A PRELIMINARY REPORT ON
THE USE OF METHENAMINE SALTS AND ASCORBIC ACID
IN THE CATHETERIZED SPINAL CORD INJURED PATIENT

by

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UNIVERSITY OF UTAH COLLEGE OF PHARMACY

FINAL READING APPROVAL

TO THE DOCTOR OF PHARMACY COMMITTEE OF THE UNIVERSITY OF UTAH COLLEGE OF PHARMACY:

I have read the clinical research project report of STEVEN FRANCIS BAUWENS in its final form and have found that 1) its format, citations, and bibliographic style are consistent and acceptable; 2) its illustrative materials including figures, tables, and charts are in place; and 3) the final manuscript is satisfactory to the Supervisory Committee and is ready for submission to the Doctor of Pharmacy Committee.

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Date

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UNIVERSITY OF UTAH COLLEGE OF PHARMACY

SUPERVISORY COMMITTEE APPROVAL

of a clinical research project report submitted by

STEVEN FRANCIS BAUWENS

We, the undersigned, have read this clinical research project report and have found it to be of satisfactory quality for a Doctor of Pharmacy Degree.

20 May 1980
Date

Chairman, Supervisory Committee

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INTRODUCTION

Patients with spinal cord injury often have a complex array of medical problems. Among the most commonly recognized is the flaccid type of neurogenic bladder dysfunction. This bladder dysfunction predisposes these patients to days or weeks of indwelling or intermittent urethral catheterization (9,29,30,31). Due to the prolonged period during which catheterization is required, these patients are at increased risk of developing recurrent or chronic urinary tract infections (29).

When the spinal cord is injured, complete suppression of reflex activity of the spinal segments below the level of the injury occurs. This is referred to as spinal shock. During the first few weeks following the spinal cord injury, micturation reflexes are completely suppressed, due to a sudden loss of facilitatory impulses from the cerebellum. Micturation is the reflex process through which the bladder empties. The process of micturation is dependent on an intact pathway from the cerebellum through the sacral spinal segments to the pelvic nerves innervating the bladder musculature. As the spinal shock resolves, the neurons gradually regain their excitability.

During spinal shock, the bladder should not be allowed to distend (4,32). Should this occur, a high threshold for the stimulus necessary to initiate micturation may occur, or even permanent inhibition of the micturation reflex is possible. Overdistention can be prevented through the use of indwelling urethral catheters.

As spinal shock resolves, therapy usually includes attempts to stimulate normal micturation reflexes, i.e.: retrain the bladder. This is accomplished by removing the indwelling catheter and inter-

mittently inserting a urethral catheter to empty the bladder throughout the day. Concurrent with catheterization, pharmacological interventions are frequently used to help stimulate bladder contraction. Once the patient voids actively, intermittent catheterization is no longer necessary (4,32).

The need to catheterize patients with spinal shock or the flaccid type of neurogenic bladder dysfunction predisposes them to increased risk for developing recurrent or chronic urinary tract infections (5,9,17,28,29,30,36,39). Indwelling catheters and repeated intermittent catheterization produces a continuous bacteriuria, even with proper catheter insertion and care (5,17,28,36,39). Consequently, microorganisms are able to ascend the urethra and colonize in the bladder (29,30).

Clinically, it is common to administer agents which keep the colony counts low enough so that the patient does not manifest signs or symptoms of a urinary tract infection. This therapeutic intervention is referred to as suppressive therapy. The methenamine salts, methenamine mandelate and methenamine hippurate, are among a variety of pharmacological agents used extensively for this purpose.

Formaldehyde is the antibacterial compound liberated when the methenamine salts are exposed to urine which has an acid pH (16,23). Optimal levels of formaldehyde are produced when the urine pH is less than 5.5, but concentrations of formaldehyde greater than 25 mcG/mL are produced when the urine pH is maintained at less than 6.0 (16,23). Formaldehyde is active against most Gram-positive and Gram-negative bacteria fungi responsible for urinary tract infections (16). Methenamine salts are not effective against urease-producing organisms,

such as the Proteus species. Urease-producing organisms generate ammonia making the urine alkaline. As a result, routine acifification is not possible, and formaldehyde is not liberated from the methenamine salts (25).

Musher et al have provided extensive data on the pharmacodynamics of methenamine (23,24). By using static and dynamic in-vitro models simulating the human genitourinary system, they showed that the antimicrobial effects of formaldehyde were dependent on: 1. the pH of the urine, which influences the degree to which methenamine liberates formaldehyde; 2. the concentration of formaldehyde produced in the urine; 3. the contact time of the formaldehyde in the urine. Musher et al also used their in-vitro model to determine the optimal formaldehyde concentration necessary to keep colonies of bacteria low enough in the urine preventing clinical signs and symptoms of a urinary tract infection, i.e.: bacteriostasis. The authors found that bacteriostasis was achieved when bacteria were exposed to 25 mcG/mL or more of formaldehyde for a minimum of two hours.

In-vivo testing of methenmaine salts in normal volunteers has shown that urine formaldehyde concentrations greater than 16 mcG/mL were bacteriostatic (7,21). Bacteriostasis in these studies was determined by gross visual inspection of the specimen tubes. Pearman et al (31) found that bacteriostasis was achieved when urine formaldehyde concentrations were maintained at a mean concentration of 18 mcG/mL, with a range of 11 to 22 mcG/mL. Bacteriostasis in this study was determined using bacterial colony counts.

Vainrub and Musher (39) studied thirty-two spinal cord injured patients participating in either an indwelling or intermittent urethral catheter program. These authors concluded that the methenamine salts were ineffective as bacteriostatic agents in catheterized patients. Similar conclusions have been made based on the results of other studies in catheterized patients (3,8,28). However, in all cases the lack of efficacy of the methenamine salts was not documented in the presence of bacteriostatic concentrations of formaldehyde in the urine.

Despite these data discussed above, the methenamine salts are commonly used clinically as suppressive agents. Likewise, it is a common practice to administer a urinary acidifying agent such as ascorbic acid concurrently. This is done to produce urine pH less than 6.0 so that optimal bacteriostatic concentrations of formaldehyde are produced (23,24). However, there are conflicting data concerning the use of ascorbic acid as an effective urinary acidifying agent (11,12, 18,22,23,33,38).

The literature does not permit the clinician to make an objective decision as to whether or not methenamine salts are effective urinary microbial suppressives in the spinal cord injured patient. Furthermore, the question of using ascorbic acid as a urinary acidifier concurrently with methenamine salts remains to be answered for this patient population. As a result, this study was undertaken to:
1. determine in spinal cord injured patients with permanent bladder dysfunction whether any difference exists in the concentration of formaldehyde produced in the urine between two methenamine salts: methenamine mandelate and methenamine hippurate in commonly used doses; 2. to determine the concentration of urine formaldehyde

attained in spinal cord injured patients with bladder dysfunction during indwelling or intermittent urethral catheterization program;

3. to determine if concurrent administration of ascorbic acid with the methenamine salts has a significant effect on the levels of formaldehyde produced in the urine.

