A Study in Human Pharmacology:
Evaluation of Four Diuretics and a Placebo

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with the collaboration of
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THE advent of the thiazides in 1958 marked the beginning of a new era in diuretic therapy. Their superiority over previously available agents was such that, for a time, it was felt that there could be little further improvement in this area of therapeutics. Today, they are considered standards of reference for the evaluation of newer diuretic agents.

Recently, two new non-thiazide agents have been made available, and are the objects of the present study: triamterene and furosemide.

Triamterene is an aminopteridine derivative which has been reported to show milder diuretic and natriuretic potency than the thiazides.[1-4] Unlike the latter, it exerts a potassium-sparing effect which is well documented,[5-9] and which is the basis of triamterene's distinctive advantages in conditions such as congestive heart failure where digitalis is used, and in cirrhosis. Triamterene is considered to be useful primarily as an adjunct to the thiazides.[5] For this reason, the combination of triamterene and hydrochlorothiazide was soon made available and was shown to be superior to either agent alone.[10, 11]

Furosemide is one of the latest additions to the list of unique diuretics. This monosulfamylanthranilic acid derivative is characterized by an intense diuretic effect of short duration.[12] It is said to be a more effective and rapid diuretic and natriuretic agent than hydrochlorothiazide.[13, 14] The intense effect of furosemide makes it particularly useful in clinical emergencies such as hypertensive attacks and cerebral and pulmonary edema.[15]

In this paper are reported the results of an experiment carried out by 131 medical and pharmacy student volunteers, in which both time-effect and dose-response relationships among four diuretics and a matching placebo were studied. Accepted principles of human pharmacology (use of objective parameters for comparison of the active compounds, double-blind conditions with appropriate controls) were applied so as to permit statistical treatment of the data. With regard to controls, an attempt was made to determine whether results of placebo administration under double-blind conditions differed from those obtained when subjects received a known placebo or no drug at all. The study method used was a modification of several published techniques.[16-18]

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METHOD

Experimental Conditions

One hundred and fifteen healthy male students, aged between 20 and 25 years, volunteered to participate in the experiment. They were divided into two groups: 88 participated in a time-effect study and 27 in a dose-response study.

Each of the 88 students in the time-effect study was allocated in a random fashion to one of six treatment groups, each of which comprised approximately 15 individuals comparable as to age, weight and physical condition. Each was given a code number. This number was the key to the whole experiment, as it was used to designate: the space allocated to each volunteer in the laboratory; the material necessary to carry out the various determinations; the observation sheet on which the data were to be entered; the containers in which each of the urine specimens was to be collected for biochemical analyses; the sealed envelope containing the medication; the senior student serving as monitor; the plates containing the food furnished for the breakfast and lunches; and any other report requested of the student during the experiment.

The single-dose regimens are shown in Table I.

Since commercially available tablets were used, there was a problem in matching them with an identical placebo. This was obviated by using placebos identical to each active drug. Therefore, by examining the tablet, the student could find the name or mark identifying the

TABLE I.—TIME-EFFECT STUDY REGIMENS

Generic name	*Brand name*	*Dose (tablet)*	*Number of volunteers*
Hydrochlorothiazide (HCT)...	Esidrix*	50 mg.	15
Triamterene/HCT (T/HCT)..	Dyazide†	50/25 mg.	15
Furosemide (F).....	Lasix‡	40 mg.	15
Coded placebo.....	—	q.s.	15
Known placebo.....	—	q.s.	12
No drug.....	—	—	16
			88

*Ciba Company Limited.
†Smith Kline & French Inter-American Corporation.
‡Hoechst Pharmaceuticals.

manufacturer and thus the drug, but he could not determine whether it was active or not.

The 27 students in the dose-response study were randomly allocated to treatment groups and dosage subgroups (Table II) which were comparable as to age, weight and physical condition.

