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Phase I Clinical and Pharmacological Study of Chloroquinoxaline Sulfonamide[1]

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ABSTRACT

Chloroquinoxaline sulfonamide (CQS) is a halogenated heterocyclic sulfanilamide identified by the *in vitro* human tumor colony-forming assay as an active agent in a variety of human solid tumors. In this phase I study, 182 courses of CQS were administered intravenously every 28 days to 88 patients at doses ranging from 18 to 4870 mg/m². Hypoglycemia associated with hyperinsulinemia was the dose-limiting adverse effect at 4870 mg/m². Supraventricular tachyarrhythmias were observed at doses >4000 mg/m². Less common reactions included infusion site phlebitis, nausea, anemia, alopecia, perioral numbness, and diarrhea. Cumulative toxicity was not observed. Minor objective antitumor responses were noted in 7 patients; 6 of the 7 responses occurred in patients with non-small cell lung cancer.

Results of pharmacokinetic studies were consistent with the preclinical observations that CQS is highly bound to plasma protein. Plasma elimination followed a two-compartment model; the mean $t_{1/2}\alpha$ was 2.7 ± 0.3 h and the $t_{1/2}\beta$ was 52 ± 6 h (± SE). The total body clearance and the volume of distribution at steady state of CQS both increased with the dose (distribution at steady state, 3.7–10.5 liter/m²; total body clearance, 53–264 ml/h/m² for doses of 18–4060 mg/m²) and may reflect saturation of the protein binding and "free" drug clearance.

Although inactive against common animal tumors in preclinical screening systems both *in vitro* and *in vivo*, CQS has demonstrated definite activity in the human tumor stem cell colony-forming assays, as well as modest anticancer activity in this phase I study in patients with advanced solid tumors. The pharmacokinetic results and the limiting effect of transient hypoglycemia suggest that considerably higher cumulative doses of CQS could be administered using a more frequent dosing schedule.

INTRODUCTION

CQS[3] (Fig. 1) is a halogenated derivative of sulfaquinoxaline, an antibiotic commonly used in veterinary medicine. In conventional preclinical screens in which animal tumors were used, CQS was inactive against P388 leukemia *in vitro* and was also ineffective against *in vivo* tests in nude mice bearing B16 melanoma, L1210 leukemia, colon 38 carcinoma, CD8F mammary cancer, and M5076 sarcoma. While ordinarily this level of activity would have precluded further consideration as an anticancer drug, CQS showed high activity when tested in the human tumor colony-forming assay (1, 2). In this assay, CQS demonstrated excellent colony inhibition in 6 of 11 common tumors. At a concentration of 10 μg/ml, responses were observed in 8 of 14 breast cancer specimens and 20 of 36 lung tumors. A similarly high incidence of response was observed in melanoma (8 of 18) and carcinomas of the ovary (10 of 22), kidney (4 of 13), and colon (5 of 17). In the human tumor colony-forming assays, the overall response rate at 10 μg/ml was 47.2% (60 of 127) and decreased to 18.3 (19 of 104) and 2.0% (2 of 102) at concentrations of 1.0 and 0.1 μg/ml, respectively.

Preclinical toxicological testing in mice yielded fatal events proceeded by central nervous system dysfunction. The estimated dose yielding a 50% mortality was 1821 mg/m² with a single dose and 7005 mg/m² on a daily times 5 dose schedule, suggesting that the toxicity of CQS was related to peak plasma concentrations. Plasma CQS concentrations of ≥10 μg/ml were readily achieved in mice without causing significant toxicity. In rats, single doses of 3600 mg/m² were lethal, causing an immediate toxic effect on the central nervous system with labored breathing, ataxia, and diminished activity. Histopathological examination suggested that the liver, kidney, thymus, and testis were the principal target organs of toxicity. Dogs were markedly more sensitive to the toxic effects of CQS; a single dose of 240 mg/m² was lethal because of fulminant bloody diarrhea. The toxicity was dose related, delayed in onset, and prolonged in duration; toxic effects were observed in bone marrow, lymphoid tissues, gastrointestinal tract, pancreas, adrenal gland, and testis. A single dose of 180 mg/m² resulted in mild, reversible gastrointestinal adverse effects. Owing to the marked sensitivity in dogs, the proposed starting dose for human studies was one-tenth of the minimally toxic dose in dogs or 18 mg/m².

