Synergism between Ciprofloxacin and Fosfomycin In Vitro

Because of the mode of action of 4-quinolones, for theoretical reasons a synergism or antagonism is not to be expected in combinations with β-lactams or aminoglycosides. On the contrary, the interaction of the substances is likely to be indifferent, as was also observed in the investigations of *Haller* (1), in which the combination effect of ciprofloxacin with nine different β-lactam antibiotics was as a rule additive or indifferent against Enterobacteriaceae and Pseudomonadaceae. In an earlier study, the interaction of nalidixic acid and fosfomycin was investigated in multiresistant Enterobacteriaceae and *Pseudomonas aeruginosa* strains (2, 3). Synergism was observed in a major proportion. For this reason the interaction of the new quinolone ciprofloxacin with fosfomycin was analysed against *P. aeruginosa* and *Staphylococcus aureus*.

All microorganisms were freshly isolated from clinical material of patients from two surgical intensive-care units. Reference strains were *P. aeruginosa* ATCC 15442 and *S. aureus* ATCC 25923. Fosfomycin (Boehringer Mannheim, FRG) was used in concentrations of 128 to 0.25 mg/l, and ciprofloxacin (Bayer AG, Leverkusen, FRG) from 2 to 0.03 mg/l. The investigation of the combination effect was carried out with checkerboard titration using microtiter plates; test medium was Mueller-Hinton substrate (CM 405, Oxoid, Wesel) which was not supplemented with glucose-6-phosphate. The bacterial inoculum was 10^6/ml. After incubation for 18 h at 36°C ±1° C, the minimum inhibitory concentrations (MIC's) were estimated visually. The following interpretation was applied for the calculation of the fractional inhibitory concentration index (FIC index) (4): FIC ≤ 0.5: synergism, FIC = 0.51–1.0: addition, FIC > 1–2: indifference, FIC >2: antagonism.

The results are summarized in Table 1. There was synergism against *P. aeruginosa* in 78% and additive behavior in 22% of the strains; the combination showed synergism against *S. aureus* in 95% and additive effects in only one strain of this species. For example, the MIC of fosfomycin for *P. aeruginosa* (8 mg/l) was reduced to 0.5 mg/l in the presence of 0.25 mg/l ciprofloxacin.

Table 1: Results of the combination study between ciprofloxacin and fosfomycin.

Bacterial species	Effect	
	Synergistic	Additive
Pseudomonas aeruginosa (n = 37)	29 (78%)	8 (22%)
Staphylococcus aureus (n = 20)	19 (95%)	1 (5%)

With *S. aureus*, for example, there is a reduction of the MIC of fosfomycin from 128 to 2 mg/l in the presence of 0.5 mg/l ciprofloxacin in one strain.

As a rule, very few microorganisms additionally investigated, such as *Escherichia coli, Klebsiella pneumoniae, Proteus mirabilis* and also *Streptococcus faecalis* strains, showed indifferent or additive effects in the combination of fosfomycin/ciprofloxacin.

The molecular biological basis is unclear for the synergism observed between fosfomycin and ciprofloxacin. In an early growth phase, fosfomycin inhibits the cell wall biosynthesis by inactivating phosphoenolpyruvate and thus the muramic acid synthesis. Glycerol-3-phosphate and glucose-6-phosphate act as inducers for the transport system of fosfomycin into the cytoplasm (5). On the other hand, 4-quinolones inhibit bacterial gyrase activity (6). It is conceivable that a channeling-in effect of fosfomycin into the bacterial cell for 4-quinolones in certain species leads to the bactericidal effect which then has a rapid onset. The synergistic action of the combination of fosfomycin and ciprofloxacin might be of clinical interest in severe *S. aureus* or *P. aeruginosa* infections, especially since the two substances also have bactericidal efficacy against microorganisms located intracellularly.

