Estimating Compliance with Diuretic Therapy: Urinary Hydrochlorothiazide-Creatinine Ratios in Normal Subjects

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SUMMARY We gave 21 healthy young men 100 mg of hydrochlorothiazide daily to determine whether or not urinary detection of the drug was feasible as a measure of compliance on a standard antihypertensive regimen. All subjects took the drug daily for 6 days, after which they were divided into four groups with differing patterns of medication administration. Urine hydrochlorothiazide and creatinine measurements were obtained to validate the urinary hydrochlorothiazide-creatinine ratio (UHCR) as an accurate quantitative index of compliance. The subjects achieved a constant level of UHCR of 13 ± 3.0 within 48 hours of hydrochlorothiazide administration. The UHCR levels decreased to 5.0 ± 0.8 48 hours after discontinuation of the drug (p < 0.001). UHCR values in the range of 13 ± 6 indicate that the subject has ingested hydrochlorothiazide 24 hours previously. The UHCR is a potentially useful means of assessing compliance in hypertensive patients taking hydrochlorothiazide. (Hypertension 1: 537-542, 1979)

KEY WORDS • compliance • diuretic • hydrochlorothiazide • urinary hydrochlorothiazide

HYPERTENSION, a major public health problem in the United States today, affects approximately 12-18% of the general population. Treatment that effectively reduces blood pressure decreases morbidity and mortality, but only about 54% of the hypertensive population is receiving therapy, and blood pressure is controlled in only about 38% of all hypertensive individuals. Furthermore, 50% of newly identified hypertensive patients discontinue therapy within 1 year of the initiation of treatment. This rate increases to 75% at 5 years.

Since mild-to-moderate hypertension is usually asymptomatic, patients frequently do not place importance on taking medication regularly for the purpose of decreasing the risk of future complications such as stroke, congestive heart failure, and renal disease. Compliance with medical treatment is therefore a difficult problem; yet close adherence to a regimen of medication is necessary in the management of hypertension. Previous studies attempting to identify factors that influence compliance have demonstrated varied and often contradictory results, owing primarily to the lack of objective measures of compliance. Compliance studies are dependent upon accurate assessment of dose and frequency of administered medication. Interviews using a questionnaire, pill counts, and blood pressure recordings have been used individually and in combination. Each of these methods, however, poses problems of accuracy in assessing compliance. Interviews using a questionnaire depend upon the patient's truthfulness, how much the patient wishes to please the investigator, and the interview techniques employed. Pill counts do not prove that the patient has actually ingested the drug. Since antihypertensive medications may reduce the level of blood pressure (BP), measurement of BP often provides a more accurate guide to compliance than...
pill counts or questionnaires. However, compliant hypertensive patients frequently do not respond to a given antihypertensive drug with a decrease in BP. Consequently, BP measurement may not reflect close patient compliance with a medical regimen.

Direct measurement of antihypertensive drugs offers a useful approach for monitoring compliance. Quantitative serum and urine measurements of most hypertensive medications have been developed, and compliance studies have utilized measurements of serum methyldopa and propranolol concentrations. However, quantitative techniques are not widely available and have not been adopted for large-scale use.

We have developed a rapid, automated, simple method of quantitatively measuring hydrochlorothiazide in the urine. The present study was undertaken to validate this method as an accurate quantitative index of compliance with a standard hydrochlorothiazide regimen given for 10 days to normal subjects.

Materials and Methods

Twenty-one normotensive male volunteer subjects 22–32 years old and without evidence of renal or hepatic disease were used for the study after the nature of the procedure was fully explained and informed consent was obtained. The subjects were within two standard deviations of their ideal body weight. Prior to initiation of the study, blood was obtained from each subject for cell counts and chemistry determinations, and urinalysis was done. Subsequently, the subjects reported daily between 8:00 a.m. and 9:00 a.m. to the Medical Clinic of the University of Virginia Hospital, where blood pressure was measured, urine was obtained, and hydrochlorothiazide, 100 mg, was given orally under direct observation.

