COMPARATIVE AMINOGLYCOSIDE INACTIVATION BY β-LACTAM ANTIBIOTICS

EFFECT OF A CEPHALOSPORIN AND SIX PENICILLINS ON FIVE AMINOGLYCOSIDES

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Gentamicin, tobramycin, netilmicin, kanamycin and amikacin were evaluated over time for biologic activity in human serum, in combination with 6 β-lactams. Simple addition of aminoglycoside and 250 μg/ml penicillin produced aminoglycoside inactivation at 8~48 hours. However, all β-lactam antibiotics exhibited decay in human serum at 37°C, even when present as a single component.

All aminoglycosides could be inactivated by penicillins but differed markedly in their susceptibility. Amikacin, at 20 μg/ml, was the least inactivated by any penicillin; netilmicin, at 10 μg/ml, was the next least inactivated. Tobramycin had pronounced loss of biological activity exceeding that of any aminoglycoside, appearing as early as 8 hours.

The ability of the various penicillins to produce aminoglycoside inactivation, in approximate descending order, was; carbenicillin, ticarcillin, penicillin G, oxacillin, methicillin, ampicillin. Cephalothin produced minimal inactivation.

Aminoglycoside inactivation also occurred at 25°C, and with many samples stored at 4°C, although at proportionately slower rates. For samples stored at −20°C, only tobramycin had substantial loss of activity. These data indicate that adequate handling and prompt assay of the specimen are important.

The inactivation of gentamicin by carbenicillin has been well characterized and is widely known[1~18]. The introduction of the aminoglycosides amikacin, tobramycin, and the experimental netilmicin and their use in combination with variety of β-lactam antibiotics has made the study of their interaction necessary.

Certain information concerning the relative stability of some of these combinations is available. However, the evaluation of several commonly used combinations is incomplete; and for other combinations, technical and methodological problems have contributed to inaccuracies.

Because complete data would be very useful, a timed analysis was made of 30 penicillin-aminoglycoside interactions, with emphasis on the more likely combinations. We studied the stability of five aminoglycosides in combination with six penicillins and a cephalosporin under a variety of conditions, including periodic additions of the β-lactam agent. Because β-lactam antibiotics in human serum at 37°C will exhibit rapid and pronounced decay, maintenance of an adequate concentration of biologically active β-lactam is essential for an accurate assessment of aminoglycoside inactivation[19].

Materials and Methods

β-Lactam antibiotics, penicillin G, ampicillin, methicillin, oxacillin, carbenicillin, ticarcillin and cephalothin, at final concentrations of 250, 500 and 1,000 μg/ml were mixed with aminoglycoside antibiotics gentamicin, tobramycin and netilmicin, at a final concentrations of 10 μg/ml, kanamycin at 20 μg/ml.

Penicillin serum concentrations of 250 μg/ml or higher are not uncommon particularly with carbenicillin and ticarcillin; for uniformity of comparison, this was the minimal concentration of penicillin examined. All antibiotic solutions were prepared from laboratory standard powder of assayed potency: gentamicin and netilmicin were supplied by Schering Laboratories, Bloomfield, New Jersey; tobramycin by Eli Lilly Laboratories, Indianapolis, Indiana; amikacin, kanamycin, methicillin, and oxacillin by Bristol Laboratories, Syracuse, New York; penicillin G by Squibb Laboratories, Princeton, New Jersey; ampicillin, Lederle Laboratories, Pearl River, New York; carbenicillin, Pfizer Laboratories, Groton, Connecticut; ticarcillin, Beecham Laboratories, Bristol, Tennessee. Antibiotics were initially dissolved and also diluted and mixed in pooled human serum (Difco). Solutions of a single antibiotic and mixtures of antibiotics were kept at 37°C in a constant-temperature incubator; at 39°C in a water bath; at 4°C in a refrigerator; or multiple aliquots were stored in a freezer at −20°C. For the pulse-addition studies, 0.03 or 0.04 ml of the respective β-lactam antibiotic, at a concentration of 5 or 10 mg/ml (150~400 μg total) was added to a working volume of 2.0 ml of the β-lactam/aminoglycoside mixture. β-Lactam additions were made at 7~12 hours intervals of incubation.