TABLE II.—DOSE-RESPONSE STUDY REGIMENS*

Generic name	*Brand name*	*Dose (tablet)*	*Number of volunteers*
Hydrochlorothiazide (HCT).....	Esidrix	25 mg. (½ tablet)	3
		50 mg. (1 ")	3
		75 mg. (1½ ")	3
Triamterene (T).....	Dyrenium†‡	50 mg. (½ tablet)	3
		100 mg. (1 ")	3
		150 mg. (1½ ")	3
Furosemide (F).....	Lasix	20 mg. (½ tablet)	3
		40 mg. (1 ")	3
		60 mg. (1½ ")	3
			27

*To ensure accuracy in dosage in the half-tablets supplied, a tablet was first weighed on a precision scale and then cut in two. The larger part was scraped gently until it weighed exactly half of the total tablet weight.
†Smith Kline & French I.A.C.
‡Not to be confused with Dyazide, used in the time-effect study.

Each volunteer in the two studies followed exactly the same protocol and had the following material at his disposition: a 250-ml. beaker for saline solution; a sealed envelope containing the medication; an observation sheet; a 1000-ml. wide-mouth polystyrene container for collecting the urine; a urinometer; a roll of "Combistix"* paper for pH determination; a 100-ml. graduated cylinder to measure the sample for biochemical analysis, and ten 200-ml. labelled specimen cups (for urine collection).

Every piece of material was identified by the code number of the volunteer using it. Furthermore, for each four students there was a 1000-ml. graduated cylinder for use in measuring the volume of the urine. Screens were placed all around the laboratory to provide isolation booths for the voiding of the urine. Several physician's scales were available for the weighing of the students. One week earlier 16 students from the third year in Medicine and Pharmacy had served as volunteers in a pilot study. They had followed exactly the same protocol as that designed for the time-effect study. Four students had submitted to each of four regimens: hydrochlorothiazide 50 mg.; triamterene/hydrochlorothiazide 50/25 mg.; furosemide 40 mg.; and matching placebos. Having taken part themselves in the experiment, these students were well prepared to supervise their junior colleagues.

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Technique

The technique described by Martz[16] was adapted to our purposes. On the night before the experiment the students were instructed to take 400 ml. of water before retiring, and to report to the laboratory at 8:00 the next morning without having breakfasted. Between 8:00 a.m. and 8:30 a.m. they ate breakfast, voided and discarded the urine. At 8:30 a.m. all recorded their weight. Shortly before 9:30 a.m. they were asked to void urine into their individual containers, and were then handed the sealed envelope containing the medication. At 9:30 a.m. they took the single dose of the drug with 250 ml. of normal saline solution (0.9%). Each volunteer then proceeded to do the following: measure total urine volume collected in the previous hour; record volume, specific gravity and pH on his observation sheet, and submit 100 ml. of urine in the appropriate specimen cup for biochemical determination of Na, K and Cl. This was repeated every hour until 5:30 p.m. Throughout the time senior students monitored the protocol and supervised the volunteers. From 10:30 a.m. to 5:30 p.m. the subjects ingested 100 ml. of normal saline solution every hour.

A specially prepared steak dinner (without salt) was served in the cafeteria at 6:30 p.m., after which the subjects were free to go home. They were instructed to abstain from alcoholic beverages and salted food (peanuts, chips, etc.) and to collect in their individual containers all of the urine voided between 5:30 p.m. and 8:30 the next morning. They were allowed 12 ounces of liquid during the evening in the form of soft drinks or water. At 8:00 the next morning they returned to the laboratory with their collected urine and without having had breakfast. They voided a last time and made the same determinations to complete the 24-hour collection. Finally, after being weighed again, they handed in their observation sheets, which had been checked for completeness and accuracy by the monitors.

All of the food served to the students was prepared under the supervision of a dietitian. The menu was the same for everyone. It consisted of a breakfast at 8:30 a.m., three light lunches at 11:30 a.m., 1:30 p.m. and 3:30 p.m., and the steak dinner. The total caloric content

was approximately 2500. During the periods between meals, the students were allowed to have *ad libitum* hard candy containing a negligible amount of electrolytes. The approximate total sodium ingestion for the day amounted to 200 mEq.

During the intervals between the various determinations, the students were occupied by watching scientific films and attending a conference.

A serious effort was made to maintain the double-blind technique in this experiment through a random assignment of coded treatments and the use of identical placebos. However, unavoidable discussion among the students regarding urine volume output may have revealed parts of the code.