MATERIALS AND METHODS

Patient Selection. Eligibility requirements included: histological documentation of cancer, age ≥18 years, Karnofsky performance status ≥50, no radiation therapy or chemotherapy in the preceding 28 days, no use of sulfonamide or sulfonylurea medications in the preceding 14 days, leukocyte count ≥3500/μl, platelet count ≥100,000/μl, serum bilirubin ≥1.5 mg/dl, serum creatinine ≥1.5 mg/dl or creatinine clearance ≥50 ml/min/1.7 m², and a normal erythrocyte level of glucose-6-phosphate dehydrogenase. Patients with leukemia, hemolytic anemia, central nervous system metastases, epilepsy, sulfonamide allergies, and lactating or pregnant women were excluded. Written informed consent was obtained, and the study was approved in advance by this center's Institutional Review Board.

Study Design. All patients underwent a complete physical examination, and a medical history was obtained. Initial laboratory studies included complete blood cell counts, serum glucose and multichannel biochemical screening profile, prothrombin time, and activated partial thromboplastin time. These studies were repeated approximately every 2 weeks and before each subsequent dose of CQS. Standard criteria for response and toxicity were used.

The prescribed dose of CQS was infused over 1 h every 28 days. At least three patients were entered at each dose level; doses were escalated using a modified Fibonacci progression from the starting dose (18 mg/m²) up to 180 mg/m². Thereafter, subsequent doses were escalated by 20% of the preceding level. At levels at which potential drug-related toxicity was observed, additional patients were studied to better define the adverse reactions. Dose escalation within an individual patient was

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[3] The abbreviations used are: CQS, chloroquinoxaline sulfonamide {NSC-339004; benzenesulfonamide (4-amino-*N*[5(on 8)-chloro-2-quinoxalinyl])}; AUC, area under the curve; HPLC, high-performance liquid chromatography; Vd_{ss}, distribution at steady state; K_{ATP}, ATP-sensitive potassium.

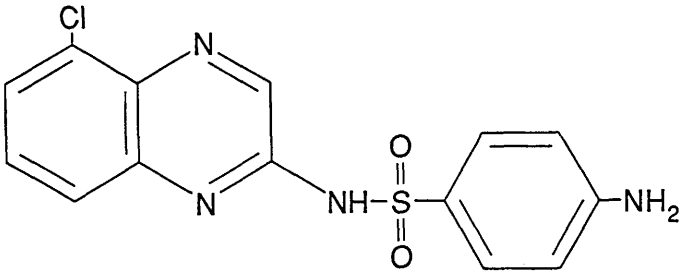

Fig. 1. Chemical structure of chloroquinoxaline sulfonamide {benzenesulfonamide (4-amino-*N*[5(on 8)-chloro-2-quinoxalinyl])}. Molecular formula $C_{14}H_{11}ClN_4O_2S$ and molecular weight 334.79.

not permitted. The maximum tolerated dose was defined as that dose which produced reversible toxicity more than grade 2+ in 70% of patients or grade 3+ toxicity in ≥30% of patients.

CQS was supplied as a yellow lyophilized powder by the Division of Cancer Treatment, National Cancer Institute, Bethesda, MD (3). Each drug vial containing 500 mg of CQS with 750 mg of *N*-methylglucamine was reconstituted with 9.2 ml of sterile water for injection (USP) at a pH of 9.5–10.5. Initially, the dose of CQS (18–1960 mg/m²) was resuspended in 50 ml of 5% dextrose or 0.9% NaCl. Doses of 2350–3385 mg/m² were resuspended in 150 ml, and a volume of 250 ml was used for doses ≥4000 mg/m².

