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In Vivo Activities Of Amoxicillin And Amoxicillin-Clavulanate Against Streptococcus Pneumoniae: A Review

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Abstract:

The purpose of the review was to determine if the efficacy of amoxicillin-clavulanate against penicillin-resistant streptococcus pneumoniae could be improved by increasing the pediatric amoxicillin unit dose (90 versus 45 mg/kg of body weight/day) while the clavulanate unit dose maintain at 6.4 mg/kg/day. In this method a rat pneumonia model was used. In that model approximately 6 $\log_{10}$ CFU of one of four strains of S. Pneumoniae (amoxicillin MICs, 2 ug/ml of one strain, and 4 µg/ml two strains, and 8 µg/ml of one strain) were instilled into the bronchi of rat.

The intravenous infusion of amoxicillin-clavulanate was given by computer controlled infusion to approximate the concentrations achieved in the plasma of children following the administration of oral doses of 45/6.4 mg/g/day or 90/6.4 mg/g/g/day divided every 12 h or saline as a control for a total of 3 days. After 2 h of cessation of infusion, the bacterial growth in the lungs were significantly reduced by the 90/6.4 mg/g/day equivalent dosage for strain for which amoxicillin MICs were 2 or 4 µg/ml.

Amoxicillin-clavulanate is an most effective drug for the treatment of respiratory tract infection generally cause by the bacteria streptococcus pneumoniae. Amoxicillin-clavulanate is still accepted as one of the most active oral agent against S. pneumoniae. Clinically, medium level penicillin resistance may be overcome by increasing the dose of penicillin. Some investigators have recommended the use of amoxicillin plus amoxicillin-clavulanate in combination this increase the efficacy and resistance against S. pneumoniae and also retain the activity against other, beta-lactamase producing pathogens of the respiratory tract is H. influenzae and M. catarrhalis. The high dose of amoxicillin-clavulanate has improved activity against penicillin non susceptible strains of S. pneumoniae by using an in vitro model simulating pharmacokinetics in humans and suggested that the dose of amoxicillin of 70 to 90 mg/kg of body weight/day may be sufficient to provide coverage against these strains.

The recommended approved dose of amoxicillin-clavulanate for pediatric use is up to 25/3.2 mg/g/divided every 12 h for less severe infection and 45/6.4 mg/kg/day divided every 12 h for otitis media and other more severe infections. The purpose of this was to determine if the activity of amoxicillin-clavulanate against S. pneumoniae could be extended to include more resistant strains by the use of a higher amoxicillin dosage (90 versus 45 mg of amoxicillin per kg/day).

Keywords: Amoxicillin, amoxicillin-clavulante, streptococcus pneumoniae, penicillin G.

Introduction:

Amoxicillin is the most commonly used antibiotic in the primary treatment of infection. It belongs to the group of β-lactam antibiotics. It is a derivative of penicillin, made by adding an extra amino group to penicillin. Amoxicillin resist the wide range of infection cause by gram negative bacteria as compare to penicillin.

The in vivo activities of amoxicillin and amoxicillin-clavulanate against 17 strains of streptococcus pneumoniae with penicillin MICs of 0.12-8.0 mg/liter were assessed in a cyclophosphamide-induced neutropenic murine thigh infection model. By administration of uranyl nitrate it produced renal impairment to prolong the amoxicillin half-life in the mice from 21 to 65 minutes, simulating human pharmacokinetics. After thigh infection of two hours with 10^5 to 10^6 CFU, for 1 to 4 days group of mice were treated with 7mg of amoxicillin per kg of body weight alone or in combination with clavulanate (ratio, 4:1) for every 8 hours. Organisms for which MICs were 2 mg/liter or less were killed at 1.4 to 4.2 and 1.6 to 4.1 $\log_{10}$ CFU/thigh at 24 h by amoxicillin and amoxicillin-clavulanate, respectively. At 24 h despite therapy with amoxicillin-clavulanate the four strains for which MICs were >4 mg/liter grew 0.2 to 2.6 and 0.6 to 2.3 logs, respectively.

Materials and methods:

Animals: specific pathogen-free Sprague-Dawley rats. It weight about 200 g were used to study. Animal were housed two to a cage. The animal use for this study was proved by smithline beecham animal care and usage committee.

Cannulae implantation: Animal was anesthetized (with N_2O-O_2, in ratio of 1:1 and 3% isoflurane) and the animal were prepare for surgery. The jugular vein and carotid artery were cannulated for blood sampling and administration of antibiotic, respectively, with polythene tubing with internal diameter 0.4 mm and outside diameter 0.8 mm. Both canunulae were illustrated dorsally and extended to the top of the cage through a flexible metal sheath. A polytetrafluoroethylene flange attached to one end of the metal sheath was implanted subcutaneously on back of the rat, and the distal end was fixed to a brass ferrule and swivel joint. This model allowed full movement of rat and also prevent the sheath from being pulled into the cage. Local anesthetic i.e. xylocaine was applied after wound closure. The animal was kept aside for at least 2 days to establishment of infection. The cannulae were kept patent by regular flushing with 0.9% sodium chloride with heparin at 50 μ/ml. A filter was fixed to the swivel joint to ensure the sterility of the infusion fluid.

Respiratory tract infection model:

For collection of clinical isolates from 4 strains of S. pneumoniae were selected. Awareness to amoxicillin-clavulanate, amoxicillin, and penicillin G are present in table 1. Organisms were grew in a night on agar plates of nutrient which containing 7% defibrinated horse blood. Preparation of inocula were done by harvesting the growth from three plates and transfer this in 2 ml of Todd-Hewitt broth, which contained approximately 8 $\log_{10}$ CFU/ml. Immediately the culture was diluted 1:10 in molten nutrient agar which is maintained at 40°C to give a final bacterial inoculums of approximately 6 $\log_{10}$ CFU in 50 µl of molten agar.

