Dose adjustment of drugs in Libyan patients with renal insufficiency: a study at some hospitals of Tripoli

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Abstract: Drugs that are eliminated primarily by renal excretion would accumulate excessively in patients with renal insufficiency. Undesirable side effects and/or toxicity will be produced unless the dosage regimens are modified. Some hospitals in Tripoli (Libya) were selected to investigate how drug doses being adjusted in patients with renal insufficiency. A total of 798 files were reviewed, data from renal insufficiency patient's files were collected and creatinine clearance was estimated. The results revealed that, the issue of dosage adjustment for renal insufficiency patients has not been put in prospective at the hospitals involved in this study. It was found that 61%, 47% and 62% of drugs that have to be adjusted were administered in the normal dose to patients with renal insufficiency at Tripoli Medical Center, Tripoli Kidney Center and Tripoli Diabetic Center, respectively. It is concluded that serum creatinine concentration test is a must to be performed, for making the dose adjustment of drugs possible in case of renal insufficiency. Including clinical pharmacist as a member of the medical team has an important role in checking out the drugs administered, dosing and dosing interval.

Keywords: Renal impairment, dose adjustment, renal insufficiency, renal failure, Libya

Introduction

In the last few decades, clinical scientists have directed the attention in their studies concerning the use of drugs to patients rather than healthy subjects (1). Such studies have demonstrated the value of applying pharmacokinetic parameters to the clinical settings and its variability was greater in sick than in healthy people (2). Disease affects various organ systems of the body and, moreover, affects the way drugs are absorbed, distributed, metabolized and excreted (3, 4). Renal disease is a major one that affects the use of drugs to patients, and directly affects their excretion. Patients with renal insuff-iciency need to be treated with a variety of drugs, both for their disease and inter-current illness. Renal insuff-iciency or failure impairs the urinary excretion of drugs that are eliminated primarily by renal excretion; these drugs will accumulate excessively in

patients with renal insufficiency, unless the dose and/or dosage regimen is modified (5). The usual standard dosage regimen may result in excessive accumulation of drug to levels potentially producing undesirable side effects and toxicity in patients with impaired renal function (6). To avoid toxic reactions, particularly if the drug has a low therapeutic index, information on which drugs accumulate in renal failure and, how to adjust drug administration to achieve an optimal therapeutic response are needed to make a judgment, using pharmacokinetics principles, on the necessity for altering drug administration in renal impairment. This eventually requires an estimate of both kidney function and the contribution of the renal route to total elimination (7, 8). The aim of the present study is to highlight the importance of the title "Dosage Adjustment in Renal Impairment" through carrying out a survey at some hospitals of Tripoli to evaluate how drug doses being adjusted in patients with renal insufficiency.

Materials and methods

A number of hospitals at Tripoli area were selected for the present study: Tripoli Medical Center (TMC), Tripoli Kidney Center (TKC) and Tripoli Diabetic Center (TDC). About 500 files at TMC, 98 files at TKC and 200 files at TDC (a total of 798 files) were studied. Data of age, sex, serum creatinine concentration, drugs administered, dose given, and dosing interval used were collected. Discussions were held with the medical staff whenever possible. Creatinine clearance (Cl_{cr}) was calculated using the Cockroft-Gault formula (9):

$$Cl_{cr} = \frac{(140-age)(body\ weight)}{72\ x\ S_{cc}} \quad \ldots (1)$$

Age is expressed in years, body weight in kg, and S_{cc} (serum creatinine concentration) in mg/dl. Equation (1) may be further simplified since the average male adult weighs about 70 kg, thus canceling out the number 72, and equation (2) becomes (9):

$$Cl_{cr} = \frac{140-age}{S_{cc}} \quad \ldots\ldots\ldots\ldots\ldots (2)$$

Equation (2) was used for both male and female patients, but the value obtained was reduced by 15% for females (2, 9-11). Accordingly, dose and/or interval adjustment of drugs were presented.

Results and discussion

From all files studied, the data of renal insufficiency patients collected at TMC (47 patients), TKC (11 patients), and TDC (20 patients) were presented in Tables 1, 2 and 3. The dose and/or interval adjustments which should be done when drugs administered to patients with renal insufficiently are also presented in the same tables for comparison. For useful and better interpretation of data, each hospital will be encountered alone.

