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Lack of quinolone-induced arthropathy in children

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The newly developed derivatives of nalidixic acid, the fluoroquinolones, have been studied extensively in the laboratory and in clinical trials. Compared with nalidixic acid the new quinolones exhibit an expanded antimicrobial spectrum, greatly enhanced bactericidal activity, and substantial pharmacokinetic advantages. Numerous clinical studies have proved the efficacy and safety of these compounds for various infections in adult patients.

Many experts have advised against performing studies on the efficacy and safety of these promising agents in children because of potential adverse effects, limited activity against streptococci, and lack of adequate pharmacokinetic evaluation. In particular, the risk of cartilage toxicity in weight-bearing joints, which was observed in experiments with some young animals whose skeletal growth was incomplete, was thought to represent a contraindication for the use of quinolones in paediatric patients.

When administered to immature animals (dogs, rabbits, rats, marmosets, pigs) all the quinolones studied—older and newer derivatives—caused arthropathic effects in major, usually weight-bearing synovial joints (Gough *et al.*, 1979; Schlüter, 1986, 1989; Christ, Lehnert & Ulbrich, 1988; Burkhardt *et al.*, 1990; Stahlmann *et al.*, 1990). This arthropathy evolves within days to weeks and is characterized by cartilage toxicity accompanied by non-inflammatory joint effusion. Histopathological findings are localized blister formation and erosions in joint cartilage (Gough *et al.*, 1979; Schlüter, 1986; Christ *et al.*, 1988). Clusters of chondrocytes are found, indicating attempted cartilage repair. Recently, electron microscopic examination of such cartilage showed necrotic chrondrocytes and dissolution of matrix (Burkhardt *et al.*, 1990; Stahlmann *et al.*, 1990). These quinolone-induced cartilage lesions are usually irreversible, and the reduced quality of cartilage may promote degeneration, including arthropathia deformans. If clinically symptomatic, such arthropathy in animals manifests as acute arthritis, including limp and swelling. These toxic effects are dose-dependent, but occur at different dosages in different species. Moreover, animal cartilage toxicity varies between quinolone compounds: this could be ascribed to either true heterogeneity of arthropathogenicity or differences in pharmacokinetics. In all these animal experiments the older compounds (e.g. pipedimic acid, nalidixic acid) showed substantially greater arthropathogenicity than the fluoroquinolones.

The pathogenesis of quinolone-induced arthropathy in animals remains unexplained. The primary target of all quinolones is a bacterial DNA gyrase (topoisomerase II), an essential bacterial enzyme for DNA replication and certain aspects of transcription, DNA repair, recombination, and transposition (Smith, 1986). Although it is generally accepted that the fluoroquinolones are specific for prokaryotic enzymes, there are reports of in-vitro experiments indicating some inhibition of eukaryotic DNA replication (Castora, Vissering & Simpson, 1983; Gootz, Barrett & Sutcliffe, 1990). In immature rats dosed with ofloxacin, chondrocytes of the intermediate zone showed a transient decrease and subsequent increase in uptake of tritiated thymidine (Kato & Onodera, 1988). This observation could reflect early depression of DNA synthesis by the drug followed by reparative reaction of the chondrocytes. The hypothesis that quinolones might inhibit mitochondrial DNA in immature, metabolically active chondrocytes of certain animal species requires further investigation.

Because of the obvious advantages of the fluoroquinolones and the absence of joint pathology in follow-up studies of children treated with nalidixic acid (Schaad & Wedgwood, 1987; Adam, 1989), many paediatricians have started to prescribe these antibacterial agents for some of their patients on a compassionate use basis. By early 1992, published data on fluoroquinolone use in children included over 1000 pre-pubertal patients (Black *et al.*, 1990; Cheesbrough *et al.*, 1991; Chysky *et al.*, 1991; LeBel, 1991; Schaad, 1991). These studies report good to excellent efficacies, and usually mild and always revers-

ible adverse reactions in 5–15%. So far, there is no documented case of unequivocal quinolone-induced arthropathy in humans. Reversible arthralgia with possible or probable relation to quinolone therapy occurred in approximately 1% of patients, most of whom were adolescents with cystic fibrosis (LeBel, 1991). In older patients with cystic fibrosis, arthropathies are estimated to occur in 7–8% (Phillips & David, 1986). The majority of these joint diseases are either explained by hyperimmune mechanisms (so-called cystic fibrosis arthropathy) or by hypertrophic pulmonary osteoarthropathy. Definite diagnosis of these arthropathies is often difficult, and is only possible after exclusion of coincidental joint disease. Therefore, the relationship of joint symptoms to drug therapy in patients with cystic fibrosis requires very cautious interpretation.

