

# European Journal of Medical Research

Official Organ » Deutsche AIDS-Gesellschaft« B1 32

VOLUME 9 / NUMBER 7

JULY 30, 2004

Editorial

Impact Factor .....333

*F. W. Schardt*

Clinical Effects of Fluconazole in Patients  
with Neuroborreliosis .....334

*O. Kilian, J. Flesch, S. Wenisch, B. Taborski,  
A. Jork, R. Schnettler, T. Jonick*

Effects of Platelet Growth Factors on  
Human Mesenchymal Stem Cells and  
Human Endothelial Cells in vitro .....337

*B. Willershausen, B. Hagedorn, H. Tekyatan,  
B. Briseño Marroquin*

Effect of Calcium Hydroxide and  
Chlorhexidine Based Gutta-Percha Points  
on Gingival Fibroblasts and Epithelial  
Tumor Cells .....345

*H. J. Hamre, C. Becker-Witt, A. Glockmann,  
R. Ziegler, S. N. Willich, H. Kiene*

Anthroposophic Therapies in Chronic  
Disease: The Anthroposophic Medicine  
Outcomes Study (AMOS) .....351

*F. Hanisch, H. W. Kölmel*

Genotype-phenotype Analysis in  
Early-onset Alzheimer's Disease due to  
Presenilin-1 Mutations at Codon 139 .....361

*U. R. Juergens, M. Stöber, H. Libertas,  
W. Darlath, A. Gillissen, H. Vetter*

Different Mechanisms of Action of  
Beta2-adrenergic Receptor Agonists:  
A Comparison of Reproterol, Fenoterol  
and Salbutamol on Monocyte Cyclic-AMP  
and Leukotriene B4 Production in vitro .....365

Eur J Med Res 9(7):333-370(2004)

ISSN 0949-2321

Indexed in: Index Medicus and MEDLINE

Indexed in: SciSearch® (Science Citation Index-Expanded), ISI Alerting Services (incl. Research Alert®),  
Current Contents®/Clinical Medicine

Indexed in: Chemical Abstracts

Medical Scientific Publications



I. Holzapfel Munich Germany

## CLINICAL EFFECTS OF FLUCONAZOLE IN PATIENTS WITH NEUROBORRELIOSIS

Bayerische Julius-Maximilians-Universität Würzburg, Germany

**Abstract:** Eleven patients with neuro-borreliosis had been treated with 200 mg fluconazole daily for 25 days after an unsuccessful therapy with antibiotics. At the end of treatment eight patients had no borreliosis symptoms and remained free of relapse in a follow-up examination one year later. In the remaining four patients, symptoms were considerably improved. At the end of therapy immune reactivity (IgM+) disappeared in three patients. Since *Borrelia* spp. are almost exclusively localised intracellular, they may depend on certain metabolites of their eucaryotic host cell. Inhibition of P450 and other cytochromes by fluconazole may incapacitate *Borrelia* upon longterm exposure.

**Key words:** neuro-borreliosis; fluconazole

### INTRODUCTION

Borreliosis is a bacterial infectious disease transmitted by tick bites. It occurs throughout the world except for areas with extreme climatic conditions [1, 2, 3]. Neuroborreliosis is the most prevalent form of stage II borreliosis in many regions of Europe and Northern America [4, 5]. Whereas in most patients borreliosis has a good prognosis with and without antibacterial chemotherapy, neuroborreliosis is a common complication of *Borrelia* infections. Stage II borreliosis (duration < 6 months) is characterized by the following symptoms: spinal and cranial meningoradiculitis, isolated meningitis and/or mononeuritis or polyneuritis in conjunction with chronic erythema migrans. In stage III (duration 6 to 9 months) chronic atrophic acrodermatitis is commonly seen associated with mononeuritis, polyneuritis or chronic progressive encephalomyelitis [6]. Cerebrovascular neuroborreliosis can occur in both stages of the disease. Arthritic disorders, cardiac arrhythmia or parenchymal liver damage (increase in serum aminotransferases) may be causally related to chronic borrelia infections [7, 8, 9, 10, 11, 12, 13]. Further symptoms may include panic attacks, depressive disorders or cerebral stroke [14, 15, 30, 31]. Whereas in children high success rates are seen after treatment with penicillin G, therapy of adults with intravenous penicillin G, doxycycline or ceftriaxone is frequently ineffective [16, 17, 25].

### CASE REPORT

Borreliosis is highly prevalent in forestry workers attending occupational health service in our institution

[18]. Neuro-borreliosis was diagnosed in three patients of this population (EF, HW, RH).