Pharmacokinetics Studies. Pharmacokinetic studies were performed during the first treatment course on 3 patients each at dose levels of 18, 36, 90, 150, 216, 1360, and 4060 mg/m². Heparinized blood samples were obtained before treatment, at 5, 10, 15, 30, 60, 120, 240, and 360 min on the first day of treatment, and then twice daily on days 2–5 days after the drug infusion. Urine was collected in aliquots after 4, 8, and 24 h on day 1 and then daily on days 2–4. CQS plasma concentrations were also measured at limited sampling intervals (2 and 24 h after the drug infusion) at 2350, 2820, 3385, 4060, and 4870 mg/m² dose levels to estimate the AUC. Blood samples were immediately separated by centrifugation, and the plasma was stored at −70°C. Urine volumes were recorded, and aliquots were stored at −70°C.

Analytic Methods. Erythrocyte glucose-6-phosphate dehydrogenase (oxidoreductase, EC 1.1.1.49) activity was determined quantitatively by a spectrophotometric method (Sigma Diagnostics, St. Louis MO). Plasma and urinary levels of CQS were analyzed by HPLC with UV detection using the modified method of Tong *et al.* (4). Briefly, separations were performed using an Alltech Econosphere C_{18} column (5-μm particle size; 4.6 x 250 mm) protected by a guard column (Alltech C_{18} Adsorbosphere: 4.6 x 10 mm). The mobile phase was 70% HPLC grade water containing KH_2PO_4 (50 mM) and 30% acetonitrile. Triethylamine (0.02%) was added to the mobile phase, and the final pH of the mobile phase was adjusted to 6.1. The flow rate was 1 ml/min, and detection was evaluated at 254 nm. The internal standard was acetophenone (10^{-5} M) which yielded a retention time of approximately 13–15 min; CQS appeared at 11–12 min. This HPLC method has the sensitivity to detect CQS concentrations of 5 μg/ml, and the standard CQS concentrations curve from 12.5 to 200 μg/ml has an r^2 of 0.99. Pretreatment samples were monitored for interference.

Pharmacokinetic Calculations. Plasma chloroquinoxaline sulfonamide concentrations were determined by peak to area ratios of the internal standard *versus* compound. Pharmacokinetic parameters were estimated using computerized software (MKMODEL version 4.42; Biosoft, Ferguson, MO).

RESULTS

Clinical Study. Eighty-eight patients were entered into this study from April 1989 to December 1991. A total of 182 CQS treatment courses were administered; 172 courses (94.5%) were deemed adequate to assess toxicity. Inevaluable courses occurred in 6 patients who failed to complete 28 days of evaluation due to rapid disease progression (4 patients) or early death (2 patients) without drug-related toxicity. Relevant clinical characteristics of the patient population are presented in Table 1. A summary of dose levels, courses of therapy (Table 2), and incidence of principal adverse events are presented (Table 3).

Metabolic Effects. Hypoglycemia which increased in incidence and severity with dose represented the limiting toxicity of CQS. Grade 4+ hypoglycemia (serum glucose <30 mg/dl) was observed in 2 of 7 patients who received 4870 mg/m² of CQS (Table 2). Of the 14 patients who received >4000 mg/m² of CQS, symptomatic hypoglycemia developed in 4; 8 of 9 patients receiving these doses and who underwent frequent glucose monitoring were found to have a blood glucose concentration ≤40 mg/dl. In all cases, hypoglycemia developed within 4 h of the CQS infusion; several patients required an initial bolus of i.v. glucose, while others required a second bolus of glucose followed by a 24- to 48-h infusion of glucose to reestablish normoglycemia. No patient required infused glucose for >48 h.

Simultaneous serum insulin and glucose levels were measured in 3 patients who received 4060 mg/m² of CQS. An inappropriate increase in serum insulin concentration relative to the serum glucose concentration was found. The elevation in serum insulin occurred 30–60 min following the CQS infusion and remained inappropriately elevated for the serum glucose concentration from 5–38 h after CQS (Fig. 2). The insulin to glucose ratio returned to normal after 5 h in one patient, while in 2 cases the ratio remained elevated for 27–38 h. Cumulative metabolic abnormalities were not observed; one patient received 4060 mg/m² of CQS once/month for 10 months without any change in the fasting glucose concentrations or abnormality in a glucose tolerance test at the completion of treatment.

