Drug-induced thrombotic microangiopathy: Experience of the Oklahoma Registry and the BloodCenter of Wisconsin

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Many drugs have been reported to cause thrombotic microangiopathy (TMA), often described as thrombotic thrombocytopenic purpura (TTP) or hemolytic-uremic syndrome (HUS). We recently established criteria to evaluate the evidence for a causal association of a drug with TMA and then we systematically reviewed all published reports of drug-induced TMA (DITMA) to determine the level of evidence supporting a causal association of the suspected drug with TMA. On the basis of this experience, we used these evaluation criteria to assess the Oklahoma TTP-HUS Registry patients who had been previously categorized as drug-induced, 1989–2014. We also reviewed the experience of the BloodCenter of Wisconsin with testing for drug-dependent antibodies reactive with platelets and neutrophils in patients with suspected immune-mediated DITMA, 1988–2014. Among 58 patients in the Oklahoma Registry previously categorized as drug-induced (15 suspected drugs), 21 patients (three drugs: gemcitabine, pentostatin, quinine) had evidence supporting a definite association with TMA; 19 (90%) of the 21 patients had quinine-induced TMA. The BloodCenter of Wisconsin tested 40 patients with suspected DITMA (eight drugs); drug-dependent antibodies, supporting a definite association with TMA, were identified in 30 patients (three drugs: oxaliplatin, quinine, vancomycin); 28 (93%) of the 30 patients had quinine-induced TMA. Combining the data from these two sources, 51 patients (five drugs) have been identified with evidence supporting a definite association with TMA. DITMA was attributed to quinine in 47 (92%) of these 51 patients.


Introduction

Adverse drug reactions are a potential cause of thrombotic microangiopathy (TMA), characterized clinically by microangiopathic hemolytic anemia and thrombocytopenia [1]. In some patients with drug-induced TMA (DITMA), kidney injury is severe and patients are often described as having hemolytic-uremic syndrome (HUS). Other patients with minimal kidney function abnormalities are often described as having thrombotic thrombocytopenic purpura (TPP). In this report, we use the term “DITMA” to describe all patients, including patients previously described as drug-induced HUS or TTP.

Similar to other adverse drug reactions, drugs can cause TMA by multiple mechanisms [2]. In some patients, DITMA results from an acute, immune-mediated reaction, presenting with the sudden onset of severe systemic symptoms, often associated with anuric acute kidney injury. DITMA can also result from dose-dependent reactions which may be acute, caused by a toxic dose of an approved or illegal drug, or chronic, occurring after weeks or months of drug administration. Dose-dependent, toxicity-mediated TMA is also often associated with kidney injury.

Using criteria we previously developed to assess published reports of DITMA [3], we reassessed the patients previously categorized as drug-induced in the Oklahoma TTP-HUS Registry. As an additional resource to identify drugs that can cause TMA, we also report the experience of the BloodCenter of Wisconsin with testing for drug-dependent antibodies in patients with suspected immune-mediated DITMA. These data provide reproducible clinical and laboratory methods for evaluating the causal association of a suspected drug with TMA. These methods can provide support for clinicians in their evaluation of patients with suspected drug-induced TMA.

Methods

Oklahoma TTP-HUS. The Registry, established in 1989, is a population-based inception cohort of all consecutive patients within a defined region of the State of Oklahoma identified by a request Registry to the Oklahoma Blood Institute (OBI) for plasma exchange treatment for a patient with suspected TTP, HUS, or TMA [4]. There are no exclusion criteria; all identified patients have been enrolled. For this study we included all patients enrolled through 2014 with their first episode of clinically suspected acquired TTP (474 patients) and also all patients in whom TMA was first identified by a kidney biopsy (12 patients). Not included in this study were the 13 patients who were enrolled

Conflict of interest: The authors have no conflict with this topic or these data.

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at the time of a recurrent episode of TTP. These patients are not in our cohort of consecutive patients; none were suspected to have a drug-induced etiology; all had acquired TTP with severe ADAMTS13 deficiency. One patient with hereditary TTP was also excluded. The Registry is approved by the Institutional Review Boards of the University of Oklahoma Health Sciences Center and all participating community hospitals.