The specimen cups containing the urine samples from each collection were kept in a refrigerator during the interval between collection and analysis. The sodium and potassium determinations were made by flame spectrophotometry and the chloride determination by an electrochemical method. The handling of over 1000 urine samples was a formidable task, and here again the pilot study proved most valuable in establishing the best method.

In summary, a straight group comparison was made of three active diuretics and three control regimens, using single-dose administration and measuring several parameters over a 24-hour period in the first study (the time-effect one). In the second study (dose-response) three dose levels of three active diuretics were compared in the same manner.

ANALYSES OF DATA

Statistical analyses considered two aspects of this study. The most obvious concern was to compare total volume, and quantities of sodium, potassium and chloride excreted during the 23-hour post-drug interval. To do this most efficiently, all analyses comparing 23-hour totals used the pre-drug body weight and the one-hour pre-drug specimen data as covariates in standard covariance analyses. In this way, all results were adjusted to a common body weight. The pre-drug urine specimen data were used as a variable to control for potential differences among volunteers' urine characteristics. Results are referred to as adjusted totals in subsequent tables.

All studies were first analyzed individually. The time-effect study and the pilot-study data were combined for one pooled analysis per criterion. The dose-response study was actually a factorial design; thus, the standard statistical analyses automatically pooled the data for the three different doses of the same drug. In this way, compounds could be compared directly.

A second and equally important set of analyses considered the results reported for the individual urine specimens. These analyses will be referred to as "time-pattern" comparisons. In statistical language, these were investigations of the time-by-drug interactions. In other words, we were attempting to determine if the average quantities were parallel when two regimens were plotted against the same time axis.

The collection intervals used in this study provided one complication for the time-pattern analyses. Most of the regimen-discriminating data were known to be in the eight hourly post-drug specimen data. Yet the 9th to 23rd hour collection always contained the largest quantities and had a tendency to dominate the analyses. To eliminate this domination, data for the last collection were divided by 15, to express the results on an hourly basis.

The dose-response study required an additional analysis. Because each compound in the study was administered at three different dose levels, the analyses sought dose-response relationships "within" each compound for each of the four criteria reported. Very few relationships developed. This can be attributed to two factors in the protocol—sample sizes were too small for the inherent variation in the study technique; and dose-response relationships are more readily seen when the study doses are administered in fixed multiples of the first dose.

There were a few missing observations in this study for which it was possible to compensate by using standard statistical missing plot technique. All analyses were carried out on an electronic computer.

RESULTS

One hundred and fifteen students completed the two formal studies and 16 students the pilot study. The calculations were based on the observation sheets turned in by these 131 students and the associated biochemical analysis reports.

In this section, we will present the average results for the time-effect study and the pilot study. Data for the three control regimens (coded placebo, known placebo and no drug) were all pooled for one control group, since no statistically significant differences were found among these regimens.

Part I: Time-Effect Relationships

Tables in this section show hourly averages for the time-effect study and total quantity averages pooled for the time-effect and pilot studies.

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TABLE III.—TOTAL URINARY VOLUMES (ml.)

Collection intervals	Regimen averages: HCT 50 mg.	T/HCT 50/25 mg.	F 40 mg.	Controls
Pre-drug	47	60	51	41
1st hour	130	142	241	89
2nd hour	210	222	508	79
3rd hour	204	284	395	98
4th hour	243	306	251	111
5th hour	114	133	181	46
6th hour	133	173	139	65
7th hour	115	158	59	63
8th hour	146	178	56	86
9th to 23rd hours	679	701	455	687
Adjusted total	1973 ± 87.34	2269 ± 89.73	2279 ± 87.38	1337 ± 42.66
Pooled total*	1917	2122	2188	1334

*Includes time-effect and pilot study totals.

Comparison of the total volumes in Table III reveals several differences. Control regimen average volume is significantly less ($P < .01$) than that found for any active regimen; HCT total volume is significantly smaller ($P < .05$) than that of T/HCT or F, and there is no difference between T/HCT and F total volume averages. Thus, following single doses, the average total urinary volumes excreted for T/HCT and F are approximately equivalent and both are greater than that found for HCT.

