The Journal of Toxicological Sciences (J. Toxicol. Sci.)
Vol.35, No.4, 459-464, 2010

Original Article

Pharmacokinetic study of sulbactomax

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(Received March 10, 2010; Accepted May 11, 2010)

ABSTRACT — We have evaluated pharmacokinetics of a fixed dose combination (FDC) of ceftriaxone and sulbactam (2:1) or sulbactomax in eight healthy volunteers. A 1.5 g dose of sulbactomax, 1 g dose of ceftriaxone and 0.5 g sulbactam were given intravenously in a balanced two-ways cross-over study. Serially collected plasma sample was analyzed for ceftriaxone and sulbactam by high performance liquid chromatography (HPLC). The mean peaks of ceftriaxone and sulbactam concentrations in plasma were 152.06 ± 6.65 μg/ml and 21.32 ± 1.80 μg/ml, respectively and plasma half-lives for ceftriaxone and sulbactam were 5.2 ± 0.35 hr and 0.94 ± 0.038 hr, respectively. The AUC0-24 for ceftriaxone and sulbactam was 760.16 ± 27.68 μg.hr/ml and 20.74 ± 2.34 μg.hr/ml, respectively, with elimination rate constant of 0.133 ± 0.009 hr^{-1} and 0.732 ± 0.029 hr^{-1}, respectively. The kinetics of ceftriaxone and sulbactum did not change in combination as compared to the alone treatment. Also, concentration of the ceftriaxone after 24 hr is higher than the minimum inhibitory concentration (MIC) of the most of the gram positive and gram negative bacteria indicating that one dose in a day is sufficient to treat the disease caused by these organisms.

Key words: Ceftriaxone-sulbactam, Sulbactomax, Pharmacokinetics

INTRODUCTION

The third generation cephalosporins were introduced into clinical practice in the early 1980s and since then they have served as efficacious and fairly safe agents for the management of many serious infections (Donowitz and Masndell, 1998). Cephalosporins are a class of beta-lactam antibiotics. Ceftriaxone is a broad-spectrum, semi-synthetic third-generation cephalosporin with a potent bactericidal activity against a wide range of gram-positive and gram-negative bacteria (Carmeli *et al*., 1999). The antibacterial activity of ceftriaxone is due to the inhibition of cell wall synthesis (Goldstein *et al*., 1995).

Sulbactam has recently been approved in many countries including India and is being combined with beta-lactam antibiotics (Levin, 2002). It is a molecule which inhibits beta-lactamase, an enzyme produced by bacteria that destroy antibiotics (Totir *et al*., 2007). It is a potent, highly specific inhibitor of a wide variety of β-lactamases produced by common gram-negative and gram-positive aerobes and anaerobes (Bhattacharjee *et al*., 2008). By forming a protein complex with β-lactamases, sulbactam irreversibly blocks their destructive hydrolytic activity (Betrosian *et al*., 2008). Thus, the full potential of ceftriaxone against enterobacter and pseudomonas species is restored by the addition of sulbactam (Corbella *et al*., 1998).

Third generation cephalosporins are potent antibiotic substances being used in the treatment of life-threatening infections. In the last few years, however, an increase in resistance, especially among *Enterobacteriaceae*, has been reported, resulting from a continuous spread of broad-spectrum β-lactamases. Guerra-Romero *et al*. (1991) reported a combination of a penicillin-derivative drug (ampicillin) and sulbactam, for the treatment of experimental meningitis caused by a β-lactamase producing strain of *E. coli* K-1.

Later, a combination of a cephalosporin (ceftriaxone) and a β-lactamase inhibitor (sulbactam) is introduced to prevent the emergence of resistant bacteria (Caron *et al*., 1990; Chambers and Fournier, 1993).

