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Misdiagnosis in Patients With Diclofenac-Induced Hemolysis: New Cases and a Concise Review

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Diclofenac has been implicated in many cases of life-threatening immune hemolytic anemia (IHA). Nevertheless, confusion still occurs at the bedside and in the laboratory. Herein we report nine new patients and summarize all published cases (total, $n = 61$). Direct and indirect antiglobulin tests were performed according to standard procedures. Tests for drug-dependent antibodies were performed in the presence and absence of the target drugs and their ex vivo antigens (in the urine of patients treated with the drug). Diclofenac- and/or ex-vivo-antigen-dependent red cell antibodies were detected in all new cases. We identified nine new cases with diclofenac-dependent IHA. All cases were initially suspected to have an abdominal illness and/or autoimmune hemolytic anemia of warm type. Acute renal failure was present in three of the 9 new patients and in 20 of 37 published patients. Seven of the 46 patients died (15%), and clinical information is lacking in 15 other published cases. Diclofenac-dependent and/or ex-vivo-antigen-dependent IHA should always be considered when a patient on diclofenac develops acute renal failure and/or IHA. Am. J. Hematol. 81:128–131, 2006. © 2006 Wiley-Liss, Inc.

Key words: drug-induced hemolysis; drug-induced acute renal failure; drug-dependent antibodies; diclofenac; immune hemolytic anemia

INTRODUCTION

Diclofenac is a widely used nonsteroidal anti-inflammatory drug (NSAID) that has regained acceptance following the debate on cardiovascular side effects of COX-2-specific inhibitors (rofecoxib, celecoxib, valdecoxib) [1]. Diclofenac is available for oral, intravenous, and intramuscular use and as suppositories. Evidence has shown that the drug or its metabolites may lead to the production of drug-dependent antibodies (ddab) and/or autoantibodies (aab) to red blood cells (RBC) [2,3]. The resulting immune hemolytic anemia (IHA) is usually acute, and often associated with renal failure. Nevertheless, there are no cardinal symptoms, and the diagnosis must be established based on sound serologic investigations [4]. 52 cases of diclofenac-induced IHA have been published in the literature to date (Table I).

We found that diagnostic confusion at onset is extremely high. Many of the affected patients develop life-threatening complications, which are sometimes fatal. During the last few years, we identified nine new cases that have not been published yet. The data on these and all previously published patients will be presented and discussed in this article.

PATIENTS AND METHODS

The patients were admitted to various hospitals in Germany during the last few years. Blood samples were sent to our laboratory because of unclear serologic findings. For tests in the laboratory, diclofenac for intravenous use (Ratiopharm, Ulm, Germany) was diluted (1 mg/mL) in phosphate-buffered saline. Urine containing the drug and its metabolites (ex vivo

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TABLE I. Reported Cases With Diclofenac-Induced Hemolysis

No. of patients	Renal failure	Death	Ref.
2	0/2	0	[15]
1	0/1	0	[16]
1	1/1	0	[17]
1	1/1	0	[18]
1	1/1	1	[2]
1	1/1	0	[19]
2	1/2	0	[3]
1	0/1	0	[20]
1	1/1	0	[21]
1	1/1	0	[22]
15[a]	9/15	2	[5]
1	1/1	0	[23]
1	1/1	0	[24]
1	0/1	0	[25]
3	NA	NA	[26]
1	0/1	0	[27]
1	1/1	1	[28]
2	0/2	0	[8]
2[b]	0/2	0	[9]
12	NA	NA	[14]
1	1/1	0	[29]
9	3/9	3	This study
61	23/46	7/23	Total

[a]Two of the 17 reported patients were previously described [3].
[b]This report includes one patient with asymptomatic diclofenac-dependent red-cell antibodies.