In one of these patients (FS) suffering from stage III neuro-borreliosis who was treated with fluconazole (200 mg/d) for concurrent oropharyngeal candidiasis, symptoms of meningoradiculitis and lower limb polyneuritis disappeared after 6 days of therapy with the antimycotic. The same patient had been treated with doxycyclin (200 mg/d for two weeks) in acute stage borreliosis and later on with intravenous ceftriaxone (500 mg/d) without considerable effects. Since in this patient longterm - for ten years - disappearance of neuro-borreliosis symptoms was observed after treatment with fluconazole for an unrelated condition, the effects of the antimycotic in further cases of neuro-borreliosis was explored in this prospective analysis.

### MATERIALS AND METHODS

All included patients had been treated with antibiotics in acute as well as chronic stage borreliosis. Neuroborreliosis had been diagnosed in all 11 cases by outside neurologists or at the Department of Neurology of the University of Würzburg. All patients had been treated with antibiotics in this stage of the disease. Fluconazole was applied orally (100 mg twice daily) for 25 days. Before and one week after completion of therapy, blood samples were taken for serologic examination (ELISA: anti-*Borrelia* IgM, IgG). In addition *Borrelia* immunoreactive bands B 19, 31, 34, 41, 65 and 94 were detected in IgG Immunoblot using fluorescent monoclonal antibodies (collaboration with Max-von-Pettenkofer-Institut, München) [29]. Symptoms were comprehensively documented and compared before and after therapy.

### RESULTS

Substantial improvement of symptoms was observed in four patients (FS, CK, WS, VK) as early as 3 to 6 days of therapy. At the end of treatment eight patients had no borreliosis symptoms and remained free of relapse in a follow-up examination one year later. One patient (HG) showed signs of improvement during and shortly after therapy. The duration of improvement could not be determined since he had cerebral stroke with consequent left side hemiplegia 4 weeks after therapy. In the remaining three patients, symptoms were considerably improved after 25 days of therapy. However, low grade symptoms persisted at the end of therapy as well in the 3 months follow-up.

Table 1. Serology, symptoms and success of therapy with fluconazole.

Initials	Age & Gender	Anti-Borrelia Ig status		Symptoms	Outcome
		before treatment	after treatment		
FS	46 male	IgM+/IgG+	IgM-/IgG+	polyneuritis tachyarrhythmia	cured
RH	49 male	IgM-/IgG+	IgM-/IgG+	encephalomyelitis depressive disorder	improved
WS	44 male	IgM-/IgG+	IgM-/IgG+	meningoradiculitis arthritis	cured
BNT	42 female	IgM+/IgG+	IgM+/IgG+	polyneuritis arthritis	improved
HG	78 male	IgM-/IgG+	IgM-/IgG+	meningoradiculitis	slightly improved
GZ	36 female	IgM-/IgG+	IgM-/IgG+	polyneuritis acrodermatitis	cured
CK	30 male	IgM+/IgG+	IgM-/IgG+	meningoradiculitis	cured
VK	42 female	IgM+/IgG+	IgM-/IgG+	radiculitis panic disorder	cured
EF	50 male	IgM-/IgG+	IgM-/IgG+	polyneuritis	cured
HW	49 male	IgM-/IgG+	IgM-/IgG+	radiculitis	cured
NE	68 male	IgM-/IgG+	IgM-/IgG+	polyneuritis	cured

In the interesting case of patient RH, in spite of serologic analysis that indicated complete cure of borreliosis, symptoms of polyneuritis were present and CSF analysis gave highly positive findings. Treatment with fluconazole resulted in substantial improvement in this case as well. Two patients stopped taking fluconazole after 4 and 6 days, respectively, when they noticed considerable amelioration of their neurologic symptoms. A few weeks later the same symptoms reappeared in almost the same intensity. However, longterm clinical success was observed after a second course of fluconazole (2 x 100 mg/d). In immunoblots, 2 or 3 of the Borrelia-specific bands had been detected in each patient before therapy. At the end of therapy, immune reactivity disappeared in patients FS, CK and VK. Anti-Borrelia IgM was undetectable in patients FS, CK and VK after therapy. These serological results correlate with longterm disease and/or late stage borreliosis (stage II or III). Clinical and laboratory results are summarized in Table 1.