A large number of studies available on pharmacokinetics of ceftriaxone and sulbactam alone in healthy volunteers and patients (Patel *et al*., 1981; Foulds *et al*., 1983;

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Caine *et al*., 1984; Zhou *et al*., 1985; Sar *et al*., 2008). However, studies on pharmacokinetics of fixed dose combination (FDC) of ceftriaxone and sulbactam (sulbactomax) in healthy individuals are lacking. Therefore, the present investigation was planned to study the pharmacokinetics of sulbactomax, ceftriaxone and sulbactam alone in healthy individuals to determine changes in the pharmacokinetic profiles of FDC. Also, we have determined the minimum inhibitory concentration (MIC) of sulbactomax against certain gram positive and gram negative orgnisms to establish dose regimen of new FDC.

MATERIALS AND METHODS

Subjects

A total of eight healthy male volunteers meeting inclusion and exclusion criteria were enrolled for an open labeled, comparative pharmacokinetic study.

Inclusion criteria

Healthy volunteers, ranging from 22 to 32 years in age, and from 55 to 80 kg in weight, were selected. All volunteer's were non-smokers, nonalcoholic, with no evidence of underlying disease on physical examination, medical disorder or impairment. All selected volunteers have not been participated in any of the clinical trials since last 3 months and have been provided written informed consent.

Exclusion criteria

The volunteers were excluded if they had a history of hypersensitivity to the drug or related products, renal or liver function abnormalities, any clinically significant illness during the 4 weeks prior to this study or hospitalized during 3 months prior to the commencement of this study.

Dropouts and withdrawals

The volunteers are free to leave the study at any time without giving the reason. The volunteer's participation in the trial can be discontinued for any of the following reasons: adverse reaction, inter current illness, non-compliance and volunteer decision not to continue. If a subject does not follow pre-study directions regarding alcohol, drug use, fasting condition etc. can be removed from the study.

Concurrent medication

All volunteers were informed not to take any medications for 14 days prior to the study. In addition, non-concomitant medication was permitted during the study period. The trial was conducted in accordance with declaration of Helsinki and ethical approval obtained from the independent institutional ethics committee.

Physical examination

All the volunteers were evaluated physically and medically two days before the start of the study.

Study design

Dose and route of administration

The overnight fasten volunteers were given a single intravenous dose of sulbactomax (1.5 g) as a 30 min infusion in a 50 ml normal saline. The fast was continued for an additional 3 hr after drug administration. After 15 days of washing period volunteers were give ceftriaoxne (1 g) and after another 15 days of washing period sulbactam (500 mg) was administered to the volunteers.

Blood sample collection & sampling schedule

Blood samples were obtained at 15 min before the infusion and 0.5, 1, 1.5, 2, 4, 8, 12 and 24 hr after the infusion. Blood samples were collected in heparinized navy-blue vacutainer tubes and centrifuged immediately. Plasma was separated and stored at -20°C until use.

Hematological parameters

Blood samples were subjected for hematological parameters such as total leukocyte counts (TLC), erythrocyte sedimentation rate (ESR), hemoglobin (Hb).

Biochemical parameters

Biochemical parameters such as serum gluatmic oxaloacetic transaminase (SGOT), serum gluatmic pyruvic transaminase (SGPT), alkaline phosphatase (ALP) activities, sugar, urea and creatinine were evaluated in plasma. All parameters were studied by Merck semi auto analyzer using Merck kits.

HPLC analysis of ceftriaxone and sulbactam

Ceftraixone and sulbactam were detected in the plasma using high performance liquid chromatography (HPLC Agilant 1,200 series, Santa Clara, CA, USA) equipped with G1311A quaternary pump, Agilent variable UV/Visible detector and a G1329A auto injector.

Mobile phase

A buffer solution consisted of 50 ml of tetrabutyl ammonium hydroxide (TBAH) in 1,000 ml of distilled water was prepared and adjusted to pH 7.0 with orthophosphoric acid. The solvent used for mobile phase was a

mixture of buffer–acetonitrile (70:30). The mobile phase was passed through membrane filter (Millipore corp., Billerica, MA, USA), 0.45 µm pore size and degassed under reduced pressure.

