Efficacy of Empirically Administered Erythromycin and Doxycycline in Children with Reactive Arthritis

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The objective of the present study was to evaluate the efficacy of empirically prescribed erythromycin and doxycycline in children with reactive arthritis (ReA).

Ninety-two children with ReA aged 2 to 16 years were examined. Patients having no other cause of disease than infection during a one-month period before onset of arthritis, disease duration till 3 months and having got only nonsteroidal antiinflammatory drugs for the treatment entered the study. Depending on the antibacterial treatment the patients were divided into 3 groups: 1) erythromycin; 2) doxycycline; 3) control group without antibiotics. The duration of the course of antibiotics was 10–14-days or 28-days. The results of the study were evaluated in per cent of patients that after 1 and 3 months of observation had no clinical and laboratory signs of disease activity. No significant difference was found between the groups of patients treated with antibiotics and without antibacterial treatment. The efficacy of treatment was the same in patients that had been prescribed 10–14-day or 28-day courses of antibiotics. Conclusion: in children ReA, empiric prescription of erythromycin or doxycycline in 10–14-day or 28-day courses had no advantage in the rate of disappearance of disease activity as compared to patients that had been managed without antibiotics.

Key words: reactive arthritis, antibacterial therapy, children

INTRODUCTION

Reactive arthritis (ReA) is an infection-associated disease. It develops in genetically predisposed individuals after a suitable infection. The list of microbes able to trigger ReA is long, but in adults most commonly the initial infection affects the digestive or urogenital tract and the terms enteroarthritis or uroarthritis are used respectively. In children, in more than a half of patients arthritis develops after upper respiratory tract infection (URTI) (1). The aetiopathogenesis of ReA associated with urogenital and digestive tract infection has been studied in the last decade in adults. It has been shown that *Chlamydia trachomatis* can persist in the joint in a viable form and is metabolically active (2). Viable Yersinia are able to reach the joint also (3). So, it is likely that antibacterials can exhibit a beneficial effect in ReA. From the studies devoted to this question in adults with applying short-term (4) or long-term courses of antibiotics of tetracycline group and ciprofloxacin it could be concluded that the positive effect was shown in Chlamydia-induced arthritis when in arthritis associated with enteric pathogens antibacterial treatment has no advantage over placebo (5–7). It seems that antibiotics of tetracycline group have a priority in their effect in ReA, as there is a growing number of reports that ciprofloxacin has no difference from placebo when applied in 3-month (8) or 12-month courses (9). In an experimental model of chlamydia-induced arthritis the disease severity was reduced by early tetracycline therapy and exacerbated by ciprofloxacin (10).

In children, chlamydia infection as a trigger of ReA takes place also. *Chlamydia trachomatis* can be transmitted to the child from the mother during the birth, and in young children arthritis with the ocular manifestations caused by *Chlamydia trachomatis* has been described (11). The role of mycoplasmas as arthritis-inducing microorganisms has been discussed for about three decades (12). *Mycoplasma pneumoniae*, mycoplasmas of urogenital tract and *Ureaplasma urealyticum* can cause an arthritis in children and adults (13–16). They were found in the synovial fluid in juvenile arthritis (16). *Mycoplasma pneumoniae* is primarily a respiratory pathogen. Polyarthralgia and polyarthritis have been described as occuring in 9% of patients with pneumonia caused by *Mycoplasma pneumoniae* (14). There is a growing number of publications on ReA other than rheumatic fever due to pharyngeal *Streptococcus pyogenes* infection (17, 18). ReA can be caused

by gastrointestinal pathogens in children (19) and in adults. In children ReA may experience recurrent episodes and lead to chronic arthritis and significant disability (20). When the chronicity develops, the clinical presentation of the disease corresponds to one of the subgroups of juvenile idiopathic arthritis (21). Such a variety of bacterial triggers of ReA raisis the question of empiric prescription of antibacterials. The results of antibacterial therapy seeking for the better outcome of ReA cannot be transferred directly from the studies on adults because of different localization and frequency of bacterial triggers and differences in the prescription of antibiotics – tetracyclines can be prescribed only for children older than 8 years, while ciprofloxacin is not advisable at all.

When an antichlamydial or antimycoplasmal activity of antibiotic is needed, in young children tetracyclines would be replaced by macrolides, most often by erythromycin.

