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Successful treatment of ozena with ciprofloxacin*

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SUMMARY

Rhinitis chronica foetida, or ozena, is a rare chronic inflammatory disease. The aetiology and pathogenesis are still not satisfactory explained. For many years various medical and surgical methods for the treatment of this slowly progressive and disabling disease have been tried without permanent success so far. The new fluoroquinolones with excellent effect on gram-negative bacteria and high suitability for oral use offer a potentially attractive treatment for ozena. We review our experience in the treatment of 10 patients with ciprofloxacin in a daily dose of 500–750 mg b.i.d. for 1-3 months. The patients have been followed regularly for up to 26–74 months after treatment and in all of them we registered permanent disappearance of odour, crusting, and growth of Klebsiella ozenae. We conclude that ciprofloxacin provides a step towards better conservative therapy for patients with ozena.

Key words: rhinitis chronica foetida, ozena, antibiotic therapy, fluoroquinolones, ciprofloxacin

INTRODUCTION

Ozena is a well-recognized clinical entity of chronic rhinitis with a long-standing history, often for decades, and with a typical picture of atrophy of the mucous membranes and underlying structures leading to abnormal patency of the nasal cavities. Many different theories about its aetiology have been proposed, including infection, and bacteriological as well as histopathological findings support the theory of a prolonged infection as an important factor in the development and progression of ozena (Holopainen, 1967; Abdel-Latif et al., 1987). Cultures from the nasopharyngeal tract often reveal species belonging to the *Enterobacteriaceae* group. One of the most commonly isolated bacteria is *Klebsiella ozenae* (Goldstein et al., 1978). Many authors state this microbe to be necessary for confirmation of the diagnosis.

The symptoms of ozena are discharge, crusting, sensation of obstruction, hyposmia, anosmia, and often an offensive foetor causing major social problems for the patient.

Specific treatment remains a difficult problem and no therapy has up to now been found that definitely cures the disease. Several anti-bacterial drugs have been used (Thornell, 1950; Dudley, 1987) with only a temporary effect and without eradication of the bacteria, and some authors consider that systemic antibiotics have no place in the treatment of ozena (Chapnik et al., 1984)

The fluoroquinolones, a new group of antibiotic drugs, are highly active against gram-negative bacteria and can be administered orally. Ciprofloxacin is one of these substances and its favourable pharmacokinetical and anti-bacterial properties (Neu, 1987; Bergan, 1988; Norris et al., 1988; Sanders, 1988) make it interesting to try this drug in the treatment of ozena.

The aims of the study were to evaluate the efficacy of ciprofloxacin in the treatment of ozena and to measure the concentration of ciprofloxacin simultaneously in serum, nasal mucosa, and nasal secretion. Finally, and for us especially important, the intention was to follow the patients clinically and microbiologically at regular intervals during and after treatment as long as possible.

MATERIAL AND METHODS

Ten patients with ozena and long-standing carriage of *Klebsiella ozenae* were prospectively included in this study from February 1987 to March 1991. All these patients had failed to respond to prior antibiotic therapy.

The group studied consisted of four men and six women. The mean age was 45 years, ranging from 24 to 70 years. The duration of symptoms varied from 5–50 years, and in all patients the disease had started in early youth. Five of the patients were immigrants, three from Eastern Europe and two from the Middle East. The diagnosis was established by medical history, clinical examination, and microbiological findings. Four of the

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patients were treated at the outpatient department whereas the other six patients were hospitalized for a few days - principally for intensified local treatment, but also for supplementary tests. At admission, a detailed medical history was taken and a thorough physical examination was carried out before the treatment was started. New cultures were obtained from the nose for identification and testing of the susceptibility of the bacteria to ciprofloxacin and determination of the MIC of ciprofloxacin against *Klebsiella ozenae*. Laboratory analysis including routine haematological values and analysis of serum proteins by electrophoresis and IgG subclasses, was performed, and X-rays of the paranasal sinuses were included in the standard examination.