Ceftriaxone and sulbactam drug analysis

Ceftriaxone and sulbactam drugs were analyzed by the method of Shrivastava *et al*. (2009a). For the analysis of ceftriaxone and sulbactam concentrations in plasma samples, 200 µl of sample was mixed with 150 µl of mobile phase and shaken vigorously. The chromatographic separation of ceftriaxone and sulbactam drugs was performed by HPLC with a mobile phase. A C-18 hypersil ODS (5 µ, 4.6 x 250 mm) column was used for the analysis. The flow rate and column temperature were maintained at 1.5 ml/min at 25°C respectively. After an equilibration of column with mobile phase for 2 hr, 20 µl of sample was injected and detection of ceftriaxone and sulbactam antibiotics was performed at 220 nm UV wavelength. Under the above mentioned chromatographic conditions, the retention time of ceftriaxone and sulbactam were found to be 5.2 and 3.3 min, respectively.

Statistical analysis

Pharmacokinetic parameters were analyzed statistically by two-way analysis of variance to determine the influence of dose. The dose effects were then compared by employing the two-tailed paired t-test.

RESULTS

No adverse effects or events were observed in any of the volunteers confirming the safety of the FDC of ceftriaxone-sulbactam.

The average plasma concentrations of ceftriaxone and sulbactam after 30 min intravenous administration are presented in (Table 1). The maximum plasma concentrations of ceftriaxone and sulbactam after administration of sulbactomax were 152.06 ± 6.55 µg/ml and 21.32 ± 1.79 µg/ml, respectively. The peak plasma concentrations of ceftraixone and sulbactam when administered alone in the same volunteers after the washing period were 153.75 ± 6.43 µg/ml and 21.42 ± 1.28 µg/ml, respectively. After twenty four hours of drug administration, the mean plasma concentrations of ceftriaxone of sulbactomax and ceftriaxone alone were 8.38 ± 1.96 µg/ml and 6.18 ± 1.62 µg/ml, respectively. There were no significant changes observed in the plasma concentrations of ceftriaxone and sulbactam of sulbactomax as compared to the ceftriaxone and sulbactam when administered alone.

Half-life and AUC for ceftraixone after administration of sulbactomax were 5.2 ± 0.35 hr and 760.16 ± 27.68 µg.hr/ml, respectively. Half life and AUC after administration of ceftriaxone alone were 5.6 ± 0.436 hr and 742 ± 29.56 µg.hr/ml, respectively. No significant changes were noted in the half-life and AUC of ceftriaxone of sulbactomax as compared to the ceftriaxone alone. Half life and AUC for sulbactam after administration of sulbactomax were 0.94 ± 0.038 hr and 20.74 ± 2.347 µg.hr/ml, respectively. Half life and AUC after administration of sulbactam alone were 0.985 ± 0.107 hr and 19.75 ± 1.876 µg.hr/ml, respectively. No significant changes were noted in the half-life and AUC of sulbactam of sulbactomax as compared to the sulbactam alone (Table 2).

Elimination rate constant for ceftriaxone after administration of sulbactomax was 0.133 ± 0.009 hr^{-1}. The elimi-

Table 1. Average plasma concentrations of ceftriaxone, sulbactam alone and sulbactomax

Time (hr)	Ceftriaxone µg/ml	Sulbactam µg/ml	Sulbactomax	
			Ceftriaxone µg/ml	Sulbactam µg/ml
0.5	153.75 ± 6.43	21.42 ± 1.28	152.06 ± 6.55	21.32 ± 1.79
1	112.66 ± 6.88	9.8 ± 1.12	109.3 ± 5.09	11.01 ± 1.47
1.5	93.85 ± 3.35	6.08 ± 1.03	92.56 ± 3.79	7.05 ± 1.63
2	83.41 ± 2.61	3.77 ± 0.46	86.5 ± 2.22	3.93 ± 0.63
4	64.61 ± 2.99	1.57 ± 0.53	63.85 ± 5.29	1.47 ± 0.23
8	33.55 ± 1.13		39.88 ± 1.30	
12	14.76 ± 1.97		15.66 ± 2.146	
24	8.38 ± 1.96		6.18 ± 1.62	

nation rate constant for ceftriaxone alone was 0.123 ± 0.01 hr $^{-1}$. No significant changes were noted in the elimination rate constant of ceftriaxone of sulbactomax as compared to the ceftriaxone alone. The elimination rate constant for sulbactam after administration of sulbactomax was 0.732 ± 0.029 hr $^{-1}$. The elimination rate constant for sulbactam alone was 0.707 ± 0.07 hr $^{-1}$. No significant changes were noted in the elimination rate constant of sulbactam of sulbactomax as compared to the sulbactam alone.