Assay of antibiotic mixture were preformed at 0, 4, 7 or 8, 24 and 48 hours. Control for each mixture was the same concentration of the aminoglycoside as a single component, kept at the same conditions as the β-lactam/aminoglycoside mixture.

Assay of antibiotic activity was performed in duplicate or triplicate by agar-well diffusion[3]. For aminoglycoside, concentrated penicillinase was incorporated into the agar; each assay plate contained freshly made aminoglycoside standards and a control of the initial starting concentration (250, 500 or 1,000 μg/ml) of the respective β-lactam agent to ensure complete inactivation. Assay of the β-lactam was performed in a similar manner, using 4% NaCl in the agar for inhibition of the aminoglycoside. Each assay plate contained freshly made β-lactam standards and a control of the starting concentration of the aminoglycoside. In some experiments, radioimmunoassay of gentamicin (Diagnostic Products), tobramycin and amikacin (Monitor Science) was utilized as an additional assay of each sample.

Results

The β-lactam antibiotics progressively lost antibacterial activity at 37°C in human serum, as shown in Table 1. With a temperature of 39°C the loss was minimally increased from that shown. Methicillin had better stability at 24 hours than the other β-lactam agents examined.

Table 1. Stability of β-lactam antibiotics in human serum at 37°C.

Time (hours)	μg/ml (% activity remaining)						
	Penicillin G	Ampicillin	Methicillin	Oxacillin	Carbenicillin	Ticarcillin	Cephalothin
0	245	260	245	250	240	240	250
24	82 (33)	109 (42)	158 (65)	61 (24)	109 (45)	106 (44)	60 (24)
48	14 (5)	21 (8)	60 (24)	4 (2)	58 (24)	27 (11)	5 (2)

To compensate for this decay, high concentration penicillin was added at various intervals (pulse addition) to increase the activity to former levels. The effect resembled that obtained clinically with repeated doses. The results of pulse addition, as compared to a single initial starting concentration kept at 37°C, are shown in Fig. 1 for penicillin G. The values shown are similar to those obtained with pulse addition for the other β-lactam antibiotics used in these studies.

Single *vs.* Pulse Addition of Penicillin

Fig. 2 illustrates the differences in aminoglycoside activity produced by simple incubation with penicillin (single addition at time 0), compared to pulse (timed, multiple) addition. With a single addition

Fig. 1. Concentration of penicillin G in human serum at 37°C.; single *vs.* multiple additions of drug.
1. Penicillin G added (single addition) at time 0.
2. Penicillin G concentration with multiple additions (arrows indicate addition of drug).

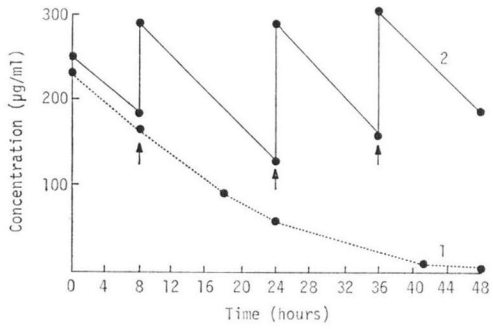
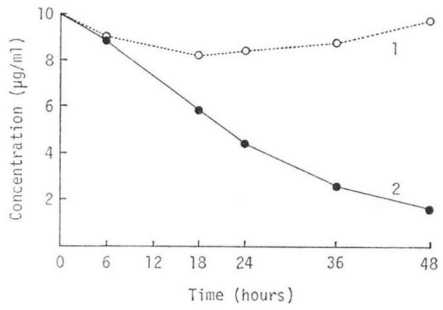


Fig. 2. Differences in aminoglycoside activity produced by single addition of penicillin *vs.* multiple additions of penicillin.
Tobramycin 10 μg/ml, initial concentration.
Penicillin 250 μg/ml; 1. Single addition at time 0. 2. Addition of concentrated penicillin G every 12 hours, to return final concentration to 250 μg/ml.



of penicillin to the aminoglycoside, inactivation was much slower and less extensive. This slowed or arrested inactivation of aminoglycoside correlated with the progressively diminished concentration of penicillin noted with prolonged incubation (*cf.* Table 1, Fig. 1). When the penicillin concentration was periodically augmented to compensate for the natural decay in activity, both the rate and amount of aminoglycoside inactivation were increased.