Tripoli Medical Center

The most important at this center is that serum creatinine measurement is performed routinely, from where creatinine clearance was estimated using Cockroft-Gault equation. Many drugs were given in normal or standard doses, where they should have been adjusted before administration (Table 1 shows the correct adjusted dose and/or interval that should have been applied 'Shadowed areas"). Table 1 reveals that 46 out of 76 drugs (61%) were given as for normal patients not for renal impairment patients (dose and/or interval not adjusted). When asked how dose adjustment of drugs was performed in patients with renal insufficiency, consultant physicians at the medicine department of this center answered that they try to avoid common nephrotoxic drugs by decrease the doses especially for most well-known drugs, aminoglycosides and digoxin. Some physicians (not consultants) seemed to have no idea about the issue of dosage adjustment. Patients with severe chronic renal failure, and having other complications (e.g. chest infection or congestive heart failure) were given the necessary treatment mostly without considering dosage adjustment of many drugs which accumulate in this case. They also referred to specialized kidney hospitals such as Al-Zahra Hospital or Tripoli kidney center.

Table 1: Dose adjustments based on estimation of creatinine clearance using Cockroft-Gault equation for renal insufficiency patients at Tripoli Medical Center

Pt. No.	Sex	Age	S_{cc}	Drug given, dose & interval	Cl_{cr}	Dose & interval adjustments
1	M	29	10.3	Hydralazine 25 mg (1x3)	10.8	25 mg (1x3)
2	F	39	5.0	Methyldopa 250 mg (1x3) Captopril 12.5 mg (1x2)	17.2	250 mg (1x3) 12.5 mg (1x2)
3	M	48	7.2	Diclofenac 25 mg (1x3)	13.5	6 – 12.5 mg (1x2)
4	M	48	6.8	Captopril 25 mg (1x3)	13.5	18.5 mg, q (12-18 h)
5	F	50	2.7	Digoxin 0.125 mg (1x1) Captopril 12.5 mg (1x3)	28	0.125 mg (1x1) 12.5 mg (1x3)
6	F	52	2.6	Captopril 12.5 mg (1x3) Coamoxiclav 1.2 g (1x2)	29	12.5 mg (1x3) 1.2 g (1x2)

7	F	54	2.8	Captopril 12.5 mg (1x3) Spironolactone 25 mg (1x1)	26.5	12.5 mg (1x3) 25 mg (1x1)
8	M	54	1.9	Captopril 12.5 mg (1x3) Spironolactone 50 mg (1x1)	45	12.5 mg (1x3) 25 mg, q(12-24 h)
9	F	55	3.0	Captopril 50 mg (1x3)	24	18 mg, q(12-18 h)
10	F	60	3.4	Captopril 12.5 mg (1x2)	23.5	12.5 mg (1x2)
11	F	60	1.8	Lisinopril 5 mg (1x1) Cefotaxime i.v. 1 g (1x2)	44.5	5 mg (1x1) 1 g (1x2)
12	M	60	3.2	Digoxin 0.0625 mg (1x1) Coamoxiclav 1.2 g (1x3)	25	0.0625 mg (1x1) 1.2 g (1x3)
13	M	61	2.2	Digoxin 0.25 mg (1x1) Allopurinol 300 mg (1x1)	36	0.0625-0.125 mg, q (36 h) 75-150 mg (1x1)
14	F	61	5.0	Captopril 12.5 mg (1x3) Ceftriaxone 1 g (1x2)	13.5	12.5 mg, q (12-18 h) 1 g (1x2)
15	F	62	5.4	Digoxin 0.25 mg (1x1) Coamoxiclav i.v 1.2g (1x2)	12.5	0.0625-0.125 mg, or increase I to 36 h 1.2 mg, (1x2)
16	F	63	3.6	Digoxin 0.5 mg followed by 0.25 mg (1x2) Cimetidine 400 mg (1x2)	18.5	0.0625-0.125 mg or increase Int. to 36 h 200 mg (1x2)
17	F	65	8.6	Atenolol 50 mg (1x1) Cimetidine 200 mg (1x2)	7.25	15-25 mg or increase Interval to 36 h 100 mg (1x2)
18	F	65	4.1	Captopril 25 mg (1x3)	16	18 mg, q (12-18 h)
19	M	65	4.5	Ampicillin 1.2g (1x2)	16.5	1.2g (1x2)
20	M	65	2.9	Spironolactone 50 mg (1x1)	26	25 mg, q (12-24 h)
21	M	65	4.0	Digoxin 0.125 mg (1x1) Cimetidine 400 mg (1x1)	19	0.125 mg (1x1) 200 mg (1x2)
22	M	66	4.5	Cefotaxime i.v 1g (1x2) Cimetidine 400 mg (1x1)	16.5	1g (1x2) 200 mg (1x2)
23	F	67	4.0	Digoxin 0.125 mg (1x1)	15.5	0.125 mg, q (36 h)