In order to study the effects of different compliance regimens of hydrochlorothiazide, each of the first 20 individuals was allocated randomly to one of four treatment groups - A, B, C, or D (table 1). The twenty-first volunteer was assigned to Group D. All subjects took hydrochlorothiazide for the first 6 days of the study; thereafter the regimens differed according to the assigned group as shown in table 1. Group A subjects omitted the dose of hydrochlorothiazide on Day 7 taking one last dose on Day 8. Group B omitted doses on Days 7 and 8, taking the last dose on Day 9. Group C omitted the Day-7 dose, took the medication on Day 8, omitted the Day-9 dose and took the last dose on Day 10. Group D subjects took the last dose on Day 7. In order to determine the peak level of hydrochlorothiazide, subjects in Group D collected spot urine specimens every 2 hours for 8 hours after administration of hydrochlorothiazide on Day 7. All subjects had repeat blood studies 24 hours following the last doses of hydrochlorothiazide. Urine samples also were obtained 2 weeks after completion of the protocol.

Blood pressure measurements were obtained with a mercury sphygmomanometer in the left arm with the individual in the sitting position. The fifth Korotkoff sound was used to determine the diastolic reading.

Each urine specimen was collected before the observed administration of the hydrochlorothiazide tablet. The urine specimens were analyzed for hydrochlorothiazide and creatinine concentration. Three determinations of urine hydrochlorothiazide were not used, because one subject was unable to produce a urine specimen prior to the hydrochlorothiazide administration and two subjects were absent one morning each.

Analytical Methods

The hematological and chemical studies were performed in the Clinical Laboratory of the University of Virginia Hospital. The procedure used to assay for hydrochlorothiazide in urine is an adaptation of a manual colorimetric procedure described by Sheppard et al. We have adapted their method to an automated instrument (Auto Analyzer, Technicon Instruments, Terrytown, NY). In our procedure, urine is extracted with ethyl acetate, the solvent removed and the residue reconstituted in NaOH, hydrolyzed by heat and sampled by the auto analyzer. The reagents include sodium nitrate, ammonium sulfamate, N-(1-naphthyl) ethylene diamine dihydrochloride and HCl. The colored product formed is read at 505 nm and traced on a recorder. Blank urine and urine containing various levels of added hydrochlorothiazide for standards are run by the same method. Urine levels up to 100 μg/ml may be determined without dilution. A urine control at 50 μg/ml is included in each run. Reproducibility studies yielded an average coefficient of variation of 7.3%.

In order to reduce the variability of urinary hydrochlorothiazide concentrations due to variability of urine volume and osmolality, the individual hydrochlorothiazide concentrations were divided by the concentration of the urine creatinine measured on the same specimen. The resultant ratio multiplied by 100 was termed the urinary hydrochlorothiazide-creatinine ratio (UHCR).

Statistical Methods

Results are expressed as the mean ± 1 standard deviation. Statistical analysis for the data in normal subjects was carried out using the Student's t test for paired and non-paired data where appropriate.
Results

The UHCR for all 21 subjects, each receiving 100 mg of hydrochlorothiazide on Days 1–6, is shown in figure 1. The UHCR rose to 8 ± 1.7 on Day 2 and to 13 ± 3.0 (p < 0.001) on Day 3. Thereafter, the UHCR remained elevated but did not change from values on Day 3. On Day 8, the UHCR for 15 of the subjects who had discontinued taking hydrochlorothiazide on Day 7 was 5.0 ± 0.8 (p < 0.001). Considerable individual variation was noted on Days 3–7.

