USE OF CEFOPERAZONE - SULBACTAM 2:1 IN PATIENTS WITH COMPROMISED RENAL FUNCTION

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Summary

Acute renal failure (ARF) is a common complication in patients admitted to the intensive care unit. Impaired renal functions in these patients can have profound effects on the pharmacokinetics of antibacterial agents. Hydrophilic antimicrobials (e.g. β-lactams, aminoglycosides and glycopeptides) and renally excreted, moderately lipophilic antimicrobials (e.g. ciprofloxacin, gatifloxacin and levofloxacin) have to be considered at much higher risk of presenting substantial daily fluctuations in plasma concentrations that may require repeated dosage adjustments. Cefoperazone-sulbactam, a novel beta lactamase- beta lactamase inhibitor is a commonly used drug combination in India. Present review focuses on the effects of renal insufficiency on antibiotic pharmacokinetics and how alterations in dose and or frequency of administration of cefoperazone :sulbactam would be warranted to ensure optimum response.

Key words: Cefoperazone, Sulbactam, Renal Impairment, Pharmacokinetics

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Introduction

Acute renal failure (ARF) is a common complication in patients admitted to the intensive care unit (ICU).[1] 35 to 50% of ARF cases in the ICU can be attributed to sepsis.[2,3,4,5,6] with reported annual death toll comparable to that of acute myocardial infarction.[2] Mortality in this subgroup of patients is considerably higher than in other subgroups.[1,3,5,6] common reason for ARF in ICUs are concomitant nephrotoxic agents including aminoglycosides, radiocontrast, NSAIDS etc. ARF is also seen in high number of patients developing ventilator associated pneumonia.[7]

Impaired renal functions can have profound effects on the pharmacokinetics of antibacterial agents. This could lead to frequent dose adjustment, & change in frequency of administration.[8] Thus, the present review focuses on the effects of renal insufficiency on antibiotic pharmacokinetics and how alterations in dose and or frequency of administration of cefoperazone :sulbactam would be warranted to ensure optimum response.

Acute Renal Failure in ICU

Acute renal failure occurs in a high proportion of patients with septic shock when blood cultures are positive. It occurs in approximately 19 percent of patients with moderate sepsis, 23 percent with severe sepsis, and 51 percent with septic shock when blood cultures are positive. [9]*(Table 1)*

Table 1: Acute renal failure and sepsis

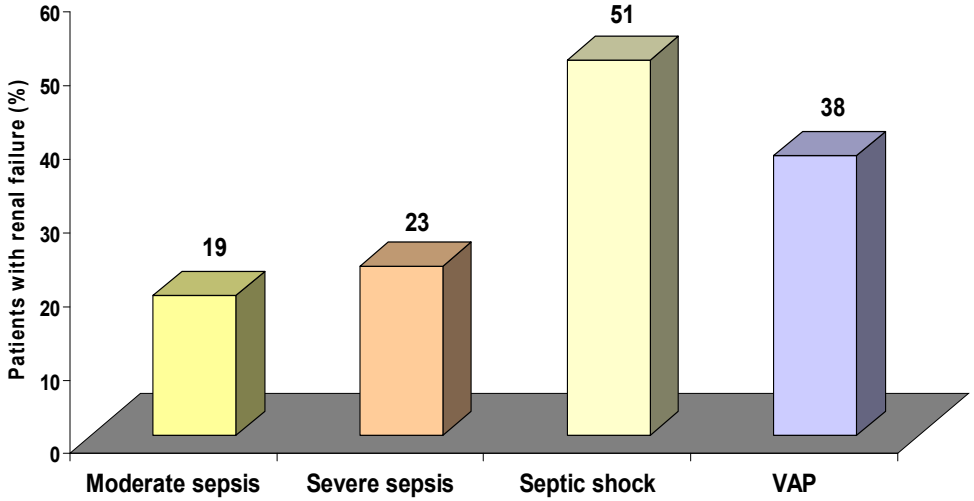
Condition	Moderate Sepsis (N=649)	Severe Sepsis (N=467)	Septic Shock (N=110)
		percent	
Acute renal failure			
Positive culture	19	23	51
Negative culture	5	16	38

Incidence of ARF increases with increase in the severity of sepsis. Ventilator-associated pneumonia, is also one of the most frequent infections in ICU and these patients have a high incidence of ARF (38%)[7] Postoperative ARF is the most common form of ARF in surgical ICU patients and markedly increases perioperative morbidity and mortality. [10]

Multiple risk factors, including old age, comorbidities like long standing diabetes and hypertension, cardiac disease, sepsis, and concurrent use of nephrotoxic agents, such as aminoglycosides, radiocontrast dye and non-steroidal anti-inflammatory agents, influence the incidence of ARF in ICU patients. [10]

Table 2 shows percentage of patients with sepsis and VAP developing renal failure.