Ciprofloxacin was administered in a dose of 1.0–1.5 g daily, divided into two oral doses, to all patients. Meticulous instrumental cleansing of the nose was performed daily for a few days and the patients were instructed how to clean the nose at home regularly with an isotonic saline solution, preferably using a squeezable plastic bottle with a nozzle. The six hospitalized patients underwent additional tests with a biopsy from the concha media for histopathological and electron microscopical analysis. Aspirated nasal secretion and specimen from the nasal mucosa of the concha inferior were obtained and analysed in order to determine the concentration of ciprofloxacin. Simultaneously, a blood sample was taken for determination of the serum concentration of ciprofloxacin. The concentration of ciprofloxacin was determined by the agar-well diffusion method. The medium was Muller-Hinton agar, pH 7.4, and the test strain was *Escherichia coli KP*.

The treatment with ciprofloxacin was maintained for 1–3 months. All the patients have been followed regularly with regard to their clinical status and in order to perform microbiological cultures with susceptibility tests. These check-ups were performed once a week under treatment until the first month and then monthly for about half a year. After that, the examinations have continued every third month for the first year and then once yearly. Two of the patients with a septal deviation causing obstruction underwent septoplasty one year after treatment. Simultaneously, a new biopsy of the nasal mucosa was taken from the concha media for histopathological analysis to investigate whether the therapy was followed by obvious changes in the nasal mucosa.

RESULTS

Klebsiella ozenae sensitive to ciprofloxacin was cultured from the nasal secretion of all patients. Apart from the common respiratory tract pathogen *Haemophilus influenzae*, no other gram-negative pathogens were isolated in cultures before treatment. On the other hand, *Staphylococcus aureus* and *Streptococcus pneumoniae* were present in some cases. With regard to standard haematological monitoring, all values were in the normal range except in one patient, in whom a slight iron-deficiency anaemia was noticed. Serum electrophoresis showed no pathological changes of the immunoglobulins and determination of IgG subclasses showed normal values. X-ray examination of the paranasal sinuses was normal in nine patients. In one patient there was a slight diffuse opacity of the maxillary sinus on both sides.

Table 1. Concentrations of ciprofloxacin.

patient	time (h)*	dose (mg)	serum (mg/l)	nasal secretion (mg/l)	nasal mucosa (mg/kg)	secretion/ serum ratio	mucosa/ serum ratio
KM	2	750	3.6	1.4	2.7	0.4	0.8
SM	4	500	2.6	1.6	3.2	0.6	1.2
TM	4	500	1.4	1.0	1.3	0 7	0.9
ÖML	5	750	2.8	3.2	1.4	1.1	0.5
NE	5	750	1.3	1.6	3.5	1.2	2.6
KS	16	750	0.6	1.4	1.4	2.3	2.3

*: Interval between drug intake and sampling of serum, secretion and tissue.

Table 2. Ciprofloxacin treatment of ozena.

patient	age	dose (g/day)	duration of treatment (months)	observation post-treatment (months)	culture of *Klebsiella ozenae* after treatment
DA*	35	1.0	3	74	no
EI	68	1.5	1	70	no
KM*	31	1.5	3	67	no
NE	70	1.5	3	61	no
AI	62	1.0	1.5+5	59	transient
ÖML	66	1.5	3	50	no
SM*	28	1.0	3	50	no
KS	42	1.5	3	50	no
TM*	25	1.0	2	44	no
SD*	24	1.0	2	26	no

*: immigrants

The MIC values of ciprofloxacin for *Klebsiella ozenae* were for all isolates extremely low, varying between 0.005 and 0.031 μg/ml before the start of treatment except for one isolate, for which the MIC value turned out to be as high as 0.5 μg/ml when double-checked on two separate occasions.

In the six hospitalized patients, histopathological examination of the nasal mucosa showed a picture of atrophic rhinitis with unspecific chronic inflammatory changes compatible with ozena. Additional electron microscopical analysis showed in five patients total loss of the normal ciliated epithelium and only a more or less pronounced metaplasia of the mucosa. An almost normal ciliated mucous membrane was seen in one patient, and this patient also had the shortest history of disease.