				Cimetidine 400 mg (1x1)		200 mg (1x2)
24	F	67	3.6	Captopril 25 mg (1x3) Diclofenac 50 mg (1x3)	17	18 mg, q (12-18 h) 12.5-25 mg (1x2)
25	M	67	2.8	Cimetidine 400 mg (1x2) Ampicillin 1g (1x4) Captopril 12.5 mg (1x3)	26	200 mg (1x2) 1g, q (6-12) 12.5 mg, q (12-18 h)
26	F	68	1.9	Captopril 12.5 mg (1x3) Coamoxiclav 375 mg (1x3)	32	12.5 mg, q (12-24 h) 375 mg (1x3)
27	M	68	3.4	Digoxin 0.125 mg (1x1) Captopril 25 mg (1x3) Amoxil 500 mg (1x3)	21	0.125 mg, q (36 h) 18 mg, q (12-18 h) 500 mg, (1x3)
28	M	69	4.3	Diclofenac 50 mg (1x3)	16.5	6.25-32.5 mg (1x2)
29	F	70	1.9	Metformin 500 mg (1x2) Atenolol 50 mg (1x1)	31.5	125-212.5 mg (1x2) 25-50 mg, q (48 h)
30	F	70	4.6	Ceftriaxone 1g (1x2)	12.5	1g (1x2)
31	M	70	1.8	Captopril 50 mg (1x3)	39	18 mg, q (12-18 h)
32	F	70	3.5	Ampicillin 1g (1x4)	17	1g, q (6-12 h)
33	M	70	3.1	Digoxin 0.125 mg (1x1) Cefotaxime 1g (1x2)	22.5	0.125 mg, q (36 h) 1g (1x2)
34	F	70	2.4	Digoxin 0.0625 mg (1x1) Voltarin 50 mg (1x1)	24.75	0.0625 mg (1x1) 6.25-32.5 mg (1x2)
35	F	70	2.1	Digoxin 0.25 mg (1x1)	28.5	0.0625-0.125 mg, q (36 h)
36	M	71	2.6	Coamoxiclav 1.2 g (1x3) Allopurinol 300 mg (1x1)	26.5	1.2 g (1x3) 75-150 mg (1x1)
37	F	72	2.0	Digoxin 0.125 mg (1x1) Cefotaxime 1g (1x2)	29	0.125 mg, q (36 h) 1g (1x2)
38	F	73	2.2	Eralpril 5 mg (1x1)	26	2.5 mg (1x1)
39	F	72	2.8	Cimetidine 400 mg (1x2) Ampicillin 1g (1x4)	20.5	200 mg,(1x2) 1g, q (6-12 h)

40	M	74	2.8	Captopril 12.5 mg (1x3)	23.5	12.5 mg, q (12-18 h)
41	F	75	5.0	Captopril 25 mg (1x3)	11	12.5-18mg, q(12-18 h)
42	M	75	1.8	Digoxin 0.125 mg (1x1)	36	0.125 mg, q (36 h)
43	F	75	5.2	Digoxin 0.0625 mg (1x1)	10.75	0.0625 mg, q (36 h)
44	F	80	3.3	Coamoxiclav 1.2g (1x3) Voltarin 50 mg (1x3)	15.25	1.2g (1x3) 6.25-32.5 mg (1x2)
45	M	80	2.0	Captopril 12.5 mg (1x3)	30	12.5 mg, q (12-18 h)
46	M	80	8.7	Lisinopril 5 mg (1x1)	6.9	1.25-5mg (1x1)
47	F	85	5.6	Cimetidine 400 mg (1x2) Morphine 25 mg (1x2)	8.25	100 mg (1x2) 10-12 mg, q (4 h)

Note: Age in years, S_{cc} in mg/dl, and Cl_{cr} in ml/min. (Shadowed areas show the correct adjusted dose and/or interval that should have been applied).