Cardiac Effects. Rapid atrial fibrillation or other supraventricular tachyarrhythmia that required antiarrhythmic treatment developed in 4 patients; each had received CQS doses >4000 mg/m². Two of the 4 patients were receiving chronic digoxin therapy for intermittent atrial fibrillation when rapid atrial fibrillation developed within 1 h following the infusion of CQS. Atrial arrhythmias occurred 3 and 4 days following the CQS infusion in 2 additional patients. Thyroid dysfunction, hypoglycemia, and myocardial infarction were eliminated as potential causes. All 4 of these patients also had abnormal echocardiograms which showed either chamber enlargement or tumor extension to the pericardium.

Table 1 *Patient characteristics*

	No.
Patients	88
Age (yr)	
Median	58
Range	22–85
Male:female	44:44
Karnofsky performance status	
80–100	41
60–70	44
50	3
Primary site of cancer	
Non-small cell lung	53
Colorectal	10
Sarcoma	5
Melanoma	4
Breast	4
Gastric	3
Head and Neck	3
Other	6
Prior therapy	
None	1
Chemotherapy	87
Radiation	37
Surgery	45

Table 2 *Dose levels and courses of CQS*

Dose (mg/m²)	No. of patients	No. of courses
18	3	6
36	3	1
60	3	4
90	3	15
120	3	7
150	4	4
180	3	10
216	3	8
260	3	3
312	3	3
375	4	16
450	3	3
540	3	4
650	3	4
780	3	3
940	3	3
1130	3	9
1360	5	5
1630	3	13
1960	3	3
2350	3	8
2820	3	5
3385	4	9
4060	7	16
4870	7	10

Table 3 *Chloroquinoxaline sulfonamide toxicity*

	Highest National Cancer Institute toxicity grade for each patient				
Toxicity	0	1	2	3	4
Anemia	29	21	30	7	1
Cardiac dysrhythmia	72	12	0	2	2
Diarrhea	76	10	2	0	0
Fever	66	17	5	0	0
Hypoglycemia	81	0	4	1	2
Leukopenia	81	5	2	0	0
Local inflammatory	81	0	7	0	0
Thrombocytopenia	73	12	1	2	0
Vomiting	74	9	5	0	0

Hematological Effects. Anemia was the most common hematological effect; 22% of patients experienced grade 2+ or greater hemoglobin depression with no clinical evidence of hemolysis. Grade 3+ thrombocytopenia developed 2 patients: in association with peritonitis in one patient receiving 312 mg/m² and with progressive pancreatic cancer complicated by disseminated intravascular coagulation in the other receiving 1360 mg/m². Grade 3+ or greater leukopenia developed in no patient during the study.

Miscellaneous Effects. Alopecia, diarrhea, and vomiting were dose related and occurred most commonly at doses ≥4000 mg/m². Phlebitis at the i.v. site was noted at doses ≥2000 mg/m²; this effect was ameliorated by progressively increasing the drug dilution. Six patients reported perioral numbness and tingling after the infusion of CQS unrelated to hypoglycemia. Two patients experienced a mild transient increase in serum creatinine. Hyperbilirubinemia developed in one patient with known periportal lymphadenopathy. A diffuse, nonpruritic, macular, erythematous rash developed in one patient after 10 monthly doses of CQS that resolved with diphenhydramine treatment. No evidence of cumulative toxicity was noted.

Antitumor Response. Seven minor antitumor regressions were observed and were not clearly dose related. The median duration of the minor responses was 7 months. Six of the 7 responses occurred in patients with non-small cell lung cancer. One patient with metastatic colon cancer also achieved a minor response at a dose of 180 mg/m² that lasted 8 months. Three other patients with non-small cell lung cancer achieved prolonged disease stabilization (11–12 months).