In this work, the efficacy of erythromycin and doxycycline empirically prescribed to children with ReA is evaluated.

MATERIALS AND METHODS

The efficacy of antibiotics was evaluated in 92 patients aged 2 to 16 years with active arthritis after preceding infection. Other causes of disease were excluded, except infection during a one-month period before the onset of arthritis. The infection was verified from parent's words and by the available medical documentation. Such diagnostic evaluation of ReA corresponds to the diagnostic criteria for ReA based on the results of the Third International Workshop on ReA (22). Nasopharyngitis, laryngitis, tonsillitis, maxillitis and otitis were included into the term URTI. Patients with the active joints during the first evaluation, the duration of disease up to 3 months and having got only monsteroidal antiinflammatory drugs for the treatment entered the study. The state of patients was evaluated at the beginning of the study, after 1 month and after 3 months of observation: the number of active joints was counted, analysis of peripheral blood and urine was carried out. Roentgenologic examination, consultations of ophthalmologist or other specialists were done during the study if needed. The patients, depending on the antibacterial treatment, were divided into 3 groups: 1) erythromycin; 2) doxycycline; 3) control group without antibiotics. Erythromycin and doxycycline were administered at an average dose according to patient's age. The course of antibacterial treatment lasted 10–14 or 28 days. Doxycycline was prescribed only to patients older than 8 years. The results of treatment were evaluated in per cent of patients that after 1 and 3 months of observation had no clinical and laboratory signs of the disease activity. The data were calculated by a chi square test for comparison of proportions. Differences were considered statistically significant at $p < 0.05$.

Table 1. **Characteristic of observed patients with reactive arthritis**

Patient groups	n	Sex		Mean age (years)	Duration of disease (months)		Pattern of joint damage	
		boys	girls		< 1	1–3	oligoartic.	polyartic.
Erythromycin	26	11	15	8.0	18	8	12	14
Doxycycline	24	10	14	10.2	16	8	10	14
All patients treated with antibiotics	50	21	29	9.1	34	16	22	28
Control group without antibiotics	42	16	26	8.8	22	20	18	24

Table 2. **Localization of infections during 1 month before presentation of arthritis**

Patient groups	n	Infections (% of patients)			
		Upper respiratory tract infections	Gastrointestinal	Urogenital	Skin
Erythromycin	26	61.5	23.1	15.3	7.7
Doxycycline	24	66.7	25.0	20.8	12.5
All patients treated with antibiotics	50	64.0	24.0	18.0	10.0
Control group without antibiotics	42	71.4	26.2	14.3	7.1
All patients observed	92	67.4	25.0	16.3	8.7

RESULTS

As is shown in Table 1, the main groups of patients are comparable in the main characteristics. A pattern of disease in more than a half of patients was polyarticular and differed in this characteristic from the adult patients in which the oligoarticular pattern of disease in ReA is characteristic (22). In two thirds of patients arthritis developed after URTI (Table 2). In 17.4% of all patients clinical manifestations of more than one localization of infection before the onset of arthritis was observed.

Table 3. **Efficacy of empirically prescribed erythromycin and doxycycline in the treatment of children with reactive arthritis**

Patient groups	n	No signs of disease activity (% patients)		Adverse reactions
		after 1 month of observation	after 3 months of observation	
Erythromycin	26	23.1	73.1	15.4
Doxycycline	24	29.2	66.7	29.2
All patients treated with antibiotics	50	26.0	70.0	22.0
Control group without antibiotics	42	11.9	61.9	4.8

Table 4. **Dependence of antibiotic efficacy on disease duration in children with reactive arthritis**

Patient groups	Duration of disease (months)	n	No signs of disease activity (% of patients)	
			after 1 month of observation	after 3 months of observation
Erythromycin	< 1	18	22.2	77.8
	1–3	8	25.0	62.5
Doxycycline	<1	16	31.2	75.0
	1–3	8	25.0	50.0
All patients treated with antibiotics	< 1	34	26.5	76.5
	1–3	16	25.0	56.3
Control group without antibiotics	< 1	22	13.6	68.2
	1–3	20	10.0	55.0

Table 5. **Dependence of efficacy of antibiotics on their course duration in children with reactive arthritis**