Statistically no significant changes in the hematological and clinical biochemical parameters were observed after the administration of sulbactomax as compared to the start of the dosing indicating that the FDC of ceftriaxone and sulbactam is neither hepatoxtoxic nor nephrotoxic (Table 3). MIC of sulbactomax were also calculated against certain organisms to determine the dosing schedule of sulbactomax (Table 4).

DISCUSSION

Ceftriaxone is a broad spectrum antibiotic that displays potent activity against gram-positive and gram-negative bacteria (Angehrn *et al*., 1980). The pharmacokinteic parameters of ceftriaxone and sulbactam alone has been reported in several literatures (Foulds *et al*., 1983; Patel *et al*., 1981; Meyers *et al*., 1983). The combination of sulbactam and ceftriaxone is active against all the organisms sensitive to ceftriaxone. In addition, it demonstrates synergistic activity (reduction in MIC for the combination versus those of each component) in a variety of organisms (Shrivastava *et al*., 2009b). There are no pharmacokinetic changes between the two drugs from the compound preparation, and there is no drug interaction between them (Yonghong *et al*., 2006).

The present study was conducted for pharmacokinetics of sulbactomax in comparison with ceftraixone and sulbactam administered alone after intravenous infusion. The results of the study demonstrate that when 1.5 g of sulbactomax containing 1 g of ceftriaxone was administered, the plasma concentrations of ceftriaoxone at different time intervals were found to be simillar as reported by the earlier researchers for 1 g of ceftriaxone (Patel *et al*., 1981; Meyers *et al*., 1983). The concentrations of sulbactam after intravenous infusion observed in our study

Table 2. Pharmacokinetic parameters of ceftriaxone, sulbactam alone and sulbactomax

Pharmacokinetic parameter	Ceftriaxone	Sulbactam	Sulbactomax	
			Ceftriaxone	Sulbactam
Half life $t_{1/2}$ (hr)	5.6 ± 0.436	0.985 ± 0.107	5.2 ± 0.35	0.94 ± 0.038
Elimination rate constant K_{el} (hr $^{-1}$)	0.123 ± 0.01	0.707 ± 0.07	0.133 ± 0.009	0.732 ± 0.029
AUC0-24 (µg.hr/ml)	742 ± 29.56	19.75 ± 1.876	760.16 ± 27.68	20.74 ± 2.347
Cmax (µg/ml)	153.75 ± 6.43	21.83 ± 1.41	152.06 ± 6.65	21.32 ± 1.80

Table 3. Hematological and biochemical parameters

Parameters	Before treatment	On completion of treatment	Normal range
TLC (/mm^3)	8500.25 ± 652.14	8181.25 ± 715.40	4000-10800
ESR (mm/hr)	6.0 ± 1.46	6.4 ± 1.13	Up to 10
Hb (g%)	14.4 ± 0.33	14.11 ± 0.34	14-18
Plasma sugar fasting (mg/dl)	90.0 ± 10.38	80.3 ± 14.39	70-110
Urea (mg/dl)	28.09 ± 2.91	27.18 ± 2.30	Up to 40
Creatinine (mg/dl)	0.78 ± 0.08	0.77 ± 0.09	Up to 1.0
SGOT (IU/l)	25.41 ± 4.86	24.68 ± 3.12	Up to 35
SGPT (IU/l)	28.2 ± 3.90	27.50 ± 2.90	Up to 35
ALP (IU/l)	160.63 ± 7.84	173.25 ± 12.84	65-306

Table 4. MIC and dosing schedule of sulbactomax in organisms causing infections

Sr.No.	Microorganisms	MIC (µg/ml)	Dosing schedule
1.	*E.coli*	0.25	q24 h
2.	*P.vulgaris*	0.50	q24 h
3.	*S.aureus*	32	q8 h
4.	*B.subtilis*	4	q24 h
5.	*A.baumanni*	0.125	q24 h
6.	*K.pneumoniae*	0.625	q24 h
7.	*C.braaki*	2	q24 h
8.	*P.aeruginosa*	2	q24 h
9.	*E.cloacae*	4	q24 h

were agreed with the previous data (Foulds *et al*., 1983).