Pharmacokinetic Results. Detailed pharmacokinetic studies were performed in 22 patients. Two- and 24-h CQS levels were obtained in 18 additional patients receiving CQS doses of 2350–4870 mg/m² to estimate AUC. These limited sampling intervals at 2 and 24 h were representative of the AUC established by the data obtained from the patients who underwent complete pharmacokinetic evaluation with a correlation coefficient of 0.91. Derived pharmacokinetic parameters are summarized in Table 4. Samples from 3 patients could not be analyzed because of an interfering substance, naproxen, which coeluted with CQS.

CQS displayed biexponential elimination from plasma with a $t_{½}\alpha$ of 2.7 ± 0.3 h (mean ± SE; range, 0.4–4.5 h) and $t_{½}\beta$ of 52 ± 6 h (range, 25–104 h). The plasma concentration × time profiles for individual patients receiving 216, 1360, and 4060 mg/m² are shown in Fig. 3. The rate of drug clearance was slow; however, as the administered dose increased, the observed clearance progressively increased. The total body clearance increased from 53 ml/h/m² at 18 mg/m² to 264 ml/h/m² at 4060 mg/m². In contrast to observations in mice (4), saturation of the clearance mechanism(s) was not observed at the maximum tolerated dose of 4870 mg/m². In human subjects, the AUC for CQS failed to increase exponentially with the doses evaluated in this study (Fig. 4). This is contrast to the murine dose escalation

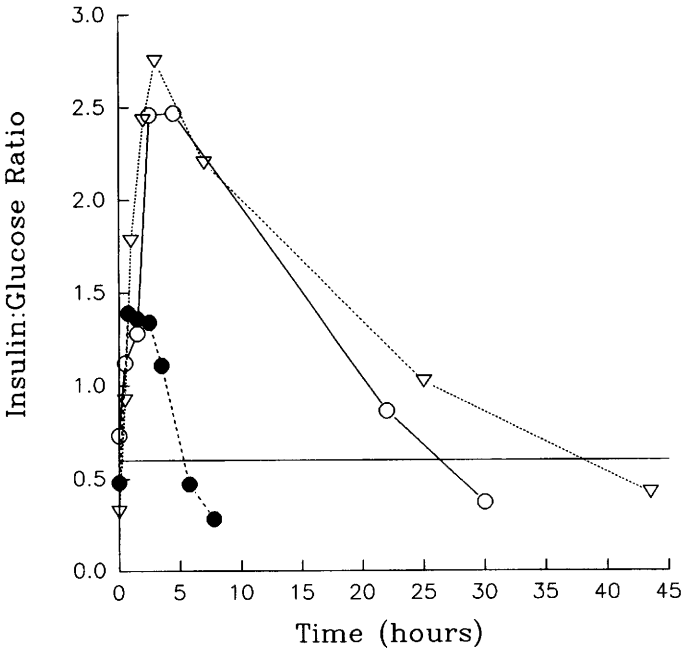

Fig. 2. Effects of chloroquinoxaline sulfonamide on the ratio of plasma insulin (μunits/ml) to plasma glucose (mg/dl) *versus* time for three patients receiving 4060 mg/m² of the drug. ——, normal upper limit for the insulin to glucose ratio of 0.6 is indicated.

Table 4 *Pharmacokinetic parameters of CQS*

Dose (mg/m²)	No. of Patients	$t_{1/2}\alpha$ (h)	$t_{1/2}\beta$ (h)	MRT[a] (h)	AUC (μg·h/ml)	Cl_{tb}[a] (ml/h/m²)	Vd_{ss} (liters/m²)
18	2	2.7	53	71	342	53	3.7
36	2	2.4	71	95	539	67	6.3
90	2	3.5	94	127	1408	50	6.4
150	3	3.0	56	75	1783	125	8.3
216	3	2.6	67	89	2349	114	8.8
1360	3	2.8	38	52	7852	196	9.6
4060	4	2.6	29	41	15962	264	10.5

[a] Cl_{tb}, total body clearance; MRT, mean residence time.

