**Table XI—Stepwise Summary of Discriminant Analysis for Number of Septic Episodes in Patients Who Survived [a]**

| Step | Variable | Wilks Lambda | Significance Level | Change in $r^2$ | Rao's V | Change in Rao's V | Significance Level |
|---|---|---|---|---|---|---|---|
| 1 | Age | 0.87 | 0.002 | 0.13 | 7.37 | 7.37 | 0.007 |
| 2 | Pharmacokinetics | 0.78 | 0.002 | 0.09 | 14.22 | 6.86 | 0.009 |
| 3 | Onset of sepsis | 0.70[a] | 0.002 | 0.08 | 18.01 | 3.79 | 0.050 |

[a] $\chi^2$ (3 *df*) = 15.35; $p < 0.002$.

partially to apply a practical cost–benefit decision model that could be used by the decision maker to determine the desirability of establishing and operating a clinical pharmacokinetics service within the hospital environment. Beginning with a considerable volume of theoretical, economic, and mathematical literature, this work set out to bridge the gap between the theoretical discussion of cost–benefit analysis and its practical application to evaluating clinical pharmacy services.

Cost–benefit analysis proved to be a satisfactory technique in evaluating the use of clinical pharmacokinetics in the treatment of burn patients. A major contribution of cost–benefit analysis was identifying the specific costs and benefits associated with the pharmacokinetics program. This step is important if one is ultimately interested in making the operation more efficient in terms of maximizing the cost–benefit ratio.

The major conclusion to be made from this study is that the pharmacokinetics service evaluated may be beneficial not only to the burn patient who develops Gram-negative infections secondary to a third-degree burn wound but also to society. In other words, this study demonstrated that the ability of the pharmacist to provide services related to the application of pharmacokinetics in the treatment of burn wound infections may improve the quality, as well as the cost–benefit, of patient care as related to drug therapy.

As stated by McLeod (3), the continued success of clinical pharmacy will be proportional to its contribution to patient care and public welfare. It appears that cost–benefit analysis can be a mechanism to document successfully and accurately the contributions of the clinical pharmacist.

**Table XII—Discriminant Analysis Coefficients for Number of Septic Episodes in Patients Who Survived**

| Variable | Standardized Coefficient | Unstandardized Coefficient |
|---|---|---|
| Age | −0.99 | −0.05 |
| Pharmacokinetics | 0.70 | 1.63 |
| Onset of sepsis | −0.47 | −0.05 |
| Constant | | 0.76 |

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# Effect of Obtrusive Measures on Antibiotic Compliance


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**Abstract** □ The influence of compliance measurement activities on patient behavior was studied. The project measured the relationship among physical capsule counts, patient interviews, and the amounts of excreted ampicillin. The capsule counts and patient interviews were conducted in a manner that disguised their intent. Sixty college-age patients were assigned to one of three experimental groups: a telephone interview, a personal interview and capsule count, or a control group. Stimulation (interviews) occurred on the 2nd day of the prescribed regimen, and urine was collected on random days thereafter. Results indicated that both stimulation types were associated with more positive compliance rates. The influence diminished rapidly. The reactive influence of experimentor intervention associated with personal and phone communication was demonstrated.



**Keyphrases** □ Compliance—effect of measurement activities on patient behavior □ Dosage regimens—effect of compliance measurement activities on patient behavior


Since 1954, when Jenkins (1) reported that the "average patient" consumed only about half of the total number of prescribed doses, members of the health community have responded with increased interest in the prevalence, associated factors, and methods of improving medication compliance. Most published research studies regarding