The half life of ceftriaxone of sulbactomax and ceftriaxone alone that we obtained is comparable with that of reported by other researchers (Patel *et al*., 1981; Meyers *et al*., 1983). The half life of sulbactam of sulbactomax and sulbactam alone is also very close to that of reported by Foulds *et al*. (1983). The elimination rate constant of ceftriaxone of sulbactomax and ceftriaxone alone after intravenous administration that we obtained is very close to reported by Luderer *et al*. (1984). The elimination rate constant of sulbactam of sulbactomax and sulbactam alone after intravenous administration that we obtained is lower to that of reported by Foulds *et al*. (1983).

The area under curve of ceftriaxone of sulbactomax and ceftriaxone alone after intravenous administration that we obtained is slightly lower to reported by Meyers *et al*. (1983). The area under curve of sulbactam of sulbactomax and sulbactam alone after intravenous administration that we obtained is comparable to that of reported by Foulds *et al*. (1983). Our results clearly indicate that there are no pharmcokinetic interactions between two components (ceftriaxone + sulbactam) of the combination.

The concentrations of ceftriaxone of sulbactomax in the plasma remain maintained above the MIC for twenty four hours after intravenous administration of the sulbactomax suggesting that one dose of sulbactomax will be adequete to treat most of the gram-positive and gram-negative bacteria. These observations were agreement with the findings of other researchers (Shannon *et al*., 1980; Wise *et al*., 1980). However, MIC for *S.aureus* is 32 µg/ml because *S. aureus* expresses an additional penicillin binding protein 2 (PBP2) with reduced affinity for beta-lactam antibiotics, therefore it has little bit higher MIC value (Taylor, 2003).

There is no significant alteration in any of the hematological parameters before and after treatment with sulbactomax. Cephalosporin-induced hepatoxicity is rarely observed. Common adverse effects are gallstones (cholelithiasis) or bile lumps. Despite the fact that only a few cases of elevated liver enzymes caused by ceftriaxone have been reported (Longo *et al*., 1998; Bell *et al*., 2005). Lee *et al*. (2009) also reported that ceftriaxone has less side effects. However, in this study, there were no significant changes in SGOT, SGPT and ALP before and after treatment with sulbactomax indicating that sulbacomax is not hepatotoxic. Nechifor *et al*. (1992) also reported that there is no treatment related changes in organs of any species.

Nephrotoxicity has never been reported with any of the broad spectrum cephalosporins (Fekety, 1990). Beauchamp *et al.* (1994) reported that ceftriaxone by itself had no detrimental effects on renal function, lysosomal enzymatic profile, or cellular regeneration. Our results also showed that there is no alteration in any of the parameters of kidney function test after administration of sulbactomax indicating that sulbactomax is safe and not causes nephrotoxicity.

In conclusion, our results indicate that there are no alterations in the pharmacokinetic parameters of the sulbactomax as compared to ceftriaxone and sulbactam administered alone. And based on the MIC and concentration of sulbactomax at different time interval, one dose of the sulbactomax at every twenty four hours is sufficient to treat the infections caused by these organisms.

ACKNOWLEDGMENT

Authors are thankful to management of Venus Medicine Research Centre for providing infrastructure and necessary grant for carrying out this study.

REFERENCES

Angehrn, P., Probst, P.J., Reiner, R. and Then, R.L. (1980): Ro 13-9904, a long-acting broad-spectrum cephalosporin: *in vitro* and *in vivo* studies. Antimicrob. Agents Chemother., **18**, 913-921.

Beauchamp, D., Thériault, G., Grenier, L., Gourde, P., Perron, S., Bergeron, Y., Fontaine, L. and Bergeron, M.G. (1994): Ceftriaxone protects against tobramycin nephrotoxicity. Antimicrob. Agents Chemother., **38**, 750-756.