METHODOLOGY

Patient Selection

Spinal cord injured patients admitted to the Physical Medicine and Rehabilitation Service at University Hospital, University of Utah, were considered for participation in this study. Inclusion criteria required that patients have a diagnosis of neurogenic bladder dysfunction of the flaccid type and be on an indwelling or intermittent urethral catheter protocol. Patients were excluded from entry into the study based on any of the following criteria: evidence of urethral obstruction, history of gastric or peptic ulcer disease, serum creatinine greater than 1.5 mg/dl, clinical signs or symptoms of a urinary tract infection (i.e.: spiking temperatures, fever, chills), or current antimicrobial therapy for any active infection.

This study was approved by the Review Committee for Research with Human Subjects, and informed written consent was obtained. Each patient was nonrandomly assigned to either the indwelling or intermittent urethral catheter group depending on the patients catheter status at the time of admission. Patients in the indwelling catheter group were designated as Group I and patients with intermittent catheters were designated as Group II.

Drug Administration

Each patient who entered the study completed four oral drug regimens. These regimens consisted of:

A. Methenamine mandelate (Mandelamine^{R}, Warner-Chilcott) one gram orally four times a day at 8 A.M., Noon, 5 P.M., and 8 P.M. for three days;

B. Methenamine mandelate and ascorbic acid, one gram orally of each, four times a day at 8 A.M., noon, 5 P.M., and 8 P.M. for three days;

C. Methenamine hippurate (Hiprex[R], Merrill-National) one gram orally twice a day at 8 A.M. and 5 P.M. for three days;

D. Methenamine hippurate one gram daily twice a day at 8 A.M., and 5 P.M., and ascorbic acid one gram orally four times a day at 8 A.M., noon, 5 P.M., and 8 P.M. for three days.

The specific administration times for the drug regimens were chosen to simulate the approximate administration times that patients normally use when they take the medications at home.

Approximately 5 ml of urine was collected to determine the urine formaldehyde concentration on the third day of each dosing regimen. The first urine sample was collected at 6:30 A.M. on each sampling day. After this initial urine sample was obtained, the methenamine salt with or without ascorbic acid was administered. On the sample days, this initial dose was given one and one-half hours early. All remaining doses were administered according to the prescribed schedule outlined above. The initial urine sample was obtained at 6:30 A.M. since this corresponded with the first catheterization of the morning for the intermittent catheter group. To maintain continuity of methodology, 6:30 A.M. was also designated as the first urine sample to be obtained from the indwelling catheter patients.

Urine samples were collected from the indwelling catheter patients at 6:30 A.M., 7:30 A.M., 8:30 A.M., 9:30 A.M., 12:30 P.M., 3:30 P.M., and 6:30 P.M. The samples were obtained by clamping the urethral catheter below the "Y" joint for a minimum of five minutes using a screw clamp. The area above the screw clamp was cleansed with

70% isopropyl alcohol. A 25 gauge hypodermic needle was introduced into the catheter lumen and approximately 5 ml of urine was aspirated. The screw clamp was then removed to allow for normal drainage. Patients with intermittent catheters were instructed to collect a minimum of 5 ml of urine at 6:30 A.M., 12:30 P.M., and 6:30 A.M. These collection times corresponded to the patient's regular intermittent catheterization schedule.

Formaldehyde Assay

All urine samples were centrifuged (International Clinical Centrifuge, Model CL, International Equipment Company, Needham, Massachusetts) at 6000 RPM for five minutes. The supernatant was removed and the urinary sediment discarded. Urine pH was then determined by a pH meter (Corning pH Meter, Model 7, Scientific Instruments, Corning, N.Y.) and phenaphthazine paper (Nitrazine Paper, E.R. Squibb and Sons, Princeton, N.J.). The presence of protein, blood, and ketones in the urine was tested for using a multiple reagent urine dip stick (Multistix^{R}, Ames Division, Miles Laboratories, Elkart, Ind.).

Urine formaldehyde concentrations were determined using a modification of the Jackson and Stamey Method (13). A dilution of 0.1 ml urine and 0.9 ml deionized water was made. The assay consists of a reaction of phenylhydrazine oxalate (Research Organics, Cleveland, Oh.) with dilute urine containing formaldehyde to form phenylhydrazone which can be quantitated colorimetrically. Phenylhydrazone was quantitated using the Coleman Junior II, Model 6-20, Spectrophotometer (Coleman Scientific Instruments, Maywood, Ill.).

Six of the samples were frozen immediately after dilution at 10^0 F for a maximum of twelve hours prior to the formaldehyde assay being performed on them. Urine samples which were frozen are indicated in Table I. Unpublished data are available on the reproducibility of urine formaldehyde concentrations when the urine is diluted and frozen immediately (Sonsalla P: Personal Communication). Samples not frozen were diluted and assayed within thirty minutes of collection.

Statistical Analysis

The data were subjected to analysis using the Split-Plot Design (15). This analysis is useful when two or more treatments are to be compared and each treatment has two or more variables which might affect it. In the present study, urine formaldehyde concentration and urine pH were the dependent variables. These two variables were analyzed in relation to their interactions with the following variances: the methenamine salt administered, presence or absence of ascorbic acid in the drug regimen, the time period when the sample was collected and the catheter grouping.

The analyses were performed using a BMDP2V computer program (2). The program was run through the DEC-20 computer system. For the purposes of analysis, only the 6:30 A.M., 12:30 P.M., and 6:30 P.M. sample results were used. These were the three sampling times both catheter groups had in common which allowed equal analysis between the two groups. When two variances analysed with a dependent variable produced a significant interaction, the test for simple main effects was performed. This test is used with the Split-Plot Design and is applied to gain a better level of understanding as to where the significance between the variances and dependent variable was occurring.

RESULTS

Patient Characteristics

Sixteen catheter patients, seven indwelling and nine intermittent, were entered into the study. Ten patients completed the study. The six patients who dropped out of the study did so because they were discharged from the unit prior to completing all four drug regimens. Four patients were in Group I, the indwelling urethral catheter group and six were in Group II, the intermittent catheter group. The raw data for the results of formaldehyde concentrations and urine pH on these ten patients are presented in Tables I and II, respectively.

Effect of Variances on Urine Formaldehyde Concentration

Table III shows the results of analysis of the variances on the production of formaldehyde in the urine. The individual variances contributing to significant changes in the urine formaldehyde concentrations were: the methenamine salt administered ($p<.001$) and the concentration of formaldehyde produced across the sampling times ($p=0.048$).

The concentration of formaldehyde produced in the urine was consistently higher with methenamine mandelate than with methenamine hippurate ($p<0.001$). As shown in Table IV, the mean urine formaldehyde concentrations were: 55.2 ± 31.7 mcG/mL (mean ± 1 Standard Deviation), 40.5 ± 26.9 mcG/mL, and 38.3 ± 22.9 mcG/mL at the zero, six, and 12 hour time intervals. The respective ranges in urine formaldehyde levels were: 0 to 131 mcG/mL, 4 to 77 mcG/mL, and 7 to 75 mcG/mL. Methenamine hippurate produced mean urine formaldehyde concentrations at zero, six, and 12 hours of 32.7 ± 21.3 mcG/mL, 34.9 ± 33.5 mcG/mL,

and 17.3 ± 13.2 mcG/mL. The respective ranges in urine formaldehyde concentrations were: 0 to 83 mcG/mL, 0 to 155 mcG/mL, and 0 to 50 mcG/mL.

The urine formaldehyde concentrations of the six and 12 hour samples were significantly lower from the zero hour sample for methenamine mandelate (p=0.001). These data are listed in Figure 1.

There was no significant difference between the catheter grouping and the concentration of formaldehyde produced in the urine (p=0.44). Likewise, the administration of ascorbic acid with either methenamine salt did not result in a significant difference in the concentration of formaldehyde produced in the urine (p=0.455).

Effect of the Variances on Urine pH

Table V lists the results of the analysis of the variances on urine pH. A significant difference on urine pH was seen between patients receiving methenamine mandelate rather than methenamine hippurate (p=0.023). A mean urine pH of 5.75 ± .49 (mean urine pH ± 1 Standard Deviation) with a range of 5.3 to 7.5 was measured in patients receiving methenamine mandelate. This was significantly lower than the mean urine pH of 6.09 ± 0.08, with a range of 5.2 to 7.9 measured from the patients receiving methenamine hippurate. These data are shown in Table VI. The administration of ascorbic acid did not produce significant effects on urine pH regardless of the methenamine salt used (p=0.154).

When the three sample times were analyzed for effect on urine pH, a statistically significant effect was found (p=0.014). Significance was also achieved when the combination of sample time and catheter

group was analyzed for its effect on urine pH (p=0.002). This interaction is shown in Figure II. When the test for simple main effects was performed on the sample time - catheter group interaction, the urine pH produced by patients in the indwelling catheter group was significant (p=0.029). No significant interaction occurred with the intermittent catheter group (p=0.52). These data are presented in Table VII. When the three sample times were analyzed alone across the catheter groups in relation to their effect on urine pH, no significant interaction was seen for the zero (p=0.94) or six (p=0.61) hour samples. Significance was seen, however, at the 12 hour sample (p=0.001). These results are summarized in Table VIII.

The results of the analysis in Table V show that when the sample time is analyzed in relation to both methenamine salts administered for their effect on urine pH, a significant difference was seen (p=0.006). Results of the test for simple main effects for the effect of the two methenamine salts across sample times resulted in no significant difference with either methenamine mandelate (p=0.1) or methenamine hippurate (p=0.59). These data are shown in Table IX. When the test for simple main effects was performed on each sample time, significance was not achieved at the zero (p=0.64), six (p=0.99) or 12 (p=0.73) hour samples. This is illustrated in Table X.

Statistical analyses were not performed on all the data collected from the patients with indwelling catheters. This was not possible since it was necessary to use sampling times from the indwelling catheter group which corresponded with the three sampling times of the intermittent catheter groups to insure that equal analysis of the data occurred. The complete data for the indwelling catheter patients

are shown in Table XI. Urine formaldehyde concentrations were consistently greater than 10 mcG/mL in one of the four indwelling patients who particpated in this study. Of the twenty-eight total urine formaldehyde concentrations determined for each indwelling catheter patient in this study, 13 (46%), 16 (57%), 26 (93%), and 12 (43%) of the samples for patients one, two, three, and four respectively, had urine formaldehyde concentrations greater than or equal to 10 mcG/mL.

DISCUSSION

There was a wide range of intrapatient variability in the indwelling catheter group as observed from the data in Table XI. Although 43% to 93% of the urine formaldehyde concentrations were equal to or greater than 10 mcG/mL, this does not assure that bacteriostasis would be seen. Contrary to Musher et al (23,24), a pH of five to six in the indwelling catheter patients did not assure a concentration of urine formaldehyde greater than 25 mcG/mL. For example, patient one had a urine formaldehyde concentration of six and two mcG/mL at the nine and 12 hour samples, with a corresponding urine pH of 5.2 and 5.4 respectively. Likewise, patient four had a urine formaldehyde concentration of zero, with a urine pH of 6.0 at the three hour sample. These and other similar data are listed in Table XI.

Gerstein et al (8) and Norrman and Wibell (28) found that the methenamine salts were not effective as suppressive agents in patients with indwelling catheters. However, in both studies, urine cultures showed bacteria in excess of 10^5 colonies prior to the start of therapy indicating that infection was present and not merely colonization. At no time was the urine formaldehyde concentration measured to determine whether bacteriostatic concentrations of formaldehyde were in fact being produced in the urine of these patients.

Vainrub and Musher (39) found that the methenamine salts failed to suppress bacteriuria of less than 10^5 in patients with indwelling or intermittent urethral catheters. Although urine formaldehyde concentrations were not determined, urine pH's of 5-6 were measured. Since Musher et al (23,24) had shown earlier that bacteriostatic concentrations of formaldehyde were produced when the urine pH was five and six,

Vainrub and Musher assumed that the urine contained formaldehyde concentrations greater than 25 mcG/mL and concluded that the methenamine salts were ineffective in the catheterized patient. The earlier data produced by Musher et al (23,24), however, were generated from an _in-vitro_ model which simulated the normal human genitourinary system. Musher concluded from the earlier works that urine flow was a major determinant for the concentration of formaldehyde produced in urine. Yet in this study with Vainrub, data were not presented concerning daily fluid intake or total urine volume.

Several authors have shown that the methenamine salts are efficacious as bacteriostatic agents in patients with urethral catheters (7,21,31). Pearman et al (31) found that bacteriostasis was seen when bacteria were innoculated into urine containing 10 mcG/mL of formaldehyde and allowed to stand for twenty-four hours. At the end of twenty-four hours, urine formaldehyde concentrations were 18 mcG/mL with a range of 11 to 22 mcG/mL. A bacteriostatic effect was seen against all organisms seen when colony counts were performed.

These results are similar to those of Gandelman who found that urine formaldehyde concentrations greater than 16.6 mcG/mL were associated with effective bacteriostasis (7). However, Gandelman estimated bacteriostasis by gross visual inspection of the urine cultures rather than by colony counts. Likewise, Miller and Phillips (21) found that urine formaldehyde concentrations greater than 18 mcG/mL were bacteriostatic against all organisms tested. Like Gandelman, Miller and Phillips determined bacteriostasis by gross visual inspection rather than by colony counts.

In the present study, the bacteriostatic effect of formaldehyde was not studied. However, based on the above discussions, it is reasonable to conclude that urine formaldehyde concentrations greater than 10 mcG/mL are bacteriostatic for some patients. Since the mean urine formaldehyde concentration produced in the present study was 33 ± 28.2 mcG/mL, with a range of zero to 155 mcG/mL, it appears that bacteriostasis is attainable in some patients.

The administration of ascorbic acid with either methenamine salt was not shown to have a significant effect on urine pH in the present study (p=0.154). The controversy of the efficacy of ascorbic acid as a urinary acidifier has been discussed by numerous authors (12,18,22,27,38). None of these studies was well controlled and the dosage of ascorbic acid ranged from 2.5 to 36 grams daily. Pharmacokinetic studies have shown that absorption of ascorbic acid is a saturable process (1,20). Large single doses of ascorbic acid may be poorly absorbed from the intestines, ultimately producing much lower urine concentrations than expected. Angel et al (1) reported that whether a dose of three or five grams of ascorbic acid was given, only 1.5 grams was recivered in the urine. Also, these studies only considered the effects of ascorbic acid on urine pH when administered alone. Further, the authors of these studies did not consider the fact that mandelic acid or hippuric acid are combined with methenamine to aid in decreasing the urine pH thus enhancing the generation of formaldehyde (41). Although these organic acids alone may not have a significant effect on urine pH (8), it cannot be determined from the above data whether the combination of the organic acid and ascorbic acid with methenamine might have an additive effect on

decreasing the urine pH. Travis et al (38) studied ten patients given 1.5 to 12 grams of ascorbic acid daily in four divided doses. They demonstrated that when ascorbic acid was used alone, pH was not consistently lowered to 5.5 or less. Even in those patients whose urine pH was lowered to 5.5, large intrapatient variations were noted. When the total daily dose was divided into six equal doses, the urine pH remained closer to 5.5 more consistently, although the total number of patients reaching the urine pH of 5.5 was unchanged. When ascorbic acid was given with methenamine mandelate, the combination of 1.5 to 4.5 grams of ascorbic acid and four grams of methenamine mandelate each given four times daily in divided doses consistently lowered urine pH. An even greater decrease in urine pH was seen when the dose of methenamine mandelate remained the same, but the dose of ascorbic acid was given in six equally divided doses. The results appear to have clinical significance although the data were not subjected to statistical analysis.

The results of the present study also show that the mean urine pH of 5.75 ± 0.49 in patients receiving methenamine mandelate was lower than the mean pH of 6.09 ± 0.08 seen in patients receiving methenamine hippurate. This difference is statistically significant ($p < .001$). These results contradict previous data by Naccarto et al (26), who found no difference between the pH measured in patients taking the two methenamine salts. A possible explanation for this difference might be that only four of ten patients in the present study had indwelling catheters, where Naccarto's patient population of seventy-three were all indwelling catheter patients. Figure II illustrates that in the present patient population, the intermittent

catheter group had a trend toward lower urine pH's than did the indwelling catheter patients. Although this was not statistically significant, it is possible that the patient population of six intermittent catheter patients was not sufficient to achieve significance.

CONCLUSION

The results of the present study show that concentrations of urine formaldehyde, commonly accepted as being bacteriostatic, are attainable in the urine of spinal cord injured patients. One cannot conclude, however, that microbial suppression is necessarily achieved until further testing is completed in a larger series of patients. These data show that methenamine mandelate produces significantly higher urine formaldehyde levels and a lower urine pH than methenamine hippurate. Perhaps methenamine mandelate should be recommended over methenamine hippurate, even though it is more expensive, or the commonly used daily doses of methenamine hippurate are not adequate in the spinal cord injured patient. In the indwelling catheter patients, it appears from the data that maintaining a urine pH between five and six does not assure that levels of formaldehyde greater than 10 to 25 mcG/mL are produced in the urine.

The use of four grams of ascorbic acid in divided doses does not appear to be beneficial. Based on the results of this study, ascorbic acid may not be indicated in conjunction with the methenamine salts for the purpose of urinary acidification.

Since the present study contained so few patients, and the standard deviations of our mean results were large, one should not extrapolate these results to the whole population of spinal cord injured patients. These results suggest that controlled studies involving larger numbers of patients are warranted.

Future studies on the bacteriostatic effects of methenamine salts in this patient population are also needed. If bacteriostasis is found to be associated with a given urine formaldehyde level in catheterized

patients, then urine formaldehyde assays may become routine. This seems reasonable in view of the wide range of urine formaldehyde concentrations, and unexpected urine formaldehyde concentrations produced by a particular urine pH measured in this study.

APPENDIX A

TABLE I: URINE FORMALDEHYDE CONCENTRATIONS (mcG/mL) ACCORDING TO PATIENT, SAMPLE TIME, AND DRUG REGIMEN

PATIENT NUMBER	METHENAMINE MANDELATE			METHENAMINE MANDELATE AND ASCORBIC ACID			METHENAMINE HIPPURATE			METHENAMINE HIPPURATE AND ASCORBIC ACID		
	ZERO HOUR	SIX HOUR	TWELVE HOUR	ZERO HOUR	SIX HOUR	TWELVE HOUR	ZERO HOUR	SIX HOUR	TWELVE HOUR	ZERO HOUR	SIX HOUR	TWELVE HOUR
1	14	17	63	17	11	12	3	28	4	3	27	2
2	43	22	19	27	4	19	13	11	2	13	6	6
3	131	60*	70	102	74	74*	83	155	22*	46	45	36
4	+	12	7*	5	7	14*	+	+	+	+	11	11*
5	35	23	13	48	19	16	39	19	6	28	9	13
6	69	37	60	105	32	75	62	48	34	38	53	30
7	81	48	20	67	51	33	9	9	2	48	61	21
8	46	77	54	41	76	40	39	27	22	47	62	50
9	45	58	43	60	26	55	15	14	13	24	10	+
10	66	100	58	46	56	21	21	29	16	58	37	21

*Samples which were frozen prior to assay

+Quantity of urine not sufficient for assay

Patient Numbers 1 - 4: Indwelling Catheter Group

Patient Numbers 5 - 10: Intermittent Catheter Group

TABLE II: URINE pH ACCORDING TO PATIENT, SAMPLE TIME, AND DRUG REGIMEN

PATIENT NUMBER	METHENAMINE MANDELATE			METHENAMINE MANDELATE AND ASCORBIC ACID			METHENAMINE HIPPURATE			METHENAMINE HIPPURATE AND ASCORBIC ACID		
	ZERO HOUR	SIX HOUR	TWELVE HOUR	ZERO HOUR	SIX HOUR	TWELVE HOUR	ZERO HOUR	SIX HOUR	TWELVE HOUR	ZERO HOUR	SIX HOUR	TWELVE HOUR
1	6.6	7.5	+	6.5	6.9	5.8	6.8	5.4	5.6	5.2	5.4	5.4
2	5.7	6.7	6.1	6.0	6.8	6.3	6.5	7.9	7.5	6.7	8.1	5.9
3	5.3	6.6	5.5	5.7	5.5	+	5.4	5.5	6.6	5.2	6.3	5.8
4	7.2	7.1	+	6.0	6.8	5.9	6.8	7.8	6.4	7.1	+	5.3
5	6.0	6.5	6.6	5.9	6.4	6.5	5.8	6.6	6.8	5.7	6.4	6.5
6	5.5	6.3	5.7	5.6	6.1	6.8	5.6	5.6	5.8	6.1	5.7	5.6
7	5.7	6.1	5.9	5.7	5.9	5.6	7.9	6.5	6.8	5.6	5.7	5.9
8	6.0	5.9	5.9	5.7	5.6	5.9	5.8	6.2	6.3	5.7	5.8	5.9
9	5.6	5.7	5.7	5.7	5.5	5.5	5.8	6.2	6.3	5.5	6.1	6.7
10	5.7	5.6	5.7	5.7	6.0	6.3	7.2	6.2	6.3	5.9	5.9	6.0

+Quantity of urine not sufficient for pH determination

Patient Numbers 1 - 4: Indwelling Catheter Group

Patient Numbers 5 - 10: Intermittent Catheter Group

TABLE III: RESULTS OF SPLIT-PLOT ANALYSIS: EFFECT OF VARIANCES ON URINE FORMALDEHYDE CONCENTRATION

VARIANT	SUM OF SQUARES	DEGREES OF FREEDOM	MEAN SQUARE	F	LEVEL OF SIGNIFICANCE
G	3622.5	1	3622.5	0.66	0.440
D	8154.7	1	8154.7	33.14	0.001*
D-G	570.7	1	570.7	2.32	0.166
V	201.6	1	201.6	0.62	0.455
V-G	1029.6	1	1029.6	3.15	0.114
D-V	262.81	1	262.81	0.45	0.522
D-V-T	456.01	1	456.01	0.78	0.403
T	3531.85	2	1765.9	3.68	0.048*
T-G	389.72	2	194.86	0.41	0.673
D-T	2143.95	2	1071.98	2.74	0.095
D-T-G	1365.55	2	682.78	1.74	0.206
V-T	337.11	2	168.55	0.88	0.433
V-T-G	203.51	2	101.75	0.53	0.597
D-V-T	152.11	2	76.05	0.35	0.708
D-V-T-G	1144.9	2	572.45	2.65	0.101

*Statistically Significant

G = Catheter Group D = Methenamine Salts V = Ascorbic Acid
T = Sample Time

TABLE IV: MEAN URINE FORMALDEHYDE CONCENTRATIONS (mcG/mL)
ACCORDING TO METHENAMINE SALT AND SAMPLE TIME

METHENAMINE SALT AND SAMPLE TIME	MEAN URINE FORMALDEHYDE CONCENTRATION (mcG/mL)*	RANGE (mcG/mL)
Methenamine Mandelate		
Zero Hour	55.2 ± 31.7	5 - 131
Six Hour	40.5 ± 26.9	4 - 100
Twelve Hour	38.3 ± 22.9	7 - 74
Methenamine Hippurate		
Zero Hour	32.7 ± 21.3	3 - 83
Six Hour	34.9 ± 33.5	6 - 155
Twelve Hour	17.3 ± 13.2	2 - 50

*Mean urine formaldehyde concentration (mcG/mL) ± 1 Standard Deviation

TABLE V: RESULTS OF SPLIT-PLOT ANALYSIS: EFFECT OF VARIANCES ON URINE pH

VARIANT	SUM OF SQUARES	DEGREES OF FREEDOM	MEAN SQUARE	F	LEVEL OF SIGNIFICANCE
G	1.67	1	1.67	0.85	0.384
D	3.79	1	3.79	7.81	0.023*
D-T	0.57	1	0.57	1.17	0.310
V	1.93	1	1.93	2.54	0.150
V-G	0.142	1	0.142	0.18	0.677
D-V	5.32	1	5.32	2.47	0.154
D-V-G	1.45	1	1.45	0.67	0.436
T	8.93	2	4.47	5.61	0.014*
T-G	14.60	2	7.30	9.17	0.002*
D-T-G	12.97	2	6.49	6.50	0.006*
V-T	2.92	2	1.46	0.72	0.009*
V-T-G	2.18	2	1.09	0.54	0.593
D-V-T	1.62	2	0.81	0.63	0.547
D-V-T-G	1.79	2	0.89	0.68	0.516

*Statistically Significant

G = Catheter Group D = Methenamine Salts V = Ascorbic Acid

T = Sample Time

TABLE VI: MEAN URINE pH MEASURED WITH EACH METHENAMINE SALT ACROSS SAMPLE TIMES

MANDELAMINE SALT	ZERO HOUR SAMPLE	SIX HOUR SAMPLE	TWELVE HOUR SAMPLE	MEAN URINE pH ACROSS SAMPLE TIME
Methenamine Mandelate				
Mean pH ± 1 S.D.*	5.89 ± 0.43	6.28 ± 0.56	5.09 ± 0.38	5.75 ± 0.49
Range	5.3 - 7.2	5.5 - 7.5	5.5 - 6.8	
Methenamine Hippurate				
Mean pH ± 1 S.D.*	6.12 ± 0.73	5.97 ± 0.80	6.18 ± 0.53	6.09 ± 0.08
Range	5.2 - 7.9	5.4 - 8.1	5.3 - 7.5	

*Mean urine pH ± 1 Standard Deviation

The mean urine pH of patients in either catheter group receiving methenamine mandelate was significantly lower than the mean urine pH values produced by patients receiving methenamine hippurate ($p = 0.001$).

TABLE VII: RESULTS OF TEST FOR SIMPLE MAIN EFFECTS: ANALYSIS OF URETHRAL CATHETER GROUPS ACROSS SAMPLE TIMES ON MEAN URINE pH

CATHETER GROUP	MEAN pH FOR ZERO HOUR SAMPLE	MEAN pH FOR SIX HOUR SAMPLE	MEAN pH FOR TWELVE HOUR SAMPLE	F	DEGREES OF FREEDOM	LEVEL OF SIGNIFICANCE
Indwelling						
Mean ± 1 S.D.*	6.17 ± 0.68	6.27 ± 0.89	6.0 ± 0.57	2.2	2,16	0.028**
Range	5.2 - 7.2	5.2 - 7.9	5.3 - 7.5			
Intermittent						
Mean ± 1 S.D.	5.89 ± 0.58	6.02 ± 0.32	6.13 ± 0.42	0.68	2,16	0.52
Range	5.5 - 7.9	5.5 - 6.5	5.5 - 6.8			

*Mean urine pH ± 1 Standard Deviation **Statistically significant

The mean urine pH produced by patients with indwelling urethral catheters were significantly lower (p = 0.028) than the mean urine pH produced by patients with intermittent catheters (p = 0.52).

TABLE VIII: RESULTS OF TEST FOR SIMPLE MAIN EFFECTS: ANALYSIS OF SAMPLE TIMES ACROSS URETHRAL CATHETER GROUPS ON URINE pH

SAMPLE TIME	MEAN pH FOR INDWELLING CATHETER GROUP	MEAN pH FOR INTERMITTENT CATHETER GROUP	F	DEGREES OF FREEDOM	LEVEL OF SIGNIFICANCE
Zero Hour					
Mean ± 1 S.D.*	6.17 ± 0.68	5.89 ± 0.58	0.062	2,16	0.94
Range	5.2 - 7.2	5.5 - 7.9			
Six Hour					
Mean ± 1 S.D.*	6.27 ± 0.89	6.02 ± 0.32	0.497	2,16	0.61
Range	5.2 - 7.9	5.5 - 6.5			
Twelve Hour					
Mean ± 1 S.D.*	5.89 ± 0.57	6.13 ± 0.42	12.67	2,16	0.001**
Range	5.3 - 7.5	5.5 - 6.8			

*Mean urine pH ± 1 Standard Deviation

**Statistically Significant

Statistical significance was achieved at the twelve hour sample only ($p = 0.001$) when the effect of each sampling time on urine pH was analyzed across the two urethral catheter groups.