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**Table I—Design of the Experiment**

| Experimental Group | Day of Regimen 2 | 3 | 4 | 5 | 6 | 7 |
|---|---|---|---|---|---|---|
| 1 | S1[a] | 0[b] | | | | |
| | S1 | | 0 | | | |
| | S1 | | | 0 | | |
| | S1 | | | | 0 | |
| | S1 | | | | | 0 |
| 2 | S2[c] | 0 | | | | |
| | S2 | | 0 | | | |
| | S2 | | | 0 | | |
| | S2 | | | | 0 | |
| | S2 | | | | | 0 |
| 3 | NS[d] | 0 | | | | |
| | NS | | 0 | | | |
| | NS | | | 0 | | |
| | NS | | | | 0 | |
| | NS | | | | | 0 |

[a] S1 = patients subjected to a telephone interview. [b] 0 = day on which patient provided urine sample. [c] S2 = patients subjected to a personal interview and capsule count. [d] NS = patients not subjected to either stimulus (control group).

drug compliance utilized the basic measurement techniques of personal interviews, dosage unit counts, and body fluid analyses.

Different measurement techniques were utilized jointly, but comparative results were often lacking (2, 3). Experimentor intervention was unavoidable in many situations. The act of counting capsules or obtaining fluid samples in itself is stimulation. Unfortunately, a conscious effort to avoid experimental intervention has been undocumented in patient compliance literature or it has been little recognized as a potential source of error.

The objective of this project was to identify the influence of measurement activities on compliance behavior patterns. The assumption of noninfluence on patient behavior in previous studies was evaluated. Two obtrusive measures of patient compliance, telephone interviews and physical capsule counts, and the amount of excreted ampicillin were studied. By isolating the effects of the obtrusive stimulations from the dependent variable measure, the results validly described the influence of experimentor bias.

## EXPERIMENTAL

A quantitative urinalysis for ampicillin utilizing UV spectrophotometry (4, 5) was tested and found applicable to the project. A Beer's law equation for concentrations in the 5.0–1250.0-μg/ml range was developed. The coefficient of correlation ($r$) was 0.9998.

**Operational Definition of Compliant Behavior**—The objective of the first phase of the study was to define compliant behavior based on excreted quantities of ampicillin. Twenty college-age students each consumed a single 250-mg capsule of ampicillin trihydrate from the same lot. The administration time was recorded, and the subjects were instructed to conduct normal patterns of food and beverage consumption and urine excretion. Urine samples were collected from each subject at 12 and 24 hr following consumption.

Collected urine samples were analyzed, and concentrations of excreted ampicillin were recorded. A paired $t$ test was calculated to determine if the mean values for the two periods differed significantly. The 12-hr data were selected as a reference standard, and a 70% confidence interval ($\alpha = 0.30$, $df = 19$) was calculated for the 12-hr mean concentration. The 70% confidence interval was chosen to reduce the probability of a type II error. A type II error is accepting the hypothesis that an individual is a member of the same population from which the 12-hr sample members were drawn when, in fact, that individual is not a member of the same population.

After the confidence interval was calculated, the operational definition of compliant behavior was formulated. Individuals who consumed at least a single 250-mg dose of ampicillin less than 12 hr before sampling were expected to excrete larger quantities of ampicillin than the noncompliant reference group.

Compliant behavior was then defined by urinalysis quantities greater than the upper tail of the 70% confidence interval.

**Table II—Analysis of Variance (Two Factor, 5 × 3)**

| Source | $df$ | Sum of Squares | Mean Square | $F$ Value | $PF$ |
|---|---|---|---|---|---|
| Experimental group | 2 | 203817.78 | 101908.89 | 2.31 | 0.11 |
| Day of regimen | 4 | 296935.84 | 74233.96 | 1.68 | 0.17 |
| Interaction | 8 | 534769.27 | 66846.16 | 0.52 | 0.18 |
| Error | 45 | 1983014.92 | 44067.00 | | |
| Corrected total | 59 | 3018537.80 | | | |

**Experimental Design and Procedures**—The project separated the urine collection procedure from the other measurement techniques by treating the interview and capsule count as stimuli rather than as measurement procedures. The experimental design is given in Table I. Four subjects were randomly assigned to each experimental cell.

