Quinine-Associated Thrombotic Thrombocytopenic Purpura–Hemolytic Uremic Syndrome: Frequency, Clinical Features, and Long-Term Outcomes

Kiarash Kojouri, MD, MPH; Sara K. Vesely, PhD; and James N. George, MD

Background: **Quinine-associated thrombotic thrombocytopenic purpura–hemolytic uremic syndrome (TTP–HUS) is thought to be uncommon and to have a good prognosis.**

Objective: **To describe the frequency, clinical features, and long-term outcomes of quinine-associated TTP–HUS.**

Design: **Case series.**

Setting: **Hospitals in central-western Oklahoma.**

Patients: **225 consecutive patients with TTP–HUS, 1989–2000.**

Measurements: **Presenting features and clinical outcomes.**

Results: **Thrombotic thrombocytopenic purpura–hemolytic uremic syndrome was associated with quinine in 17 patients. Four patients died, and 7 survivors currently have chronic renal failure. Since 1 July 1995, 132 patients with clinically suspected TTP–HUS were explicitly asked about drug exposure. Fourteen (11%) had taken quinine, and 7 had taken other drugs associated with TTP–HUS. Neurologic abnormalities were as severe in patients with quinine-associated TTP–HUS as in the 118 patients who had not taken quinine.**

Conclusions: **Quinine is a common cause of drug-associated TTP–HUS and can cause death and chronic renal failure. When the disorder is described as TTP–HUS rather than only as HUS, the severity of neurologic abnormalities and the occasional absence of renal failure are emphasized. If recurrent disease is to be prevented, clinicians must recognize quinine as a possible cause.**

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For author affiliations, current addresses, and contributions, see end of text.

In 1994, Gottschall and coworkers published a report of 9 patients with thrombocytopenia, microangiopathic hemolytic anemia, and acute renal failure after ingestion of quinine (1, 2). That report, along with previous reports involving 8 patients, established quinine-associated thrombotic thrombocytopenic purpura–hemolytic uremic syndrome (TTP–HUS) as a new clinical entity. Five additional patients with quinine-associated TTP–HUS have subsequently been described (3). Of these 22 patients, 1 died and 2 developed chronic renal failure. These findings suggested that quinine-associated TTP–HUS was rare and that the prognosis for complete recovery was good.

We have found that quinine is a common cause of TTP–HUS and that death and chronic renal failure are frequent. The frequency of quinine-associated TTP–HUS may be related to continued use of quinine for nocturnal leg cramps despite a 1994 ban by the U.S. Food and Drug Administration on over-the-counter marketing (4). The purpose of our report is to describe the frequency, clinical features, and long-term outcomes of quinine-associated TTP–HUS.

Methods

Patients

All patients with clinically suspected TTP–HUS who are referred to the Oklahoma Blood Institute for plasma exchange treatment are included in the Oklahoma TTP–HUS Registry. This allows identification of all patients in our region with clinically suspected TTP–HUS. The Oklahoma Blood Institute is the sole provider of plasma exchange in our region, and it is standard practice to treat all adult patients who have TTP or HUS with plasma exchange.

The registry has complete clinical and laboratory data on 225 consecutive patients who experienced an initial episode of clinically suspected TTP–HUS between 1 January 1989 and 31 December 2000. We excluded patients who developed TTP–HUS after bone marrow transplantation ($n = 19$) and therapy with mitomycin C ($n = 9$) because their disease course was determined by their primary malignant disease (27 of 28 died). Since 1 January 1995, the third author has been involved in the care of 132 of 142 patients from the registry (93%). Follow-up is complete for 111 of 112 surviving patients (99%). The institutional review

boards of the University of Oklahoma and community hospitals have approved the registry.