The concentrations of ciprofloxacin in nasal mucosa and nasal secretion were measured in the same six patients. Simultaneously, a blood sample was taken for the same purpose. The samples of the nasal secretion and the specimen from the concha inferior for analysis were obtained after about 4 days of treatment and 2–5 h after the last dose of ciprofloxacin. In one patient all the samples were inadvertently taken 16 h after intake of ciprofloxacin. The serum concentrations of ciprofloxacin varied between 0.6 and 3.6 mg/l, the concentrations in the nasal mucosa between 1.3 and 3.5 mg/kg, and those in the nasal secretion between 1.0 and 3.2 mg/l, thus well exceeding the MIC-values for *Klebsiella ozenae* (Table 1). In general, the concentration of ciprofloxacin in secretions exceeded the serum concentration after 5 h, and were more than twice as high in secretions after 16 h in the patient who by mistake did not get the medication as planned in the morning before the investigation.

In nine of the patients the *Klebsiella ozenae* disappeared during the first week of treatment and the bacteria have not returned during a follow-up period of up to now 26–74 months (Table 2). In the patient with a MIC of 0.5 μg/ml the bacterium was present occasionally during the treatment and in one culture six weeks after the start showed resistance to ciprofloxacin. The resistance was reversible and after a few weeks the treatment could be started again. The bacterium disappeared and has not returned in 50 months of observation. Perhaps the relapse in this patient could be explained by low compliance, as the patient's intake of ciprofloxacin was very irregular and because she forgot to take her medication for some days.

During the treatment, a wide range of other gram-negative organisms were found temporarily in the nasal secretion, mostly *Pseudomonas maltophilia*, which was seen in nearly all the patients. More infrequently, *Pseudomonas aeruginosa*, *Escherichia coli*, *Proteus vulgaris* and *Acinetobacter sp.* were found for shorter periods. In eight of the patients *Streptococcus pneumoniae* could be cultured despite treatment.

After treatment, cultures from the nasopharyngeal tract showed only *Streptococcus pneumoniae* and *Haemophilus influenzae*. In three of the patients we found temporary growth of *Pseudomonas aeruginosa*, mostly during the first six to nine months. Occasionally, we also noted growth of *Staphylococcus aureus*.

In the long-term clinical follow-up, we noticed that the crusts disappeared almost completely after a few weeks and after 1–3 months the nasal cavities were usually almost clean. The local changes of the nasal mucosa improved considerably, and although the clinical picture of atrophic rhinitis persisted, the offensive odour disappeared in all patients after only a couple of days. Some of the patients (4/10) had some sense of their smell left and they all noticed a subjective improvement after treatment.

In the two patients who underwent septoplasty one year after treatment, we had the opportunity to obtain a new biopsy of the nasal mucosa of the concha media; histopathological examination still showed chronic inflammation compatible with ozena and the picture was almost unchanged compared with the first biopsy. In spite of this, they were both clinically improved with essentially clean nasal cavities; cultures taken repeatedly after treatment in these two patients never showed bacteria belonging to the *Enterobacteriaceae* group.

After a long period of observation, we can now note that two of the patients have totally stopped the irrigation of their nose and that another four patients irrigate with great irregularity. Nevertheless, these patients with low compliance for local treatment are free or almost free from symptoms and clinically we cannot detect a markedly greater tendency for crust formation.

DISCUSSION

Ozena is a nasal disease still ranking as an unsolved problem in otorhinolaryngology, and there is much controversy concerning its treatment. It is quite a common clinical diagnosis in many countries, although in our part of the world it has become unusual. Causal therapy is not available and gentle daily irrigation of the nose with isotonic saline solution is the most common mode of treatment and in most cases sufficient to relieve the most troublesome symptoms, especially the more extensive formation of crusts and the offensive odour. This kind of treatment should also probably form the basis of the conservative treatment of ozena. However, some of the patients are not prepared to co-operate fully, neglecting to continue nasal rinsing, which lessens the efficacy of this kind of treatment.

