Efficacy of Two Dosage Schedules of Cephalexin in Dermatologic Infections

Arthur F. DiMattia, MD, Michael J. Sexton, Md, Chester R. Smialowicz, MD, and Wallace H. Knapp, Jr., MD
Peabody, Massachusetts, San Diego, California, Pennsauken, New Jersey, and Corvallis, Oregon

Is the administration of oral antibiotics four times a day as necessary as some pharmacokinetic studies indicate? The efficacy of cephalexin administered twice a day was compared to the same drug administered four times a day for the treatment of skin and skin structure infections due to staphylococcus and/or streptococcus. The 154 outpatients in this four-clinic study ranged in age from 1 month to more than 70 years. A random number table was used to assign patients to either the twice a day or the four times a day regimen. The total daily dosage was the same in each regimen. Administration twice a day proved equally effective to the four times a day regimen. Both regimens were more than 97 percent effective and side effects were minimal.

Nearly a decade of experience has shown cephalexin (Keflex) to be effective in the treatment of skin and skin structure infections when caused by staphylococci and/or streptococci.[1-5]

This oral cephalosporin antibiotic has been particularly useful to the pediatrician and the family physician because it is relatively safe and it eliminates the need for intramuscular administration of penicillin.

Most oral antibiotics, including cephalexin, traditionally are administered three or four times a day. While some pharmacokinetic studies suggest administration four times a day is necessary, clinical studies in various infections have shown the effectiveness of cephalexin when administered twice a day. In addition, as Fischer[6] recently pointed out, simplifying drug regimens can improve patient compliance.

From Peabody, Massachusetts, San Diego, California, Pennsauken, New Jersey, and Corvallis, Oregon. Requests for reprints should be addressed to Dr. Arthur F. DiMattia, North Shore Medical Park, Essex Center Drive, Peabody, MA 01960.

For these reasons, the efficacy of 250 mg of cephalexin administered four times a day (qid) was compared with the same total daily dose administered as 500 mg twice a day (bid) in the management of skin and skin structure infections. (Dosage for children was 20 to 30 mg/kg/day.) The study was conducted by four investigators in four different centers, but identical protocols were used, thus making a multiclinic assessment possible. This paper presents the results of the pooled data.

Methods

A total of 154 patients were enrolled in the study. The patients varied in age from 1 month to 70 years or more. The age distribution of the two groups was similar. The largest number of patients in each group was less than 15 years of age: 35 percent in the bid group and 36 percent in the qid group (Table 1).

A medical history was taken and a physical examination was performed on each patient before

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Table 1. Distribution by Patient Age

	<15	15-25	26-45	46-65	66+	Total
Cephalexin bid	28	20	19	8	5	80
Cephalexin qid	27	12	20	12	3	74

being enrolled in the study. The purpose of the study was explained to each patient (or parent-guardian) and informed consent was obtained.

Pathogen identification was undertaken in all infections (furuncle, impetigo, skin ulcer, subcutaneous abscess) that offered culturable material. Pretherapy cultures were taken not more than 72 hours prior to treatment. The infecting organism was identified and susceptibility determined. Therapy was not delayed pending susceptibility test results.

Patients with nonculturable infections (cellulitis, lymphangitis, adenitis) that were judged to be due to staphylococci or streptococci also were treated.

Patients were excluded from the study if the skin infection was complicated by foreign material or more serious systemic infections, the causative pathogen(s) was resistant to the cephalosporins, the patient was pregnant (unless in the opinion of the investigator the benefits of therapy outweighed the risks), the patient was hypersensitive to penicillin or the cephalosporins, or the patient had received prior treatment with an agent that would preclude evaluation of therapy.

Patients were assigned to either a twice a day or a four times a day regimen according to a computer derived randomization table.

The usual duration of therapy was four to ten days; however, a minimum of four days' therapy was considered necessary in order to evaluate any given case. Laboratory studies were conducted when indicated.

Additional therapy consisted of incision and drainage of eight of the subcutaneous abscesses. Spontaneous drainage was present in four abscesses, and six yielded to hot compresses. Thorough daily cleansing of the skin was stressed, and the continued use of compresses was urged in some cases.

The following clinical and bacteriologic criteria were used to determine whether the treatment was satisfactory.

Clinical

Satisfactory: Signs and symptoms disappeared or improved, or signs and symptoms improved or disappeared during therapy but recurred.

Unsatisfactory: No improvement in signs or symptoms.

Bacteriologic

Cure: The pathogen was eliminated with clearing of inflammation, or the infection recurred with a new pathogen.

Failure: The lesion persisted with significant numbers of the original pathogen, or the lesion improved but recurred with a culture that was positive with the same pathogen.

Results

Of the 154 patients originally enrolled, 21 cases could not be evaluated for various reasons, including negative precultures, violation of the random dosage sequence, and lack of pathogen identification.