Thrombotic thrombocytopenic purpura–hemolytic uremic syndrome was diagnosed by the presence of thrombocytopenia and microangiopathic hemolytic anemia without another apparent cause (5, 6). The syndrome was designated as quinine-associated if the patient ingested quinine regularly, either daily or at least several times each week, at the time of onset and if the syndrome did not recur in the absence of quinine ingestion.

Statistical Analysis

We used the nonparametric Wilcoxon rank-sum test (interval–ratio data) and the chi-square test or the Fisher exact test (categorical data) to compare patients who consumed quinine and those who did not. Patients with quinine-associated TTP–HUS were divided into two groups according to the presence or absence of chronic renal failure and were compared by using the Wilcoxon rank-sum test. We used SAS software, version 6.12 (SAS Institute, Inc., Cary, North Carolina), for all analyses.

Results

Relation of Quinine Ingestion to Onset of Symptoms

Seventeen patients had quinine-associated TTP–HUS (**Table 1**). All patients had used quinine tablets for nocturnal leg cramps for many years. In each patient, TTP–HUS was apparently provoked by a single tablet. Six patients reported taking quinine tablets regularly. In 11 patients, the mean time since taking the previous quinine tablet was 5 months (range, 2 weeks to 2 years). Four of 17 patients had had abdominal symptoms, headache, or fever and chills after previous quinine ingestions, often multiple times, which suggests quinine hypersensitivity. In patients 2 and 5, quinine was confirmed as the cause of TTP–HUS because the syndrome recurred immediately after ingestion of quinine 3 to 6 months after the initial episodes (**Table 1**).

Presenting Clinical and Laboratory Features

Abdominal pain, nausea, vomiting, and diarrhea were the most common presenting symptoms. Symptoms often began suddenly, within several hours of ingesting quinine. Most patients reported chills and fever; sepsis was a common initial diagnosis (7). Although no patient had a history of renal disease, 16 patients were oliguric or anuric during their initial episode. Patient 2, who had acute renal failure during her first episode, had no renal failure during her two subsequent episodes. Six patients were leukopenic, and 2 patients had hypofibrinogenemia. Eight patients had abnormal results on liver function tests; of these, 2 received an initial diagnosis of hepatitis. These abnormalities have previously been associated with quinine (8–10). Five of 14 patients tested positive for quinine-dependent antiplatelet antibodies (2).

Clinical Course and Treatment

Fourteen of 16 patients required hemodialysis. (Patient 17 died before beginning treatment.) Two patients required permanent dialysis, while the remaining 12 required a median of 6 hemodialysis sessions (range, 2 to 31 sessions). Eleven of these 12 patients survived, and their urine output normalized in a median of 13 days (range, 6 to 25 days). In 6 patients, the serum creatinine concentration normalized in a median of 38 days (range, 19 to 380 days).

Four patients died: Three died during the initial episode, and 1 died of heart failure while receiving continual hemodialysis 5 years after her second episode. Eight of 14 patients who survived the initial episode (57%) developed chronic renal failure; they were older than the other 6 patients (68 years vs. 55 years; $P = 0.04$). Five of the 8 patients with chronic renal failure had a history of hypertension or diabetes, compared with 1 of the 6 patients without renal failure ($P = 0.14$).

Comparison of Patients with Quinine-Induced TTP–HUS and Other Patients in Whom TTP–HUS Was Clinically Suspected

Beginning on 1 July 1995, all patients presenting with first episodes of clinically suspected TTP–HUS ($n = 132$), as well as their families, were explicitly asked about quinine tablets and quinine-containing remedies and beverages (11). Fourteen patients (11%) had taken quinine tablets, and 118 had not. Seven had taken other drugs reported to cause TTP–HUS (12): cyclosporine ($n = 3$), ticlopidine ($n = 2$), gemcitabine ($n = 1$), and pentostatin ($n = 1$). Patients with quinine-associated TTP–HUS were all women and were older than patients who had not taken quinine (**Table 2**). Neurologic abnormalities, thrombocytopenia and anemia, death,