Table 2: Percentage of patients of sepsis and VAP with renal failure



The mortality due to acute renal failure (ARF) is 50-80% in critically ill patients and there has been no significant decline despite numerous advances in critical care strategies and renal replacement technologies over several decades. [10]

Effects of Renal Insufficiency on Antibiotic Pharmacokinetics

Patients with renal insufficiency, are prescribed multiple medications to manage not only their underlying disease, but also symptoms related to renal impairment.[11]

Renal insufficiency can affect the absorption, bioavailability, distribution, metabolism and excretion of many drugs. Diabetic or uremic gastroparesis in patients with renal impairment can alter rates of absorption of drugs. Edema or ascites may increase volume of distribution for protein-bound or water-soluble drugs such as vancomycin (possibly requiring a larger loading dose to achieve therapeutic drug concentrations).[11] Excretion of the drug is altered in renal insufficiency due to three factors - glomerular filtration, tubular secretion and reabsorption. Generally it is assumed that all 3 factors can decline. Creatinine clearance is the guiding factor for drug dosage in patients with renal impairment. The ranges of normal and decreased creatinine clearance are given in *Table 3*. [11, 12, 13]

Table 3: Ranges of normal and decreased creatinine clearance

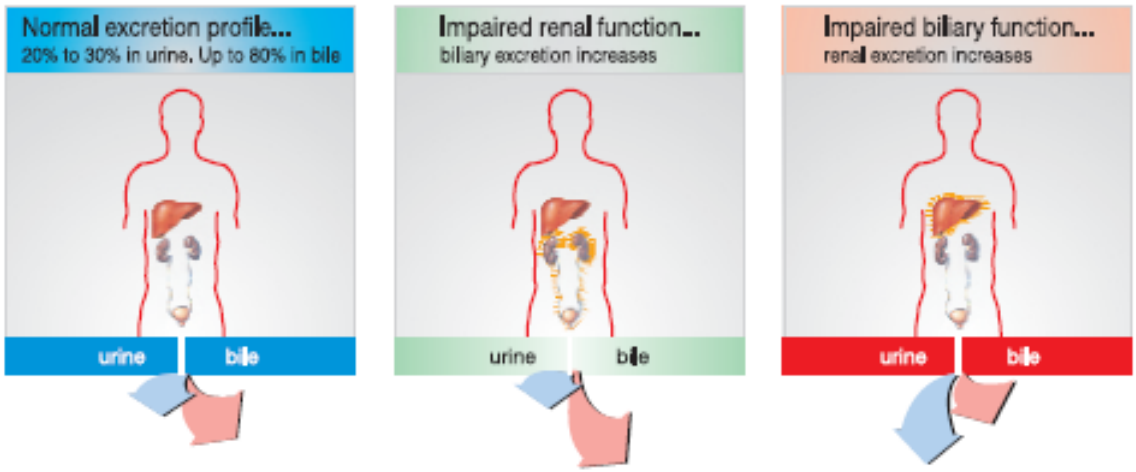
	Serum creatinine	Serum creatinine
Normal renal function Men Women	 95-145 ml/min 75-115 ml/min	 (1.58-2.42 ml/s) (1.25-1.92 ml/s)
Mild renal insufficiency*	50-70 ml/min	(0.83-1.17 ml/s)
Moderate renal insufficiency*	25-50 ml/min	(0.42-0.83 ml/s)
Severe renal insufficiency*	< 25 ml/min	(< 0.42 ml/s)
*Please note that there is considerable controversy regarding what constitutes mild, moderate and severe renal insufficiency. It is also important to note that creatinine clearance declines by 1 ml/min per year (0.02 ml/s per year) after the age of 40 years. Therefore, these guidelines are for women and men aged < 65 years.		