#### DISCUSSION

Because Borrelia spp. can penetrate the central nervous system in acute as well as chronic stages of the infection, neuro-borreliosis is a quite common complication. Therapy may not effectively prevent CNS penetration since only penicillins penetrate the blood/brain barrier in case of meningitis. Other antibiotics used in the treatment of Borrelia infections (doxycyclin, erythromycin, cephalosporins) do not achieve effective CSF concentrations. This fact

may explain the low response rates on antibiotic therapy in neuro-borreliosis patients [19]. In this study, 7/11 patients were clinically cured and 4/11 were improved after three weeks of treatment with fluconazole. Patients that were anti-Borrelia IgM-positive before treatment turned negative after therapy.

Fluconazole achieves high concentrations in many tissues as well as in CSF [20, 21, 22, 23, 24, 26, 27, 28, 32, 33]. No previously published data exists on efficacy of fluconazole against Borrelia in vivo. In vitro investigations failed to reveal a direct antibacterial effect of fluconazole on Borrelia spp [34]. Concerning the mechanism of the therapeutic effect observed in our patients, we may speculate on a potential bacteriostatic impact of fluconazole due to its inhibitory action on cytochrome P450. Since in vivo Borrelia spp. are almost exclusively localized intracellularly, they may depend on certain metabolites of their eucaryotic host cell for replication and long-term persistence [35]. Inhibition of P450 and other cytochromes may incapacitate Borrelia spp. upon longterm exposure. This appears to correlate with the fact that in this study improvement/cure was observed in most cases only after 25 days of fluconazole treatment. Perhaps a longer therapy could have improved the results.

The eleven cases presented here provide preliminary evidence of a potential therapeutic usefulness of fluconazole in neuro-borreliosis. The observed clinical effects after fluconazole treatment certainly warrant further investigation in vitro as well as in controlled clinical trials.