The experimental groups were those patients who were subjected to a telephone interview (S1), those patients who were subjected to a personal interview and capsule count (S2), and those patients who were not subjected to either stimulus (NS) on the 2nd day of the drug regimen. The control received no stimulation.

College age student patients[1] for whom a normal ampicillin regimen was prescribed were eligible for the study. Subjects were selected if:

1. The ampicillin prescription was written for a 250-mg capsule to be taken four times a day for 7–10 days.
2. The brand dispensed when the patient received the prescription matched the selected brand and lot number of ampicillin.
3. The patient did not receive any other confounding medication, particularly penicillin, during the ampicillin regimen.
4. The patient was seen only on an out-patient basis during the ampicillin regimen.
5. The patient agreed to release his/her pharmaceutical information by signing the release form at the time the ampicillin prescription was received. The release forms were collected daily and were designed to minimize association with the compliance study.

Subject stimulation took place the day after the patient received the prescription. The primary researcher, posing as a graduate student currently enrolled in a sociology course, conducted both the telephone and personal interviews. Subjects, told that they were randomly selected from the University's telephone directory, were administered the "Survey of Self-Medication Habits of College Age Adults."

The subjects assigned to the experimental group receiving a personal interview were asked to show the interviewer all medication they were currently taking; the interviewer pretended not to know how to spell the names of the medications and requested to see the containers. Patients in the second experimental group were administered the questionnaire by telephone. They also were asked if they were currently taking any medication and the name(s) of the medication(s).

All subjects were contacted by telephone on the evening prior to the randomly assigned day for sampling of the student's urine and were requested to present themselves at the College of Pharmacy to provide "data" for the Northeast Georgia Drug Study. The nature of the data was not specifically identified. The subjects were promised $10 for their cooperation.

If the subject agreed to provide data and did appear at the College, he/she was then informed of the exact nature and purpose of the data collection. Upon receipt of the urine sample, the researcher analyzed the sample spectrophotometrically.

## RESULTS

Urine samples collected from the 20 selected subjects at 12 and 24 hr following dosing yielded mean concentrations of excreted ampicillin equal to 89.72 and 26.92 μg/mg, respectively. The standard deviations were 52.53 and 24.42 for the 12- and 24-hr periods, respectively. The paired comparison $t$ test, using a pooled standard deviation of 9.79, yielded a calculated value of 6.41. Therefore, it was concluded that excretion of ampicillin decreased in concentration between the two time periods.

The 70% confidence interval calculated for the 12-hr sample was

[1] At the University of Georgia Gilbert Health Center.

**Table III—Experimental Cell Means**

| Experimental Group | Day of Regimen | | | | |
|---|---|---|---|---|---|
| | 3 | 4 | 5 | 6 | 7 |
| 1 | 107.50 | 133.13 | 290.69 | 588.75 | 121.13 |
| 2 | 137.56 | 228.75 | 143.81 | 122.50 | 78.06 |
| 3 | 57.50 | 75.63 | 22.69 | 200.00 | 206.50 |

76.86–102.58 μg/ml. Therefore, sampled patients who exhibited urine concentrations of ampicillin less than 102.58 μg/ml were defined as noncompliant. They were defined as having consumed not more than a single 250-mg dose, 12 hr prior to urine sampling.

A total of 92 students released their pharmaceutical information to the Northeast Georgia Drug Compliance Study between July 1 and October 18, 1976. Thirty-two students were not included because some could not be contacted while others failed to comply with one or more of the selection criteria.

A two-factor analysis of variance was conducted utilizing the SAS ANOVA computer program (6). The analysis of variance table and $F$ values calculated by this procedure are found in Table II.

The analysis of variance demonstrated that neither the main effects (experimental group and day of regimen) nor the two-way interaction contributed significantly to the total variation in the data.