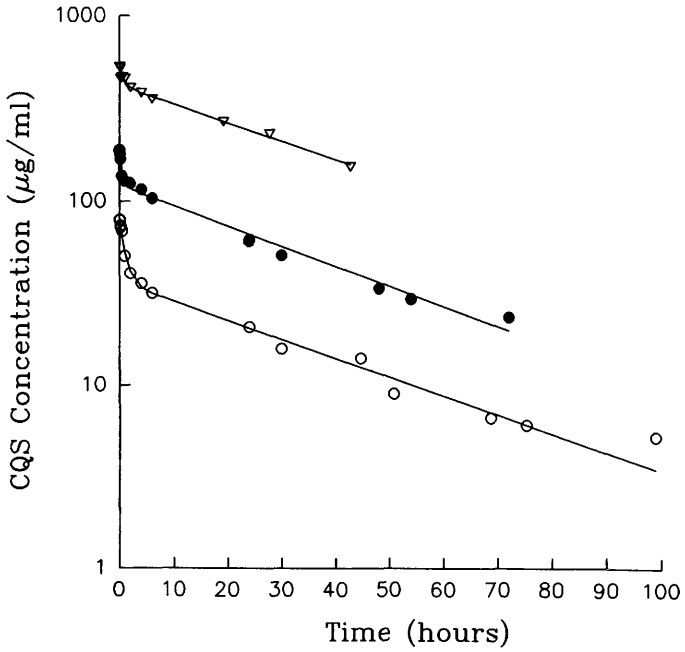

Fig. 3. Representative plasma concentration *versus* time plots of the elimination of chloroquinoxaline sulfonamide for three patients following a 1-h infusion of 216 mg/m² (○), 1360 mg/m² (●), and 4060 mg/m² (▽).

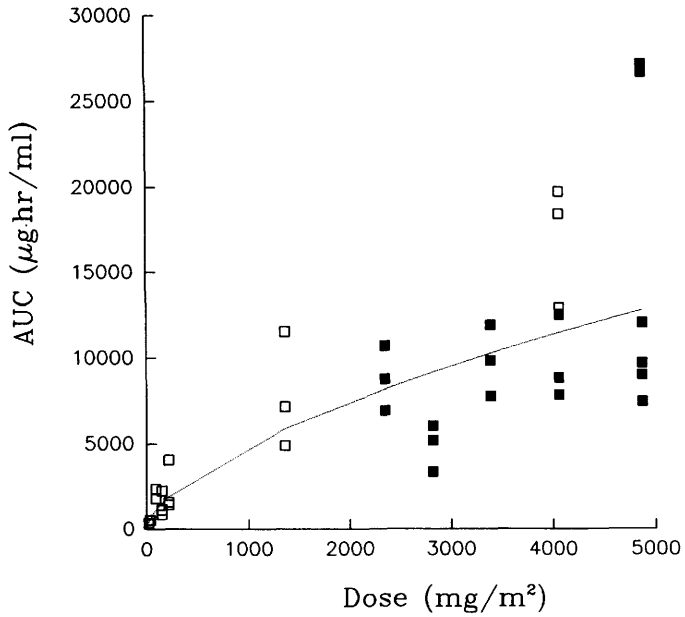

Fig. 4. Plasma chloroquinoxaline sulfonamide AUC based on the complete pharmacokinetic data (□) and 2- and 24-h limited sampling data (■) following 1 h infusion of the drug. *Dotted line*, least squares fit predicting AUC from dose for 18 (n = 2), 36 (n = 2), 90 (n = 2), 150 (n = 3), 216 (n = 3), 1360 (n = 3), 2350 (n = 3), 2820 (n = 3), 3385 (n = 3), 4060 (n = 6), and 4870 (n = 6) mg/m².