Comparative Aminoglycoside Inactivation

Utilizing pulse addition of the penicillins, the activity of five aminoglycosides was assayed at various times, as shown in Table 2. The aminoglycosides are listed in groups, corresponding to attainable clinical serum concentrations (gentamicin, tobramycin, netilmicin at 10 μg/ml; kanamycin and amikacin at 20 μg/ml).

Tobramycin had marked loss of activity with all penicillins, exceeding that of any other aminoglycoside. It lost 20% or more of its activity at 7 hours in combination with all penicillins except ampicillin, and at 48 hours tobramycin routinely lost 50 to 75% of its initial activity. Gentamicin was somewhat more stable; it lost considerable activity with carbenicillin and ticarcillin, but maintained over 90% of its activity at 7 hours with ampicillin, oxacillin and methicillin. Netilmicin was the most stable of the aminoglycosides used at the 10 μg/ml concentration. It maintained acceptable activity (less than 20% loss) with all penicillins for at least 7 hours, and evidenced less than 30% loss at 24 hours. At 20 μg/ml, kanamycin exhibited marked inactivation by all penicillins except ampicillin. Amikacin was little affected by any penicillin studied at 250 μg/ml, and retained its activity with minor changes even at 48 hours.

The augmentation of the β-lactam resulted in an initial excess of 50~100 μg/ml immediately following its addition, as can be seen by the values for the penicillins which are shown in parentheses in Table 2. However, the average penicillin concentration was 200~250 μg/ml for the time of the study (Fig. 1). Cephalothin, not shown on the Table, was the least inactivating β-lactam tested. In combination with any aminoglycoside, cephalothin produced a minimal decrease in aminoglycoside activity at 24 hours (5~10%) and only a 15~20% loss of activity at 48 hours.

Table 2. Comparative aminoglycoside inactivation.

	Time	Penicillin G	Ampicillin	Methicillin	Oxacillin	Carbenicillin	Ticarcillin
Gentamicin (μg/ml)	0	9.8 (252)*	10.5 (256)	9.9 (259)	10.0 (241)	9.6 (235)	9.0 (253)
	4	9.3	10.1	9.3	10.1	8.8	8.5
	7	8.3 (290)	10.0 (340)	9.1 (239)	9.5 (278)	8.2 (270)	8.5 (256)
	24	7.7 (320)	8.3 (286)	7.6 (250)	8.8 (312)	5.8 (268)	5.7 (269)
	48	4.0 (182)	6.5 (102)	5.2 (116)	6.8 (187)	3.1 (153)	3.5 (133)
Tobramycin (μg/ml)	0	10.0 (250)	10.1 (307)	9.7 (248)	9.6 (250)	10.0 (240)	10.5 (248)
	4	8.7	9.6	8.6	8.9	8.5	8.0
	7	8.1 (300)	9.3 (309)	8.2 (240)	8.2 (302)	7.1 (274)	7.0 (256)
	24	6.2 (302)	8.1 (300)	6.6 (264)	6.6 (308)	4.4 (298)	5.3 (282)
	48	3.0 (211)	6.0 (99)	5.0 (118)	4.4 (145)	2.4 (180)	3.0 (133)
Netilmicin (μg/ml)	0	10.0 (264)	10.7 (261)	10.0 (248)	10.1 (248)	9.0 (260)	10.2 (268)
	4	9.3	10.6	9.1	9.2	9.0	9.0
	7	9.2 (308)	10.0 (340)	8.3 (268)	9.3 (291)	8.3 (285)	9.2 (250)
	24	8.2 (340)	10.0 (268)	7.8 (263)	9.6 (271)	7.7 (268)	7.7 (276)
	48	5.0 (179)	8.3 (106)	6.1 (127)	7.1 (155)	4.6 (155)	6.1 (139)
Kanamycin (μg/ml)	0	21.1 (268)	20.2 (242)	20.3 (278)	22.8 (252)	20.8 (268)	20.2 (256)
	4	18.5	20.0	17.5	19.5	18.8	16.5
	7	17.4 (281)	19.3 (330)	16.2 (252)	17.5 (308)	16.5 (289)	16.5 (232)
	24	13.2 (352)	17.1 (281)	13.0 (291)	15.4 (288)	12.3 (312)	14.0 (248)
	48	6.2 (215)	14.9 (115)	8.5 (157)	12.2 (124)	8.7 (173)	8.8 (109)
Amikacin (μg/ml)	0	20.2 (292)	19.7 (238)	19.8 (239)	20.0 (248)	19.0 (250)	18.7 (250)
	4	20.0	19.3	19.3	19.3	19.3	18.7
	7	20.1 (302)	18.9 (310)	18.4 (262)	18.6 (282)	19.2 (282)	18.6 (250)
	24	19.8 (302)	17.3 (275)	17.4 (250)	16.5 (360)	19.3 (360)	16.5 (248)
	48	16.3 (103)	15.9 (104)	16.1 (116)	16.1 (280)	15.2 (280)	15.4 (106)

