Furthermore, the vaginal absorption of phenolsulfonphthalein after the consecutive administration resulted in an enhanced absorption with less variance, regardless of the initial stage of the estrous cycle (Fig. 4). The better absorption supports the halt of the cycle at diestrus and possibly reveals the thinner epithelial membrane.

In long-term therapy with vaginal application of leuprolide, the reproductive cycle effects would be leveled off by continuous administration, either parenterally or vaginally, although some fluctuation in absorption may be unavoidable at the initial period of administration. The authors' previous proposal of the vaginal application of leuprolide as a rational method for long-term anticancer therapy was supported by the findings of the present study.

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Methaqualone–Diphenhydramine Interaction Study in Humans

K. W. HINDMARSH *x, S. M. WALLACE *, C. B. SCHNEIDER *, and E. D. KORCHINSKI ‡

Received November 3, 1981, from the **College of Pharmacy and* ‡*College of Medicine, University of Saskatchewan, Saskatoon, Saskatchewan, Canada S7N 0W0.* Accepted for publication April 12, 1982.

Abstract □ Twelve healthy subjects received three single oral doses (250 mg) of methaqualone alone or in combination with diphenhydramine (25 mg). Blood samples were collected for a 48-hr period after each dose and analyzed for methaqualone and its major metabolite, 2-methyl-3-(2′-hydroxymethylphenyl)-4(3H)-quinazolinone. Peak blood concentrations ranging from 1.0 to 2.7 μg/ml occurred ~1–2 hr after the oral dose. The area under the blood level–time curve, peak plasma level, and elimination half-life for methaqualone were not significantly different (three-way ANOVA, $p > 0.05$) when methaqualone was administered alone, in combination with a diphenhydramine elixir or as a commercial product (capsule) containing both methaqualone and diphenhydramine. Statistically significant intersubject differences in the area under the curve were eliminated if the area was corrected for subject differences in elimination. Blood levels of the metabolite reached an average peak of 314 ng/ml (±107) between 4 and 8 hr after the dose and remained elevated for the 48-hr sampling period. The areas under the blood level time curve of the metabolite were not significantly different for the three treatments. Diphenhydramine administered at the dosage level used in therapeutic combination products did not alter the blood levels of methaqualone or its metabolite. In addition, no significant differences in methaqualone availability from the two commercial formulations tested could be detected.

Keyphrases □ Methaqualone—interaction study with diphenhydramine in humans, elimination, metabolism □ Diphenhydramine—interaction study with methaqualone in humans, elimination, metabolism □ Elimination—methaqualone–diphenhydramine interaction study in humans, metabolism □ Metabolism—methaqualone–diphenhydramine interaction study in humans, elimination

Although the therapeutic use of the methaqualone–diphenhydramine combination has declined, abuse continues to flourish (1–3). The reasons for the enhanced CNS effects claimed by drug abusers is not clearly understood.

Metabolism of methaqualone by the 10,000-g supernatant fraction of rat liver homogenates is inhibited *in vitro* by diphenhydramine (4). Concurrent oral administration of methaqualone and diphenhydramine to rats increases the blood and brain levels of methaqualone (3), whereas concurrent intravenous administration has no significant effect (5).

In humans, diphenhydramine has been credited with increasing the sedative-hypnotic effect of methaqualone (6), although the mechanism has not been elucidated. A previous study (7) compared methaqualone plasma concentrations achieved after administration of two commercially available diphenhydramine–methaqualone combination products and three methaqualone products. Differences in plasma levels were noted and attributed to formulation factors. An earlier study (8), comparing plasma levels after single dose administration of commercial products containing methaqualone, methaqualone hydrochloride, and methaqualone plus diphenhydramine, is difficult to interpret since no subject appears to have received more than one formulation. In a subsequent study (9) reduction of buccal absorption was reported when methaqualone powder was administered with diphenhydramine powder, but there was no difference in plasma levels after oral administration of the combination.

The objective of the present study was to compare, in healthy subjects, the concentrations of methaqualone and its major metabolite in blood (2-methyl-3-(2′-hydroxymethylphenyl)-4(3H)-quinazolinone), after administration of methaqualone alone and in combination with diphenhydramine. The possibility of a formulation effect was anticipated by including in the study design administration of diphenhydramine–methaqualone as a commercial combination product and as a mixture of a methaqualone capsule and diphenhydramine elixir.