Fig. 1 shows that not all time patterns are similar. Control and active drug patterns are different ($P < .01$). The F pattern is distinctly different ($P < .01$) from the T/HCT patterns. On the other hand, T/HCT and HCT time patterns are parallel.

F very definitely shows a "flushing" response, i.e. a marked diuresis of short duration. The averages show a big surge of volume during the first three or four hours after administration. This is most clearly seen in the magnitude of the peak response just two hours after administration. The unit dose of T/HCT appears to be providing "more" diuretic action than twice as much HCT alone.

The sodium excretion results in Table IV discriminate further among the regimens. Total

TABLE IV.—TOTAL MILLIEQUIVALENTS OF SODIUM EXCRETED PER SPECIMEN

Collection intervals	Regimen averages: HCT 50 mg.	T/HCT 50/25 mg.	F 40 mg.	Controls
Pre-drug	6	8	8	7
1st hour	10	13	24	9
2nd hour	20	31	50	8
3rd hour	28	43	48	9
4th hour	26	34	28	8
5th hour	17	20	18	5
6th hour	19	20	13	6
7th hour	16	21	5	6
8th hour	16	18	4	7
9th to 23rd hours	94	76	40	86
Adjusted total	247 ± 10.67	279 ± 10.85	229 + 10.65	141 ± 5.15
Pooled total*	253	259	219	142

*Includes time-effect and pilot study totals.

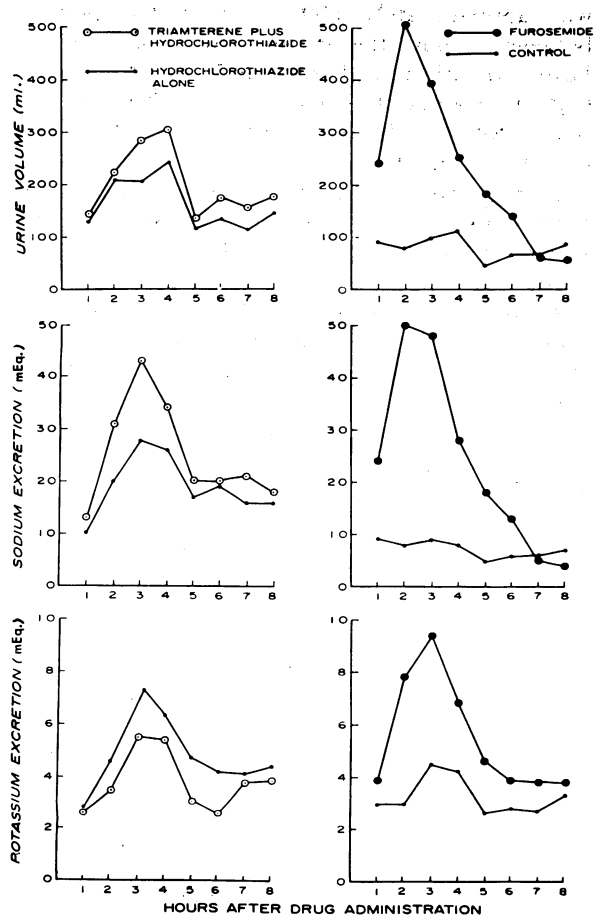

Fig. 1.—Time-effect study regimen averages.

excretion for T/HCT is significantly greater ($P < .01$) than that reported for F. HCT provides more sodium excretion than F ($P < .05$). As with the total urine volume, controls are again much lower ($P < .01$) than any active drug. Results of time-pattern analyses follow those reported for the volumes (Fig. 1).

Thus, in total sodium excreted, T/HCT provides at least as much natriuretic action as twice the dose of HCT alone. F again shows the prompt "flushing" effect with a peak at two hours after administration. After six hours the volunteers on F appeared to go into a negative balance. As a result the total sodium excreted for 23 hours following F is less than that reported for either of the other two active regimens.

Although the original Martz[16] report did not include potassium excretion as a criterion, the results for this electrolyte enhance the discrimination among the regimens in this study. In Table V, the differences between T/HCT and HCT or F are both statistically significant ($P < .05$). The difference between T/HCT and control does not approach statistical significance. HCT and F appear equivalent, and both exceed control levels ($P < .01$) (Fig. 1).