Patient groups	Duration of the course (days)	n	No signs of disease activity (% of patients)	
			after 1 month of observation	after 3 months of observation
Erythromycin	10–14	10	20.0	70.0
	28	16	25.0	75.0
Doxycycline	10–14	8	37.5	62.5
	28	16	25.0	68.8
All patients treated with antibiotics	10–14	18	27.8	66.7
	28	32	25.0	71.9
Control group without antibiotics		42	11.9	61.9

After 1 month of observation the percentage of patients having no signs of disease activity was higher in the groups with antibacterial treatment than in control group in which patients were managed without antibiotics, but this difference was not significant. After 3 months of observation, the results in patients that had been prescribed antibiotics did not differ essentially from those who got no antibiotics (Table 3). Adverse reactions in doxycycline group and in the group of all patients treated with antibiotics were more frequent than in control group ($p = 0.02$ and $p = 0.04$, respectively). In doxycycline group adverse reactions were observed in 29.9% of patients. They developed in the gastrointestinal tract and hemopoietic system: leucopenia ($< 4.0 \times 10^9$/l) or platelet-deficiency ($< 200.0 \times 10^9$/l). No one patient required discontinuation of antibacterial therapy because of adverse reactions.

Analysis of the efficacy of antibacterials depending on the duration of disease revealed no significant difference between the patients with the duration of disease up to 1 month and the patients with a longer disease duration (Table 4). No essential difference in the efficacy of antibiotics and in the results of 10–14-day and 28-day antibacterial courses was observed (Table 5).

DISCUSSION

This work showed no advantage of erythromycin or doxycycline in the disappearance of signs of disease activity in comparison with ReA patients that were treated without antibiotics, even when these antibiotics were applied in

an early phase of disease. Thus, the results of this study which was carried out in children are comparable with the conclusions of works analysing the efficacy of tetracyclines and ciprofloxacin in adult ReA (4–7). It was reported in the literature that viable *Chlamydiae* may persist in the joint tissue in patients treated with antibiotics (23). Ciprofloxacin exacerbates experimental chlamydia-induced arthritis (10), tetracyclines can induce arthritis (24) and lupus-like syndrome with arthritis (25) in man, intestine-born bacterial triggers of ReA are not susceptible to erythromycin. So, these antibiotics may be not the best choice for empiric antibacterial therapy in ReA. In our other work it was shown that amoxicillin and amoxicillin+clavulanic acid exhibit a benefitial effect in the early ReA in children (unpublished observations). Thus, it may be that in children streptococcal, staphylococcal infection and other bacteria of upper respiratorry tract (*Haemophilus influenzae, Maraxella catarrhalis and Streptococcus pneumoniae*) which are susceptible to amoxicillin and especially amoxicillin+clavulanic acid (26) play a more important role than chlamydial and mycoplasmal infection. *Staphylococcus aureus*, especially its methicillin-resistant strains, has attracted rheumatologists' attention recently. It is the most frequent causative microorganism of septic arthritis in children (27), but it may be a trigger of ReA also (28). In our earlier work it was showed that the frequency of growing of *Staphylococcus aureus* in the passages from tonsils was significantly higher than the growing of *Streptococcus pyogenes* in children with ReA and juvenile chronic arthritis (29) and differed from the strains grown from tonsils of healthy children in the phagotypic characteristics and significantly more often methicillin-resistance (30). Experimental data showed that the superantigen produced by *Staphylococcus aureus* can reactivate arthritis that has been triggered by *Streptococcus pyogenes* cell wall polymers (31), so it can have an arthritis-promoting effect. It is suggested that sometimes ReA can be caused by the existence of several bacterial triggers (32, 33) and in children Lyme arthritis an additional course of other antibacterials after the failure of ceftriaxone could be successful (33).

CONCLUSION

In children ReA, empiric prescription of erythromycin or doxycycline in 10–14-day or 28-day courses has no advantage in the rate of disappearance of disease activity as compared to cases managed without antibiotics.