antigen) was collected from patients receiving 150 mg of the drug daily, as described previously [5]. Antibody screening and direct (DAT) and indirect antiglobulin tests (IAT) were performed by the standard gel technique (DiaMed, Cressier sur Morat, Switzerland) [6]. All antiglobulin reagents used were from commercial sources (anti-C3d—Dako, Copenhagen, Denmark; anti-IgG, anti-IgA, and anti-IgM—Biotest, Dreieich, Germany). RBC-bound antibodies were eluted by the acid method (Immucor, Rödermark, Germany). Drug-dependent antibodies were assessed by the tube and/or the gel technique, as described previously [5,7], i.e., IAT-negative patient sera (25 μL) were incubated with donor RBCs (50 μL of a 1% v/v suspension) in the absence (25 μL of saline, controls) or presence of diclofenac (25 μL) or its ex vivo antigen (50 μL). Sera that were positive in the IAT before the addition of diclofenac were dialyzed to eliminate residual drug and/or metabolites and then tested. Drug-dependent antibodies were separated from autoantibodies as has been described earlier [5].

RESULTS

Diclofenac-dependent IHA was not suspected on admission in any of the nine new cases (Table II). Initially, acute abdomen and later AIHA (nos. 3 and 4) or a transient ischemic attack (no. 9) were suspected in three patients, all of whom died shortly after the onset of hemolysis (42, 20, and 72 hr after the last diclofenac application, respectively). The remaining six patients (nos. 1, 2, 5–8) developed jaundice, and were initially thought to have AIHA due to warm-reactive autoantibodies. These patients recovered after discontinuation of diclofenac and inpatient glucocorticoid treatment (12–20 days).

The serologic test results at our laboratory suggested drug-induced IHA. Further investigation revealed that all patients had been treated with diclofenac. Drug-dependent antibodies against diclofenac and/or its metabolites were identified in all patients (Table III). In addition, the indirect antiglobulin test was positive in the absence of diclofenac and its metabolites in six cases, indicating the presence of

TABLE II. Clinical Data on Newly Diagnosed Patients With Diclofenac-Dependent Red Cell Antibodies

Patient no.	Age (years)	Sex	Initial symptom(s)	Initial diagnosis[a]	Treatment	Complications	Outcome
1	79	F	Shock	AIHA	Unknown	None	Full recovery
2	60	M	Jaundice	AIHA	Glucocorticoids, iv IgG, RBCs	None	Full recovery
3	71	F	Itching rash, abdominal pain, vomiting	Aortal aneurysm, myocardial infarction, gastric ulcer bleeding	Glucocorticoids, plasma exchange, RBCs	Multiorgan failure	Fatal
4	82	F	Lumbar pain, jaundice, vomiting	Mesenteric infarction and paralytic ileus	Glucocorticoids	Multiorgan failure	Fatal
5	63	F	Jaundice	AIHA	Unknown	Unknown	Full recovery
6	75	M	Jaundice	AIHA	RBCs	None	Full recovery
7	74	M	Jaundice	AIHA	Glucocorticoids	None	Full recovery
8	78	F	Weakness, palor	AIHA	Unknown	None	Full recovery
9	78	F	Somnolence	TIA	Unknown	Multiorgan failure	Fatal

[a]AIHA, autoimmune hemolytic anemia; TIA, transitory ischemic attack.

TABLE III. Serological Data on Newly Diagnosed Patients With Diclofenac-Dependent Red Cell Antibodies*

		DAT		aab		
Patient no.	Hb (g/dL)	C3d	IgG	Eluate	IAT	ddab
1	6.9	+	+	+	–	+
2	5.0	+	+	NA	+	+
3	6.9	+	+	+	+	+
4	9.1	+	+	+	+[a]	+
5	7.3	–	+	+	+[a]	+
6	7.1	+	+	+	+	+
7	7.9	+	+	+	–	+
8	7.0	+	+	+	+	+
9	NA	+	+	–	–	+

*Abbreviations: aab, autoantibodies; DAT, direct antiglobulin test; ddab, drug-dependent antibodies reactive with testing RBCs in the presence of the drug or its metabolites; Hb, lowest hemoglobin value measured during hemolysis; IAT, indirect antiglobulin test; NA, not available.
[a]Autoantibodies in patients no. 4 and 5 had partial C specificity.

drug-induced autoantibodies in addition to the drug-dependent antibodies.