Since renal impairment is known to alter the pharmacokinetics of the drug, dosage adjustment would be required for many antibiotics. [14]

Hydrophilic antimicrobials (e.g. β-lactams, aminoglycosides and glycopeptides) and renally excreted, moderately lipophilic antimicrobials (e.g. ciprofloxacin, gatifloxacin and levofloxacin) have to be considered at much higher risk of presenting substantial daily fluctuations in plasma concentrations that may require repeated dosage adjustments. The presence of an oedematous status, regardless of the underlying pathogenic mechanism, plays a major role in altering the distribution of antimicrobials. Therefore, higher dosages for most hydrophilic antimicrobials should be considered to ensure therapeutic concentrations. Overhydration through intravenous (i.v.) fluid therapies, total parenteral nutrition, pleural effusion, mediastinitis, peritoneal exudate and ascites, by causing an increase in the extracellular compartment fluid, may lead to a significant increase in volume of distribution (*V*d), justifying higher dosages. In surgical patients, indwelling drainages may represent a pathway of antimicrobial loss and contribute to lower antimicrobial levels. [14]

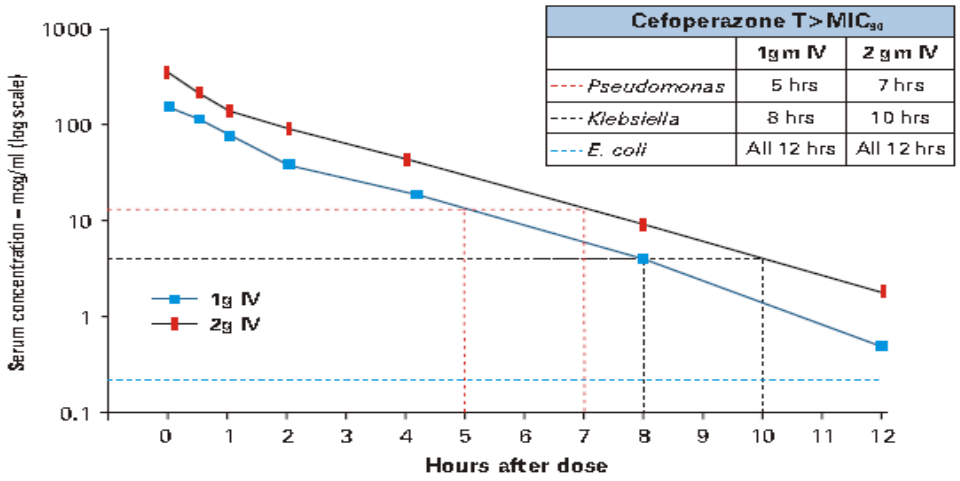
Use of Cefoperazone and Sulbactam 2:1 in Renal Failure

Cefoperazone is a cephalosporin with a broad spectrum of activity whereas sulbactam inhibits hydrolysis of penicillins and cephalosporins by β-lactamases.[15]
Cefoperazone has a dual and compensated excretion, normally excreted more by kidneys which may increase if the patient has impaired biliary function and similarly biliary excretion would compensate for decreased renal function if any.[15,16,17] Sulbactam is cleared primarily by kidneys.



Cefoperazone is known to have dose dependent increase in the serum concentrations. It was administered in the dose of 1 and 2 gram intravenously every 12 hours and the serum concentrations were plotted against time. *(Graph 1)*. It was observed that there was a linear increase in the concentration when cefoperazone was administered in the dose of 2 gram iv as compared to 1 gram iv.[15] Minimal inhibitory concentration (MIC) values for *pseudomonas* (12), *klebsiella* (6.2), *E.coli* (0.4) were plotted to find out the duration for which concentration remained above MIC_{90} (t>MIC).[18] As shown in the graph, t>MIC was 7 hrs with 2 gram dose for *Pseudomonas spp.* as compared 5 hrs observed with 1 gram dose. Similarly values are mentioned for *klebsiella* and *E.coli.*[15,18] As noted from the graph, increasing the dose will be able to increase the t>MIC.

Graph 1: Cefoperazone: Serum concentration versus hours after dose



In infection models and in clinical studies, inhibition of growth is likely if the drug concentration exceeds the MIC for at least 40% of the dosing interval, and a maximal bacteriological response is predicted if the drug concentration exceeds the MIC for at least 60–70% of the dosing interval.[19]

This would be maximized if the dose of cefoperazone is increased. Benefits of higher dose of cefoperazone have been reported in literature. Higher dose of cefoperazone might be useful in patients with severe sepsis in order to obtain high bactericidal activity and possibly to overcome resistance.[20] This would be useful if the patients are not responding to the lower dose of cefoperazone possibly due to resistance.