155

## REFERENCES

- 1 Berglund J, Hansen BU, Eitrem R (1995) Lyme arthritis - a common manifestation in a highly endemic area in Sweden. *J Rheumatol* 22: 695-701
- 2 Wilske B, Busch U, Fingerle V, Jauris Heipke S, Preac Mursic V, Rossler D, Will G (1996) Immunological and molecular variability of OspA and OspC. Implications for *Borrelia* vaccine development. *Infection* 24: 208-212
- 3 Wilske B, Busch U, Eiffert H, Fingerle V, Pfister HW, Roessler D, Preac Mursic V (1996) Diversity of OspA and OspC among cerebrospinal fluid isolates of *Borrelia burgdorferi* sensu lato from patients with neuroborreliosis in Germany. *Med Microbiol Immunol* 184: 195-201
- 4 Kaiser R (1998) Neuroborreliosis. *J Neurol* 245: 247-255
- 5 Oschmann P, Wellensiek HJ, Zhong W, Dorndorf W, Pflughaupt KW (1997) Relationship between the *Borrelia burgdorferi* specific immune response and different stages and syndromes in neuroborreliosis. *Infection* 25: 292-297
- 6 Kindstrand E, Nilsson BY, Hovmark A, Pirskanen R, Asbrink E (1997) Peripheral neuropathy in acrodermatitis chronica atrophicans - a late *Borrelia* manifestation. *Acta Neurol Scand* 95: 338-345
- 7 Alpeter ES, Meier C (1991) The epidemiology of neuroborreliosis in Switzerland. *Schweiz Med Wochenschr* 122: 22-26
- 8 Bohmer R, Tiller FW (1996) Lyme borreliosis 1996: State of the art. *Klin Labor* 42: 835-841
- 9 Garcia Monco JC, Benach JL (1995) Lyme neuroborreliosis. *Annals of Neurology* 37: 691-702
- 10 Haass A, Treib (1996): Neurologic manifestation and classification of borreliosis. *Infection* 24: 467-469
- 11 Hansen K (1994) Lyme neuroborreliosis: improvement of the laboratory diagnosis and a survey of epidemiological and clinical features in Denmark 1985-1990. *Acta Neurol Scand Suppl* 151: 1-44
- 12 Peter O, Bretz AG, Postic D, Dayer F (1997) Association of distinct species of *Borrelia burgdorferi* sensu lato with neuroborreliosis in Switzerland. *Clin Microbiol Infect* 3: 423-431
- 13 Pfadenhauer K, Schoensteiner T, Stoehr M (1998) Thoracoabdominal manifestation of stage II Lyme neuroborreliosis. *Nervenarzt* 69: 296-299
- 14 Fallon BA, Nields JA (1994) Lyme disease: a neuropsychiatric illness. *Am J Psychiatry* 151: 1571-1583
- 15 Hammers Berggren S, Grondahl A, Karlsson M, von Arbin M, Carlsson A, Sturnstedt G (1993) Screening for neuroborreliosis in patients with stroke. *Stroke* 24: 1393-1396
- 16 Christen HJ (1996) Lyme neuroborreliosis in children. *Ann Med* 28: 235-240
- 17 Verdon ME, Sigal LH (1997) Recognition and management of lyme disease. *Am Family Physician* 56:427-36
- 18 Huisse C, von-Stenglin M (1995) Incidence of Lyme borreliosis in Mecklenburg-Vorpommern. *Gesundheitswesen* 57: 21-24
- 19 Nowakowski J, Nadelman RB, Forseter G, McKenna D, Wormser GP (1995) Doxycycline versus tetracycline therapy for lyme disease associated with erythema migrans. *J Am Acad Dermatol* 32: 223-227
- 20 Bergan T (1995) Pharmacokinetics of the Azole Antifungal Agents: Distinguishing Differences. *Antifungal Drugs Chemother* 13: 149-159
- 21 Brammer KW, Farrow PR, Faulkner JK (1990) Clinical Pharmacology - Pharmacokinetics and Tissue Penetration of Fluconazole in Humans. *Rev Infect Dis* 12: 318-326
22. Debruyne D (1997) Clinical Pharmacokinetics of Fluconazole in Superficial and Systemic Mycoses. *Clin Pharmacokineter* 33: 52-77
23. Ebden P, Neill P, Farrow PR (1989) Sputum Levels of Fluconazole in Humans. *Antimicrobial Agents and Chemotherapy* 33: 963-964
24. Goa KL, Barradell LB (1995) Fluconazole - An Update of its Pharmacodynamic and Pharmacokinetic Properties and Therapeutic Use in Major Superficial and Systemic Mycoses in Immunocompromised Patients. *Drugs* 50: 658-690
25. Kaplan RF, Trevino RP, Johnson GM, Levy L, Dornbush R, Hu LT, Evans J, Weinstein A, Schmid CH, Klempner MS (2003) Cognitive function in post-treatment Lyme disease - Do additional antibiotics help? *60(12)*: 1916-22
26. Koks CHW, Meenhorst PL, Hillebrand MJX, Bult A, Beijnen JH (1996) Pharmacokinetics of Fluconazole in Saliva and Plasma after Administration of an Oral suspension and Capsules. *Antimicrob Agents Chemother* 40:1935-1937
27. Laufen H, Yeates RA, Zimmermann T, De Los Reyes C (1995) Pharmacokinetic Optimization of the Treatment of Oral Candidiasis with Fluconazole: Studies with a Suspension. *Drugs Exp Clin Res* 21:23-28
28. Nicolau DP, Crowe H, Nightingale CH, Quintiliani R (1995) Bioavailability of fluconazole administered via a feeding tube in intensive care unit patients. *J Antimicrob Chemother* 36: 395-401
29. Panielus J, Lahdenne P, Saxen H, et al. (2003) Diagnosis of Lyme neuro-borreliosis with antibodies to recombinant proteins DbpA, BBK32, and OspC, and VisE IR6 peptide *250(11)*: 1318-27
30. Ramesh G, Alvarez AL, Roberts ED, et al. (2003) Pathogenesis of Lyme neuro-borreliosis - *Borrelia burgdorferi* lipoproteins induce both proliferation and apoptosis in rhesus monkey astrocytes *33(9)*: 2539-50
31. Scheid R, Hund-Georgiadis M, von Cramon DY (2003) Intracerebral haemorrhage as a manifestation of Lyme neuro-borreliosis *10(1)*: 99-101
32. Shiba K, Saito A, Miyahara T (1990) Safety and Pharmacokinetics of Single Oral and Intravenous Doses of Fluconazole in Healthy Subjects. *Clinical Therapeutics* 12: 206-215
33. Wildfeuer A, Pfaff G, Zimmermann T, Lach P, Yeates R, Sarnow E, Haferkamp O (1991) Pharmakokinetisches Profil von Fluconazol, einem systemischen Antimykotikum. *Die Medizinische Welt* 42: 42-49
34. Troke PF, Andrews RJ, Pye GW, Richardson K (1990) Fluconazole and Other Azoles: Translation of in Vitro Activity to in Vivo and Clinical Efficacy. *Rev Infect Dis* 12: 276-280
35. Girschick HJ, Huppertz HI, Rüssmann H, Krenn V, Karch H (1996) Intracellular persistence of *Borrelia burgdorferi* in human synovial cells. *Rheumatol Int* 16: 125-132

Received: February 16, 2004 / Accepted: March 8, 2004

Address for correspondence:

D-97070 Würzburg, Germany

Tel.:

Fax:

E-mail: