Heterogeneity of Drug-Dependent Platelet Antigens and Their Antibodies in Quinine- and Quinidine-Induced Thrombocytopenia: Involvement of Glycoproteins Ib, IIb, IIIa, and IX

By Sharron L. Pfueller, Robyn A. Bilston, Dana Logan, Jannine M. Gibson, and Barry G. Firkin

The molecular nature of platelet receptors for quinine- and quinidine-dependent antiplatelet antibodies (Q.Ab and Qd.Ab) was studied by immunoblotting. One Q.Ab caused quinine-dependent IgG binding to platelet proteins with molecular weights (mol wts) of 174 Kd and 93 Kd and another to only a 93-Kd protein. A third Q.Ab caused binding to 174-, 140-, 93-, and 57-Kd proteins, while a fourth Q.Ab and a Qd.Ab caused IgG binding to 174- and 18-Kd proteins. Using platelets from patients with Glanzmann's thrombasthenia or Bernard Soulier syndrome and purified GPIIb, these proteins were shown to be GPIIb, GPIIa, GPIIIa, GPIX, and an unidentified 57-Kd protein missing in Bernard Soulier syndrome. Absorption of one Q.Ab with Glanzmann's thrombasthenia platelets revealed different populations of antibodies with different specificities within the one patient. Thus Q.Ab and Qd.Ab are heterogeneous and may be directed toward different epitopes on major platelet glycoproteins.

METHODS

Patient material. Q.Ab and Qd.Ab were obtained from patients who developed thrombocytopenia more than five days after commencement of quinine (DH, SM, MS, TH) or quinidine (WB). Drug-dependent antibodies in serum were detected by their ability to cause drug-specific increases in IgG binding to normal platelets in an enzyme-linked immunosorbent assay (ELISA) (see below).

Platelets from a patient with Glanzmann's thrombasthenia (JM) described previously were further characterized by labeling of surface glycoproteins (see Results) and by measuring the binding of a monoclonal antibody (Hu-Pl-M1) (see below). One patient with Bernard-Soulier syndrome was described by Berndt et al. A second patient was diagnosed as having Bernard-Soulier syndrome because he had giant platelets, a platelet count of 2 x 10^9/L, absent aggregation with ristocetin (1 and 2 mg/mL), but normal aggregation responses to adenosine diphosphate (ADP), collagen, and adrenalin. Analysis of surface glycoproteins by periodate-Na[B]borohydride labeling confirmed the diagnosis.

IgG binding to platelets. Drug-dependent IgG binding was measured by ELISA as previously described in the presence and absence of quinine or quinidine hydrochlorides (1 mmol/L). Briefly, platelets coated on plastic microtiter plates were incubated with patient or normal serum in the presence or absence of the appropriate drug followed by incubation with alkaline phosphatase-linked anti-IgG (Sigma Chemical Co, St Louis). Hydrolysis of the substrate p-nitrophenol phosphate was measured as absorbance at 405 nm. Results were expressed as corrected net A_405nm calculated as the difference between serum and buffer samples. The presence of Q.Ab

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or Qd.Ab was indicated by a drug-induced increase in $A_{405\,nm}$ greater than drug-independent increases in $A_{405\,nm}$ (mean + 2 SD) obtained with serum from 11 normal donors.

Binding of monoclonal antibody to the GPIb/IIIa complex was measured by a modification of the above technique. Doubling dilutions of platelets from either the patient with Glanzmann’s thrombasthenia or normal controls were coated on microtitre plates that, after blocking with bovine serum albumin, were incubated with Hu-PI-M1 (Australian Monoclonal Development, Sydney, Australia) (diluted 1/200) followed by alkaline-phosphatase linked anti-mouse IgG (Sigma). The curve relating log platelet count and $A_{405\,nm}$ was used to calculate the monoclonal IgG binding to patient platelets expressed as a percent of the controls.

**Blood products.** Serum was obtained after incubating whole blood in glass tubes for two hours at 37°C and 18 hours at 2°C. Platelet-rich plasma (PRP) was prepared from blood collected into one-tenth volume 3.8% trisodium citrate by centrifugation at 800 g for ten minutes. Platelet-poor plasma (PPP) was obtained by centrifugation of citrated blood at 2,200 g for 20 minutes.

To prepare washed platelet suspensions for electrophoresis, PRP was diluted in an equal volume of 0.01 mol/L Tris, 0.14 mol/L NaCl, 0.027 mol/L glucose, 0.005 mol/L Na$_2$EDTA, pH 7.4 (TNGE) and sedimented by centrifugation at 2,200 g for ten minutes. Platelets were washed by three cycles of resuspension in TNGE and centrifugation, and finally suspended to 7.8 x 10$^9$/mL in 0.14 mol/L NaCl, 0.065 mol/L K$_2$EDTA, 0.01 mol/L Tris, pH 7.4 (TNE) containing 11 mg/mL soybean trypsin inhibitor, 10 mmol/L tosyl arginine methyl ester, 10 mmol/L benzamidine, 10$^{-2}$ M/L trisylol (Bayer, Leverkusen, Germany), 1 g/L sodium azide, 1 mmol/L phenyl methyl sulfonyl fluoride, and 200 mg/L leupeptin.