Table 1. **Clinical Features and Outcomes of 17 Women with Quinine-Associated TTP–HUS***

Patient	Age	Ethnicity	Date	Presenting Symptoms	Fever, Chills	Initial Oliguria or Anuria	Neurologic Abnormalities	Presenting Laboratory Data†					Creatinine Clearance at 1 Year‡	Death
								Platelet Count	Hematocrit	LDH Level§	Leukocyte Count	Creatinine Concentration		
	y							*×10⁹ cells/L*		*μkat/L (U/L)*	*×10⁹ cells/L*	*μmol/L (mg/dL)*	*mL/s (mL/min)*	
1	58	W	1994	Abdominal pain, diarrhea	Yes	Yes	Confusion, dysarthria	14	0.21	70 (4175)	9.2	804 (9.1)	1.37 (82)	No
2	47	W	1995	Vomiting, diarrhea	Yes	Yes	Confusion, dysarthria	24	0.23	16 (964)	2.6	575 (6.5)	–	No
			1995	Vomiting, diarrhea	Yes	No	None	58	0.23	17 (1015)	1.5	88 (1.0)	–	No
			1995	Vomiting, diarrhea	Yes	No	None	87	0.24	6 (352)	0.7	88 (1.0)	1.42 (85)	No
3	81	W	1995	Abdominal pain, vomiting	Yes	Yes	None	18	0.22	23 (1348)	2	548 (6.2)	0.52 (31)	No
4	79	W	1995	Syncope, vomiting	Yes	Yes	Confusion, combativeness	17	0.21	30 (1775)	2.2	672 (7.6)	0.35 (21)	No
5	64	W	1995	Abdominal pain, vomiting, diarrhea	Yes	Yes	None	17	0.22	73 (4358)	1.5	619 (7.0)	–	No
			1996	Vomiting, diarrhea	Yes	Yes	None	33	0.22	15 (908)	0.1	681 (7.7)	–	Yes
6	55	W	1996	Vomiting, bloody diarrhea	Yes	Yes	Headache, stiff neck	41	0.23	23 (1398)	0.6	530 (6.0)	1.00 (60)	No
7	63	W	1996	Abdominal pain, vomiting	Yes	Yes	Lethargy, confusion	54	0.23	53 (3193)	17.9	813 (9.2)	0.23 (14)	No
8	49	W	1997	Vomiting, diarrhea	No	Yes	Headache	11	0.21	98 (5878)	14.7	946 (10.7)	0.87 (52)	No
9	59	W	1997	Vomiting, diarrhea	No	Yes	Confusion, aphasia	47	0.21	60 (3577)	30.1	831 (9.4)	0.50 (30)	No
10	70	W	1997	Abdominal pain, vomiting	No	Yes	Lethargy, confusion	56	0.35	55 (3314)	13.3	230 (2.6)	–	Yes
11	67	W	1997	Chest and abdominal pain, vomiting, diarrhea	Yes	Yes	Recent memory loss	6	0.21	27 (1628)	3.3	530 (6.0)	0.60 (36)	No
12	79	NA	1999	Chest pain, cough, hemoptysis	No	No	Confusion, disorientation	50	0.23	25 (1493)	7.9	80 (0.9)	0.82 (49)	No
13	64	W	1999	Abdominal pain, vomiting, diarrhea	No	Yes	Seizures, coma	61	0.25	36 (2143)	31	769 (8.7)	–	Yes
14	56	W	1999	Abdominal pain, vomiting, diarrhea	No	Yes	None	41	0.27	16 (949)	28.9	734 (8.3)	–	No
15	42	W	2000	Vomiting, bloody diarrhea	Yes	Yes	None	10	0.19	88 (5290)	14.5	1344 (15.2)	1.22 (73)	No
16	77	W	2000	Abdominal pain, vomiting, hypotension	No	Yes	None	26	0.22	29 (1739)	9.2	857 (9.7)	0.25 (15)	No
17	61	W	2000	Abdominal pain	No	Yes	Lethargy	13	0.28	49 (2946)	14.9	557 (6.3)	–	Yes