Results of the individual treatment groups (Days 8–11) are summarized in figure 2. All groups received hydrochlorothiazide on Day 6, and all levels on Day 7 were within two standard deviations of values on Days 3–6. Only Group D was given hydrochlorothiazide on Day 7. On Day 8, the levels of five of the six members of Group D were within two standard deviations of the mean values on Days 3–7, whereas all of the individual ratios of Groups A, B, and C fell below this level. Only Groups A and C were given hydrochlorothiazide on Day 8, and on Day 9 all ratios of these two groups rose to within two standard deviations of mean values on Days 3–7. Likewise, all of the ratios of individuals of Groups B and C, when given hydrochlorothiazide on Days 9 and 10, respectively, rose within two standard deviations of the following days. Except for one member of Group D on Day 9, all the ratios fell below two standard deviations 2 days after each individual discontinued hydrochlorothiazide. The only other exception noted was another member of Group D whose ratios failed to rise within two standard deviations on Day 8 after administration of hydrochlorothiazide on Day 7. Except for these two instances, individual UHCR determinations included within two standard deviations of the mean for Days 3–7 correspond to the administration of hydrochlorothiazide to that individual on the previous day. Similarly, values below two standard deviations represent discontinuation of hydrochlorothiazide at least 24 hours previously. Hydrochlorothiazide was not detectable 2 weeks after the protocol was discontinued.

The UHCR values for Group D monitored every 2 hours are shown in figure 3. The UHCR peaks at 4 hours. At 8 hours, the UHCR does not decrease below 48, a value significantly higher (p < 0.001) than noted at 24 hours. The time at which the 24-hour baseline UHCR levels were reached was not determined.

Results of chemical determinations obtained prior to the study and on the day following the last hydrochlorothiazide administration are compared in table 2. No significant differences were noted for hematocrit, white blood cell count, serum bicarbonate, blood urea nitrogen, blood glucose, serum
calcium, phosphorus, bilirubin, and alkaline phosphatase. No side effects due to hydrochlorothiazide were observed in any of the subjects during the study.

A comparison was made of the blood pressures obtained at the start of the study with those obtained after 6 days of hydrochlorothiazide administration to all of the subjects. Mean arterial blood pressure decreased from 90 to 86 mm Hg ($p < 0.05$). Average systolic blood pressure decreased from 126 to 119 mm Hg ($p < 0.005$), and average diastolic blood pressure decreased from 75 to 67 mm Hg ($p < 0.001$).

**Discussion**

Although hydrochlorothiazide has a half-life of approximately 5 hours, the results of this study indicate that it can be detected in the urine of normal subjects for at least 4 days. The calculated UHCR reached a steady state 48 hours after the groups began ingesting the drug. In this state UHCR values in the range of 7-19 indicate that the subjects had taken the drug 24 hours previously. When the drug was omitted, the UHCR in all groups with one individual exception fell below two standard deviations from the mean (less than seven).

The results of the treatment Groups A, B, and C in which doses were omitted in varying patterns, showed that the UHCR values fell below seven after omission of the drug on the previous day and rose to a range of 7-19 on the day after the drug was administered. Interestingly, this rise occurred in Group B on Day 10 after doses had been omitted on Days 7 and 8 before administration of the drug on Day 9. The present data do not indicate how many doses may be omitted prior to taking the medication in order to observe a UHCR value above seven. However, the UHCR values for the whole group on Day 2 after the initial administration of hydrochlorothiazide do not show a uniform rise above seven.

The data indicate, therefore, that the UHCR values may be useful in detecting those individuals who have omitted the doses of hydrochlorothiazide on the previous day. Whether or not the individuals had omitted other previous doses as well could not be evaluated by the UHCR value unless the value was zero indicating complete noncompliance. If UHCR levels are below seven, one may identify those individuals who are not taking hydrochlorothiazide at all, those who have skipped a dose the previous day, and those who take medicine so sporadically as to never reach a steady state.
The results of the UHCR measurements in Group D at 2-hour intervals indicate peak values at 4 hours with a gradual return to the range of 7–19. Although the exact time for the return of the UHCR values to this range was not determined, the data suggest that this may take 12 hours. If this is true, some latitude would be allowed in the time during which meaningful UHCR values could be measured. A UHCR value greater than 19, however, probably indicates that the individual has ingested hydrochlorothiazide within 8 hours of urine collection.