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Figure 1—*Gas chromatograms of extracts of blood. Key: (A) control blood sample with imipramine added; (B) blood from subject receiving methaqualone (Peak I) with imipramine (Peak II) added.*

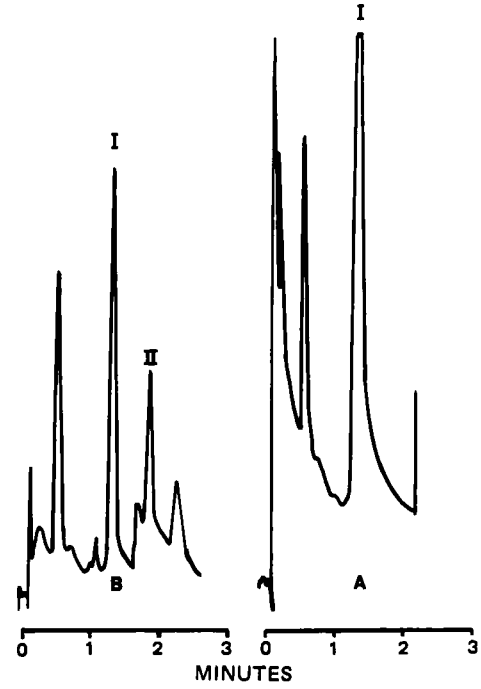

Figure 2—*Gas chromatograms of silylated extracts of blood. Key: (A) control blood sample with imipramine (Peak I) added; (B) blood from subject receiving methaqualone, Peak I imipramine, Peak II 2-methyl-3-(2'-hydroxymethylphenyl)-4(3H)-quinazolinone.*

EXPERIMENTAL

Materials—Methaqualone hydrochloride[1], 1-chlorobutane[2], ammonium carbonate[3], imipramine hydrochloride[4], bis-(trimethylsilyl)-trifluroacetamide with trimethylchlorosilane (1%)[5], dichloromethane[6], ethyl acetate[6], and glacial acetic acid[7] were obtained commercially and appropriate aqueous or methanolic solutions were prepared as required. The solvent used for extracting biological fluids was prepared by mixing dichloromethane with ether (11:14 v/v) (10). An acetate buffer (pH 5.2) was prepared by mixing 21 ml of 0.1 *M* acetic acid with 79 ml of 0.1 *M* sodium acetate.

***In Vitro* Blood–Plasma Distribution Studies**—Methaqualone hydrochloride (1 μg/ml of solution in methanol) was added to Erlenmyer flasks in sufficient quantity to produce a final methaqualone hydrochloride concentration of 1–20 μg/ml (0.87–17.5 μg/ml of methaqualone). The methanol was evaporated and 20 ml of blood[8] added. The flasks were covered[9] and incubated[10] for 2 hr (37°). Two hours had been established previously as sufficient time to ensure equilibration. A portion of the blood from each flask was centrifuged[11] to separate plasma. Aliquots (1 ml) of blood and plasma were extracted and methaqualone concentrations were determined by GLC. Hematocrits were determined[12] and red blood cell concentrations were calculated (11).

Study Design—Twelve volunteers (4 female, 8 male) weighing between 50.2 and 83.9 kg each and ranging in age from 21 to 38 years participated in the study. All subjects received a medical examination and a series of standard laboratory tests prior to entering the study. All subjects gave their written informed consent according to an approved[13] *protocol.*

Each subject received a single dose each of methaqualone hydrochloride in a 250-mg capsule[14], methaqualone hydrochloride capsule[14] plus 25 mg of diphenhydramine hydrochloride [elixir][15] and a methaqualone (250 mg)–diphenhydramine hydrochloride (25 mg) capsule[16]. The order of treatments was randomized according to a Latin-square design with a minimum period of 2 weeks between each treatment (*i.e.*, each drug administration). Drugs were administered with water after a 12-hr fast. Food was not consumed until at least 4 hr after the drugs had been administered. One subject received a fourth treatment of methaqualone hydrochloride and 50 mg of diphenhydramine hydrochloride[17].

Blood samples (7 ml) were collected[18] at 0, 0.5, 1, 2, 4, 8, 24, 32, and 48 hr after each drug administration, and were refrigerated until extracted and analyzed for methaqualone concentration by GLC. For 9 of the 12 subjects, blood samples were also analyzed for 2-methyl-3-(2'-hydroxymethylphenyl)-4(3H)-quinazolinone by GLC. All samples were extracted within 48 hr of collection.

A portion of the blood collected for five of the subjects, after one of the drug doses, was centrifuged[11] to separate plasma. Both plasma and blood samples were analyzed for methaqualone by GLC.

GLC–mass spectrometry was performed on a GLC-mass spectrometer linked to a data system[19].

Extraction of Biological Fluids—For samples from *in vitro* studies, aliquots (1 ml) of blood and plasma were added to centrifuge tubes containing the internal standard, imipramine (4 μg). The samples were diluted with distilled water (1 ml), basified (10 *M* NaOH) and extracted[20] twice with 1-chlorobutane (5 ml) for 1.0 min. The pooled organic layers were evaporated[21] (at 85°) to dryness under a flow of air. The residue was quantitatively transferred to glass vials (1 ml)[22] using small portions of methanol. The methanol was evaporated[23]. The residue was dissolved in methanol (20 μl) and 1–2 μl injected onto the GLC.

[1] William H. Rorer (Canada) Ltd., Bramalea, Ontario, Canada.
[2] J. T. Baker Chemical Co., Phillipsburg, NJ.
[3] British Drug Houses (Canada) Ltd., Toronto, Ontario, Canada.
[4] Geigy Pharmaceuticals, Division of Ciba-Geigy Canada Ltd., Dorval, Quebec, Canada.
[5] Pierce Chemical Co., Rockford, Ill.
[6] Caledon Laboratories Ltd., Georgetown, Ontario, Canada.
[7] Fisher Scientific Co., Fair Lawn, NJ.
[8] Canadian Red Cross Society Blood Bank, Saskatoon, Saskatchewan, Canada.
[9] Parafilm, American Can Co., Greenwich, Conn.
[10] Model G-76, Gyrotory Water bath shaker, New Brunswick Scientific Co., Inc., New Brunswick, NJ.
[11] Model IEC-HN-S centrifuge, Damon/IEC Division, Needham Heights, Mass.
[12] Readacrit centrifuge, Clay Adams Division of Becton, Dickinson and Co., Parsippany, NJ.
[13] President's Committee on Ethics in Human Experimentation, University of Saskatchewan, Saskatoon, Saskatchewan, Canada.
[14] Mequelon capsules, 250 mg, Charles E. Frosst and Co., Pointe Claire-Dorval, Quebec, Canada.
[15] Benadryl elixir, 12.5 mg/5 ml, Parke-Davis and Co. Ltd., Scarborough, Ontario, Canada.
[16] Mandrax capsules, Roussel (Canada) Ltd., Montreal, Quebec, Canada.
[17] Benadryl capsule, 50 mg, Parke-Davis and Co. Ltd., Scarborough, Ontario, Canada.
[18] Venoject, heparinized, evacuated blood collection tubes, Kimble-Terumo, Elkton, Md.
[19] Model 3300, Finnigan GC–MS and Model 2300, Incos Data System, Finnigan Corp., Honeyville, Calif.
[20] Vortex Genie, Fisher Scientific Co., Montreal, Quebec, Canada.
[21] Thermolyne Dri-Bath, Thermolyne Corp., Dubuque, Iowa.
[22] Reacti-vials, 1 ml, Pierce Chemical Co., Rockford, Ill.
[23] Extracted at a speed setting of 10, Evapomix, Buchler Instruments, Fort Lee, NJ.

Table I—*In Vitro* Distribution of Methaqualone Between Plasma and Erythrocytes

Methaqualone Concentration, μg/ml			
Blood[a], C_B	Plasma, C_P	Erythrocytes[b], C_{RBC}	Blood–Plasma Ratio
1.0	1.25	0.60	0.80
2.0	2.37	1.41	0.84
3.0	3.30	2.52	0.91
4.0	4.71	2.87	0.85
5.0	4.47	5.72	1.12
10.0	6.20	15.1	1.61
15.0	8.20	24.2	1.83
20.0	9.03	34.8	2.21

[a] Concentration added to blood. [b] Calculated from $C_B = C_P(1 - H) + C_{RBC}(H)$, where the hematocrit (H) is 38.5% for concentrations of 1–4 μg/ml and 42.5% for concentrations of 5–20 μg/ml.

Table II—*In Vivo* Distribution of Methaqualone in Blood[a]

Time after Administration, hr	Methaqualone Concentration, μg/ml		Blood–Plasma Ratio
	Blood	Plasma	
0	0	0	
0.5	0.44 ± 0.46	0.47 ± 0.31	0.95 ± 0.03[b]
1	1.10 ± 0.64	1.21 ± 0.69	0.90 ± 0.14
2	1.18 ± 0.14	1.32 ± 0.22	0.90 ± 0.09
4	0.66 ± 0.12	0.80 ± 0.10	0.82 ± 0.09
8	0.42 ± 0.09	0.50 ± 0.07	0.82 ± 0.05
24	0.24 ± 0.02	0.25 ± 0.02	0.97 ± 0.05
32	0.21 ± 0.02	0.23 ± 0.02	0.92 ± 0.06
48	0.17 ± 0.01	0.19 ± 0.02	0.93 ± 0.09

[a] Values are the mean ± *SD* for 5 subjects (1, 6, 8, 10, and 12) with hematocrits of 0.45, 0.48, 0.52, 0.42, and 0.47, respectively. [b] Two of five blood and plasma concentrations had a value of zero at 0.5 hr.

For analysis of samples from the *in vivo* study, 1-ml aliquots of blood or plasma were diluted with 1 ml of distilled water containing 3 μg/ml of imipramine hydrochloride. Ammonium carbonate (1 g) was added, and the samples were extracted twice with 4 ml of ether–dichloromethane (14:11) for 10 min[23]. The tubes were centrifuged at 2000 rpm[11] for 10 min. The pooled organic layers were evaporated[21] at 85° under a gentle flow of nitrogen. The residue was dissolved in 500 μl of methanol. For analysis of methaqualone concentrations, 2–5-μl aliquots were injected onto the GLC. For analysis of the methaqualone metabolite in blood the remaining methanol was evaporated under a flow of nitrogen. Silyl ether derivatives were prepared by adding ethyl acetate (300 μl dried over molecular sieves) and bis-(trimethylsilyl)trifluoroacetamide with 1% trimethylchlorosilane (50 μl) to the residue in each tube. The tubes were capped and incubated[21] at 85° for 1 hr. The solvent was evaporated under a flow of nitrogen. The residue was dissolved in ethyl acetate (500 μl), and 2–5-μl aliquots were injected onto the GLC.

GLC Analysis—For analysis of samples from *in vitro* studies, a GLC[24] equipped with a flame-ionization detector was used. The chromatographic column was 1.2-m × 3.2-mm o.d. coiled, stainless-steel tubing packed with 3% methyl silicone coated on a high-performance diatomite support (80–100 mesh)[25]. The column was conditioned by maintaining the oven at 290° with low carrier gas flow for 18 hr. Operating temperatures were: injection port, 270°; column, 220°; detector, 265°.

The nitrogen flow was 30 ml/min. Hydrogen and compressed air flow rates were adjusted to give maximum response. Methaqualone concentrations were determined from a standard curve plotted as the peak height ratio (methaqualone–internal standard) against methaqualone concentration.

For analysis of methaqualone and its metabolite in blood obtained during the *in vivo* study, a GLC[26] equipped with a nitrogen–phosphorus detector was used. The chromatographic column was 1.2-m × 2.0-mm i.d. coiled-glass tubing packed with 2% methyl silicone on a high-performance diatomite support (100–120 mesh)[25]. Operating temperatures were: injection and detector ports, 300°; column, 240° (for methaqualone) or 220° (for the methaqualone metabolite). The helium flow rate was 30 ml/min, and the hydrogen and compressed air flow rates were adjusted to 3 ml/min and 50 ml/min, respectively. Concentrations of methaqualone and its metabolite were calculated from standard curves plotted as peak area (methaqualone) or peak height (metabolite) ratio (compound–internal standard) against concentration. All standard curves for analysis of samples were prepared as extracted standard curves by adding known amounts of methaqualone (or metabolite) to blood and extracting the standards as previously described.