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References

1. Kunnamo I. Infections and related risk factors of arthritis in children. Scand J Rheumatol 1987; 16: 93–9.
2. Gerard HC, Branigan PJ, Schumacher HR, Hudson AP. Synovial Chlamydia trachomatis in patients with reactive arthritis / Reiter's syndrome are viable but show aberrant gene expression. J Rheumatol 1998; 25: 734–42.
3. Gaston JSH, Cox C, Granfors K. Clinical and experimental evidence for persistent Yersinia infection in reactive arthritis. Arthritis Rheum 1999; 42 (10): 2239–42.
4. Wollenhaupt J, Hammer M, Pott HG, Zeidler H. A double-blind, placebo-controlled comparison of 2 weeks *versus* 4 months treatment with doxycycline in Chlamydia-induced arthritis. Arthritis Rheum 1997; 40: S 143.
5. Lauhio A, Leirisalo-Repo M, Lahdevirta J, Saikku P, Repo H. Double-blind, placebo-controlled study of three-month treatment with lymecycline in reactive arthritis, with special reference to Chlamydia arthritis. Artritis Rheum 1991; 34: 6–14.
6. Sieper J, Fendler C, Laitko S, Sorensen H, Gripenberg-Lerche C, Hiepe F et al. No benefit of long-term ciprofloxacin treatment in patients with reactive arthritis and undifferentiated oligoarthritis – A three-month multicenter, double-blind, randomized, placebo-controlled study. Arthritis Rheum 1999; 42 (7): 1386–96.
7. Sieper J, Braun J. Treatment of reactive arthritis with antibiotics. Br J Rheumatol 1988; 37: 717–20.
8. Yli-Kerttula T, Luukkainen R, Yli-Kerttula U, Mottonen T, Hakola M, Korpela M et al. Effect of a three month course of ciprofloxacin on the outcome of reactive arthritis. Ann Rheum Dis 2000; 59 (7): 565–70.
9. Wakefield D, Mc Cluskey P, Verma M, Aziz K, Gatus B, Carr G. Ciprofloxacin treatment does not influence course or relapse rate of reactive arthritis and anterior uveitis. Arthritis Rheum 1999; 42 (9): 1994–7.
10. Inmam RD, Chiu B. Sinoviocyte-packaged Chlamydia induces chronic aseptic arthritis: a model system Arthritis Rheum 1997; 40 (Suppl): S 331.
11. Maximov AA, Shaikov AV, Lovell DJ, Giannini EH, Soldatova SI. Chlamydia associated syndrome of arthritis and eye involvement in young children. J Rheumatol 1992; 19: 1794–7.
12. Jansson E. Mycoplasmas and arthritis. Scand J Rheumatology 1975; 4: 39–42.
13. Davis CP, Cochran S, Lisse BG, DiNuzzo AR, Weber T, Reinarz JA. Isolation of *Mycoplasma pneumoniae* from synovial fluid samples in patients with pneumonia and polyarthritis. Arch Intern Med 1988; 148: 967–70.
14. Cole BC, Griffiths MM. Triggering and exacerbation of autoimmune arthritis by the *Mycoplasma arthritidis* superantigen MAM. Arthritis Rheum 1993; 36 (7): 991–1002.
15. Franz A, Webster ADB, Furr PM, Taylor-Robinson D. Mycoplasmal arthritis in patients with primary immunoglobulin deficiency: clinical features and outcome in 18 patients. Br J Rheumatol 1997; 36: 661–8.