Tripoli Kidney Center

This center has in-patient and outpatient departments where in-patients all have end-stage renal failure. There is also an out-patient service for pre-end stage renal failure patients, where they are followed up and given the necessary treatment, to delay the onset of end stage renal failure and sometimes given treatment for other complications (e.g., hypertension, diabetes mellitus, and infection). From talking to consultant physicians in the center, it seemed that they were more aware of the dose adjustment issue of some drugs than physicians in other hospitals visited. Serum creatinine concentration and creatinine clearance tests are perfo-rmed. The files of the outpatients were seen, and it was noticed that most were given drugs which needed no dosage adjustment (Lasix, folic acid, 1-alpha, calcium carbonate etc.). In spite of that, some patients took drugs which needed dosage adjust-tment. Table 2 reveals that 9 out of 19 drugs (47%) were given as for normal patients not for renal impairment patients (dose and/or interval not adjusted).

Table 2: Dose adjustments based on estimation of creatinine clearance using Cockroft-Gault equation for renal insufficiency patients at Tripoli Kidney Center.

Pt. No.	Sex	Age	S_{cc}	Drug given, dose & interval	Cl_{cr}	Dose & interval adjustments
1	M	38	4.3	Ranitidine 150 mg (1x2)	12.7	150 mg (1x2)
2	F	44	2.9	Captopril 12.5 mg (1x2)	25.75	12.5 mg (1x2)
3	M	44	10.6	Lisinopril 50 mg (1x1) Amoxil 500 mg (1x3) Ranitidine 150 mg (1x2)	9.0	15-50 mg, q (96 h) 500 mg (1x3) 150 mg (1x2)
4	M	45	3.9	Amoxil 500 mg (1x3)	8.4	500 mg (1x3)
5	M	55	11.3	Lisinopril 100 mg (1x1)	7.5	15-50 mg, q (96 h)
6	F	55	7.0	Cimetidine 200 mg (1x2)	8	100 mg (1x2)
7	F	60	4.0	Captopril 12.5 mg (1x3) Allopurinol 150 mg (1x1) Methyldopa 250 mg (1x3)	32	12.5 mg, q (12-18 h) 150 mg (1x1) 250 mg (1x3)
8	M	61	8.5	Methyldopa 250 mg (1x1)	4.0	250 mg (1x1)
9	F	65	3.9	Ranitidine 150 mg (1x2) Amoxil 500 mg (1x3) Enalpril 5 mg (1x1)	16.3	150 mg (1x2) 500 mg (1x3) 2.5 mg (1x1)
10	F	66	3.6	Cimetidine 200 mg (1x3)	17.5	200 mg (1x2)
11	M	69	10.7	Captopril 50 mg (1x2) Allopurinol 150 mg (1x2) Methyldopa 250 mg (1x3)	6.6	12.5 mg (1x1) 32.5-75 mg (1x2) 250 mg, q (12-24 h)

Note: Age in years, S_{cc} in mg/dl, and Cl_{cr} in ml/min. (Shadowed areas show the correct adjusted dose and/or interval that should have been applied).

Tripoli Diabetic Center

As diabetic nephropathy is a common complication of diabetes, so visiting the diabetic center was essential to see how patients with mild to moderate renal failure, were treated with drugs which may accumulate excessively in case of renal insufficiency, and if dose

adjustment was carried out to these drugs. When the files were looked up, the first thing noticed was that most patients did not have serum creatinine concentration level performed, although many were diagnosed as having diabetic nephropathy, and were taking drugs which need dosage adjustment. Some data were recorded from the files as an example of patients with elevated serum creatinine concentrations, chronic renal failure or acute renal failure and taking drugs which need dosage adjustment in their cases. For some cases, serum creatinine concentration was not performed (Table 3: patient Nos. 2, 10, 11, 14, 16, 20). When a leading consultant physician was asked on how renal function is assayed, he said that serum creatinine reagent is not available and outpatients were asked to carry out the test in outside laboratories. He added that the in-patients were recognized to have renal insufficiency if they had urinary complaints such as peripheral neuropathy, lethargy, edema and all the other common findings of chronic renal failure or if they were previously diagnosed as having renal failure in another hospital. A visit was also paid to the laboratory, where the laboratory technician said that serum creatinine concentration levels were not measured on a regular basis since a long time (over four years), due to lack of machines and regular supply of reagents. Creatinine clearance and subsequent adjustment of dose and/or dosing interval for data collected are presented in table 3, which reveals that 24 out of 39 drugs (62%) were given as for normal patients not for renal impairment patients (dose and/or interval not adjusted).

