Academic Sciences International Journal of Pharmacy and Pharmaceutical Sciences

ISSN- 0975-1491 Vol 4, Suppl 4, 2012

Review Article

A REVIEW ON ANALYTICAL METHODOLOGIES FOR THE DETERMINATION OF PIPERACILLIN AND TAZOBACTAM

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Received: 15 Mar 2012, Revised and Accepted: 30 May 2012

ABSTRACT

The combination of piperacillin and tazobactam has been shown to be efficacious for the treatment of intra-abdominal infections, skin and soft tissue infections, moderately severe community-acquired pneumonia, and bacteraemia in neutropenic patients. The pharmacokinetics of piperacillin and tazobactam has been extensively investigated in human subjects. There are some analytical methods in the literature for the analysis of both compounds in the pharmaceutical preparations. In this work, we have recompiled these methods with the aim of to present the different options for the piperacillin and tazobactam determination.

Keywords: Piperacillin, Tazobactum, HPLC, Method Development.

INTRODUCTION

Piperacillin is an extended spectrum beta-lactam antibiotic of the ureidopenicillin class. Piperacillin1;[2s-[2α,5α,6β(s*)]]-6-[[[[(4-ethyl-2,3-dioxo-1-piperazinyl)carbonyl]amino] phenyl-acetyl]amino -3,3-dimethyl-7-oxo-4-thia-1-azabicyclo-[3.2.0]heptane-2-carboxylic acid. It is a semi-synthetic broad-spectrum antibacterial agent and is indicated for the treatment of serious infections caused by susceptible strains of microorganisms. Tazobactum 2; (2s,3s,5r)-3-Methyl-7-oxo-3-(1*h*-1,2,3-triazol-1-ylmethyl)-4-thia-1-a zabicyclo-[3.2.0]heptanes-2-carboxylic acid-4,4-dioxide, is a beta-lactamase antibiotic and is used in combination with beta-lactamase. Pipracillin is normally used together with a beta-lactamase inhibitor such as tazobactam. The combination drug piperacillin/tazobactam is commercially available as e.g. *Tazocin*, *Zosyn*, *Brodactam*, *Piptaz* and as *Trezora*. The combination has activity against many Gram-positiveand Gram-negative pathogens and anaerobes, including *Pseudomonas aeruginosa*.The combination of piperacillin and tazobactum is used to reduce the development of drug-resistant bacteria.. It is a penicillinate sulfone, structurally related to sulbactam being a beta-lactamase inhibitor; it is synergistic with many beta-lactamase liable drugs such as penicillins and cephalosporins[1-2].

Piperacillin is not absorbed orally, and must therefore be given by intravenous or intramuscular
injection; piperacillin/tazobactam is administered intravenously every 6 or 8 hours; the drug may also be given by continuous infusion. It has been shown that the bacteriocidal actions of the drug do not increase with concentrations of piperacillin higher than 4-6xMIC, which means that the drug is concentration-independent in terms of its actions. Piperacillin has instead shown to offer higher bacteriocidal activity when its concentration remains above the MIC for longer periods of time (50% time>MIC showing the highest activity). This higher activity (present in continuous dosing) has not been directly linked to clinical outcomes, but however does show promise of lowering possibility of resistance and decreasing mortality.

Use- Its main uses are in intensive care medicine (pneumonia, peritonitis), some diabetes-related foot infections and empirical therapy in febrile neutropenia[3]

Clinical Pharmacology

Peak plasma concentrations of piperacillin and tazobactam are attained immediately after completion of an intravenous infusion of piperacillin and tazobactam for injection. Piperacillin plasma concentrations, following a 30-minute infusion of piperacillin and tazobactam for injection, were similar to those attained when equivalent doses of piperacillin were administered alone, with mean peak plasma concentrations of approximately 134, 242, and 298 mcg/mL for the 2.25 g, 3.375 g, and 4.5 g piperacillin and tazobactam doses, respectively. The corresponding mean peak plasma concentrations of tazobactam were 15, 24 and 34 mcg/mL, respectively.