TABLE IX: RESULTS OF TEST FOR SIMPLE MAIN EFFECTS: ANALYSIS OF METHENAMINE SALTS ACROSS SAMPLE TIMES ON MEAN URINE pH

METHENAMINE SALT	MEAN pH FOR ZERO HOUR SAMPLE	MEAN pH FOR SIX HOUR SAMPLE	MEAN pH FOR TWELVE HOUR SAMPLE	F	DEGREES OF FREEDOM	LEVEL OF SIGNIFICANCE
Methenamine Mandelate						
Mean ± 1 S.D.*	5.89 ± 0.43	6.28 ± 0.56	5.98 ± 0.38	3.44	2,6	0.1
Range	5.3 - 7.2	5.5 - 7.5	5.5 - 6.8			
Methenamine Hippurate						
Mean ± 1 S.D.*	6.12 ± 0.73	6.28 ± 0.80	6.18 ± 0.53	0.576	2,6	0.59
Range	5.2 - 7.9	5.4 - 8.1	5.3 - 7.5			

*Mean urine pH ± 1 Standard Deviation

No significant effect was seen for either methenamine mandelate ($p = 0.1$) or methenamine hippurate ($p = 0.59$) when each salt was analyzed for effects on urine pH across the three sampling times.

TABLE X: RESULTS OF TEST FOR SIMPLE MAIN EFFECTS: ANALYSIS OF SAMPLE TIMES ACROSS THE METHENAMINE SALTS ON THE MEAN URINE pH

SAMPLE TIME	METHENAMINE MANDELATE	METHENAMINE HIPPURATE	F	DEGREES OF FREEDOM	LEVEL OF SIGNIFICANCE
Zero Hour					
Mean ± 1 S.D.*	5.89 ± 0.43	6.12 ± 0.73	0.507	2,4	0.64
Range	5.3 - 7.2	5.2 - 7.9			
Six Hour					
Mean ± 1 S.D.*	6.28 ± 0.56	6.28 ± 0.80	0	2,4	0.99
Range	5.5 - 7.5	5.4 - 8.1			
Twelve Hour					
Mean ± 1 S.D.*	5.98 ± 0.38	6.18 ± 0.53	0.341	2,4	0.73
Range	5.5 - 6.8	5.3 - 7.5			

*Mean urine pH ± 1 Standard Deviation

No significance was found at the zero hour ($p = 0.64$), six hour ($p = 0.99$) or twelve hour ($p = 0.73$) sample times when each was analyzed across both methenamine salts for effects on urine pH.

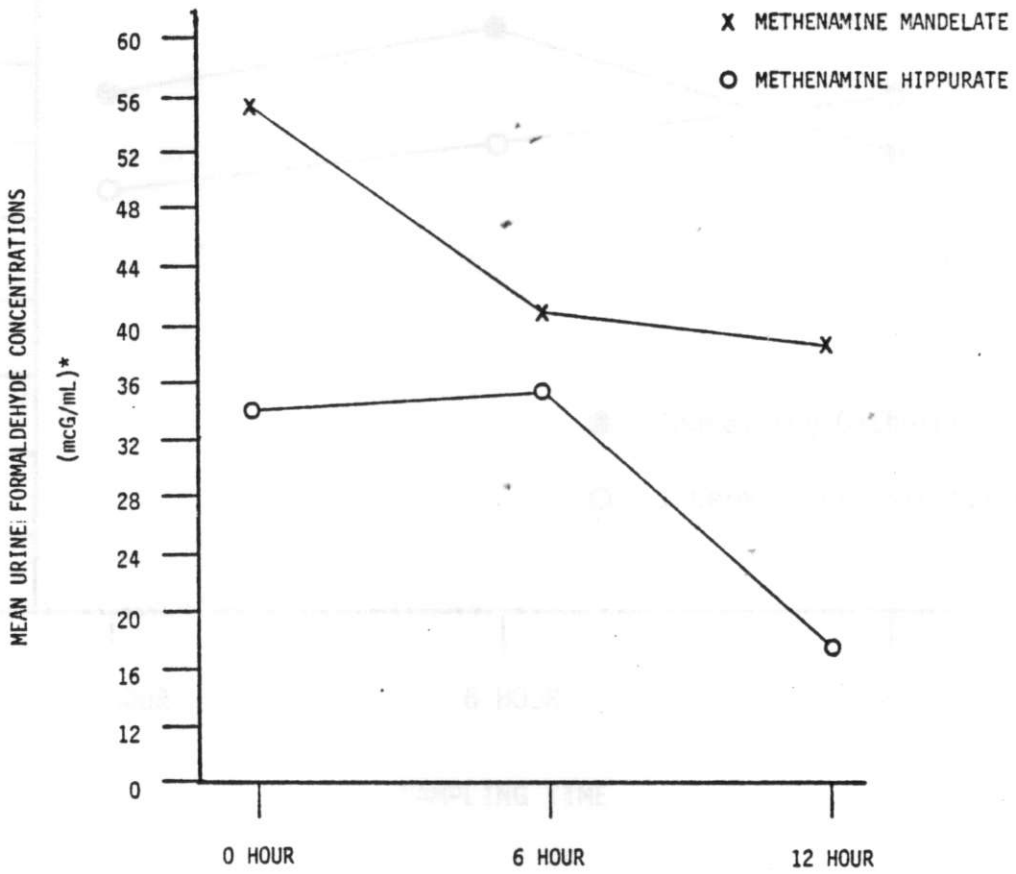
TABLE XI: URINE FORMALDEHYDE CONCENTRATIONS AND URINE pH ACROSS SAMPLE TIMES FOR INDWELLING CATHETER GROUP

SAMPLE TIME	METHENAMINE MANDELATE				METHENAMINE MANDELATE AND ASCORBIC ACID				METHENAMINE HIPPURATE				METHENAMINE HIPPURATE AND ASCORBIC ACID			
	PATIENT NUMBER				PATIENT NUMBER				PATIENT NUMBER				PATIENT NUMBER			
	1	2	3	4	1	2	3	4	1	2	3	4	1	2	3	4
ZERO HOUR																
Formaldehyde*	14	43	131	0	17	27	102	5	3	13	83	0	3	13	46	0
pH	6.6	5.7	5.3	7.2	6.5	6.0	5.7	6.0	6.8	6.5	5.4	6.8	5.2	6.7	5.2	7.1
ONE HOUR																
Formaldehyde*	4	9	148	0	8	16	107	5	9	11	58	14	7	13	37	0
pH	7.7	6.5	+	7.2	6.3	6.4	5.4	6.7	6.8	6.8	5.3	6.2	5.3	6.2	5.2	6.7
TWO HOUR																
Formaldehyde*	7	9	128	5	17	8	95	11	9	14	73	13	11	18	73	19
pH	7.2	6.6	+	6.5	6.4	6.8	5.5	6.2	6.7	6.9	5.4	6.9	5.2	+	+	5.3
THREE HOUR																
Formaldehyde*	3	8	113	15	9	18	86	11	17	10	83	0	10	5	99	15
pH	7.1	6.3	5.3	6.8	6.8	+	5.5	6.7	8.0	7.2	5.3	6.0	5.2	8.1	5.3	+
SIX HOUR																
Formaldehyde*	17	22	60	12	11	4	74	7	28	11	155	0	27	6	45	11
pH	7.5	6.7	6.6	7.1	6.9	6.8	5.5	6.8	5.4	7.9	5.5	7.8	5.4	8.1	6.3	+
NINE HOUR																
Formaldehyde*	+	19	79	33	13	5	+	14	8	2	+	0	6	2	35	13
pH	+	6.6	5.6	6.1	6.5	6.9	+	6.5	8.0	7.8	+	7.5	5.2	8.0	5.7	5.4
TWELVE HOUR																
Formaldehyde*	63	19	70	7	12	19	74	14	4	2	22	0	2	6	36	11
pH	+	6.1	5.5	+	5.8	6.3	+	5.9	5.6	7.5	6.6	6.4	5.4	5.9	5.8	5.3