Table 3: Dose adjustments based on estimation of creatinine clearance using Cockroft-Gault equation for renal insufficiency patients at Tripoli Diabetic Center

Pt. No.	Sex	Age	S_{cc}	Drug given, dose & interval	Cl_{cr}	Dose & interval adjustments
1	F	25	2.3	Captopril 50 mg (1x3)	42.5	18 mg, q (12-18 h)
2	M	41	-	Cimetidine 400 mg (1x2) Septrin 480 mg (1x2)	-	Doses & intervals needing adjustments because the patient was diagnosed as nephropathy pyelonephritis (No S_{cc} was measured)
3	F	42	6.0	Lisinopril 5 mg (1x1)	13.5	2.5-7.5 mg (1x1)
4	M	46	4.0	Captopril 25 mg (1x3)	23.5	18 mg, q (12-18 h)
5	F	50	4.7	Cimetidine 200 mg (1x3)	16	200 mg (1x2)
6	F	50	3.0	Cimetidine 200 mg (1x2)	25.5	200 mg (1x2)

				Coamoxiclav 1.2g (1x3)		1.2g (1x3)
7	M	50	2.8	Lisinopril 20 mg (1x1) Ranitidine 150 mg (1x2) Allopurinol 300mg (1x1)	32	2.5-7.5 mg (1x1) 150 mg (1x1) 150 mg (1x1)
8	F	52	5.4	Captopril 25 mg (1x2) Cimetidine 400 mg (1x1)	14	12.5-18 mg (1x2) 200 mg (1x2)
9	M	54	3.4	Coamoxiclav 1.2g (1x3) Nalidixic acid 500 mg (1x4) Captopril 12.5 mg (1x1)	25	1.2g (1x3) should be avoided 12.5 mg (1x1)
10	F	63	-	Cimetidine 200 mg (1x2) Acetaminophen 1g (1x2)	-	Doses & intervals needing adjustments because the patient was diagnosed as Acute renal failure (ARF) (No $\mathbf{S_{cc}}$ was measured)
11	F	55	-	Digoxin 0.125 mg (1x2)	-	Doses & intervals needing adjustments because the patient was diagnosed as Chronic renal failure (No $\mathbf{S_{cc}}$ was measured)
12	M	65	5.4	Captopril 12.5 mg (1x2)	14	12.5 mg (1x2)
13	F	65	3.9	Cimetidine 200 mg (1x2) Ampicillin 1g (1x4)	16	200 mg (1x2) 1g (1x4)
14	F	69	-	Captopril 12.5 mg (1x2) Allpurinol 300 mg (1x2)	-	Doses & intervals needing adjustments because the patient was diagnosed as Chronic renal failure (No $\mathbf{S_{cc}}$ was measured)
15	M	70	10.0	Captopril 25 mg (1x1) Ranitidine 150 mg (1x1) Ceftriaxone 1g (1x1)	7	12.5-18 mg (1x1) 150 mg (1x1) 1g (1x1)
16	M	73	-	Captopril 25 mg (1x3) Coamoxycillin 1g (1x4) Aminophylline 5g (1x3)	-	Doses & intervals needing adjustments because the patient was diagnosed as Chronic renal failure (No $\mathbf{S_{cc}}$ was measured)
17	M	75	3.9	Captopril 12.5 mg (1x2) Spironolactone 50 mg (1x1) Ampicillin 1g (1x4)	16.5	12.5 mg (1x2) 25 mg, q (12-24 h) 1g (1x4)

				Tetracycline500mg (1x4)		500 mg, q (12-24 h)
18	F	75	4.4	Cimetidine 200 mg (1x2) Captopril 12.5 mg (1x2)	12.75	200 mg (1x2) 12.5 mg (1x2)
19	M	77	2.9	Lisinopril 10 mg (1x1)	22	2.5-7.5 mg (1x1
20	F	78	-	Captopril 25 mg (1x3) Nalidixic acid 1g (1x2)	-	**Captopril** needing to be adjusted because the patient was diagnosed as Chronic renal failure (No S_{cc} was measured).

Note: Age in years, S_{cc} in mg/dl, and Cl_{cr} in ml/min. (Shadowed areas show the correct adjusted dose and/or interval that should have been applied).

In general, the practice of dose adjustment of drugs in patients with renal insufficiency requires a broad therapeutic knowledge and a careful clinical assessment of the patient, in addition, to a solid foundation in the pharmacokinetic principles. A clinical assessment of the patient, include the disease state being treated, the clinical condition of the patient, a complete drug dosing history, pertinent laboratory data, and assessment of concomitant drug therapy. Collection of this data is often difficult, and the medical team should all collaborate, including a competent clinical pharmacist to give the optimum dug therapy to the patient. The issue of dose adjustment of drugs in patients with renal insufficiency is of utmost importance, and requires extensive clinical skill. In the course of this study, it was noticed that this issue has not been put in perspective in the visited hospitals of Tripoli, Libya. Many clinicians are unassisted by reference books, monograms, formulae, and equations. Therefore, they are unable to make the required dose adjustment of drugs needed when a patient has renal insufficiency. Although some drugs have been adjusted, many others were administered in excess. In some hospitals, even fundamental investigations of kidney function were not done (i.e. serum creatinine concentration) making dose adjustment of drugs impossible. There are several points which need to be taken into account and put in consideration for the process of dose adjustment in patients with renal failure to be completed, among them are: Investigation of kidney function could be done in many ways, (creatinine clearance, serum creatinine concentration, blood urea nitrogen, protein urea, osmolality measurements in plasma and urine etc.) but the most important for dose adjustment of drugs in renal failure is creatinine clearance. If it is unavailable, then it can be estimated from serum creatinine concentration levels. With the exception of Tripoli kidney center, none of the hospitals that were visited carried out creatinine clearance

tests to their patients, as a regular investigation of kidney function. Because diabetes is one of the main causes, if not the main cause of end-stage renal failure, great care in administration of drugs to diabetic patients is crucial. In the diabetic center even serum creatinine concentration was not performed, making it impossible to perform a dose adjustment of drugs in case of renal impairment. Patients who are diabetic should have regular follow-up on their kidney function as diabetic nephropathy is a well-known complication of diabetes. From looking at the files of many patients, many potentially toxic drugs, and even nephrotoxic drugs were administered to diabetic patients without any consideration to dosage adjustment, which may be needed to prevent excessive accumulation of the drug. This may accelerate the development of chronic renal failure and finally end-stage renal failure and dialysis of these patients. Clinical pharmacist has an important role in checking out the drugs administered, dosing and dosing interval. None of the hospitals that were visited included clinical pharmacists as part of their medical team. In the developed countries, no drug is dispensed from the hospital pharmacy unless signed by clinical pharmacist. Clinical pharmacists can assist doctors in proper administration of the drugs, because of their greater understanding in clinical pharmacology, pharmacokinetics, pharmacodynamics, drug interactions and adverse reactions.

References

1. Husain M and Mehta MA (2011) Cognitive enhancement by drugs in health and disease. Trends Cogn Sci. 15(1), 28-36.
2. Gibaldi M (1991) Biopharmaceutics and Clinical Pharmacokinetics. 4th Ed. Lea and Febiger.
3. Notari RE (1987) Biopharmaceutics and Clinical Pharmacokinetics: An Introduction. 4th Ed. Marcel Dekker, New York.
4. Gibaldi M and Perrier D (1975) Pharmacokinetics. Marcel Dekker, New York.
5. Verbeek RK and Musuamba FT (2009) Pharmacokinetics and dosage adjustment in patients with renal dysfuction. Eur J Clin Pharmacol. 65, 757-773.
6. Gibaldi M and Levy G (1976) Pharmacokinetics in clinical practice. I. Concepts. JAMA, 235, 1864.
7. Stevens LA, Coresh J, Greene T and Levey AS (2006) Assessing kidney function – measured and estimated Glomerular filtration rate. N Engl J Med. 354, 2473-2483.
8. Graves JW (2008) Diagnosis and management of chronic kidney disease. Mayo Clin Proc 83, 1064-1069.
9. Cockroft DW and Gault MH (1976) Prediction of creatinine clearance from serum creatinine. Nephron. 16, 31-41.
10. Lott RS and Hayton WL (1978) Estimation of creatinine clearance from serum creatinine concentration. Drug Intl Clin Pharmacol. 12, 140.
11. Wheeler LA and Sheiner LB (1979) Clinical estimation of creatinine clearance. Am J Clin Pathol. 72, 27.