The blood chemistry determinations obtained after chronic hydrochlorothiazide administration to normal subjects reflect the well-known pharmacological actions of the drug. A significant decrease in potassium occurred despite the self-administration of potassium by some individuals. The finding of significantly elevated levels of lactic dehydrogenase (although still within the normal range) is unexplained. Borderline hepatic insufficiency has been noted during hydrochlorothiazide administration, but the mechanism is not understood. Although administration of hydrochlorothiazide was associated with a decrease in blood pressure in the 21 subjects, there was no control group to exclude the possibility that blood pressure declined with adaptation to examiners and surroundings.

Determination of the UHCR in normal subjects taking hydrochlorothiazide indicates that UHCR values indicative of patient compliance ought to fall in the range of 7–19. It is apparent, however, that UHCR values need to be standardized for age, sex, race, blood pressure level, and different doses and dosage schedules of hydrochlorothiazide, as well as for abnormal renal or hepatic function. In addition, the relationship of the UHCR to therapeutic serum concentration of hydrochlorothiazide is unknown.

In previous studies, the pharmacokinetics of hydrochlorothiazide have been studied, and several methods for assay of serum and urine for hydrochlorothiazide have been available. However, no previous studies have employed quantitative determinations of this drug for compliance measurements. Lowenthal et al. employed a qualitative colorimetric test to screen 172 hypertensive patients treated with hydrochlorothiazide and found 75 with uncontrolled blood pressures and positive tests. It was impossible to ascertain which patients were taking only an occasional dose of the drug.

Further studies of the UHCR are needed to assess its value in the determination of compliance in hypertension. Currently several disadvantages are apparent. The UHCR is standardized for the ingestion of hydrochlorothiazide taken 24 hours previously. Subjects must not take hydrochlorothiazide within at least 5 hours prior to urine collection to prevent a high UHCR value. The necessity of reminding patients of

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<th>Table 2. Serum Chemical Determination Before and 24 Hours After Hydrochlorothiazide Administration on the Last Study Day (n = 81)</th>
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<tr>
<td><strong>Before Hydrochlorothiazide</strong></td>
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this fact might result in bias of the compliance studies. However, the data indicate that the UHCR may return to baseline within 12 hours of hydrochlorothiazide administration, and if this is so, subjects could be instructed to take hydrochlorothiazide each evening. Urine specimens then could be collected anytime during the day. This regimen would allow much more flexibility for compliance studies.

A potential disadvantage of UHCR determination is the short half-life of hydrochlorothiazide (5 hours). If subjects only take their medication a few days before being studied for compliance, they might appear compliant because one cannot use the UHCR value to detect drug ingestion more than 24 hours earlier. Although this kind of noncompliance may be difficult to detect, multiple UHCR measurements over a prolonged period of time may identify some of these individuals.

Although obtaining a urine specimen for the UHCR determination is less invasive than obtaining a serum sample, compliance may be influenced in the informed patient. This form of bias may be important in experimental investigations of compliance, but a suitable control group would help identify the magnitude of this problem. Since multiple UHCR values should be determined over time to measure compliance, it is likely that this bias would diminish somewhat with time.

The UHCR method is more expensive than other methods of measuring compliance, such as pill counts. However, this method can easily be established in chemistry laboratories with automated equipment, and the unit cost would be determined in part by the volume of tests performed. In addition, the UHCR could be used as a reference standard for comparison of less costly measures of compliance that could ultimately be substituted.

The present data indicate that the UHCR is a useful index of compliance and that further development of this test for routine clinical use is indicated. A controlled prospective study of hydrochlorothiazide administration to a hypertensive group is needed. We plan to continue our studies of hydrochlorothiazide in order to resolve some of the difficulties mentioned. In addition, other doses of hydrochlorothiazide might be explored as well as other antihypertensive agents. Checking the UHCR in hypertensive patients could identify difficulties with medication-taking and lead to appropriate efforts promoting enhanced compliance. The ultimate outcome might be amelioration of the excessive morbidity and mortality of hypertension.

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