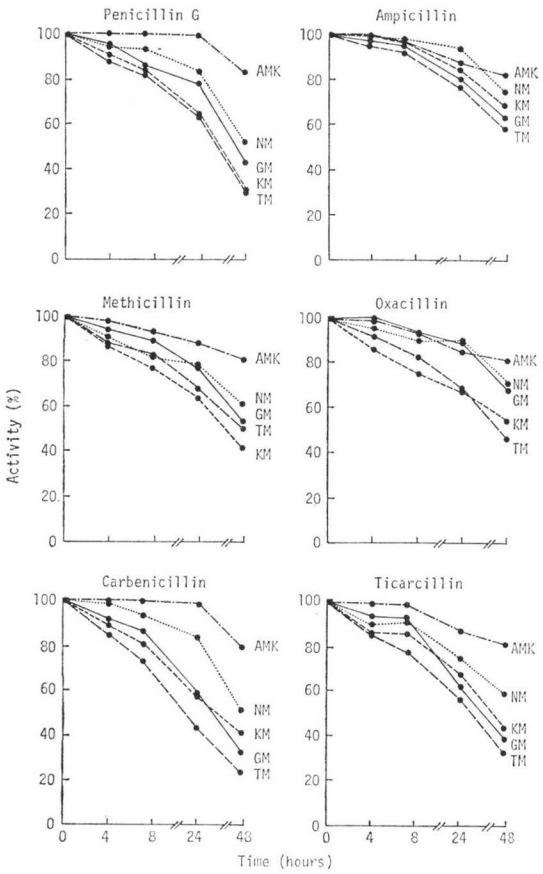
* (Resultant concentration in μg/ml of the respective penicillin added at this time point).

Comparative Effect of Various Penicillins

Fig. 3 shows the comparative changes in aminoglycoside activity produced by each of the penicillins. Penicillin G, carbenicillin and ticarcillin produced a marked decrease in activity of all aminoglycosides except amikacin (AMK). Ampicillin was the least inactivating penicillin. The β-lactamase-resistant penicillins, methicillin and oxacillin, had an intermediate effect, which appeared to vary with the aminoglycoside examined. Methicillin produced more inactivation of kanamycin (KM), netilmicin (NM) and gentamicin (GM) than did oxacillin. Tobramycin (TM) had approximately 50% inactivation at 48 hours with both methicillin and oxacillin. Amikacin was very stable in combination with all β-lactams: its activity was unchanged for at least 24 hours by penicillin G, ampicillin and carbenicillin, and even at 48 hours, no penicillin at 250μg/ml caused amikacin activity to fall below 80% of initial values.