* LDH = lactate dehydrogenase; NA = Native American; TTP–HUS = thrombotic thrombocytopenic purpura–hemolytic uremic syndrome; W = white.
† Laboratory values are the most abnormal values on the day of the first plasma exchange ± 7 days. These values were used to avoid transient effects of transfusions and to capture worsening anemia and renal failure, which often progressed after plasma exchange began.
‡ Based on the serum creatinine concentration obtained closest to 1 year after initial presentation (mean interval, 355 days). No creatinine clearance values are presented for the initial episodes of patients 2 and 5 (who had relapse within 1 year), patients 5 and 14 (who required permanent dialysis), and patients 10, 13, and 17 (who died during their initial episode).
§ Values are normalized for an upper limit of normal of 3.5 μkat/L (200 U/L).

and rate of relapse did not differ significantly between the two groups. Renal failure was more severe and elevated levels of serum lactate dehydrogenase were higher in patients with quinine-associated TTP–HUS.

Discussion

In our case series, quinine hypersensitivity was a common cause of TTP–HUS and the most common cause of drug-associated TTP–HUS. The older age of patients with quinine-associated TTP–HUS was consistent with the more common occurrence of leg cramps in older persons (13). However, it is not known why all of our patients were women, since leg cramps, and therefore presumed quinine use, are equally common in men (13). Of note, 17 of the 22 previously reported patients (77%) were women (2, 3).

In our patients, quinine-associated TTP–HUS was a serious illness. Three of 17 patients (18%) died during

Table 2. **Comparison of Patients with Quinine-Associated TTP–HUS and Patients with TTP–HUS Not Associated with Quinine***

Variable	Patients with Quinine-Associated TTP–HUS (n = 14)	Patients with Non–Quinine-Associated TTP–HUS (n = 118)	*P* Value
Characteristic			
Age (range), *y*	64 (42–79)	50 (9–91)	0.029
Female sex, %	100	64	0.004
White ethnicity, %	93	69	0.112
Clinical features, %†			
Mental status changes	57	61	>0.2
Coma	7	17	>0.2
Oliguria or anuria	93	41	0.002
Laboratory data‡			
Platelet count (range), $\times 10^9$ *cells/L*	34 (6–61)	17 (1–129)	0.088
Hematocrit (range)	0.23 (0.19–0.35)	0.22 (0.12–0.38)	>0.2
Lactose dehydrogenase level (range)			<0.001
U/L	2545 (949–5878)	1280 (138–12 587)	
μkat/L	42 (16–98)	21 (2–210)	
Creatinine concentration (range)			<0.001
mg/dL	8.0 (0.9–15.2)	3.1 (0.6–31.4)	
μmol/L	707 (80–1344)	274 (53–2776)	
Treatment			
Plasma exchange (range), *n*§	12 (6–24)	13 (0–74)	>0.2
Hemodialysis, %	85	38	0.001
Outcomes, %‖			
Death	21	41	0.162
Relapse	0	16	>0.2
Chronic renal failure	57	16	0.013

* Median values and ranges are reported for continuous data because these data were not normally distributed. TTP–HUS = thrombotic thrombocytopenic purpura–hemolytic uremic syndrome.
† Clinical features are described for the day of the first plasma exchange.
‡ Laboratory values are the most abnormal values on the day of the first plasma exchange ± 7 days. These values were used to avoid transient effects of transfusions and to capture worsening anemia and renal failure, which often progressed after plasma exchange began.
§ The median number required to achieve a hematologic and neurologic remission in surviving patients.
‖ Death = death occurring within 30 days of the last plasma exchange; relapse = recurrent TTP–HUS occurring more than 30 days after the last plasma exchange, excluding relapses caused by repeated quinine ingestion; chronic renal failure = an estimated creatinine clearance of less than 0.67 mL/s (40 mL/min) at 1 year after initial presentation, or a need for continuing dialysis.