For Days 6 and 7 of the regimen, the mean cell values of excreted ampicillin concentration of the control group increased dramatically from the three previous regimen days (Table III). This observation prompted a second two-factor analysis of variance utilizing the day-of-regimen factor with only three levels. The remaining two levels (Days 6 and 7) were deleted from this analysis.

A series of three two-factor analysis of variance procedures, each utilizing levels 3, 4, and 5 of the day-of-regimen factor, and all pair comparisons of the experimental group factor levels was conducted (Table IV). A significant difference was found among the experimental group levels, personal interview, and control and among experimental group levels, telephone interview, and control. The respective $p$ values were 0.00 and 0.01, with 1 degree of freedom associated with each $F$ value. No significant difference was found among the experimental group factor levels, telephone interview, and personal interview at $\alpha = 0.05$ with 1 degree of freedom.

Thus far, the analysis conducted utilized the raw measure of micrograms of excreted ampicillin per milliliter as the dependent variable. Comparisons between the marginal mean values of excreted ampicillin that denote compliant behavior were then conducted to determine if significant differences found between experimental groups based on the raw data corresponded to actual differences in compliance. The results indicated that the significant differences found, based on quantities of excreted ampicillin, were similar to expected differences based on the operationally defined standard of compliant behavior (Table V).

**Table IV—Analysis of Variance (Two Factor, 3 × 3)**

| Source | $df$ | Sum of Squares | Mean Square | $F$ Value | $PF$ |
|---|---|---|---|---|---|
| Experimental group | 2 | 118660.67 | 59330.4 | 7.14 | 0.00[a] |
| Day of regimen | 2 | 18890.94 | 9445.5 | 1.14 | 0.36 |
| Interaction | 4 | 86377.92 | 21594.5 | 2.60 | 0.06 |
| Error | 27 | 224420.44 | 8311.9 | | |
| Corrected total | 35 | 448349.97 | | | |

[a] Significant at $\alpha = < 0.05$.

**Table V—Comparison of Experimental Group Marginal Values to Operational Defined Level Indicative of Compliant Behavior**

| Experimental Group | Day of Regimen | | | Marginal | Compliant Marginal (≥102.58) |
|---|---|---|---|---|---|
| | 3 | 4 | 5 | | |
| 1 | 107.5 | 133.13 | 290.69 | 177.11 | Yes |
| 2 | 137.56 | 288.75 | 143.81 | 170.04 | Yes |
| 3 | 57.50 | 75.63 | 22.69 | 51.94 | No |

## DISCUSSION

Patients subjected to either physical capsule counts *via* a personal interview or to a telephone interview differed in compliance rates from patients who received no stimulation. Stimuli were associated with more positive compliance. The influence of both stimuli diminished after the 5th day of the regimen. This conclusion was based on the results of the 3 × 5 two-factor analysis of variance, which included Days 6 and 7.

Patients subjected to a personal interview differed in compliance rates from those subjected to a telephone interview. No significant difference between the two stimuli was found.

As the duration of time increased between the point of stimulation and the measurement of compliance, the medication compliance rate decreased. Based on the analysis of variance procedures, a significant day-of-regimen effect was not verified. However, the excreted quantities of ampicillin increased on the 6th and 7th regimen days for the experimental group that received no stimulation (control). The experimental group that received the telephone interview maintained high levels of excreted ampicillin throughout the last 2 regimen days measured. For the experimental group that received the personal interview, excretion levels decreased dramatically on the 7th day.

This project demonstrated that the act of measurement was of interest to the patient. Being so, it elicited more positive compliance rates. Health care personnel can benefit from this and other projects that have demonstrated the association between improved compliance habits and increased interest in the patient population.

This project has impact on the validity of previous studies that utilized either a patient interview or dosage unit count to generate a dependent measure of compliance. The act of measurement does influence resultant compliance rates to a degree that must be accounted for if accurate measures are to be achieved. Past reports of patient compliance must be weighted with the intrinsic bias isolated.

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