Bell, M.J., Stockwell, D.C., Luban, N.L., Shirey, R.S., Shaak, L., Ness, P.M. and Wong, E.C. (2005): Ceftriaxone-induced hemolytic anemia and hepatitis in an adolescent with hemoglobin SC disease. Pediatr. Crit. Care Med., **6**, 363-366.

Betrosian, A., Frantzeskaki, F., Xanthaki, A. and Douzinas, E. (2008): Efficacy and safety of high-dose ampicillin/sulbactam vs. colistin as monotherapy for the treatment of multidrug resistant Acinetobacter baumannii ventilator-associated pneumonia. J. Infect., **56**, 432-436.

Bhattacharjee, A., Sen, M.R., Prakash, P. and Anupurba, S. (2008): Role of beta-lactamase inhibitors in enterobacterial isolates producing extended-spectrum beta-lactamases. J. Antimicrob. Chemother., **61,** 309-314.

Caine, V.A., Foulds, G. and Handsfield, H.H. (1984): Therapeutic trial and pharmacokinetics of sulbactam for uncomplicated gonorrhea in men. Antimicrob. Agents Chemother., **26**, 683-685.

Carmeli, Y., Troillet, N., Karchmer, A.W. and Samore M.H. (1999): Health and economic outcomes of antibiotic resistance in *Pseudomonas aeruginosa*. Arch. Intern. Med., **159**, 1127-1132.

Caron, F., Gutmann, L., Bure, A., Pangon, B., Vallois, J.M., Pechinot, A. and Carbon, C. (1990): Ceftriaxone-sulbactam combination in rabbit endocarditis caused by a strain of *Klebsiella pneumoniae* producing extended-broad-spectrum TEM-3β-lactamase. Antimicrob. Agents Chemother., **34**, 2070-2074.

Chambers, H.F. and Fournier, M.A. (1993): Efficacy of cefoperazone in combination with sulbactam in experimental *Staphylococcus aureus* endocarditis in rabbits. J. Antimicrob. Chemother. **32**, 453-458.

Corbella, X., Ariza, J., Ardanuy, C., Vuelta, M., Tubau, F., Sora, M., Pujol, M. and Gudiol, F. (1998): Efficacy of sulbactam alone and in combination with ampicillin in nosocomial infections caused by multiresistant *Acinetobacter baumannii*. J. Antimicrob. Chemother., **42**, 793-802.

Donowitz, G.R. and Masndell, G.L. (1998): β-lactam antibiotics (second of two parts), N. Engl. J. Med., **310**, 490-500.

Fekety, F.R. (1990): Safety of parenteral third-generation cephalosporins. Am. J. Med., **88,** 38S-44S.

Foulds, G., Stankewich, J.P., Marshall, D.C., O'Brien, M.M., Hayes, S.L., Weidler, D.J. and McMahon, F.G. (1983): Pharmacokinetics of sulbactam in humans. Antimicrob. Agents Chemother., **23**, 692-699.

Goldstein, F.W., Péan, Y. and Gertner, J. (1995): Resistance to ceftriaxone and other beta-lactams in bacteria isolated in the community. The Vigil'Roc Study Group. Antimicrob. Agents Chemother., **39**, 2516-2519.

Guerra-Romero, L., Kennedy, S.L., Fournier, M.A., Tureen, J.H. and Täuber, M.G. (1991): Use of ampicillin-sulbactam for treatment of experimental meningitis caused by a beta-lactamase-producing strain of *Escherichia coli* K-1. Antimicrob. Agents Chemother., **35**, 2037-2041.

Lee, H., Jung, D., Yeom, J.S., Son, J.S., Jung, S.I., Kim, Y.S., Kim, C.K., Chang, H.H., Kim, S.W., Ki, H.K., Moon, C.S., Chung, D.R., Peck, K.R., Song, J.H. and Woo, G.J. (2009): Evaluation of ceftriaxone utilization at multicenter study. Korean J. Intern. Med., **24**, 374-380.