All aminoglycosides were tested with higher concentrations of penicillin, and gave proportionately faster rates and more extensive total inactivation with higher penicillin ratios. Amikacin, incubated with 1,000 μg/ml of carbenicillin, a 50: 1 ratio, lost approximately 30% of its activity at 24 hours, and 45% at 48 hours. The one exception occurred when amikacin was incubated with 1,000 μg/ml of ampicillin; under these conditions amikacin retained over 80% of its activity throughout the 48-hour observa-

Fig. 3. Comparative effect of various penicillins on aminoglycoside activity.



tion period. The two most stable aminoglycosides, netilmicin and amikacin, were compared at equal penicillin - aminoglycoside ratios of 50: 1. With all six penicillins, the stability of these two agents differed by only a few percent.

Effect of Temperature

Aminoglycoside inactivation by penicillins occurred even at 4°C, as shown in Table 3. While the decrease in activity was much slower than that observed at 37°C, some samples stored for 3 days or longer at refrigerator temperature gave depressed values for the aminoglycoside as compared to the starting concentration. Amikacin was little affected by any agent studied. Netilmicin was affected only by storage with carbenicillin; with all other β-lactams it retained 90% or more of its initial activity for 7 days or longer. In contrast, tobramycin had marked loss of activity with all penicillins. The loss was most pronounced with carbenicillin and ticarcillin, but also of importance with methicillin and penicillin G. Kanamycin gave depressed values when stored with ampicillin.

Most samples of aminoglycoside stored with a penicillin at −20°C for 7 and 14 days had rela-

Table 3. Aminoglycoside plus penicillin in human serum: Effect of storage at 4°C on aminoglycoside activity.

	Day	Pen G	Amp	Meth	Ox	Carb	Tcr
Tobramycin	1	92*	98	98	92	84	91
	3	81	92	74	85	65	59
	7	70	84	63	78	33	30
	14	58	65	39	72	14	14
Gentamicin	1	95	96	100	97	93	94
	3	98	97	96	102	76	75
	7	92	94	72	97	61	65
	14	87	77	65	102	45	49
Netilmicin	1	93	99	100	96	91	96
	3	88	98	94	95	87	94
	7	93	93	94	102	75	93
	14	93	99	87	102	70	87

	Day	Pen G	Amp	Meth	Ox	Carb	Tcr
Kanamycin	1	93	96	86	100	93	104
	3	81	78	86	98	78	80
	7	75	64	71	87	54	56
	14	65	47	53	87	38	41
Amikacin	1	96	100	100	97	101	98
	3	96	103	100	94	98	92
	7	98	95	96	96	99	94
	14	99	99	99	101	91	93

* Percent aminoglycoside activity remaining.

Pen G : Penicillin G
Amp : Ampicillin
Meth : Methicillin
Ox : Oxacillin
Carb : Carbenicillin
Tcr : Ticarcillin

Table 4. Comparison of bioassay and radioimmunoassay.
Measurements of gentamicin alone and following inactivation by carbenicillin.

Time (hours)	Bioassay (μg/ml)		Radioimmunoassay (μg/ml)	
	Gentamicin alone	Gentamicin+ carbenicillin	Gentamicin alone	Gentamicin+ carbenicillin
0	9.5	9.6	9.2	9.1
24	10.0	4.4	9.8	4.3
48	9.5	3.6	10.6	3.9

Starting concentrations: gentamicin 10 μg/ml, carbenicillin 500 μg/ml. Human serum, 37°C.

tively stable value. However, tobramycin lost 15~20% of its initial activity after 1 and 3 days, and 30~ 40% after 7 and 14 days.

Effect of Assay Method

As can be seen from the example in Table 4 there was excellent correlation between bioassay and radioimmunoassay with both intact and penicillin-inactivated aminoglycoside. None of the samples subjected to radioimmunoassay registered aminoglycoside that had been inactivated by penicillin.