TABLE V.—TOTAL MILLIEQUIVALENTS OF POTASSIUM EXCRETED PER SPECIMEN

Collection intervals	Regimen averages: HCT 50 mg.	T/HCT 50/25 mg.	F 40 mg.	Controls
Pre-drug	3.1	3.2	4.0	3.7
1st hour	2.8	2.6	3.9	2.9
2nd hour	4.6	3.5	7.8	3.0
3rd hour	7.3	5.5	9.4	4.5
4th hour	6.3	5.4	6.8	4.2
5th hour	4.7	3.1	4.6	2.6
6th hour	4.2	2.6	3.9	2.8
7th hour	4.1	3.8	3.8	2.7
8th hour	4.4	3.9	3.8	3.3
9th to 23rd hours	34.9	34.4	29.6	31.5
Adjusted total	74.1 ± 3.96	66.1 ± 4.01	73.1 ± 3.96	57.0 ± 1.91
Pooled total*	74.1	61.3	74.8	58.4

*Includes time-effect and pilot study totals.

The time patterns were parallel to those reported above. Potassium excretion is reasonably low and tends to peak at about the same time for all regimens. F again shows a "flushing" effect different ($P < .01$) from T/HCT and HCT. For F, results at all times are greater than the control data.

These potassium excretion data clearly discriminate among the active study regimens. Potassium excretion following T/HCT is comparable to the controls, clearly supporting the potassium-sparing claims for this combination. HCT alone shows a potassium loss. This demonstrates the benefit of adding the triamterene component in the combination. Total excretion after F administration is as great as with HCT and follows the flushing pattern seen in the urine volume data. However, the potassium pattern for F does not show a negative balance in the late study hours.

When adjusted totals for chloride excretion are compared (Table VI), only the active versus control results are statistically significant ($P < .01$). Inherent study variation in the chloride data was too great to support any statistically significant differences among active study regimens.

TABLE VI.—TOTAL MILLIEQUIVALENTS OF CHLORIDE EXCRETED PER SPECIMEN

Collection intervals	Regimen averages: HCT 50 mg.	T/HCT 50/25 mg.	F 40 mg.	Controls
Pre-drug	8	10	10	9
1st hour	13	15	26	12
2nd hour	27	36	66	10
3rd hour	32	41	61	12
4th hour	30	34	37	10
5th hour	23	23	26	6
6th hour	24	23	18	7
7th hour	20	22	8	7
8th hour	20	21	6	8
9th to 23rd hours	100	84	32	77
Adjusted total	291 ± 10.69	307 ± 10.87	278 ± 10.67	145 ± 5.16
Pooled total*	290	279	262	145

*Includes time-effect and pilot study totals.

Part II: Dose-Response Relationships

This study was conducted along with the time-effect study, the controls being common for the two. Three doses of each active drug were chosen to be one-half, one, and one-and-one-half times the unit dose. One objective was to produce graded responses "within" each drug's data. In retrospect, it appears that three volunteers per dose level of each drug may have been too small a number to illustrate clearly the expected dose-response relationships among the averages.

Since all regimen assignments were balanced in terms of proportions of the dose studied, pooled results over all three doses provided a meaningful comparison between regimens. Though the data did not indicate the expected dose-response relationships, they corroborate some of the results of the time-effect study. These data are shown in Table VII, the content of which is self-evident.

Of the various comparisons in Table VII, the one concerning potassium deserves particular mention. HCT and F are about equivalent in total potassium excretion and both greater ($P < .01$) than the total for T. The time-effect study reported a control average excretion of 58.4 mEq. of potassium (Table V), which is not statistically different from that of T (53.5 mEq.) in the dose-response study. This would suggest that the T activity may not have induced any potassium loss in these volunteers, thus corroborating the potassium-sparing effect of the T/HCT combination evaluated in the time-effect study.

In general, the time-pattern analyses in this section are parallel to those of the time-effect study.