the initial hospitalization, and 8 of 14 patients who survived the initial episode developed chronic renal failure. One patient died of complications of chronic renal failure 5 years after a second episode. Even in the 6 patients whose serum creatinine concentrations returned to normal, complete recovery was initially uncertain because the high initial serum creatinine concentrations (mean, 716 μmol/L [8.1 mg/dL]) (**Table 1**) and brief duration of symptoms (8 hours to 4 days) suggested preexisting renal disease. However, serum creatinine concentrations can increase very rapidly in patients with TTP–HUS (14), probably because of severe tissue ischemia indicated by the extreme elevation of serum lactate dehydrogenase levels (15). The mean initial value of lactate dehydrogenase in these 6 patients was 53 μkat/L [3200 U/L]).

Quinine-associated TTP–HUS is probably caused by drug-dependent antibodies, since it can be triggered by a single quinine tablet taken many months after a previous exposure or even by quinine-containing beverages, such as tonic water (1, 16). This is distinct from TTP–HUS caused by mitomycin C and cyclosporine, which is dose-dependent (12). The broad spectrum of clinical abnormalities suggests a broad spectrum of quinine-dependent antibody specificity. Previous case reports have documented quinine-dependent antibodies to platelets, granulocytes, lymphocytes, and endothelial cells (1, 2, 8). Measurements of von Willebrand factor–cleaving protease activity have not been reported in patients with quinine-associated TTP–HUS.

A designation of TTP–HUS is supported by the severity of neurologic complications, thrombocytopenia, hemolysis, and the occasional absence of renal failure. Since all previously reported patients were described as

having HUS, not TTP, quinine was omitted from some discussions of drug-associated TTP (17, 18). Therefore, clinicians could fail to consider quinine as a possible cause if a patient with severe neurologic abnormalities, thrombocytopenia, and hemolysis is thought to have TTP rather than HUS.

Our data are limited by our case definition, which is based on referral for plasma exchange treatment and excludes patients in whom quinine hypersensitivity is manifested principally by abnormalities that are uncommon in TTP–HUS (7–10). However, our case definition also allowed prospective, consecutive identification of all patients in our region with clinically suspected TTP–HUS.

In summary, recognition of quinine hypersensitivity is critical to prevent recurrences of TTP–HUS. Although the U.S. Food and Drug Administration has banned over-the-counter marketing of quinine (4), it remains readily available in beverages and from nutrition stores, pharmacies, and Internet sites. In addition, patients may not report it among their medications, creating a potentially dangerous diagnostic problem (11).

From University of Oklahoma Health Sciences Center, Oklahoma City, Oklahoma.

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Requests for Single Reprints: James N. George, MD, Hematology–Oncology Section, Department of Medicine, University of Oklahoma Health Sciences Center, Box 26901, Oklahoma City, OK 73190; e-mail, Jim-George@OUHSC.edu.

Current Author Addresses: Drs. Kojouri, Vesely, and George: Hematology–Oncology Section, Department of Medicine, University of Oklahoma Health Sciences Center, Box 26901, Oklahoma City, OK 73190.

Author Contributions: Conception and design: K. Kojouri, S.K. Vesely, J.N. George.
Analysis and interpretation of the data: K. Kojouri, S.K. Vesely, J.N. George.
Drafting of the article: K. Kojouri, S.K. Vesely, J.N. George.
Critical revision of the article for important intellectual content: K. Kojouri, S.K. Vesely, J.N. George.
Final approval of the article: K. Kojouri, S.K. Vesely, J.N. George.
Statistical expertise: K. Kojouri, S.K. Vesely, J.N. George.
Collection and assembly of data: K. Kojouri, S.K. Vesely, J.N. George.

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