Data Analysis—Slope and intercept of standard curves were calculated by least-squares linear regression[27]. The disposition rate constant (β) for methaqualone was determined by log-linear regression[27] of the last 3–4 data points of the blood level–time curve. The biological half-life ($t_{1/2\beta}$) was calculated as $0.693/\beta$. The area under the blood level time curve for methaqualone (AUC_0^{48}) and its metabolite ($AUC_{0\,met}^{48}$) was estimated using the trapezoidal rule. To obtain the total area under the curve for methaqualone (AUC_0^∞), the area from the last sampling point to infinity (plasma level at 48 hr/β) was added to AUC_0^{48}. All parameters, except the time of peak plasma levels (t_{max}) and $t_{1/2\beta}$, were corrected for subject differences in the milligram per kilogram dose (*i.e.*, by dividing by the ratio of the dose of methaqualone base to the subject's weight) (12). The AUC_0^∞ was corrected for changes in elimination by multiplying by β ($AUC_0^\infty\,\beta$). All parameters (AUC_0^{48}, AUC_0^∞, $AUC_0^\infty\beta$, $AUC_{0\,met}^{48}$, t_{max}, C_{max}, and $t_{1/2\beta}$) were then analyzed statistically by three-way ANOVA[28] for treatment, period (*i.e.*, order of treatment), and subject effects; effects were considered significant if $p \leq 0.05$.

RESULTS AND DISCUSSION

GLC analysis of blood extracts revealed a well-defined peak (I, Fig. 1B) adequately separated from the internal standard, imipramine, (Peak II, Fig. 1B) and endogenous material (Fig. 1A). Peak I was identified, by GLC–mass spectrometry, as methaqualone. A molecular ion at m/z 250 and the base peak at m/z 235 due to the loss of the methyl group at the 2-position of the molecular ion were noted. A column temperature of 240° gave a relative retention time (with respect to imipramine) of 0.86 min for methaqualone. The standard curve for the GLC analysis of methaqualone was linear (r^2, coefficient of determination = 0.996) over a concentration range of 0.15–2.40 μg/ml.

Chromatography of silylated blood samples revealed one major peak (Peak II, Fig. 2B) not found in control blood extracts (Fig. 2A). Peak II (Fig. 2B) had a relative retention time of 1.39 min with respect to the internal standard, imipramine (Peak I, 2B). GLC–MS confirmed that Peak II was the trimethylsilyl derivative of the monohydroxy methaqualone metabolite, 2-methyl-3-(2′-hydroxymethylphenyl)-4(3H)-quinazolinone. Similar fragment ions to those previously reported for this metabolite (13, 14) were detected. The standard curve for GLC analysis of the metabolite was linear (r^2, coefficient of determination = 0.99) over a concentration range of 0.06–0.96 μg/ml. Mean recoveries of methaqualone and the metabolite from blood were 89.4 ± 6.6 (*SD*) and 87.2 ± 11.2%, respectively.

While forensic studies of methaqualone overdosage tend to report blood levels of the drug (15–17), pharmacokinetic studies measure the concentration of the drug in plasma or serum (18–20). Erythrocyte concentrations at <50% of the corresponding plasma concentration have been reported (9, 21). Another study (22) claimed >90% of the methaqualone in plasma phase with little, if any, bound to the cellular elements of blood. In the present report, however, concentrations of methaqualone in blood and plasma did not differ greatly except for blood concentrations of 5 μg/ml or greater (Table I).

After administration of a single 250-mg dose of methaqualone to healthy subjects, the blood–plasma ratio of methaqualone concentrations ranged from 0.82 to 0.97 over the 48-hr period studied (Table II). *In vitro* distribution studies yielded similar results for the concentration range of 1–4 μg/ml of blood. At higher blood concentrations, *in vitro*, erythrocyte concentrations of methaqualone were significantly greater than plasma concentrations (Table I). A larger fraction free in plasma would not account for the changing blood–plasma ratios, since a relatively constant fraction (95%) of methaqualone is bound *in vitro* to human plasma proteins over the concentration range of 5–20 μg/ml plasma (unpublished observations).