Discussion

The inactivation of gentamicin by carbenicillin was originally reported by McLAUGHLIN and REEVES[1]. RIFF and JACKSON[2,3,4] noted that with admixture of the drugs in solutions, the aminoglycoside inactivation was relatively rapid; in contrast, the reaction between these compounds in serum was much slower. This physiochemical property has been reported between other aminoglycoside/penicillin combinations[3,4,7~18]. An amino group of the aminoglycoside opens the β-lactam ring of the penicillin forming an amide resulting in inactivation of both compounds[20] (personal communication P.J. DANIELS). The one-for-one inactivation has far more effect on the concentration of active aminoglycoside than it dose on the penicillin because the amount of penicillin is typically 10~15 times greater than that of the aminoglycoside. The biologically active aminoglycoside remaining is decreased substantially, while the decrease in penicillin is minimal.

In vitro studies reporting inactivation of aminoglycosides by penicillins, show the process to be dependent upon time, concentration, temperature, and composition of the medium[4,7,12].

It has been reported[22] and has been generally assumed that older, commonly used penicillins do not inactivate aminoglycosides. However, all penicillins have limited stability once dissolved in an aqueous medium[19,20]; refrigeration prolongs penicillin stability in an aqueous solution, but the life of the intact molecule is markedly shortened by exposure to 25°C (room temperature) and further shortened at 37°C (body and incubation temperatures). The loss of activity is due to opening of the lactam ring. All the β-lactams studied exhibited decay in activity with time at 37°C as shown in Table 1. An intact β-lactam molecule is essential for the inactivation of an aminoglycoside[4,7]. The reaction between penicillin and aminoglycoside does not occur if the integrity of the β-lactam ring is destoyed.

The general assumption that little or no interaction occurs between aminoglycosides and older penicillins is a result of the rapid decay of the penicillin being studied. There was not sufficient intact penicillin to accomplish the inactivation of the aminoglycoside.

The periodic administration (pulse addition) of penicillin was designed to return the concentration of penicillin to its original amount, and compensate for the loss of penicillin activity (Fig. 2).

Replacing the decayed penicillin by periodic additions clearly produced greater inactivation of the aminoglycoside than did a single addition. When aminoglycosides were exposed to penicillins whose biologically active concentrations had been replenished by periodic addition, all penicillins were capable of inactivating aminoglycosides (Table 2, Fig. 3). Moreover, the pulse addition, which more nearly

simulates the clinical situation, resulted in greater total inactivation of aminoglycoside than previously has been reported[10,16,18].

Cephalothin produced the least inactivation of any β-lactam studied. Ampicillin was the least inactivating penicillin studied. The β-lactamase resistant penicillins, methicillin and oxacillin, inactivated the aminoglycosides less than carbenicillin and ticarcillin. As previously reported both *in vitro* and *in vivo*[11,12,14,16,18], ticarcillin inactivated aminoglycosides to a lesser extent than did carbenicillin. This observation suggests that the combination of ticarcillin and aminoglycoside may be more acceptable as an antibiotic combination. Amikacin was the least inactivated by any of the penicillins studied, while tobramycin had the greatest loss. If other factors are equal, amikacin and ticarcillin would seem to be a logical combination for therapy of serious Gram-negative infections.

Measurement of peak and trough levels of aminoglycosides has become essential to avoid the risks of toxicity, yet maintain adequate serum concentration for antibacterial activity. Specimens should be processed rapidly, since significant inactivation of the aminoglycosides can occur *in vitro* in serum containing an aminoglycoside/penicillin combination. Placing the specimen on ice may be helpful to slow this reaction; however, the inactivation of the aminoglycoside can occur even at lower temperatures. Samples lose activity at 25°C (room temperature) and at 4°C (refrigerator) (Table 3). Kanamycin gave depressed values when stored with ampicillin. Freezing did not totally prevent aminoglycoside inactivation by penicillins. Storage of samples for months prior to assay can result in significant loss of activity. Samples to be stored for long periods of time prior to assay should have the penicillin inactivated by a penicillinase prior to freezing.

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