Levin, A.S. (2002): Multiresistant Acinetobacter infections: a role for sulbactam combinations in overcoming an emerging worldwide problem. Clin. Microbiol. Infect., **8**, 144-153.

Longo, F., Hastier, P., Buckley, M.J., Chichmanian, R.M. and Delmont, J.P. (1998): Acute hepatitis, autoimmune hemolytic anemia, and erythroblastocytopenia induced by ceftriaxone. Am. J. Gastroenterol., **93**, 836-837.

Luderer, J.R., Patel, I.H., Durkin, J. and Schneck, D.W. (1984): Age and ceftriaxone kinetics. Clin. Pharmacol. Therapeut., **35**, 19-25.

Meyers, B.R., Srulevitch, E.S., Jacobson, J. and Hirschman, S.Z. (1983): Crossover study of the pharmacokinetics of ceftriaxone administered intravenously or intramuscularly to healthy volunteers. Antimicro. Agents Chemother., **24,** 812-814.

Nechifor, M., Buiuc, D., Diaconu, E., Poiată, A., Teslariu E., Filip, C., Negru, A. and Antonescu, C. (1992). Pharmacological studies of sulbactam and its association with semisynthetic beta-lactam antibiotics. Rev. Med. Chir. Soc. Med. Nat. Iasi., **96**, 51-55.

Patel, I.H., Chen, S., Parsonnet, M., Hackman, M.R., Brooks, M.A. Konikoff, J. and Kaplan, S. A. (1981): Pharmacokinetics of ceftriaxone in humans. Antimicrob. Agents Chemother., **20**, 634-641.

Sar, T.K., Mandal, T.K., Das, S.K. and Chakraborty, A.K. (2008): Pharmacokinetics of ceftriaxone in carbontetrachloride-induced hepatopathic and uranyl nitrate-induced nephropathic goats following single dose intravenous administration. Drug Metab. Lett., **2**, 23-28.

Shannon, K., King, A., Warren, C. and Phillips, I. (1980): *In vitro* antibacterial activity and susceptibility of the cephalosporins Ro 13-9904 to beta-lactamases. Antimicrob. Agents Chemother., **18**, 292-298.

Shrivastav, S.M., Singh, R., Tariq, A., Siddiqui, M.R., Yadav, J., Negi, P.S. and Chaudhary, M. (2009a): A novel high performance liquid chromatograpic method for simultaneous determination of ceftraixone and sulbactam in sulbactomax. Int. J. Biomed. Sci., **5**, 37-43.

Shrivastava, S.M., Saurabh, S., Rai, D., Dwivedi, V.K. and Chaudhary, M. (2009b): *In Vitro* microbial efficacy of sulbactomax: a novel fixed dose combination of ceftriaxone sulbactam and ceftriaxone alone. Curr. Drug Ther., **4**, 73-77.

Totir, M.A., Helfand, M.S., Carey, M.P., Sheri, A., Buynak, J.D., Bonomo, R.A. and Carey, P.R. (2007): Sulbactam forms only minimal amounts of irreversible acrylate-enzyme with SHV-1 beta-lactamase. Biochemistry, **46**, 8980-8987.

Taylor, J. (2003): Overview of Antibiotic Resistance in *Staphylococcus aureus.* Expert Rev. Anti-infective Ther., **1**, 45-55.

Wise, R.A., Gillett, A.P., Andrews, J.M. and Bedford, K.A. (1980): Ro 13–9904: A cephalosporin with a high degree of activity and broad antibacterial activity: an *in vitro* comparative study. J. Antimicrob. Chemother, **6**, 595-600.

Yonghong, X., Yuan, L., Zisheng, K. and Jan, L. (2006): Tolerability and pharmacokinetics of multiple dose ceftriaxone/sulbactam injection in chinese. Chinese J. Clin. Pharmacol. Therap., **11**, 458-506.

Zhou, H.H., Chan, Y.P., Arnold, K. and Sun, M. (1985): Single-dose pharmacokinetics of ceftriaxone in healthy Chinese adults. Antimicrob. Agents Chemother., **27**, 192-196.