SYNERGISTIC ACTIVITY *IN VITRO* OF THE NEW CEPHALOSPORIN ANTIBIOTIC HR 810 WITH GENTAMICIN AND AMIKACIN AGAINST MULTIRESISTANT PATHOGENS

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The new cephalosporin antibiotic HR 810 has an outstandingly high antibacterial activity against a wide range of Gram-positive and Gram-negative bacteria[1~4]. It has been reported[4] that even against selected clinical isolates which are highly resistant to third generation cephalosporins, HR 810 possesses a considerable antibacterial activity. The minimal inhibitory concentrations (MICs) of HR 810 however against these selected strains are with $8 \sim 16$ μg/ml in most cases higher than for other clinical isolates.

The aim of this study was to investigate whether these strains with reduced susceptibility to HR 810 can be inhibited in a synergistic manner by combinations of HR 810 with aminoglycoside antibiotics.

The combined activity of HR 810 (synthesized by Hoechst AG, Frankfurt, Germany) and amikacin or gentamicin was measured using the checkerboard method in conjunction with the agar dilution test. Mueller-Hinton-Agar (Difco) was used as the test medium. Suspensions of stationary cultures, diluted 1: 10, of the test strains served as inocula. Agar plates were inoculated with a multipoint inoculator which delivered 5×10^5 colony forming units per spot. After 18 hours at 37°C, the MICs were read both from the controls containing only one of the antibiotics and from the plates containing the combinations. If the MIC of an aminoglycoside antibiotic exceeded 128 μg/ml, the strain was not included in the study with the respective antibiotic combination.

The "fractional inhibitory concentrations" were calculated from these values according to BERENBAUM[5].

Definition of Synergism: A combination of two substances is usually considered to be synergistic when both compounds together inhibit the test strain at concentrations of 1/4 of the MIC of each compound alone or less[6]. If this criterion is applied to the method of the

Table 1. Antibacterial activity of HR 810, gentamicin and amikacin alone and synergistic effect in combination against multiresistant clinical isolates.

Strain	HR 810	Gentamicin		Amikacin	
	MIC	MIC	FIC	MIC	FIC
Pseudomonas aeruginosa 4	16	128	0.19	>128	n.t.
P. aeruginosa 9	8	2	0.37	0.5	0.5
P. aeruginosa 15	8	128	0.26	8	0.5
P. aeruginosa 80	8	8	0.5	8	0.5
P. aeruginosa 42	8	4	0.5	4	0.75
P. maltophilia J 64	64	64	0.37	128	0.75
Citrobacter sp. 2901	8	16	0.37	128	0.75
Citrobacter sp. 4887	8	32	0.12	1	0.26
Enterobacter cloacae 89	4	0.125	0.5	2	0.37
Staphylococcus aureus 20924	8	16	1.0	2	1.0
S. aureus 20212	4	8	1.0	2	1.0
S. aureus 22130	8	8	0.75	2	1.0
Streptococcus sp. D 756	16	16	0.69	128	0.75
Streptococcus sp. D Ed	16	16	0.63	128	1.0
Streptococcus sp. D ATCC 23241	8	8	0.56	128	1.0
Streptococcus sp. D Ent.	64	8	0.63	>128	n.t.
Streptococcus sp. D 21777	16	16	0.63	>128	n.t.
Streptococcus sp. D 26777	16	16	0.63	>128	n.t.

n.t.=not tested.

(MIC in μg/ml)

"fractional inhibitory concentration (FIC)", an FIC value of ≤ 0.5 shows synergism, whereas an FIC value of 1.0 expresses additive action.

All bacterial strains used were selected from clinical isolates obtained from various hospitals in Germany. The strains chosen are resistant against most third generation cephalosporins (MIC $\geqq 32$ μg/ml)[3] and are moderately susceptible against HR 810 (MIC 4~64 μg/ml).

As Table 1 shows, most of the strains are moderately sensitive or resistant also to the action of the aminoglycosides. Against the three *Staphylococcus* strains tested, the action of the combined antibiotics is clearly of the additive type (FIC=1 and 0.75). Against the 6 strains of enterococci, there is a more than additive effect with the HR 810/gentamicin combination. Three of the enterococcal strains are highly resistant against amikacin (MIC >128 μg/ml) and were therefore excluded from the study. For the three strains with a MIC from amikacin of 128 μg/ml, the combination shows an additive effect.

The combination HR 810/gentamicin is highly synergistic against all 6 tested *Pseudomonas* strains, both *Citrobacter* strains and the *Enterobacter* strain.

With the HR 810/amikacin combination this effect is less pronounced and for three strains (FICs of 0.75) is a more than additive rather than a synergistic effect.

The synergism found gives cause for hope that in the chemotherapy of infections with multiresistant strains, clinical success can be obtained even in cases where HR 810 shows MICs near or even higher than the susceptibility breakpoint.

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