The pharmacokinetics of cefoperazone 2g combined with 1 g of sulbactam after a single dose administered intravenously were evaluated in 24 subjects with normal and impaired renal function. Patients in groups 1, 2 and 3 had creatinine clearance of >60, 31 to 60 and 10 to 30 mL/min/1.73 m^2 respectively. Patients in group 4 required maintenance haemodialysis and were assumed to have creatinine clearance < 10 mL/min/1.73 m^2. No significant differences in steady state volumes of distribution were noted for either cefoperazone or sulbactam amongst four groups. The concentration of cefoperazone and sulbactam remained at or above the MICs for common bacterial pathogens is shown in the *table 4*.[21]

Table 4 : Duration of cefoperazone & sulbactam concentrations above MIC values post infusion

Creatinine clearance (ml/min)	Time above MIC Cefoperazone 16 mg/L (hrs)	Time above MIC Sulbactam 8 mg/L (hrs) Maximum synergy	Time above MIC Sulbactam 2 mg/L (hrs) Minimum synergy
Group 1: >60	5.5	2.5	3
Group 2: 31-60	8	3	7.5
Group 3: 10-30	9	7	18
Group 4: <10	10.5	14	36

As it is visible in the above table, maximum synergy was noted for 16 mg/ml of cefoperazone and 8 mg/ml of sulbactam (2:1 ratio).

Following table shows time above MIC (hrs) of cefoperazone: sulbactam 2:1 combination for group1 to 4.

Table 5 : Duration of cefoperazone & sulbactam concentrations above MIC for 2:1 combination

Creatinine clearance (ml/min)	Time above MIC (hrs)
Group 1: >60	2.5
Group 2: 31-60	3
Group 3: 10-30	7
Group 4: <10	14

It is apparent from the studies that when a fixed (2:1) combination of cefoperazone and sulbactam is administered, sulbactam will reach threshold concentrations more rapidly than cefoperazone in groups 1 and 2 while remaining above threshold concentrations in groups 3 & 4. The fixed 2:1 ratio is more likely to have maintained pharmacokinetics in patients with severe renal impairment than in those with mild impairment. [21] In order to reach the sulbactam concentration which provides maximum synergy, it may be necessary to increase the sulbactam dose to a fixed 1:1 ratio in patients with only mild renal insufficiency or to increase the dosing frequency. In patients with more severe renal insufficiency, administration of cefoperazone sulbactam in a 2:1 ratio appears to provide a balanced pharmacokinetic profile.[21]. The recommended dose for cefoperazone: sulbactam 2:1 combination is as per the *table 6.* [22]

Table 6: Recommended dosage for cefoperazone: sulbactam 2:1 combination

Recommended dosage		
Normal renal function	Creatinine clearance (ml/min) 15-30	Creatinine clearance (ml/min) <15
6 to 9 gm* / day IM or IV in equally divided doses every 12 hrs	**Upto 6 gm / day IM or IV** in equally divided doses every 12 hrs	**Upto 3 gm / day IM or IV** in equally divided doses every 12 hrs

In severe infections dosages of up to 16 gram of cefoperazone daily have been given without complication in patients with normal renal status. Dosage adjustment for this drug would rarely be needed in patients with either renal or hepatic dysfunction. Cefoperazone can be given safely in these patients and it is often required to increase the total dose of cefoperazone to tackle severe infections in patients otherwise suffering from renal failure. Hence if required additional dose of cefoperazone may be administered.[22,23]

Conclusion

In conclusion, ARF is one of the common complications in patients admitted in ICU. Sepsis and VAP increases the likelihood of patients developing ARF. Altered pharmacokinetics in patients with renal failure requires dose adjustment according to the severity of renal failure especially prescribing antibiotics. Application of the knowledge of pharmacokinetics: pharmacodynamics principle in clinical practice needs to be validated in prospective randomized clinical studies. In critically ill patients with severe infections, higher dose of antibiotic may be warranted. Cefoperazone:sulbactam offers a unique combination of third generation cephalosporin and a beta lactamase inhibitor. Cefoperazone achieves higher concentrations with increase in dose which would be beneficial to overcome the resistance. In patients with normal renal function the dosing frequency may need to be increased. In patients with more severe renal insufficiency, it is desirable to administer a cefoperazone: sulbactam in a 2:1 ratio every 12 hours to obtain a balanced pharmacokinetic profile.

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