Since November 1995, serum samples have been routinely collected immediately before the first plasma exchange. ADAMTS13 activity was measured by Drs. Johanna Kremer Hovinga and Bernhard Lamml (University of Bern, Switzerland) (normal range, 50–100%). Tests for drug-dependent antibodies reactive with platelets and neutrophils were performed by the BloodCenter of Wisconsin [5]. For Oklahoma Registry patients, tests for drug-dependent antibodies were performed on serum from patients with suspected dose-dependent toxic reactions as well as suspected immune-mediated reactions, since the distinction between these two categories of adverse drug reactions may not always be clear. Testing for drug-dependent antibodies in patients with TMA attributed to dose-dependent toxic reactions was done for completeness in this research study. For routine clinical practice, testing for drug-dependent antibodies may only be appropriate for patients with suspected immune-mediated, drug-induced TMA. For some patients, tests were also performed with drugs they had taken in addition to the primary suspected drug, since the history of drug exposures was not always clear. For some drugs, tests were also performed using a metabolite of the drug, when previous experience with drug-induced thrombocytopenia had documented that drug-dependent antibodies may react with the metabolite rather than the native drug [6].

Criteria for evaluation of Oklahoma registry patients. Patients enrolled in the Registry are assigned to one of six clinical categories based on assessments at the time of their initial episode [4]. Our initial criteria assigned patients to the drug-induced category if they "were currently taking a drug previously reported to be associated with TTP-HUS" [4]. Subsequently, we also assigned patients to the drug-induced category if the acute onset of TMA was temporally associated with a drug exposure and no alternative etiology of TMA was apparent. For this study, all patients previously categorized as drug-induced were reviewed independently by two of the authors (JAR, JNG) to determine the level of evidence supporting a causal association with TMA, using the criteria we developed to evaluate published case reports (Table I) [3]. As described for our previous evaluation of published reports, different criteria were developed for DITMA resulting from either an immune-mediated reaction or a dose-dependent toxic reaction. Classification of patients as having either an immune-mediated or a dose-dependent mechanism of toxicity has been previously described [3].

BloodCenter of Wisconsin experience. The laboratories of the BloodCenter of Wisconsin are an international resource for identification and characterization of drug-dependent antibodies reactive with blood cells [5]. Data in this report are the results of testing for drug-dependent antibodies reactive with platelets and/or neutrophils in samples submitted from patients with suspected immune-mediated, drug-induced TTP, HUS, or TMA, 1988-2014. Samples from patients in the Oklahoma Registry are not included in these data.

### Results

**Reassessment of Oklahoma registry patients**

In 474 (97%) of the 487 Oklahoma Registry patients included in this study, TMA was initially suspected from the clinical features of microangiopathic hemolytic anemia and thrombocytopenia; the etiology of TMA was attributed to a drug in 52 (11%) of these patients. In the other 12 patients included in this study, TMA was initially diagnosed by kidney biopsy; the etiology of TMA was attributed to a drug in six (50%) of these patients. Patients in whom TMA was diagnosed by kidney biopsy often did not have the clinical features of TMA. Only one of the six patients categorized as drug-induced was thrombocytopenic (her platelet count was 128,000 µL⁻¹); only three had fragmented red blood cells reported on their peripheral blood smear.

Table II presents the results of reassessing the status of the 58 patients in the Oklahoma Registry who had previously been assigned to the drug-induced category, 1989–2014. These patients include one previously reported patient with TMA attributed to pentostatin [7] and 17 previously reported patients with TMA attributed to quinine [8]. Among the six patients in whom TMA was diagnosed by kidney biopsy, TMA was attributed to tacrolimus in four patients and to cyclosporine and gemicitabine in the other two patients. Using the evaluation criteria developed for our previous assessment of published reports, 21 patients (37%) had evidence supporting a definite association of the suspected drug with their episode of TMA. In 19 (90%) of these 21 patients, the etiology was attributed to quinine; 12 of the 19 patients with quinine-induced TMA has been reported previously [8]; the other seven patients with evidence supporting a definite association were diagnosed following this report. In the other two patients with evidence supporting a definite association, TMA was attributed to pentostatin (the previously reported patient [7]) and gemicitabine. Two additional patients had evidence supporting a probable association of the suspected drug with their episode of TMA (one attributed to quinine, the other to trimethoprim-sulfamethoxazole).

Among the 19 patients with evidence supporting a definite association with quinine, quinine-dependent antibodies to platelets and/or neutrophils were documented in 18 patients. One patient who had
with samples from 40 patients with suspected immune-mediated
bodies; the test were negative.

association and four patients had evidence supporting a possible association.
classes of drugs.
antibodies that was performed following the original publication [8].

have been previously published [7,8]. Reassessment of previously published patients with TMA attributed to quinine included testing for quinine-dependent antibodies that was performed following the original publication [8].

a Twelve of the 17 previously reported patients [8] had evidence supporting a definite association with TMA; one patient had evidence supporting a probable association and four patients had evidence supporting a possible association.
b This patient had also taken levaquin and therefore her serum was also tested for levaquin-dependent, platelet-reactive antibodies; the test was negative.
c This patient was also tested for quinine-dependent, platelet-reactive antibodies, since quinine may be used to dilute cocaine; the test was negative.
d This patient was also tested for quinine-dependent, platelet-reactive antibodies, since quinine may be used to dilute cocaine; the test was negative.

MDMA (3,4-methylenedioxy-N-methylamphetamine), commonly known as Ecstasy, is an empathogenic drug of the phenethylamine and amphetamine classes of drugs.

multiple episodes of systemic symptoms (abdominal pain, nausea, vomiting) with previous quinine exposures died before a serum sample for testing for drug-dependent antibodies was obtained. Eight of the 18 patients with documented quinine-dependent antibodies also had a history of systemic symptoms with previous quinine exposures. ADAMTS13 activity was measured on 16 of the 19 patients; none had severely deficient ADAMTS13 activity (mean, 65%; range, 25–100%).

The ADAMTS13 activity of the patient with evidence supporting a definite association of TMA with gemicitabine was 41%. Her test for gemicitabine-dependent, platelet-reactive antibodies was negative; this result was anticipated as her clinical course was consistent with a dose-dependent toxic mechanism. The ADAMTS13 activity of the patient with evidence supporting a definite association of TMA with pentostatin was 50%. She was not tested for pentostatin-dependent, platelet-reactive antibodies. Twenty-two of the 37 patients who did not have definite evidence supporting a causal association with the suspected drug, including 10 patients in whom the mechanism was postulated to be immune-mediated, had drug-dependent antibody tests; all were negative. Twenty-four of these 37 patients had ADAMTS13 activity measured; none were severely deficient (mean, 63%; range, 25–100%).

Among the 21 patients with evidence supporting a definite association of TMA with the suspected drug, 20 (95%) were women; all were white.

BloodCenter of Wisconsin experience with testing for drug-dependent antibodies in patients with suspected drug-induced TMA

Table III presents the experience of the BloodCenter of Wisconsin with samples from 40 patients with suspected immune-mediated DITMA submitted for identification of drug-dependent antibodies

<table>
<thead>
<tr>
<th>Drug</th>
<th>Total number of patients</th>
<th>Categories determined by re-assessment (number of patients)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Definite</td>
</tr>
<tr>
<td><strong>Immune-mediated TMA</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Quinine</td>
<td>25</td>
<td>19</td>
</tr>
<tr>
<td>Ticlopidine</td>
<td>2</td>
<td>–</td>
</tr>
<tr>
<td>Clopidogrel</td>
<td>1</td>
<td>–</td>
</tr>
<tr>
<td>Trimethoprim-sulfamethoxazole</td>
<td>1</td>
<td>–</td>
</tr>
<tr>
<td>Alendronate</td>
<td>1</td>
<td>–</td>
</tr>
<tr>
<td><strong>Dose-dependent toxicity-mediated TMA</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mitomycin</td>
<td>11</td>
<td>–</td>
</tr>
<tr>
<td>Cyclosporine</td>
<td>4</td>
<td>–</td>
</tr>
<tr>
<td>Tacrolimus</td>
<td>4</td>
<td>–</td>
</tr>
<tr>
<td>Gemicitabine</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>Carmustine</td>
<td>1</td>
<td>–</td>
</tr>
<tr>
<td>Cocaine</td>
<td>1</td>
<td>–</td>
</tr>
<tr>
<td>Cytarabine</td>
<td>1</td>
<td>–</td>
</tr>
<tr>
<td><em>Ecstasy</em></td>
<td>1</td>
<td>–</td>
</tr>
<tr>
<td>Pentostatin</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Taxotere</td>
<td>1</td>
<td>–</td>
</tr>
</tbody>
</table>