16. Poggio TV, Orlando N, Galanternik L, Grinstein S. Microbiology of acute arthropathies among children in Argentina: *Mycoplasma pneumoniae* and *hominis* and *Ureaplasma urealyticum*. Pediatr Infect Dis 1998; 17(4): 304–8.
17. Ahmed S, Ayoub EM, Scornik JC, Vang CY, She JX. Poststreptococcal reactive arthritis: clinical characteristics and association with HLA-DR alleles. Arthritis Rheum 1998; 41 (6): 1096–102.
18. Bont L, Brus F, Dijkman-Neerincx RH, Jansen TL, Meyer JW, Jenssen M. The clinical spectrum of poststreptococcal syndromes with arthritis in children. Clin Exp Rheumatol 1998; 16 (6): 750–2.
19. Ansel BM. Reactive arthritis/Reiter's syndrome in children. Clin Exp Rheumatol 1994; 12: 581–2.
20. Fink CW. Reactive arthritis. Pediatr Infect Dis J 1988; 7: 58–65.
21. Kanakoudi-Tsakalidou, Pardalos G, Pratsidou-Gertsi P, Kansouzidou-Kanakoudi A, Tsangaropoulou-Stinga H. Persistent or severe course of reactive arthritis following *Salmonella enteritidis* infection. Scand J Rheumatol 1998; 27: 431–4.
22. Kingsley G., Sieper J. Third International Workshop on Reactive Arthritis. 23–26 September 1995, Berlin, Germany. Report and abstracts. Ann Rheum Dis 1996; 55: 564–84.
23. Beutler AM, Hudson AP, Whittum-Hudson JA et al. *Chlamydia trachomatis* can persist in joint tissue after antibiotic treatment in chronic Reiter's syndrome/reactive arthritis. J Clin Rheumatol 1997; 3: 125–30.
24. Knights SE, Leandro MJ, Khamashta MA, Hughes GRV. Minocycline-induced arthritis. Clin Exp Rheumatol 1998; 16: 587–90.
25. Hess EV. Minocycline and autoimmunity. Clin Exp Rheumatol 1998; 16: 519–21.
26. Jakobs MR. Emergence of antibiotic resistance in upper and lower respiratory tract. Am J Manag Care 1999; 5 (11 Suppl): S651–61.
27. Sonnen GM, Henry NK. Pediatric bone and joint infections. Diagnosis and antimicrobial management. Pediatr Clin North Am 1996; 43 (4): 933–47.
28. Siam AR, Hammoudeh M. *Staphylococcus aureus* triggered reactive arthritis. Ann Rheum Dis 1995; 54 (2): 131–3.
29. Astrauskienė D, Rimkuvienė Z, Bižanienė G, Lapinskienė. Artritais sergančių vaikų nosiaryklės bakterinė flora. Kn: IV Lietuvos pediatrų suvažiavimo pranešimų tezės. Alytus, 1991 spalio 24–25 d.; Vilnius 1991: 32–3.
30. Astrauskienė D, Rutienė K, Brilingienė I, Bajoriūnienė A, Orlickaitė L. Phagolysing properties and susceptibility to antibiotics of *Staphylococcus aureus* cultured from children with rheumatic arthritides. Acta medica Lituanica 1996; 1: 32–8.
31. Schwab JH, Brown RR, Anderle SK, Schlievert PM. Superantigen can reactivate bacterial cell-wall-induced arthritis. J Immunol 1993; 150: 4151–9.
32. Astrauskienė D. Some problems in revealing bacterial etiology of rheumatic arthritides in children. Acta medica Lituanica 1995; 4: 77–84.
33. Huppertz HJ, Karchh H, Suscke HJ et al. Lyme arthritis in European children and adolescents. Arthritis Rheum 1995; 38 (3): 361–8.

D. Astrauskienė

EMPIRIŠKAI SKIRIAMO ERITROMICINO IR DOKSICIKLINO EFEKTYVUMAS REAKTYVIUOJU ARTRITU SERGANTIEMS VAIKAMS

S a n t r a u k a

Darbo tikslas – įvertinti empiriškai skiriamo eritromicino ir doksiciklino efektyvumą reaktyviuoju artritu (ReA) sergantiems vaikams. Ištirti 92 sergantys ReA 2–16 m amžiaus vaikai. Tyrime dalyvavo ligoniai, kuriems: 1) buvo ekskliuduoto visos galimos ligą sukėlusios priežastys išskyrus infekciją 1 mėn. laikotarpiu prieš artrito pradžią; 2) ligos trukmė buvo ne ilgesnė nei 3 mėn.; 3) iki tyrimo buvo gydoma tik nesteroidiniais priešuždegiminiais vaistais. Priklausomai nuo antibakterinio gydymo ligoniai buvo suskirstyti į 3 grupes: 1) gydomi eritromicinu; 2) gydomi doksiciklinu; 3) negaunantys antibakterinio gydymo (kontrolinė grupė). Antibiotikai buvo skiriami 10–14 dienų arba 28 dienų kursais. Tyrimo rezultatai buvo vertinami po 1 mėn. ir po 3 mėn. procentais ligonių, kuriems nebebuvo rasta klinikinių bei laboratorinių ligos aktyvumo simptomų. Tyrimo rezultatai parodė, kad gydymo efektyvumas ligoniams, gavusiems eritromiciną ar doksicikliną, iš esmės nesiskyrė nuo antibakterinio gydymo negavusių ligonių ir nepriklausė nuo gydymo antibiotikais trukmės. Daroma išvada, kad empiriškai skiriami eritromicinas ir doksiciklinas 10–14 dienų ar 28 dienų kursais esminės įtakos ligos aktyvumo išnykimo greičiui ReA sergantiems vaikams neturėjo.