From experience, we know that surgical procedures for reducing the width of the nasal passages make the subjective and objective symptoms of ozena less pronounced and since the beginning of this century different methods of operation for this purpose have been developed (Cottle, 1958; Saunders, 1958; Sinha et al., 1977; Rasmy, 1986). Most of them involve implantation of free grafts of autogenous or synthetic materials of various kinds, often with good effect - at least temporarily. However, the beneficial effect of nasal narrowing of free grafts does not persist. Encouraging results have been described following complete or almost complete closure of one or both nostrils for a period of >1 year (Young, 1967, 1971). Even after this kind of operation, reversal of the pathological changes in the micro-anatomy of the nasal mucosa have been demonstrated (Elwany, 1988).

Although many authors believe that *Klebsiella ozenae* is only an opportunistic finding in rhinitis chronica foetida, one cannot totally exclude the possibility that this bacterium is in some way involved in the pathogenesis of the disease. A notable characteristic of *Klebsiella ozenae* is the ability to form large

mucoid colonies on agar media, which is due to a prominent polysaccharide capsule. These extracapsular mucopolysaccharides seem to have a destructive effect on the normal nasal ciliated epithelium, causing a decrease in mucociliary clearance and thereby allowing colonization with *Klebsiella ozenae* and other bacteria as described and suggested by Ferguson et al. (1990).

There could, therefore, be an indication for antibiotic treatment of the disease and many antibiotics have been used. However, up to now treatment of ozena with conventional antibiotics has been difficult and of uncertain efficacy despite full *in vitro* sensitivity of *Klebsiella ozenae* to different kinds of antibiotic drugs. The efficacy has nevertheless often been limited *in vivo*, although the disease may be transiently suppressed, but not cured.

The first patient in our series, with an observation period of 74 months, had been treated before entering the study for some weeks with cotrimoxazole orally, with the bacteria fully sensitive to both trimethoprim and sulphonamide, and with a sufficient concentration of trimethoprim in the nasal secretion. Treatment with cotrimoxazole was not successful, nor was local treatment with aminoglycosides.

There are only a few publications with regard to the use of antibiotics in ozena, and no publications about the use of quinolones. Ciprofloxacin, one of the new fluoroquinolones, penetrates excellent into tissues of the upper respiratory tract, including the nose. Its penetration into nasal secretions is also excellent. These features, combined with good oral absorption, a broad anti-bacterial spectrum and especially high bactericidal activity against gram-negative organisms, make this drug attractive for the treatment of ozena.

We report in this study 10 cases of ozena treated with ciprofloxacin. All patients are after an observation period of 2–6 years completely free from foetor and also largely free from crusting. During the same period, *Klebsiella ozenae* could not be cultured at any time except in one patient, in who we noticed recurrence of the bacteria for a short period. In our patients, ciprofloxacin has been a successful treatment for their disabling disease. All the patients were satisfied with the result, especially those with a tendency to considerable crusting and those with a pronounced offensive odour for years, affecting their social life negatively.

The period of treatment was as long as 1–3 months, mainly because it usually took that time before we could notice stabilized and clean conditions in the nasal cavities but also in some cases because of the finding of various other gram-negative bacteria in cultures. Despite the long period of treatment, the tolerance was good and no serious adverse reactions were recorded. The side effects were few, with moderate gastrointestinal disturbances in two patients and *pruritus vulvae* in one patient. No patient had to stop the medication.

Our conclusion is that ciprofloxacin, with its excellent penetration into tissues and secretions, seems to be a promising drug in the treatment of ozena. This treatment, on the other hand, did not reverse the histopathological aspect of the nasal mucosa, at least not after one year of treatment in our two re-biopsied patients. For continuing successful results, we strongly suggest that careful cleansing of the nose (i.e., daily during the first week of treatment and, then, whenever necessary for 1–3 months) is extremely important. After that, regular nasal irrigation is usually sufficient, although we know that some of the patients will neglect this and apparently can do so without recurrence of the symptoms. The combination of antibiotic treatment and regular cleansing has been successful in our 10 patients. It is reasonable to believe that it is important to choose antibiotics with a high bactericidal activity against gram-negative organisms and with a high ability to penetrate tissues and secretions, as do the quinolones.

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