*Formaldehyde concentrations measured in mcG/mL +Quantity of urine not sufficient to determine value

APPENDIX B

FIGURE I: MEAN URINE FORMALDEHYDE CONCENTRATIONS (mcG/mL) PRODUCED BY EACH METHENAMINE SALT ACROSS SAMPLING TIMES



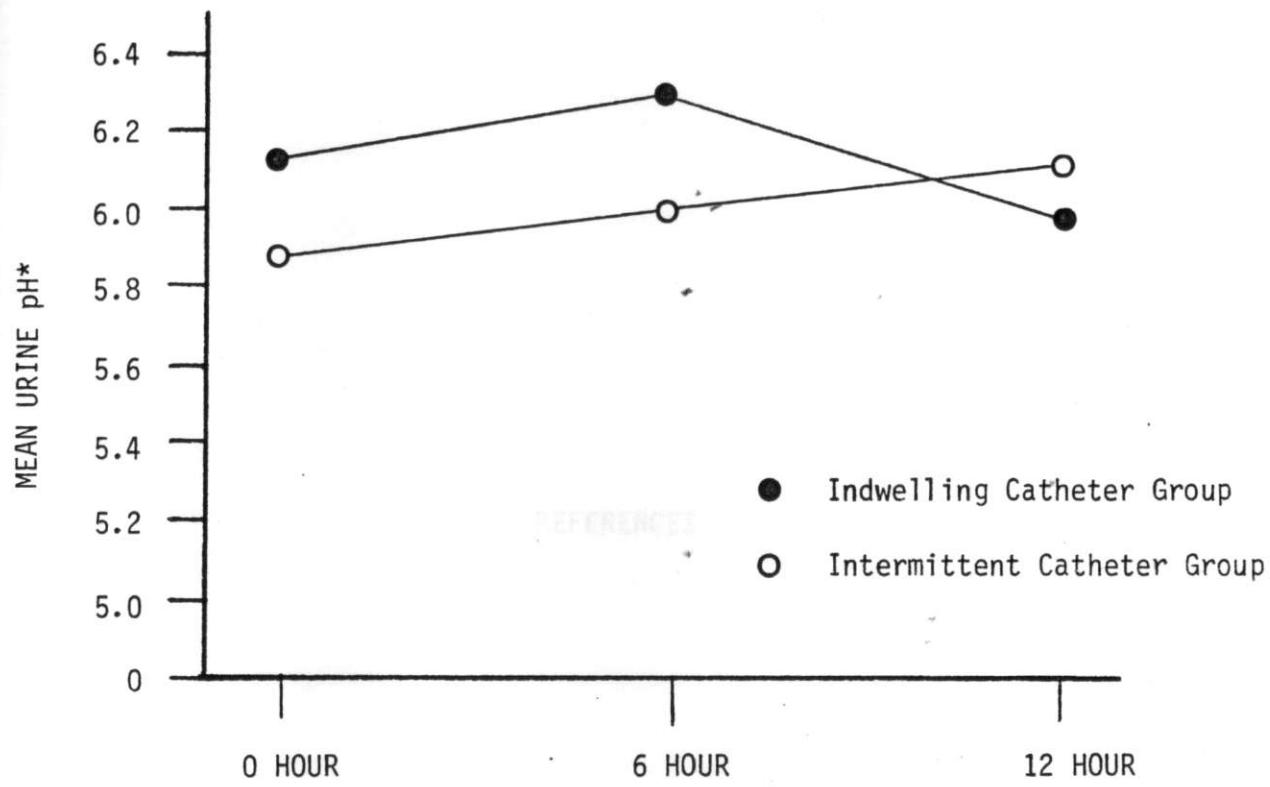
*Standard Deviations:

Methenamine Mandelate: ± 31.7, ± 26.9, and 22.9 mcG/mL for zero, six and 12 hour samples respectively

Methenamine Hippurate: ± 21.3, ± 33.5, and ± 13.2 mcG/mL for zero six and 12 hour samples respectively

The concentration or formaldehyde produced in the urine was significant for the time period the sample was obtained ($p = 0.048$). The urine formaldehyde concentrations at six and 12 hours were significantly different from the zero hour sample for methenamine mandelate. The 12 hour sample was significantly different for methenamine hippurate.

FIGURE II: MEAN URINE pH PRODUCED BY EACH METHENAMINE SALT AT EACH SAMPLING TIME



*Standard Deviations:

Indwelling Catheter Group: ± 0.68, ± 0.89, ± 0.57 at zero, six and 12 hours respectively

Intermittent Catheter Group: ± 0.58, ± 0.32, ± 0.42 at zero, six and 12 hours respectively

A significant effect was achieved when the catheter group - sampling time interaction was analyzed for effect on urine pH ($p = 0.002$). The changes in urine pH across time were significant for the indwelling catheter group only ($p = 0.028$).

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CURRICULUM VITAE

CURRICULUM VITAE

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PERSONAL

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Date and Place of Birth: April 7, 1953
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Marital Status: Single

Pharmacy Licensures: Iowa 1978-1979: #14668
Nebraska 1979-1980: #8624
Utah 1979-1980: #3233

PROFESSIONAL GOALS AND OBJECTIVES

To utilize and maintain professional competency in an academic or private institution and serve as a role model-practitioner-educator in the profession of pharmacy. To provide innovative and quality clinical pharmacy services and actively participate in an interdisciplinary approach to total patient care. To apply my expertise to the areas of adult internal medicine and special interest area of geriatric medicine within the acute and ambulatory care setting. To conduct research in relevant areas of my practice as a contribution to my profession and an aid in maintaining my competency.

EDUCATION

Undergraduate: Creighton University, 1971-1975
Omaha, Nebraska
Bachelor of Science in Pharmacy

Graduate: Doctor of Pharmacy Program, 1978 -
University of Utah
College of Pharmacy
Salt Lake City, Utah
Expected Graduation: June 1980

Faculty Advisor: George E. Dukes, Pharm.D.