studies, in which the appearance of toxicity correlated with nonlinear elevations in the 24-h concentration and AUC of CQS. In these murine studies, no lethal toxicity was observed at 900 mg/m² (24-h concentration, 31 μg/ml; AUC, 4,393 μg · h/ml), while the dose yielding a 50% mortality was reached at 1821 mg/m² (24-h concentration, 4,882 μg/ml; AUC, 90,942 μg · h/ml). At low doses of CQS, the Vd_{ss} approximated plasma volume, while with increasing dose, the Vd_{ss} also increased; at 4060 mg/m², it approximated the extracellular space (10.5 liters/m²). The central volume of distribution ranged from 1.4–9.7 liters/m², and the Vd_{ss} for CQS was similar to that observed with most sulfonylureas (5).

Three probable metabolites of CQS were observed in plasma (Fig. 5). Assuming molar equivalency in their absorbance to CQS at 254 nm, the plasma concentration of the most prominent metabolite ranged from 8% of the parent CQS concentration at 6 h to 25% at 50 h (data not shown). At the time that hypoglycemia first appeared, the total concentrations of the proposed metabolites were <10% of the circulating drug. As the hypoglycemia resolved during the ensuing 1 h, the levels of two of the metabolites remained stable, while the third (HPLC retention time, 8 min) declined in parallel with the parent CQS concentration.

DISCUSSION

Chloroquinoxaline sulfonamide was selected for clinical investigation based on its antitumor activity in the human tumor colony-forming assay. Despite the lack of antitumor activity in the traditional antitumor drug-screening program, the human tumor colony-forming assay identified CQS as an active agent in six human cancers: breast, lung, ovarian, skin, kidney, and colon. These effects were observed using total concentrations of CQS achievable in both rodents and man.

CQS binds avidly to plasma proteins on the basis of charge and hydrophobicity. Tong *et al.* (4) observed that the extent of protein binding by CQS to human plasma greatly exceeded that of all other species. The dose-related changes observed for the rate of plasma clearance and volume of distribution for CQS are consistent with preclinical protein-binding observations that increasing doses produced an increase in free CQS, which has a larger volume of distribution and more rapid clearance than protein-associated drug. Preclinically, a projection of a target plasma concentration of CQS had been made on the basis of multiday exposure of human tumor cells to CQS in the human tumor colony-forming assay (10 μg/ml). Colony inhibitory effects were regularly observed, without correcting for differences in protein binding, at CQS media concentrations of 10 μg/ml. In this study, total CQS concentrations in plasma exceeded 10 μg/ml at 24 h at all dose levels >90 mg/m² of CQS. However, the target concentration to be derived from the human tumor colony-forming assay should also be corrected for protein binding. The assays are commonly carried out in medium containing 10% fetal calf serum; Tong *et al.* noted that 12.5% fetal calf serum was capable of binding only 77% of CQS at 10 μg/ml,

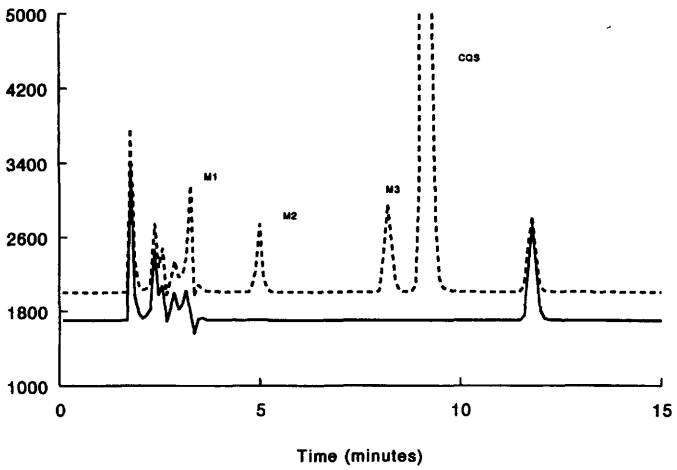

Fig. 5. Representative chromatogram from an HPLC separation prior to (——) and 2 h following (- - - - -) an infusion of 2820 mg/m² of CQS. The plot demonstrates the parent compound (CQS); retention time 9 min and the three metabolites; retention times 3 (M1), 5 (M2), and 8 (M3) min.