DISCUSSION

The aims of this study were multiple. First, there were the teaching benefits. The students had the opportunity to participate actively in a controlled drug evaluation. They were exposed to the basic methodological principles of human and clinical pharmacology, and the many difficulties involved in carrying out a well-controlled study were graphically demonstrated. In the lecture periods preceding the experiment, the protocol was explained in detail. After the experiment, the reasons for everything they had done were made clear by stressing the necessity of maintaining just as high a degree of scientific rigour when studying a drug in man as in performing animal pharmacological experiments. The students should now be in a better position to evaluate scientific and promotional literature regarding drugs.

TABLE VII.—TOTAL URINE VOLUME AND ELECTROLYTE EXCRETION (ADJUSTED TOTALS FOR 23 HOURS AFTER DRUG ADMINISTRATION)

Parameters	Regimen averages			Comparisons		
	HCT N = 9	T N = 8*	F N = 9	HCT vs T	T vs F	HCT vs F
Urine volume (ml.).....	2280 ± 162	1945 ± 193	2250 ± 171	N.S.	N.S.	N.S.
Na+ excretion (mEq.)..	297 ± 15.0	199 ± 18.0	238 ± 15.5	P < .01	N.S.	P < .05
K+ excretion (mEq.)....	81.3 ± 3.39	53.5 ± 3.87	84.0 ± 3.46	P < .01	P < .01	N.S.
Cl— excretion (mEq.)...	342 ± 13.1	187 ± 15.1	287 ± 13.3	P < .01	P < .01	P < .05

*One subject, apparently very proud of his bladder control, chose to provide specimens only every four hours. His data were too atypical to include.

Furthermore, by being subjected to the effects of a drug, the students were given some insight into a type of experience they can expect their patients to undergo when they become practising physicians. It is hoped that they will have gained respect for both the patient and the therapeutic agent.

From a strictly therapeutic viewpoint, it showed them that each one of the diuretics has unique characteristics which make it particularly valuable in specific situations—a lesson applicable throughout the whole field of drug therapy.

No significant differences were shown in the various objective parameters among the three control groups—coded placebo, known placebo and no drug. This does not mean that no differences existed, but rather that the probability of their being important is very small. This confirmed the authors' impression that, in a drug evaluation where parameters are objective and can be precisely measured, a placebo is less necessary when a standard of reference is available for comparison. This implies that the methodology has been established as sensitive to drug action.

It is true that the conclusions are based on data from normal individuals. However, Seller and Brest[19] state that diuretics are best compared in "normals" to prevent differences in drug effect from being obscured by variations in severity of disease processes.

The diuretics included in these studies were chosen for their particular characteristics. HCT was included as a standard of reference, F and T as newer diuretic agents and T/HCT as a combination of two diuretics.

The combination of drugs in a fixed ratio has been the object of criticism.[20, 21] One of the aims of this study was to find out if the combination of T and HCT had real advantages. There is no doubt that some combinations of drugs are rational and valuable therapeutic tools, and that the combination of T/HCT is one of these.[13, 14] One component (T) complements the other (HCT) to produce a combination of advantages with a lessening of disadvantages. This is readily apparent from the volume of urine, the sodium and chloride excretion, and the potassium-sparing effect as shown in the results.

Furosemide is a potent but short-acting diuretic. Most striking was the rapid and sustained decrease in output of water and electrolytes which began in the fifth hour following its administration and persisted for several hours. The urinary output during this period was less than that of the controls, though not to a statistically significant degree. This is referred to variously as the refractory phase, the antidiuretic phase or the "rebound phenomenon". Some authors[1, 22] explain it by the influence of aldosterone on the renal tubule. Sodium depletion would stimulate aldosterone secretion, the latter acting to retain this electrolyte, thus decreasing the urinary output. No references were found in the published literature to indicate a dose relationship for this rebound phenomenon, i.e., whether larger doses of furosemide and other diuretics would produce increased antidiuretic effects. It might be interesting to explore this question which, obviously, this experiment could not answer. It is possible to envision a more or less direct relationship among diuretics between potency and extent of rebound antidiuresis. This could be of practical importance in the area of applied therapeutics.