U. Ullmann

Literature

1. **Haller, J.:** Comprehensive evaluation of ciprofloxacin in combination with β-lactam antibiotics against Enterobacteriaceae and *Pseudomonas aeruginosa.* Arzneim.-Forsch./Drug. Res. 36 (1986) 226–229.
2. **Ullmann, U.:** Synergism between fosfomycin and nalidixic acid *in vitro.* J. Antimicrob. Chemother. 5 (1979) 612–613.
3. **Ullmann, U., Lindemann, B.:** *In vitro* investigations on the action of fosfomycin alone and in combination with other antibiotics on *Pseudomonas aeruginosa* and *Serratia marcescens.* Arzneim.-Forsch./ Drug Res. 30 (1980) 1247–1249.
4. **Krogstad, D., Moellering, R. C.:** Combination of antibiotics, mechanisms of interaction against bacteria. In: *Lorian, V.* (ed.): Antibiotics in Laboratory Medicine. Williams and Wilkins, Baltimore, London 1980, pp. 298–341.
5. **Kahan, F. M., Kahan, J. S., Cassidy, P. J., Kropp, H.:** The mechanism of action of fosfomycin (phosphonomycin). Ann. N. Y. Acad. Sci. 235 (1974) 364–386.
6. **Gutzler, F.:** Gyrasehemmer – eine neue Klasse von Antibiotika. Inn. Med. 12 (1985) 139–146.

Prof. Dr. *U. Ullmann,* Department of Medical Microbiology, University of Kiel, Brunswiker Str. 4, 2300 Kiel, FRG.

Human Parvovirus B19 Infection and Juvenile Chronic Polyarthritis

Introduction

The human parvovirus B19, a small single-stranded DNA virus, was discovered by counter-immunoelectrophoresis during a screening program for hepatitis B (1), and in the last few years, a wide spectrum of diseases has been associated with B19 infection. Most frequently, erythema infectiosum has been associat-

T. F. Schwarz, M.D., *M. Roggendorf,* M.D., Prof. *F. Deinhardt,* M.D., Max von Pettenkofer Institute for Hygiene and Medical Microbiology, University of Munich, Pettenkoferstr. 9a, D-8000 München 2; Prof. *H. Suschke,* M.D., Pediatric Department, University of Munich, Pettenkoferstr. 8a, D-8000 München 2.
Address for proofs and reprints: *T. F. Schwarz,* M.D.

Infection 15 (1987) Nr. 4

ed with this infection (2). Following B19 infection, aplastic crises have been observed in patients with chronic haemolytic anaemia (3), such as sickle cell anaemia, thalassaemia and hereditary spherocytosis. It has been shown that red precursor cells are target cells of this virus (4) and that an infection with B19 can inhibit erythropoesis for up to 26 days (5). B19 infection in pregnancy can cause hydrops fetalis, resulting in fetal loss in about 40% of cases (6).

The role that human parvovirus B19 plays in the etiology of chronic polyarthritis is unclear (7, 8). Rheumatoid arthritis may develop in genetically predisposed persons after B19 infection (9), and B19 infection in children may result more often in persistent disease than in adults (10).

Case Report

We report here a case of chronic juvenile polyarthritis in an eight-year-old girl. In July 1985, she had fever and headache, and a few days later complained of pain in her wrists and ankles and finally in the metacarpophalangeal joints. No rash developed. There was no personal or family history of joint disorders. Clinically, she had tender stiffness in the cervical spine, shoulders, both hips, both wrists and metacarpophalangeal joints and ankles. The blood count was normal, antinuclear factors were positive with a titer of 1:40 (IFT) and rheumatoid factor (latex agglutination) was negative. A serum sample taken four weeks after the onset of symptoms had an anti-B19 IgM titer of 10^{-5}, determined by ELISA. IgM antibodies against common viruses (EBV, CMV, rubella) were negative, and B19 was not detected in this serum sample by DNA hybridisation. HLA typing revealed the presence of HLA-DRw11 (5), which is associated with early onset of pauciarticular juvenile chronic polyarthritis.

Thirteen months after the B19 infection, the patient's metacarpophalangeal joints, elbows, knees and ankles are still swollen. The erythrocyte sedimentation rate is 48/91, and the haemoglobin concentration ranged between 9.0 and 10.6 g/dl throughout this period. Anti-B19 IgM was still detectable at a low titer (10^{-1}) and anti-B19 IgG had a titer of 10^{-5}. B19 DNA hybridisation remained negative.

