic quantitative studies of drug action in renal failure have found many differences between patients with this condition and metabolically normal people. This was comprehensively reviewed in 1977¹⁴ and many times since. Impaired excretion of drugs was known much earlier and tabulation of dosage recommendations for azotemic patients for some of these drugs began in the 1960s.

Other effects of renal failure on drug action and dose-response or drug concentration-response relationships include effect on drug metabolism, drug distribution, drug-protein binding, and drug sensitivity. All this research has led to making the response of an azotemic patient to a specific dose of a specific drug more predictable than before. Such predictability makes drug therapy both safer and more effective. It has led to the present requirement for learning how impaired renal function effects the response to a new drug before it can be approved and registered for general clinic use.

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References

1. Taussig HB. A study of the German outbreak of phocomelia. The thalidomide syndrome. *JAMA*. 1962 Jun 30;180:1106–1114. [PubMed: 13919869]
2. Smith JW, Seidl LG, Cluff LE. Studies on the epidemiology of adverse drug reactions. V. Clinical factors influencing susceptibility. *Ann Intern Med*. 1966 Oct; 65(4):629–640. [PubMed: 5926386]
3. Reidenberg MM. *Renal Function and Drug Action*. Philadelphia: W.B. Saunders Co; 1971.
4. Kunin GM. A guide to use of antibiotics in patients with renal disease. *Ann Intern Med*. 1967 Jul; 67(1):151–158. [PubMed: 6028645]
5. Bennett WM, Singer I, Golper T, Feig P, Coggins CJ. Guidelines for drug therapy in renal failure. *Ann Int Med*. 1977; 86:754–783. [PubMed: 869359]
6. Bennett WM, Muther RS, Parker RA, Feig P, Morrison G, Golper TA. Drug therapy in renal failure: dosing guidelines for adults. *Ann Int Med*. 1980; 93(part 1):62–89. [PubMed: 6994534]
7. Dettli L, Spring P, Habersang R. Drug dosage in patients with impaired renal function. *Postgrad Med J*. 1970 Oct; 46(Suppl on Cephalosporins):32–35. [PubMed: 5412562]
8. Cockcroft DW, Gault MH. Prediction of creatinine clearance from serum creatinine. *Nephron*. 1976; 16(1):31–41. [PubMed: 1244564]
9. Reidenberg MM, Kostenbauder H, Adams WP. Rate of drug metabolism in obese volunteers before and during starvation and in azotemic patients. *Metabolism*. 1969 Mar; 18(3):209–213. [PubMed: 4887616]
10. Reidenberg MM. Kidney disease and drug metabolism. *Med Clin North Am*. 1974 Sep; 58(5):1059–1062. [PubMed: 4608133]
11. Aronson JK, Grahame-Smith DG. Altered distribution of digoxin in renal failure—a cause of digoxin toxicity? *Br. J. Clin. Pharmacol*. 1976; 3:1045–1054.
12. Reidenberg MM, Odar-Cederlöf I, von Bahr C, Borgå O, Sjöqvist F. Protein binding of diphenylhydantoin and desmethylinipramine in plasma from patients with poor renal function. *N Engl J Med*. 1971 Jul 29; 285(5):264–267. [PubMed: 4378402]
13. Reidenberg MM. The binding of drugs to plasma proteins and the interpretation of measurements of plasma concentrations of drugs in patients with poor renal function. *Am J Med*. 1977 Apr; 62(4):466–469. [PubMed: 851114]
14. Reidenberg MM. Effect of disease states on plasma protein binding of drugs. *Med Clin North Am*. 1974 Sep; 58(5):1103–1109. [PubMed: 4607741]
15. Lowenthal DT, Reidenberg MM. The heart rate response to atropine in uremic patients, obese subjects before and during fasting, and patients with other chronic illnesses. *Proc Soc Exp Biol Med*. 1972 Feb; 139(2):390–393. [PubMed: 4550935]
16. Rubin AL, Stenzel KH, Reidenberg MM. Symposium on drug action and metabolism in renal failure: foreword. *Am J Med*. 1977 Apr; 62(4):459–460. [PubMed: 851112]