It should be pointed out that maximally effective doses of the study drugs were not used in this experiment. Thus, the comparison of diuretic efficacy among the active agents is not entirely valid. On the other hand, the relative diuretic response to these agents is approximated when the comparison is made on a unit-dose basis. This experiment was not intended to proclaim a winner among the diuretics used, but rather tended to show that the methodology used is sensitive to drug action. The authors are aware that, ideally, cross-over comparisons should have been made. For obvious reasons, this was not feasible.

Summary This project was undertaken as a classroom experiment designed to compare diuretic drugs, using a modified Martz technique. The newer agents, triamterene and furosemide, and the combination of triamterene and

hydrochlorothiazide, were compared, hydrochlorothiazide being included as a standard diuretic. Also included were control groups. The project was conducted under double-blind conditions.

The study provided an opportunity for students to participate actively in a controlled drug evaluation. In so doing they were exposed to several basic methodological principles. The experience should prepare them to look for individual drug characteristics and to understand some problems faced by patients.

Data for 131 volunteers included observations for a one-hour pre-drug period, eight hourly post-drug intervals, and a single 9th to 23rd hour post-drug period. The active preparations in the major study were hydrochlorothiazide 50 mg., furosemide 40 mg., and a combination of triamterene 50 mg. and hydrochlorothiazide 25 mg., administered as single doses. Statistical analyses considered total excretion for 23 hours and the hourly excretion time patterns for urinary volume, sodium, potassium and chloride. In the doses tested:

(a) The hydrochlorothiazide regimen provided a good positive diuresis response. This drug's time pattern was always parallel to that of the triamterene-hydrochlorothiazide combination. When compared to the combination, total urine volume was less and total potassium was greater ($P < .05$) for the hydrochlorothiazide regimen.

On the other hand, the hydrochlorothiazide and furosemide time patterns were very different. Total volume excreted was less ($P < .05$) with hydrochlorothiazide, while total sodium excretion was greater ($P < .01$).

(b) When diuretic activity was measured by urinary volume and sodium excretion, the combination acted like a more potent hydrochlorothiazide. Its potassium excretion response was unique. Low potassium excretion distinguishes this combination from the other active regimens in this study.

(c) Furosemide shows a rapid onset of action with a large peak at two hours after administration. This has been referred to as "flushing". The total volume excreted after furosemide was significantly less ($P < .05$), and potassium excretion was significantly greater ($P < .05$) when compared with the responses of the combination.

(d) Chloride excretion data did not add to the regimen discrimination.

A smaller study using 27 volunteers provided data to compare three doses each of hydrochlorothiazide, triamterene and furosemide. The sample sizes were too small to demonstrate dose-response relationships. The data support the hydrochlorothiazide-furosemide comparisons reported above. Data showing the potassium-sparing effect of triamterene help to explain the observed benefits of the triamterene-hydrochlorothiazide combination.

Résumé Cent trente et un étudiants en médecine et en pharmacie ont participé, lors d'une expérience pédagogique en pharmacologie humaine à l'évaluation à double-insu de quatre diurétiques et de placebos identiques. Les termes de comparaison étaient le triamtérène (T), le furosemide (F), l'hydrochlorothiazide (HCT) et l'association triamtérène-hydrochlorothiazide (T/HCT). Les relations effet-temps et effet-doses constituaient les deux aspects principaux du projet. Les données couvraient le volume urinaire ainsi que l'excrétion du Na, K et des chlorures de huit collections horaires et d'une dernière collection de 15 heures. Les résultats furent analysés statistiquement par ordinatrice électronique.

Aux doses uniques employées, les relations effet-temps de l'HCT et de l'association T/HCT sont parallèles, cette dernière provoquant une plus grande diurèse et une kaliurèse moindre. Le F se distingue par sa rapidité d'action et sa puissance avec effet maximum deux heures après administration. Le volume urinaire total excrété par le F est supérieur à celui de l'HCT. Cependant, par rapport au F l'association T/HCT a causé une plus grande élimination totale d'eau et de Na et a moins influencé le K urinaire. Cette diurèse et cette natriurèse moindres du F s'expliquent possiblement par l'antidiurèse de ressaut plus marquée qu'il déclenche.

A cause du petit nombre de sujets, aucune relation effet-dose n'a été observée.

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