One may speculate that larger blood–plasma ratios result from a cooperative binding to erythrocytes at higher methaqualone concentrations. The reasons for the apparent accumulation in erythrocytes were not investigated. Blood and plasma concentrations appear to be approximately equivalent at the lower methaqualone concentrations encountered in pharmacokinetic studies. However, in overdose cases, blood and plasma

[24] Model 5750B, Hewlett-Packard, Avondale, Pa.
[25] OV-101 on Chromosorb W, Chromatographic Specialties, Brockville, Ontario, Canada.
[26] Model 5840, Hewlett-Packard, Avondale, Pa.
[27] TI-59 Programmable Calculator, Texas Instruments Inc., Dallas, Tex.
[28] SPSS program package, University of Pittsburgh, and DEC-20 computer.

Table III—Comparison of Parameters for Methaqualone after Administration of a Single Oral Dose with and without Diphenhydramine

Parameter	Treatment[d] Methaqualone HCl Capsule	Methaqualone HCl plus Diphenhydramine Elixir	Methaqualone–Diphenhydramine Capsule	p Value for Subject Effect[a]
AUC_0^{48} μg/ml × hr[b]	5.29 ± 0.99	5.33 ± 0.97	5.22 ± 0.97	<0.001
AUC_0^{∞} μg/ml × hr[b]	8.16 ± 2.67	7.82 ± 2.20	7.81 ± 1.47	<0.001
$AUC_0^{\infty}\beta$ μg/ml[b]	0.15 ± 0.03	0.16 ± 0.02	0.15 ± 0.03	0.06
C_{max}, μg/ml[b]	0.51 ± 0.11	0.46 ± 0.11	0.50 ± 0.10	0.04
t_{max}, hr	1.5 ± 0.5	1.3 ± 0.5	1.8 ± 0.9	0.30
$t_{1/2\beta}$, hr	37.7 ± 14.1	33.4 ± 8.7	36.6 ± 11.5	0.01
$AUC_{0\,met}^{48}$[b,c] μg/ml × hr	3.47 ± 1.04	3.19 ± 1.44	3.05 ± 0.61	0.12
Dose/kg, methaqualone base	3.26 ± 0.53	3.26 ± 0.53	3.74 ± 0.61	

[a] p values >0.05 for treatment and period effects for all parameters. [b] Corrected for dose–kilogram of body weight (divide all units by mg/kg). [c] Determined for 9 of the 12 subjects. [d] Mequelon, Charles E. Frosst & Co.; Mequelon and Benadryl elixir, Parke Davis & Co. Ltd.; Mandrax, Roussel (Canada) Ltd.

levels may not be equivalent and the difference should perhaps be considered when evaluating a patient. For the purposes of the present investigation, blood was chosen as the biological fluid for analysis, because cleaner extracts with less GLC baseline interference were obtained.

To determine whether methaqualone blood levels differed when methaqualone was administered orally with diphenhydramine, blood was sampled over a 48-hr period in 12 healthy subjects. Data from subject 6 are presented as representative of methaqualone blood levels achieved with oral administration of a single dose of methaqualone with and without diphenhydramine (Fig. 3). The time of blood collection (48 hr) was too short to obtain a pharmacokinetically accurate value for the elimination half-life, but the estimates for $t_{1/2}$ were within the range previously reported for methaqualone (19.6–41.5 hr) (18). Peak blood levels ranged from 1.0–2.7 μg/ml at 1–2 hr after oral administration (Table IV). The t_{max} and $t_{1/2\beta}$ values were not significantly different for the three treatments (methaqualone HCl capsule, methaqualone HCl capsule plus diphenhydramine elixir, methaqualone–diphenhydramine capsule). All other parameters were corrected for the mg/kg dose of methaqualone administered. No treatment or formulation effect was evident for AUC_0^{48}, AUC_0^{∞}, $AUC_0^{\infty}\beta$, or C_{max} (p for treatments >0.05) (Table III). The power of the statistical test was such that a difference of 20% would have been detected (23). Significant intersubject differences (p <0.05) were noted for AUC_0^{48}, AUC_0^{∞}, C_{max}, and $t_{1/2\beta}$. No significant intersubject differences in $AUC_0^{\infty}\beta$ were apparent, thus suggesting the major factor contributing to intersubject differences in the AUC value for methaqualone was the elimination of the drug.

Maximum blood levels of the methaqualone metabolite, 2-methyl-3(2′-hydroxymethylphenyl)-4(3H)-quinazolinone), occurred between 4 and 8 hr after methaqualone administration and remained elevated over the 48-hr sampling time (Fig. 4). The average maximum metabolite level was 314 ng/ml ± 107 (SD). The $AUC_{0\,met}^{48}$ values after administration of methaqualone with and without diphenhydramine were not significantly different.

