Absorption of Orally Administered Nafcillin in Normal Healthy Volunteers

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The absorption of orally administered nafcillin sodium monohydrate buffered with calcium carbonate was studied in 10 healthy human volunteers. Dosages of 500 mg and 1 g were studied in fasting and nonfasting states. There was considerable individual variation in the absorption of nafcillin, although measurable serum concentrations were obtained in all subjects. With few exceptions, peak serum concentrations were reached faster and were more predictable in the fasting state than in the nonfasting state. In the majority of subjects, food interfered with nafcillin absorption. Measurable serum concentrations persisted for 4 h in almost all subjects, but there were no or negligible serum concentrations at 6 h. The mean serum concentrations obtained in the present study were higher than those reported in an earlier study.

Nafcillin, a semisynthetic penicillinase-resistant penicillin, is a valuable anti-staphylococcal antibiotic when it is given parenterally. However, it has been shown during clinical investigation of nafcillin that after oral administration of nafcillin, absorption was erratic in both fasting and nonfasting subjects, resulting in poor and unpredictable serum concentrations (7, 11). Consequently, oral nafcillin therapy is not usually recommended (1, 5, 8). There has been no recent study on oral nafcillin. The present investigation was designed to study the serum concentrations of nafcillin after oral ingestion of this antibiotic in a group of healthy human volunteers.

MATERIALS AND METHODS

Antibiotic. The nafcillin preparation used in this study was in the form of film-coated tablets containing nafcillin sodium as the monohydrate, equivalent to 500 mg of nafcillin, buffered with calcium carbonate. Wyeth Laboratories, Inc., Philadelphia, Pa., kindly provided the entire supply needed for this study.

Volunteers. Eight male and two female healthy adults volunteered for the study. The research protocol was approved by the Committee on Human Research, University of Cincinnati College of Medicine. Written informed consent was obtained from all subjects.

Experimental designs. The study was divided into four phases, and all 10 volunteers participated in all four phases of the study. Each phase of the study was performed in weekly intervals. During phase 1, all subjects received no food from midnight until noon of the day of the study. One tablet of nafcillin (500 mg) was ingested by each subject in the morning. Six milliliters of blood was withdrawn immediately prior to the administration of nafcillin and at 0.5, 1, 1.5, 2, 4, and 6 h after the drug was given.

Phase 2 was similar to phase 1, except that the subjects were allowed to eat breakfast and the nafcillin tablet was ingested within 1 h of breakfast. In phase 3, the procedure of phase 1 was followed, except two tablets of nafcillin (1 g) were ingested instead of one.

Phase 4 was similar to phase 3, except that the subjects were allowed to eat breakfast and the study was performed within 1 h of breakfast.

Nafcillin assay. The blood was allowed to clot and the serum was separated. The serum samples were immediately frozen at -20°C until tested. In most instances, the samples were tested within 48 h of collection. Nafcillin assay was performed by the cylinder cup-plate agar diffusion method of Bennett et al., using Sarcina lutea as the test organism (2). Antibiotic standards were diluted in pooled human serum. Antibiotic standards as well as samples were assayed in triplicate, and the average measurements were used. All serum samples from each subject during the same phase of study were assayed in the same plate.

RESULTS

Results of the study are shown in Tables 1 and 2. In the fasting subjects, measurable but markedly variable concentrations of nafcillin were obtained in all but one subject at 0.5 h. In all but one subject in each of the two fasting studies, peaked serum concentrations were attained at 1 h. One subject in each study attained peak serum concentrations at 1.5 h. There was marked variation in the individual peak serum concentration among the subjects.
At 6 h, no or negligible serum concentrations were found.

In the nonfasting studies, the serum concentrations were even more unpredictable. In the 500-mg study, no antibiotic activity was found in the 0.5-h specimens in seven subjects. However, in the remaining three subjects, peak serum concentrations were attained at 0.5 h. Peak serum concentrations were at 1.5 h in three subjects, at 2 h in three subjects, and at 4 h in the remaining subject. Again, the individual peak serum concentration varied markedly among the subjects. The peak serum concentration was the same in one, higher in three, and lower in six subjects as compared with the values obtained in the fasting state. At 6 h, no or negligible serum concentrations were found. In the nonfasting 1-g study, peak serum concentration was attained at 1 h in seven, and in one subject each at 1.5, 2, and 4 h. Marked variation in individual peak concentration also prevailed. In all subjects, the peak serum concentration was lower than that obtained in the fasting state. No or negligible serum antibiotic activity was found at 6 h.

**DISCUSSION**

The results of this study confirm the previous finding that there was considerable individual variation in the absorption of nafcillin administered orally (7, 11), although measurable serum concentrations were obtained in all subjects. Even in the same individual, the absorption was not predictable. For example, subject no. 2 absorbed poorly in the 500-mg experiments, but had good absorption in the 1-g studies. With few exceptions, peak serum concentrations were reached faster and were more predictable in the fasting state than in the nonfasting state. In the majority of subjects, food interfered with nafcillin absorption.

It is not clear to what extent individual vari-
ation in absorption occurs with other orally administered antibiotics since usually only the mean values from a group of experimental subjects are reported. However, in a recent report on josamycin and erythromycin stearate, in which values from individual volunteers were reported, there was also considerable individual variation in the serum concentrations after oral administration of either josamycin or erythromycin stearate (9). The finding of individual variation was not emphasized when the authors only discussed the mean values. Wide individual variation in absorption also occurs with the orally administered isoxazolyl penicillins. Although only mean values from a group of experimental subjects were usually given in the published reports, the wide ranges of serum concentrations obtained in volunteers after the same oral dose of any one of the isoxazolyl penicillins were evident (3, 4, 6, 10), and authors of three of these reports commented specifically on these findings (4, 6, 10).

There is only one report on oral nafcillin in the literature comparable to the present study, using the same oral preparation (1 g of nafcillin sodium monohydrate buffered with calcium carbonate) and the same antibiotic assay technique (cylinder cup-plate agar diffusion method using S. lutea as the test organism). Only mean values were given in that particular study, although in the summary and conclusion the authors commented that the serum activity varied widely in different individuals (7). A comparison of the mean nafcillin serum concentrations from that and the present studies is given in Table 3. In both studies, absorption of oral nafcillin was much better in fasting than nonfasting subjects. In both the fasting and nonfasting experiments, the mean serum concentrations from the present study were higher than those from the earlier study that was published in 1963. The significance of this finding is not known. It may be due to the mere fact that the results were from two different laboratories at two different times, or the formulation of the drug may not be exactly the same.

On the basis of the results of this and previous studies (7, 11), it is concluded that the use of nafcillin orally is not warranted.

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LITERATURE CITED