Data are reported for the 58 patients enrolled in the Oklahoma Registry, 1989–2014, who were initially assigned to the drug-induced clinical category. Evidence for a drug association with TMA was assessed using the criteria developed for evaluation of individual patient data for drugs with suspected immune-mediated or toxic reactions [3]. Seventeen of the 25 patients with TMA attributed to quinine and the patient with TMA attributed to pentostatin have been previously published [7,8]. Reassessment of previously published patients with TMA attributed to quinine included testing for quinine-dependent antibodies that was performed following the original publication [8].

### TABLE III. BloodCenter of Wisconsin Experience With Testing for Drug-dependent Antibodies in Patients With Suspected Immune-mediated, Drug-induced TMA

<table>
<thead>
<tr>
<th>Drug</th>
<th>Serum samples tested</th>
<th>Serum samples positive for drug-dependent antibodies</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Immune-mediated TMA</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Quinine</td>
<td>32</td>
<td>28</td>
</tr>
<tr>
<td>Captopril</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Hydrochlorothiazide</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Oxaliplatin</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Plaquenil</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Primadone</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Ticlopidine</td>
<td>5</td>
<td>0</td>
</tr>
<tr>
<td>Vancomycin</td>
<td>1</td>
<td>1</td>
</tr>
</tbody>
</table>

Serum samples from 40 patients with suspected immune-mediated, drug-induced TMA were sent to the BloodCenter of Wisconsin, 1988–2014, for identification of drug-dependent antibodies reactive with platelets and/or neutrophils. For two patients, testing was performed for two different drugs (quinine, ticlopidine: positive for quinine, negative for ticlopidine, and quinine, plaquenil: negative for both drugs). For one patient, testing was performed for three different drugs (vancomycin, ticlopidine, captopril: positive for vancomycin, negative for ticlopidine and captopril). These data do not include Oklahoma Registry patients.

(eight drugs), 51988–2014. These data include nine patients previously reported by the BloodCenter of Wisconsin with TMA attributed to quinine [9]. Oklahoma Registry patients are not included in this analysis. Thirty-two patients had suspected quinine-induced TMA; quinine-dependent antibodies reactive with platelets and/or neutrophils were identified in 28 of these 32 patients. Drug-dependent antibodies were also identified in one patient with suspected oxaliplatin-induced TMA and one patient with suspected vancomycin-induced TMA.


**Discussion**

There have been many reports attributing TMA to many different drugs; most reports have been repeated descriptions of previously reported drugs [3]. This suggests a bias that more frequently reported drugs are the most likely suspects when a diagnosis of DITMA is considered. Our initial Oklahoma Registry criterion for suspecting DITMA, that patients "were currently taking a drug previously reported to be associated with TTP-HUS" [4], was also subject to bias from previously published reports. Therefore, to avoid this risk for bias, we developed criteria to characterize the likelihood of a causal association of a drug with TMA that are independent from previous reports [3] and we used these criteria to reassess the patients who had been assigned to the drug-induced category in the Oklahoma Registry.

Our evaluation criteria were adapted from our previous criteria to determine the level of evidence for a causal association of a drug with isolated thrombocytopenia [5,10]. However the evaluation of patients with suspected DITMA was more difficult than evaluation of patients with suspected drug-induced isolated thrombocytopenia (DITP). For DITP, the target condition is defined simply by a platelet count less than 100,000/μL. In contrast, the clinical and pathologic features of TMA occur in multiple distinct complex disorders, making evaluation of a suspected drug etiology more difficult. Also DITP typically refers only to immune-mediated adverse drug reactions [11]; patients with thrombocytopenia caused by marrow suppressive drugs are typically not considered in descriptions of DITP. In contrast, the typical pathologic features of TMA can be caused by dose-dependent toxic adverse drug reactions, as well as by immune-mediated reactions, and these patients are included in descriptions of DITMA.