A summary of most relevant findings in all published cases ($n = 61$) is given in Table I. Unfortunately, clinical data were lacking in 15 patients. Of the remaining 46 patients, 23 developed shock and/or renal failure, and 7 of these patients died. The remaining patients appear to have survived the hemolysis without life-threatening complications.

DISCUSSION

In this study, we report nine new cases of diclofenac-induced IHA and we have summarized the data on all previously published cases (Table I). Although the clinical and serological findings were well-characterized in some of the reported cases, diagnostic confusion seemed to occur in almost all instances. Of greatest concern, some patients died because of a belated diagnosis. The clinical symptoms were variable and did not lead directly to the correct diagnosis in any of our nine new patients. In most cases, clues as to the nature of the disorder—ddab with RBC specificity—came from the serological reassessment. In our opinion, there is a general lack of awareness that diclofenac can cause this severe side effect, complicated further by limited access to quality serological testing at some local hospitals. Before learning that these patients had drug-dependent IHA due to diclofenac, AIHA due to warm-reactive autoantibodies was the usual diagnosis. Without a doubt, this diagnostic confusion is extremely dangerous for the patients, since they may receive the drug again. Moreover, the failure to administer adequate treatment to patients because of a late or wrong diagnosis can lead to even more complications, such as acute renal failure (ARF). The outcome was fatal in 7 of 46 cases (15%), and ARF occurred in 16 additional patients.

Based on these observations, we believe that explicit information about this complex problem is absolutely necessary to avoid or reduce life-threatening complications. First of all, patients receiving diclofenac must be advised that hemolysis can occur as a side effect of the drug, and they must be educated about the symptoms and clinical findings that may develop during or following diclofenac administration. In addition, all physicians involved with these patients should be familiar with the serological findings relevant to the hemolytic potential of diclofenac. Most importantly, physicians should know that diclofenac may lead to the production of autoantibodies and drug/metabolite-dependent antibodies and that the hemolysis may develop gradually or abruptly. The initial symptoms are usually characteristic of acute immune hemolytic anemia (fatigue, jaundice or pallor, back and/or abdominal pain), whereas the late symptoms may be characterized by complications normally related to decompensated hemolysis, i.e., shock and/or renal failure. Finally, the presence of autoantibodies should not invariably exclude testing for drug-dependent antibodies.

According to the Uppsala Monitoring Center, at least 82 cases of diclofenac-induced hemolytic anemia are currently known [8], indicating a higher incidence than is generally believed. Diclofenac-induced immune thrombocytopenia has also been reported in isolated cases [9], reflecting the immunogenicity of the drug. Unfortunately, it is absolutely impossible to predict which patients will be affected or to determine when immunization will take place. The reaction may develop during continuous or intermittent therapy and immediately following re-exposure to the causative drug [10].

The high frequency of acute renal failure in patients with diclofenac-induced IHA (23 of 46 = 50%) is not uncommon in drug-dependent IHA [4,10–13]. The reason for this phenomenon and why it only affects some of the patients is unclear. Apart from hemolysis, anemia, and shock, other factors seem to be involved in some cases. Therapy such as plasmapheresis, hemodialysis, and/or glucocorticoid-treatment may play a determinant role. In addition, the target antigen might be expressed on both RBCs and renal cells [11]. Products of the complement cascade and cytokines may also contribute to renal damage [12]. However, deposition of immune complexes was not found in some reported cases [13].

From our experience, we surmise that diclofenac-induced immune hemolytic anemia is far more common than has been previously assumed and that the

incidence is increasing due to the greatly reduced use of COX-2-specific inhibitors.

Misdiagnosis of diclofenac-induced IHA may be due to limited awareness of drug-dependent hemolysis and/or to oversimplification of serologic investigations. False-negative results may be obtained when the drug metabolites are omitted from testing [14]. The true incidence of diclofenac-dependent antibodies must be determined by means of controlled studies in cooperation with all manufacturers of the drug.

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