No major differences in blood levels could be detected between the methaqualone HCl capsule and methaqualone–diphenhydramine HCl capsule formulation. Diphenhydramine administered at the dosage level

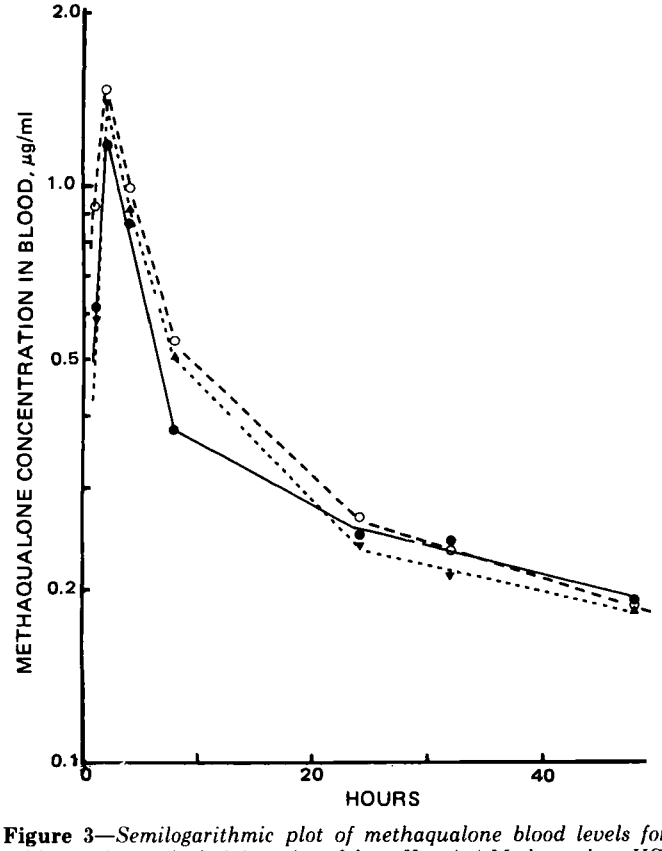

Figure 3—*Semilogarithmic plot of methaqualone blood levels for subject 6 after oral administration of drug. Key: (●) Methaqualone HCl (250 mg); (○) methaqualone HCl (250 mg) and diphenhydramine HCl (25 mg) elixir; (▼) methaqualone diphenhydramine HCl capsule (250:25 mg).*

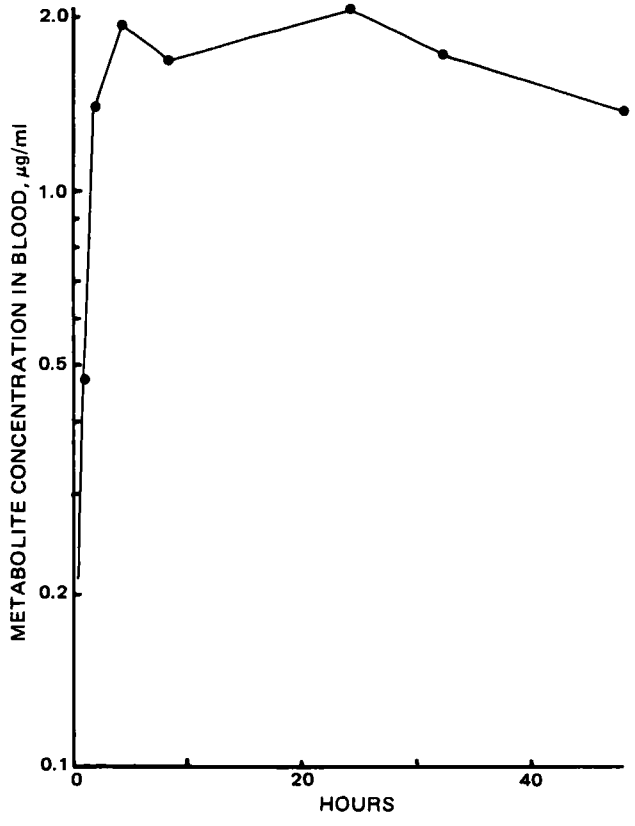

Figure 4—*Semilogarithmic plot of 2-methyl-3-(2′-hydroxymethylphenyl)-4(3H)-quinazolinone blood levels for subject 6 after administration of a methaqualone HCl (250 mg) capsule.*