leaving a free drug concentration in the stem cell colony-forming assays of at least 2.3 μg/ml. In contrast, only 0.05 μg/ml of CQS was free at a concentration of 50 μg/ml in human plasma, while, at a total CQS concentration of 300 μg/ml, 6 μg/ml was free drug. Accordingly, a human plasma total CQS equivalent of the inhibitory concentration in the human tumor colony-forming assay would be at least 100 μg/ml during a minimum of 24 h. This total CQS concentration at 24 h was achieved in this trial at doses ≥2350 mg/m^2.

The dose-limiting effect of CQS was hypoglycemia. This effect appeared to be related to the peak plasma drug concentration, consistent with preclinical observations that the toxicity of CQS was schedule and dose dependent. Clinically significant hypoglycemia developed in 5 of 7 patients who received 4870 mg/m^2. Two of these patients experienced severe hypoglycemia that required multiple infusions of concentrated glucose solutions. At doses ≤4060 mg/m^2, hypoglycemia was less common, more mild in severity, and readily reversible.

CQS is structurally similar to the oral sulfonylureas and to the sulfanilamide antibiotics (from which it was synthesized). Sulfonylureas are known to elicit pancreatic insulin release that results in hypoglycemia. The onset of action, duration of effect, degree of protein binding, and volume of distribution of CQS are similar to those observed with the oral hypoglycemic agents (5). Extracellular glucose concentrations regulate the release of insulin from the pancreatic β-cells through an effect on the K_{ATP} channels (6). Sulfonylureas have been found to bind to a specific receptor close to these channels whereby diminished flow of potassium ions through these channels causes β-cell depolarization, calcium influx, and insulin exocytosis. Recently, the β-cell sulfonylurea receptor has been partially purified by photoaffinity labeling using an analog of glyburide (7). CQS may act similarly on these receptor leading to insulin secretion. The prolonged half-life of the drug ($t_{½}\beta$, 29–94 h) and the observed duration of hypoglycemia beyond the typical 2–4 h associated with bolus insulin injections are analogous to the properties of other sulfonylureas (8). Although CQS-induced hyperinsulinemia might be evoked by a direct cytotoxic effect on the β-cell, the absence of progressive fasting hyperglycemia in any patient argues against this mechanism.

Recent evidence suggests that K_{ATP} channels are present in other tissues, including heart, skeletal muscle, and brain. Sulfonylurea receptors have also been identified in the heart; however, their affinity and effect on the K_{ATP} channels is 50-fold less than observed with pancreatic β-cells (9, 10). Conceivably, CQS might have a higher affinity for these receptors, and consequent inhibitory effects of CQS on these channels in cardiac tissue could explain the atrial arrhythmias observed in this study. All 4 cases of potentially drug-related supraventricular tachyarrhythmias in this trial occurred in advanced cancer patients with preexisting cardiac abnormalities.

CQS is the first sulfonamide to be used as an anticancer agent. In the human tumor colony-forming assay studies, CQS displayed a unique pattern of activity unlike other anticancer agents identified in screening systems primarily using animal tumors. These data may indicate a novel mechanism of action for this drug. CQS apparently does not affect DNA intercalation or induce alterations in folate homeostasis (11). However, cell cycle arrest in G_0/G_1 has been found in B16 melanoma cells and in mitogen-stimulated human peripheral blood mononuclear cells (12).

In this study, CQS showed anticancer activity in two common solid human tumors, non-small cell lung cancer and adenocarcinoma of the colon. The drug was generally well tolerated, did not cause myelosuppression, and lacked cumulative toxicity. These attributes suggest that further clinical evaluation of CQS is desirable. The pharmacokinetic results ($t_{½}\beta$, 52 ± 6 h), combined with the dose-limiting toxicity of hypoglycemia, suggest that substantially higher cumulative doses could be administered using a weekly dose schedule. Studies using a weekly schedule are now in progress.

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