Discussion

A viral etiology of juvenile chronic polyarthritis has often been discussed, but no agent has been identified. In this patient, it is highly likely that B19 triggered the onset of juvenile chronic polyarthritis. However, we do not believe that B19 is the general cause of juvenile chronic polyarthritis but think that genetically predisposed patients have a higher risk of developing juvenile chronic polyarthritis following B19 infection. It has been reported that arthralgia often occurs after B19 infection, usually associated with erythema infectiosum (9), and it seems possible that in some cases arthralgia is the first symptom of the onset of polyarthritis. In differential diagnosis, B19 infection should be considered in all cases of arthropathy following an exanthematic or flu-like disease. The influence of sex, age and HLA on the severity and duration of arthropathy associated with B19 infection should be studied further.

T. F. Schwarz, M. Roggendorf, H. Suschke, F. Deinhardt

Literature

1. **Cossart, Y. E., Cant, B., Field, A. M., Widdows, D.:** Parvovirus-like particles in human sera. Lancet I (1975) 72–73.
2. **Anderson, M. J., Lewis, E., Kidd, J. M., Hall, S. M., Cohen, B. J.:** An outbreak of erythema infectiosum associated with human parvovirus infection. J. Hyg. Camb. 93 (1984) 85–93.
3. **Lefrère, J. J., Courouce, A. M.:** Human parvovirus infections in France 1984–1986. Lancet I (1987) 166–167.
4. **Ozawa, K., Kurtzman, G., Young, N.:** Replication of the B19 parvovirus in human bone marrow cell cultures. Science 233 (1986) 883–886.
5. **Anderson, M. J., Higgins, P. G., Davis, L. R., Willman, J. S., Jones, S. E., Kidd, J. M., Pattison, J. R., Tyrrell, D. A. J.:** Experimental parvoviral infection in humans. J. Inf. Dis. 152 (1985) 257–265.
6. **Mortimer, P. P., Cohen, B. J., Buckley, M. M., Cradock-Watson, J. E., Ridehalgh, M. K., Burkhardt, F., Schilt, U.:** Human parvovirus and the fetus. Lancet II (1985) 1012.
7. **Lefrère, J. J., Meyer, O., Menkes, C. J., Beaulieu, M. J., Courouce, A. M.:** Human parvovirus and rheumatoid arthritis. Lancet I (1985) 982.
8. **White, D. G., Mortimer, P. P., Blake, D. R., Woolf, A. D., Cohen, B. J., Bacon, P. A.:** Human parvovirus arthropathy. Lancet I (1986) 419.
9. **Cohen, B. J., Buckley, M. M., Clewley, J. P., Jones, V. E., Puttick, A. H., Jacoby, R.:** Human parvovirus infection in early rheumatoid and inflammatory arthritis. Ann. Rheum. Dis. 45 (1986) 832–838.
10. **Reid, D. M., Reid, T. M. S., Brown, T., Rennie, J. A. N., Eastmond, C. J.:** Human parvovirus-associated arthritis: a clinical and laboratory description. Lancet I (1985) 422–424.

Letter to the Editor

Re: Epidemiological Aspects of Acute Viral Hepatitis in Portugal, Infection 14 (1986) p. 71

A report on 400 Portugese patients with acute viral hepatitis hospitalised during a four year observation period, revealed that the majority of episodes among children and those aged below 15 years were mainly due to hepatitis A virus (HAV) with hepatitis B virus (HBV) and Non-A, Non-B virus (NANB) having a minor role (1). The infrequent causative role of HBV in acute viral hepatitis in that age group should not appear odd or unexpected since a follow-up of 98 HBV seronegative children under five years of age in Taiwan revealed that the acquisition of HBV marker positivity was not associated with any illness that could have been recognised as acute hepatitis (2). Moreover, longitudinal studies in 12 Eskimo villages located in Southwestern Alaska also revealed clinical evidence of acute hepatitis in only 19.8% of children below four years of age, in contrast to 33.3% among adults aged 30 years or more (3). In view of the infrequent role of HBV in acute hepatitis during childhood, it may be appropriate to suggest that HAV rather than HBV is the virus responsible for acute illness in two Portugese children with serological evidence of dual viral exposure (1). Obviously the extent of HBV infection in Portugese children could be assessed through a serological survey for different HBV markers of chil-

Dr. *S. C. Arya*, M.B.B.S., Ph. D., M-122, of part 2, Greater Kailash-II, New Delhi 110048, India.