Table 2. Skin and Skin Structure Infections, bid vs qid Cephalexin

Diagnosis/Microorganism	Total Number of Patients		Satisfactory Clinical Outcome		Bacteriologic Cure	
	bid	qid	bid	qid	bid	qid
Impetigo						
S aureus	32	34	32	32	32	32 (1*)
S epidermidis	3	—	3	—	3	—
S pyogenes	1	1	1	1	1	1
Multiple organisms	4	2	4	2	4	2
Subtotal	40	37	40	35	40	35
Cellulitis						
S aureus	3	5	3	5	3	5
S epidermidis	—	2	—	2	—	2
S pyogenes	2	1	2	1	2	1
Multiple organisms	1	1	1	1	1	1
No organism isolated	1	3	1	3	1**	3**
Subtotal	7	12	7	12	7	12
Subcutaneous abscess						
S aureus	10	7	10	7	10	7
Multiple organisms	—	1	—	1	—	1
Subtotal	10	8	10	8	10	8
Miscellaneous†						
S aureus	6	6	6	6	6	6
S epidermidis	—	3	—	3	—	3
Multiple organisms	2	1	2	1	2	1
No organism isolated	—	1	—	1	—	1**
Subtotal	8	11	8	11	8	11
Total	65	68	65	66	65	66

*Pathogen eliminated but reinfected due to sibling contact in one case
**In nonculturable infections, a clinical cure implied a bacteriologic cure
†Includes postoperative infection, furuncle, ecthyma, eczema, paronychia, lymphangitis, skin ulcer, and atopic dermatitis

It was of interest that of the 136 available cultures yielding staphylococcus and/or streptococcus organisms, routine laboratory testing showed all were susceptible to cephalexin and methicillin. However, 111 staphylococci and 5 streptococci were resistant to penicillin, 78 staphylococci and 1 streptococcus were resistant to ampicillin, and 26 staphylococci were resistant to tetracycline.

The 21 cases that could not be evaluated included only 1 clinical and bacteriologic failure, and this was attributed to poor regimen compliance.

Of the remaining 133 cases that were evaluated, 68 received cephalexin four times a day, and 65 received the drug twice a day. Conditions treated included impetigo, cellulitis, subcutaneous abscess, and other infections such as postoperative and traumatic wound, eczema, ecthyma, and paronychia (Table 2).

All 65 patients on the twice a day regimen had satisfactory clinical and bacteriologic responses (Table 2). Two of the 68 patients on the four times a day regimen had unsatisfactory responses. In one case, cephalexin failed to eradicate Staphylococcus aureus from a 30-year-old white male with impetigo. While no clinical improvement was noted after 14 days of therapy, repeat cultures showed improvement, with a change from a heavy to a sparse growth of S aureus.

Another patient, a 24-year-old white female who presented with impetigo, did not improve symptomatically, although the infecting organism was eliminated.

Side Effects

Of all the 154 patients originally enrolled, side effects occurred in 6 patients, 3 in each of the two regimens. Therapy was discontinued in three patients.

Three patients in the twice a day group had dyspepsia, dry mouth, and rash respectively. Therapy was discontinued only in the patient complaining of dyspepsia, but a bacteriologic cure had been obtained after four days of therapy.

In the four times a day group, three patients complained of nausea, dyspepsia, and erythematous rash, respectively. Therapy was discontinued in the latter two patients. The relationship of the drug to the rash could not be determined.

There were no reports of abnormal laboratory data attributable to cephalexin.

Discussion

One theoretical advantage of the twice a day over the four times a day dosage is that the reduced frequency of administration would lead to greater compliance. Patient noncompliance is a part of every physician's experience, especially with oral medication in the ambulatory patient. When a patient fails to respond to treatment, the physician often is left to wonder whether the drug was ineffective or the patient failed to take the prescribed dosage at the assigned times for the specified number of days.

Numerous reviews indicate that compliance decreases as the number of drugs taken and the frequency of administration increase.[7,8] Thus, compliance could be expected to improve on a twice a day regimen because it would be easier for the patient to remember and would be more convenient. For example, a study by Ayd evaluated the influence of the frequency of administration on compliance in psychiatric patients, many of whom also had coexisting chronic physical illnesses.[9] At the end of a one-month study period, he found there was a noncompliance rate of 70 percent in the four times a day group compared with a 30 percent rate in the twice a day group.

The results of this study indicate that the administration of cephalexin twice a day for the treatment of skin and skin structure infections is fully as efficacious as administration four times a day. Although compliance was not specifically studied as part of this protocol, it may have been a factor.

It is interesting that these skin and skin structure infections responded to dosages twice a day, in spite of the fact that the serum half-life of cephalexin is 0.9 to 1.2 hours, which would suggest that more frequent administration is necessary.

The simplicity of the twice a day dosage should be of benefit to the family physician in the therapeutic management of skin and skin structure infections in the ambulatory patient.

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