CLINICAL EXPERIENCE

August 1978 - present — Pharm.D. Candidate and Teaching Fellow
College of Pharmacy
University of Utah

Responsibilites include academic and service-oriented activites. The program is patient-oriented and includes: daily patient rounds, patient counseling, pharmacokinetic drug monitoring, formal and informal in-service presentations to health professionals, and drug information responses.

Medicine: 27 weeks - University Hospital, University of Utah; Holy Cross Hospital;
Preceptors: Mary E. Russo, Pharm.D., George E. Dukes, Jr., Pharm.D.

Ambulatory Care: 10 weeks - University Hospital, University of Utah;
Preceptors: George E. Dukes, Jr., Pharm.D., Martin D. Higbee, Pharm.D.

Drug Information: 6 weeks - University Hospital, University of Utah;
Preceptor: Thomas C. Sudds, Pharm.D.

Psychiatry: 6 weeks - Salt Lake City Veteran's Administration Hospital.
Preceptor: Jean K. Devenport, Pharm.D.

Pediatrics: 6 weeks - University Hospital, University of Utah;
Preceptor: John A. Bosso, Pharm.D.

Surgery: 6 weeks - University Hospital, University of Utah;
Preceptor: John Russo, Jr., Pharm.D.

Physical Medicine and Rehabilitation: 3 weeks - University Hospital, University of Utah;
Preceptor: Jean K. Devenport, Pharm.D.

Nephrology: 6 weeks - University Hospital, University of Utah;
Preceptor: Mary E. Russo, Pharm.D.

Geriatric Medicine: 4 weeks - Salt Lake City Veteran's Administration Hospital;
Preceptor: Martin D. Higbee, Pharm.D.

Cardiology: 6 weeks - University Hospital, University of Utah;
Preceptor: Jean A. Nappi, Pharm.D.

Infectious Disease: 6 weeks - University Hospital, University of Utah;
Preceptor: Mary E. Russo, Pharm.D.

Critical Care: 6 weeks - L.D.S. Hospital, Salt Lake City;
Preceptor: John Russo, Jr., Pharm.D.

CLINICAL EXPERIENCE (Continued)

May 1976 - June 1978 — Creighton University
School of Pharmacy
Omaha, Nebraska

Preceptors: D.E. Ellerbeck, Pharm.D., Bruce D. Clayton, Pharm.D., Kyoko T. Mitsuoka, Pharm.D., Steven F. Kowalsky, Pharm.D., Paul Groth, M.S.

Areas of emphasis included providing clinical pharmacy services to: general medicine (7 weeks), geriatric medicine (4 weeks), drug information (4 weeks), general pediatrics (elective-7 weeks), general psychiatry (elective-7 weeks).

PHARMACY PRACTICE EXPERIENCE

May 1976 - June 1978 — Staff Pharmacist
Mary Greeley Memorial Hospital
Ames, Iowa

Activities included hospital pharmacy practice in a 230-bed hospital which included unit dose, I.V. additives, in-service teaching, preceptor for the Pharmacy Extern program, Drake University School of Pharmacy, Des Moines, Iowa, distribution center for Methadone Treatment program.

January 1976 - May 1976 — Community Pharmacist
Countryside Pharmacy
Omaha, Nebraska

Activities included contemporary community pharmacy practice.

May 1973 - December 1975 — Senior Pharmacy Intern
Immanuel Medical Center
Omaha, Nebraska

Activities included contemporary hospital pharmacy practice in a 400-bed hospital, aided in planning and initiation of unit dose system, and training of new pharmacy interns.

May 1973 - October 1975 — Pharmacy Intern
Field Club Pharmacy
Omaha, Nebraska

Activities included contemporary community pharmacy practice.

TEACHING EXPERIENCE

Intramural:

August 1978 - Present — Teaching Fellow
Adult Internal Medicine
Department of Pharmacy Practice
College of Pharmacy
University of Utah

TEACHING EXPERIENCE (Continued)

Responsibilities include formal classroom teaching for underclassmen in the Doctor of Pharmacy Program. Shared preceptorship responsibilities with faculty for baccalaureate pharmacy students during clinical clerkships.

Extramural: (Invited Presentations)

September - November 1978	Critical Care In-Service Education University Hospital, University of Utah TOPIC: Vasopressor Agents
November 1978	Rocky Mountain Gerontology Center Salt Lake City, Utah TOPIC: Senile Dementia
March - April 1979	Surgery ICU Nursing Staff In-Service Education, University Hospital, University of Utah TOPIC: Nitroprusside, cardiac electrophysiology, cardiac glycosides, antiarrhythmic agents, medical management of PSE
May - June 1979	Team Conference Department of Family Practice Holy Cross Hospital TOPICS: Theophylline kinetics, digoxin kinetics, lidocaine kinetics, clinical use of dopamine and dobutamine
May - June 1979	Surgery Nursing Staff In-Service Education, Holy Cross Hospital TOPIC: Clinical use of cephalosporins - special emphasis on cefamandole and cefoxitin
May - June 1979	Pharmacy Staff Conference Holy Cross Hospital TOPICS: Lidocaine kinetics, digoxin kinetics, theophylline kinetics, drug dosing in liver and kidney disease
September 1979	Participant Festival of Health Northwest Multidisciplinary Center
Novmeber 1979	Guest Lecturer Utah Pharmaceutical Association's First Annual Midyear Conference TOPIC: Panel Discussion - Critical Review of New Drugs 1978-79

TEACHING EXPERIENCE (Continued)

February 1980	Advanced Pharmacotherapeutics (ClPh 612) University of Utah College of Pharmacy TOPIC: Digitalis Glycosides
March 1980	Guest Lecturer Southeast Ladies Lions Club of Salt Lake TOPIC: Danger of mixing drugs
April 1980	Drug Use in the Elderly (ClPh 520) University of Utah College of Pharmacy TOPICS: Management of TIA's, Treatment of hypertension in the elderly

RESEARCH EXPERIENCE

January 1980 - Present	The Use of Methenamine Salts and Ascorbic Acid in Catheterized Spinal Cord Injured Patients
June 1979	A Pharmacokinetic Model for Repeated Oral Dosing

PUBLICATION

Bauwens, SF and Dukes, GE: Initial Heparin Infusion Rates, (Letter to the Editor), Am J Hosp Pharm 37(1):26-27 (1980).

HONORS AND AWARDS

APhA Student Award
Creighton University 1975

ACTIVITIES

1973-74	Sophomore Class President Creighton University School of Pharmacy
1973-74	Treasurer Creighton Student Council Creighton University School of Pharmacy
1973-75	Creighton University SAPHa Committee on Drug Abuse Lectures (Project SPEED)
1974-75	Editor-in-Chief, Pharmacy Newsletter Creighton University School of Pharmacy

ACTIVITIES (Continued)

1979-80	Graduate Student Representative Curriculum Committee University of Utah College of Pharmacy
1979-80	Student Member Pharm.D. Admissions Subcommittee University of Utah College of Pharmacy
1979-80	Journal Club University of Utah College of Pharmacy

ORGANIZATION AFFILIATIONS

American Society of Hospital Pharmacists
American Pharmaceutical Association
Utah Society of Hospital Pharmacists
Utah Heart Association

May 1980