Table IV—Methaqualone Concentrations in Blood [a] at Various Times after Administration of a Single Oral Dose with and without Diphenhydramine

Time[b], hr	Treatment: Methaqualone HCl Capsule	Methaqualone HCl plus Diphenhydramine Elixir	Methaqualone–Diphenhydramine Capsule
0.5	0.38 ± 0.44	0.24 ± 0.25	0.60 ± 0.50
1	1.39 ± 0.68	1.34 ± 0.53	1.54 ± 0.53
2	1.38 ± 0.35	1.26 ± 0.31	1.56 ± 0.48
4	0.79 ± 0.23	0.81 ± 0.23	0.92 ± 0.35
8	0.49 ± 0.15	0.51 ± 0.20	0.54 ± 0.17
24	0.24 ± 0.07	0.25 ± 0.08	0.30 ± 0.10
32	0.21 ± 0.08	0.21 ± 0.08	0.26 ± 0.09
48	0.16 ± 0.07	0.16 ± 0.07	0.18 ± 0.06

[a] Values (μg/ml) are the mean ± *SD* for 12 subjects. [b] Means were calculated using the approximate time of blood collection; exact collection times were recorded and used for *AUC* and $t_{1/2}$ determinations.

used in therapeutic combination products (25 mg) did not affect blood levels of methaqualone or its major metabolite.

An important consideration, in comparing the present study conducted in healthy humans to previous studies conducted in the rat (3), may be the relative doses of diphenhydramine and methaqualone hydrochloride administered. Although the ratio of methaqualone–diphenhydramine doses were similar (8:1 for rats and 10:1 for humans), the doses administered per kilogram of body weight were higher in animal studies (40 mg/kg for methaqualone HCl; 5 mg/kg for diphenhydramine HCl) than in human studies (3.7 mg/kg for methaqualone HCl and 0.4 mg/kg for diphenhydramine HCl). For the one subject who received a fourth dose of methaqualone in combination with a larger dose of diphenhydramine (50 mg), the $t_{1/2}$ for methaqualone increased and the urinary metabolite excretion decreased with increasing diphenhydramine dosage. While the AUC_0^∞ had increased, after correction for the increase in $t_{1/2}$, the $AUC_0^\infty\beta$ had decreased with the larger diphenhydramine dosage. Thus, larger doses of diphenhydramine, as might be favored by drug abusers, may elicit a pharmacokinetic interaction. The possibility of a dose-dependent interaction was not specifically investigated and would require further study.

This study was concerned only with investigating a pharmacokinetic interaction, and therefore does not preclude the possibility of a pharmacological interaction between methaqualone and diphenhydramine.

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Photolytic Decomposition of Hydrochlorothiazide

SWASONO R. TAMAT and DOUGLAS E. MOORE ˣ

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Abstract □ Hydrochlorothiazide decomposes upon irradiation with near-UV light ($\lambda > 310$ nm) both in methanol and aqueous solutions. In the photolysis the chlorine substituent is removed to be replaced by either —H or —OR from the solvent ROH. Hydrolysis of the thiadiazine ring is superimposed upon the dechlorination. The presence of oxygen inhibits the decomposition. The mechanism of the photolysis is suggested to involve cation radical formation which facilitates the hydrolysis step. 5-Chloro-2,4-disulphonamido-aniline, the normal hydrolysis product from hydrochlorothiazide, is also susceptible to photolytic dechlorination by a similar mechanism.

Keyphrases □ Hydrochlorothiazide—photolytic decomposition, irradiation, dechlorination, hydrolysis □ Decomposition, photolytic—hydrochlorothiazide, irradiation, dechlorination, hydrolysis □ Hydrolysis—photolytic decomposition of hydrochlorothiazide, dechlorination, irradiation

Hydrochlorothiazide [6-chloro-3,4-dihydro-1,2,4-benzothiadiazine-7-sulphonamido-1,1-dioxide] (I) is a widely used diuretic effective in small doses. Within a few years of its introduction there were reports of its implication in skin photosensitization (1). From oxygen uptake measurements and free radical polymerization (2), I and some

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