Only 21 (36%) of the 58 patients in the Oklahoma Registry who had been previously categorized as drug-induced had evidence supporting a definite association with TMA. Two additional patients had evidence supporting a probable association with TMA. On the basis of this experience, we have changed our requirement for assigning patients to the drug-induced category in the Oklahoma Registry. Patients must now meet the criteria for a "definite" or "probable" association with TMA. We acknowledge that in patients who do not have definite or probable evidence for a causal association, it remains possible that the suspected drug may have contributed to the etiology of TMA.

The biologic basis for the dramatic demographic disparities among the 21 patients with evidence supporting a definite association with TMA is not known. Twenty (95%) of the 21 patients were women, similar to but exceeding the increased frequency of women among patients with acquired autoimmune TTP (77%) [12]. All 21 patients were white, distinct from acquired autoimmune TTP, in which the relative incidence rate is seven-fold greater in blacks compared to non-blacks [12].

The experience of the BloodCenter of Wisconsin for evaluation of patients with suspected immune-mediated, drug-induced TMA was similar to the experience of the Oklahoma Registry. Most samples submitted for drug-dependent antibody testing were from patients with TMA attributed to quinine, and quinine was responsible for most drug-dependent antibodies that were identified (28 [93%] of 30) in patients with suspected DITMA. Although detection of a drug-dependent antibody provides strong evidence for a causal association with DITMA, it should be noted that failure to detect such an antibody provides less persuasive evidence against a causal association. Reasons for this include the fact that some implicated drugs are very poorly soluble in water, making serologic testing difficult, while others may induce antibodies specific for drug metabolites that are not readily available for use in testing [6].

Both the Oklahoma Registry and BloodCenter of Wisconsin experiences were similar to the data from previously published case reports. Seventy-eight drugs and other substances have been previously reported to cause TMA but only 22 had definite evidence supporting a causal association [3]. Quinine was the most commonly reported drug, accounting for 37 (35%) of the 107 patients reported with evidence supporting a definite association with TMA. Table IV compares the data for all three methods of identifying patients with evidence supporting a definite association. These data provide the best current summary of drugs documented to cause thrombotic microangiopathy. These data, including the analyses of all 387 articles reporting patients with suspected DITMA [3], are available on our website (www.oushc.edu/platelets).

The combined data suggest that quinine is the most common cause of drug-induced TMA. Quinine has been used for over 75 years as a remedy for nocturnal leg cramps [14]. Because of serious adverse events associated with quinine, the U.S. Food and Drug Administration banned over-the-counter marketing of quinine for prevention or treatment of leg cramps in 1994 because of insufficient data supporting efficacy [15]. However quinine continues to be commonly used for treatment and prevention of leg cramps and failure to recognize quinine as a cause of adverse drug reactions has been previously well described [16,17]. Patients who take quinine only occasionally, ...
sometimes obtained from family or friends (as among Oklahoma Registry patients), often fail to report it to their physicians, assuming that physicians are only interested in regularly prescribed medications [16,17]. Also (as among Oklahoma Registry patients) the source of quinine may be in a beverage containing tonic water, not from a tablet. Failure to recognize quinine or another drug as a possible cause of immune-mediated TMA may have critical consequences if the patient is re-exposed to the drug, including end-stage renal disease and death (as among Oklahoma Registry patients).

Quinine-induced TMA may provide the characteristic clinical features for immune-mediated, drug-induced TMA. The onset is sudden, occurring several hours following exposure, with severe systemic symptoms which may include headache, abdominal pain, vomiting, diarrhea, chills, and fever. Anuric acute kidney injury often occurs. In some patients liver toxicity [18] and disseminated intravascular coagulation [19] also occur.

Drugs that can cause dose-dependent toxicity-mediated TMA primarily represent three classes of drugs: chemotherapeutic agents (such as gemcitabine and mitomycin), immunosuppressive agents (such as cyclosporine and tacrolimus), and illegal drugs or narcotics taken inappropriately (such as cocaine [20] and oxymorphone [21,22]). The clinical course of these patients may be acute, as with cocaine and oxymorphone, or chronic, caused by dose-dependent toxicity, as with cyclosporine and tacrolimus. Some drugs, such as gemcitabine [13], may cause TMA by both immune-mediated and dose-dependent toxicity-mediated mechanisms.

We believe that greater awareness of drug-induced TMA together with the methods for diagnosis described in this report can provide support for clinicians who evaluate patients with suspected TMA. Recognition of DITMA and documentation of the drug etiology are essential for patient safety.

References