Many studies have stressed the excellent sensitivity of magnetic resonance imaging (MRI) in detecting early and discrete inflammatory, degenerative, or traumatic lesions of articular cartilage under both clinical and experimental conditions. MRI investigations performed in juvenile beagle dogs and piglets were found to predict ciprofloxacin-induced cartilage toxicity at the knee joint (Schlüter, 1989; Hoffman & Desprechins, 1991). In these animal experiments the formation of minimal intra-articular effusions, manifested by enlargement of the recessus suprapatellaris, was the first sign of quinolone-induced arthropathy.

We conducted clinical, laboratory, radiological and MRI studies in 13 pre-pubertal (age range 6–13 years) and five post-pubertal patients (age range 14–24 years) with cystic fibrosis. Investigations were made at the start and the end of a three-month course of ciprofloxacin (30 mg/kg/day, administered orally in two equal doses) and at follow-up examinations, 4 to 6 and 15 to 22 months later (Schaad *et al.*, 1991). Our comprehensive monitoring gave no evidence for arthropathogenicity. Detailed physical skeletal function tests, height velocity values, laboratory studies of bone metabolism, and conventional radiographs of both knees revealed no abnormalities. Moreover, serial MRI of the left knee demonstrated lack of joint effusion, intact two-layer appearance of cartilage, and unaffected thickness of articular cartilage measured at five anatomically different points.

Recently, two of our pre-pubertal patients with far-advanced cystic fibrosis died due to combined respiratory and cardiac failure, at the age of 7 and 13 years, respectively. Both patients had repeatedly received oral courses of ciprofloxacin (30 mg/kg/day in two doses), amounting to a total of 9–10 months of quinolone treatment during their last three years of life. In both patients autopsy of the left knee revealed macroscopically regular structures. There were no histopathological changes similar to those found in animal experiments, such as blister formation or erosions in joint cartilage (Schlüter, 1989; Burkardt *et al.*, 1990; Stahlmann *et al.*, 1990). Also, electron microscopic examination showed regular morphology of hyaline cartilage with intact chondrocytes, normal mitochondria and genuine matrix. Details of these studies will be published elsewhere.

Our clinical, MRI and histopathological monitoring of ciprofloxacin use, together with the published experiences of other groups, suggest that the quinolone antibiotics do not cause arthropathy in humans. Interspecies differences may account for the lack of quinolone-induced cartilage toxicity in children compared with juvenile animals. We wish to stress the need for further studies on potential quinolone toxicities to be performed in larger numbers of paediatric patients, including infants and young children, and in diseases other than cystic fibrosis. Also, long-term follow-up over many years is needed.

Nevertheless, it is our strong opinion that the data presented here justify the compassionate use of the fluoroquinolones in paediatric patients suffering from specific infections complicated by pathological or special conditions. Conditions that potentially qualify for quinolone use include oral anti-pseudomonal therapy for pulmonary exacerbation in cystic fibrosis, complicated urinary tract infection (disturbed urinary outflow due to anatomical or functional abnormality), and skeletal, aural and shunt infections. In addition to these rare indications, there is urgent need in developing countries for availability of the new quinolones for treating children with endemic and epidemic shigellosis and typhoid fever.

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BSAC: 21 years

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In November the British Society for Antimicrobial Chemotherapy will be celebrating 21 years since its inception. The foundation of the Society was based on the desire to promote knowledge, awareness and research into all aspects of antimicrobial chemotherapy. These objectives have clearly flourished. The Society is well known for the excellence of its scientific meetings, the influence of the Reports of its various Working Parties, its key role in fostering research and international outreach through the promotion of joint Society meetings. This Journal, founded by the Society in 1975, has played a major role in promoting the scientific effort of the Society across the broad field of antimicrobial chemotherapy. Congratulations to all those members, past and present, who have contributed to this success story. The article on page 417 and the scientific programme of the Autumn Meeting adopt an appropriate stance which allows reflection on some aspects of the past, while looking at present and future aspects of antimicrobial science.

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Editor-in-Chief