TABLE 1

Susceptibilities of isolates used in the experimental infection model.

strain	***MIC (µg/ml)***		
	Amoxicillin	***Amoxicillin-clavulanate***	***Penicillin G***
N1387	**2**	**2**	**2**
1439	**4**	**4**	**8**
410101	**4**	**4**	**4**
RS1	**8**	**8**	**16**

The rat was separate anesthetized by intramuscular injection of fentanyl fluanisone and diazepam. The anesthetized rats were then infected by intrabronchial instillation of 50-µl inoculums, in cooled molten agar, containing S. pneumoniae by means of nonsurgical intubation.

Antimicrobial administration:

Amoxicillin sodium and potassium clavulanate were obtained from SmithKline Beecham Pharmaceuticals. The drug was prepared as sterile solutions of 0.9% sodium chloride at concentration of 2.5 and 5mg/ml for amoxicillin for the 45 and 90 mg/g/day simulations, respectively and 0.8 mg/ml for clavulanate.

All antibiotics were administered by continuous intravenous infusions, when the drug administered orally rate adjusted to simulate the concentrations of amoxicillin-clavulanate achieved in the plasma of children at either 45/6.4 mg/kg/day of amoxicillin/clavulanate or 90/6.4 mg/kg/day in divided doses every 12 h. Dosing commenced at 24 h postinfection.

There were three groups of experimental animals i.e. first is animal receiving dosage of 45/6.4 mg/kg/day of amoxicillin-clavulanate at a simulated given in divided doses every 12 h, second is animal receiving dosage of 90/6.40mg/kg/day of amoxicillin-clavulanate at a simulated given in divided doses every 12 h, and third is untreated control animals, which infused with 0.9% sodium chloride at a rate similar to those at which the other groups were infused. In each group there were seven to eight rats included. Infusion goes for continued for 3 days, with a total of six doses being simulated.

Therapy:

The rats received 0.5 ml of oral doses of amoxicillin trihydrate or ampicillin trihydreate alone or in combination with the β-lactamase inhibitor clavulanic acid. BRL 42715 was given by subcutaneous route because of its less absorption from the GI tract. The doses were selected to produce areas under the serum concentration-time curves (AUCs) for amoxicillin and clavulanic acid similar to those produced in human serum following the administration of standard oral doses of amoxicillin-clavulanate i.e. amoxicillin-clavulanate doses of 250/125, 500/125, and 750/125 mg, respectively (***Table 2***). Therapy commenced at 24 h postinfection and continued twice daily (1000 and 2200 h) or three times daily (0900, 1600, and 2300 h) for 2 to 3 days.

Table 2:

Comparison of AUCs for amoxicillin-clavulanic acid for human and rats

Reference	Human		Rat	
	Dose (mg)	AUC (g . h/ml)	Dose (mg/kg)	AUC (g . h/ml)
Jackson et al. (16)	250/125	13.5/7.8	100/50	12.6/4.9
	500/125	22.5/5.9	200/50	24.4/4.7
Adam et al. (1)	500/125	20.4/8.0		

[a]Values for dose and AUC are expressed as those for amoxicillin/clavulanic acid.

Sampling and assessment:

In all studies, the group of four or five rats were used and sampled at 72 or 96 h after infection. Lungs of each rat are taken and homogenized in 1 ml of TH broth in a colworth stomacher for min. serial dilutions were plated onto blood agar, and the plates were incubated at 37°C for bacterial enumeration.

DISCUSSION

Escalating resistance to antimicrobial agents seen in clinical isolates of S. pneumoniae has reduced the efficacy of many oral drugs used to treat respiratory infections such as otitis media (2–4). Assessing the utility of different antimicrobial agents and respective dosing regimens against resistant pneumococci has thus become a pressing priority. The use of animal models to predict effective dosing regimens in humans is one approach to this problem (5, 7). Despite the many positive aspects of animal models, several criticisms, such as altered pharmacokinetics in animals, have precluded direct application of results to clinical practice in humans. By altering the renal kinetics of amoxicillin in the murine thigh infection model, we have simulated the serum concentration time course of this agent observed in humans. Doses of 7 mg/kg produced a kinetic elimination profile similar to that seen with a 500-mg oral dose in humans with normal renal function. However, subcutaneous absorption of amoxicillin in mice was faster than gastrointestinal absorption of the drug in humans. This resulted in similar peak concentrations but a shorter time above MIC in the mice than would be observed in humans.

Prior experiments in a murine infection model have shown that the in vivo efficacies of antimicrobial agents correlate closely with their respective in vitro activities (6, 20, 24). Several clinical studies have demonstrated a similar relationship between MICs and in vivo outcomes (1, 17). In our infection experiments, the in vivo efficacies of amoxicillin and amoxicillin-clavulanate were inversely related to the MICs for the infecting organisms over a wide range of susceptibilities, including penicillin-resistant organisms. At a dose of 7 mg/kg, bacterial killing was observed for organisms for which MICs were as high as 2 mg/liter. A recent clinical trial of augmentin in acute otitis media demonstrated equal efficacies in patients infected with penicillin-susceptible, -intermediate and resistant strains of S. pneumoniae (15). The highest MIC of amoxicillin observed in this study was 2 mg/liter.

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