Piperacillin is metabolized to a minor microbiologically active desethyl metabolite. Tazobactam is metabolized to a single metabolite that lacks pharmacological and antibacterial activities. Both piperacillin and tazobactam are eliminated via the kidney by glomerular filtration and tubular secretion. Piperacillin is excreted rapidly as unchanged drug with 68% of the administered dose excreted in the urine. Tazobactam and its metabolite are eliminated primarily by renal excretion with 80% of the administered dose excreted as unchanged drug and the remainder as the single metabolite. Piperacillin, tazobactam and desethyl piperacillin are also secreted into the bile.

Both piperacillin and tazobactam are approximately 30% bound to plasma proteins. The protein binding of either piperacillin or tazobactam is unaffected by the presence of the other compound. Protein binding of the tazobactam metabolite is negligible.

Piperacillin and tazobactam are widely distributed into tissues and body fluids including intestinal mucosa, gallbladder, lung, female reproductive tissues (uterus, ovary, and fallopian tube), interstitial fluid, and bile. Mean tissue concentrations are generally 50% to 100% of those in plasma. After the administration of single doses of piperacillin/tazobactam to subjects with renal impairment, the half-life of piperacillin and of tazobactam increases with decreasing creatinine clearance[4-7].

ANALYTICAL METHODS

Estimation In bulk and pharmaceutical dosage forms by RPHPLC method

A simple, rapid, accurate and precise reverse phase high performance liquid chromatographic method has been developed for the simultaneous determination of piperacillin and tazobactum in pharmaceutical dosage forms. Chromatography was carried out on a C-18 column using a mixture of Ammonium acetate and methanol in the ratio of 65:35 v/v as the mobile phase at a flow rate of 1.0 ml/min. and eluents are monitored at 225 nm. The calibration curves were linear over the range of 0.2-80 µg/ml for piperacillin and 0.3-30 µg/ml for tazobactum. The retention times of Piperacillin and tazobactum was found to be 4.8 and 3.2 min., respectively. The intra and inter day variation was found to be less than 1% showing high precision of assay method. Due to its simplicity, rapidness and high precision, the proposed HPLC method may be used for simultaneous determination of these two drugs in pharmaceutical dosage forms[8].

Simultaneous estimation of piperacillin and tazobactam in injection formulations

An high performance liquid chromatography method for simultaneous estimation of piperacillin and tazobactam was developed using Wakosil II, C18, 250 × 4.6 mm, 5 µm column, with mobile phase composition of methanol, phosphate buffer-pH 4 and acetonitrile in the ratio of 1:2:1 v/v/v with the flow rate of 1 ml/min and UV detection at 220 nm. The retention time for piperacillin and tazobactam was found to be 6.4 and 3.1 min respectively. Linearity was observed over the concentration range of 10-80 µg/ml for piperacillin and 2-10 µg/ml for tazobactam. Recovery was found to be 100.7-104.7% for piperacillin and 103.6-105.7% for tazobactam[9].

Estimation by Ion Pair HPLC Method

A simple, sensitive and rapid ionpair high performance liquid chromatographic method was developed for the estimation ceftriaxone sodium (CS) and tazobactum sodium (TS) in pharmaceutical dosage forms. Lichrocart R100-RP18e5)m-C18 column was used with a mobile phase containing mixture of 0.012M tetra butyl ammonium hydroxide in 0.01M potassium dihydrogen phosphate : acetonitrile in the ratio of 70:30 % v/v. The flow rate was 0.8ml/min and effluents were monitored at 220nm and eluted at 4.5 and 6.7 min for tazobactum sodium (TS) and ceftriaxone sodium (CS) respectively. Calibration curve was plotted with a range from 2 to 12) g/ml (CS) and 0.26 to 1.56 (TS) g/ml. The assay was validated for the parameters like accuracy, precision, robustness and system suitability parameters. The proposed method can be useful in the routine analysis for the determination of ceftriaxone sodium and tazobactum sodium in pharmaceutical dosage forms[10].

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