$[^{3}H]$ labeling of platelets. Washed platelets were labeled with periodate/sodium borohydride ($[^{3}H]$NaBH$_4$) as described. The amounts of GIIb and GPIIIa were quantitated by scanning with an UltroScan XL enhanced laser densitometer (LKB-Pharmacia, Uppsala, Sweden). The area under the peaks was expressed as a percentage of that of GPIb or GPIb$\alpha$.

**Electrophoresis.** Sodium dodecyl sulfate polyacrylamide gel electrophoresis (SDS-PAGE) was carried out as described using a 5% to 15% gradient as the separating gel and 3% polyacrylamide as a stacking gel.

**Immunoblotting.** Proteins were transferred to nitrocellulose (Bio-Rad) as described. The portion of paper carrying the standard immunoblot was visualised with gold-conjugated antihuman IgG by a modification of the procedure of Lowry and Langenberg except that tenfold more IgG was used. The $A_{405\,nm}$ of the conjugate was measured and 100 µL of a suspension with $A_{405\,nm}$ equal to 18.8 together with 5 mL blocking buffer (in the presence or absence of the appropriate drug) were added to each lane. In some experiments F(ab')$_2$, fragments of affinity isolated antibodies to IgG (Silenus) were used. In experiments with F(ab')$_2$ fragments of patient IgG, the gold conjugate was prepared using affinity purified antibody to human Fab fragments (ICN Immunobiologics, Lisle, IL). Pink bands were visualized after one to three hours and maximum intensity was reached in about 18 hours.

**Preparation of IgG.** IgG was obtained from patient serum by affinity chromatography on protein A sepharose (Pharmacia). F(ab')$_2$, fragments were prepared by digestion of IgG with immobilized pepsin (Pierce Chemical Co, Rockford, IL) for two hours at 37°C at pH 4.5 and further passage through a protein A column.

**Preparation of platelet membranes.** These were prepared as described and washed and resuspended in TNE containing protease inhibitors as described above. The protein concentration was measured by the procedure of Lowry and 534 µg were loaded into the large gel slot for SDS-PAGE analysis. This was one third of the amount of protein routinely used for the analysis of whole platelets.

**Typing of platelets for the PI$^{Ab}$ antigen.** Sera were typed as containing antibodies to the PI$^{Ab}$ antigen using the platelet suspension immunofluorescence test by the Red Cross Blood Bank. These sera produced strong bands of 93 Kd in the absence of any drug with platelets on immunoblots by the technique described above.

**Purification of GPIIa.** Platelet membranes were prepared and extracted as described. The extract was subjected to gel filtration on Sephacyr S-300, and the GPIIb/IIIa complex was subjected to SDS-PAGE on a preparative 5% to 15% gradient gel. A strip from the gel was cut out, stained with Coomassie Brilliant Blue R. The portion of the unstained gel corresponding to GPIIa on the stained gel was cut out and, after maceration in the sample loading buffer described above, loaded on another gradient gel for immunoblotting as described above. The amount of GPIIa for each nitrocellulose strip was calculated to be 2 µg.

**RESULTS**

**Drug-dependent IgG binding to normal platelets.** The presence of Q.Ab and Qd.Ab was demonstrated by increased IgG binding to platelets by ELISA in the presence of the drug at 1 mmol/L. Drug-dependent increases in IgG ($\Delta A_{405\,nm}$) varied with serum concentration reaching a maximum at a dilution of 1/8 to 1/64, and the results at the dilution where the drug-induced changes were maximal are shown in Table 1. In normal sera, the maximum drug-dependent changes in $A_{405\,nm}$ corresponded to the maximum deviations due to experimental error. For the Q.Ab, changes in $A_{405\,nm}$ in the presence of quinidine fell within this range. Similarly, no significant change in quinidine-dependent IgG binding was observed with the Qd.Ab. With sera MS and WB, which produced the greatest drug-dependent change in $A_{405\,nm}$ IgG binding in the absence of the drug was also above the normal range.

**Drug-dependent IgG binding to platelet proteins on Western blots.** In each of five sera from patients with drug-induced thrombocytopenia, drug-specific IgG binding to
Table 1. IgG Binding From Patient Serum to Normal Platelets

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<tr>
<th>Serum Dilution for Positive Drug-Induced IgG Binding</th>
<th>IgG Binding (Corrected net A590)</th>
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<td>Serum + Buffer</td>
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<td>Quinine-induced</td>
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<td>thrombocytopenia</td>
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<td>S.M.</td>
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<td>T.H.</td>
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IgG binding to normal platelets in the presence or absence of quinine or quinidine (1 mmol/L) was measured at a range of serum dilutions (1/4 to 1/2,048) as described in the METHODS section and is shown as corrected net A590. The values are with serum dilutions where maximum drug-induced increases in IgG binding occurred. After each value is shown the upper limit of the normal range (mean ± 2 SD) obtained with 11 normal sera.
To study the effect of quinine concentration on drug-dependent binding of IgG to platelet antigens, incubations of Western blots with the four Q.Ab, the washes of the blots, and the incubation with gold-conjugated IgG were performed in the presence of 0.1 μmol/L, 1 μmol/L, 10 μmol/L, 100 μmol/L, and 1 mmol/L quinine. With sera DH, MS, and SM, all the drug-dependent bands that were visualized at 1 mmol/L quinine began to be faintly visible at 10 μmol/L and showed increasing intensity up to 1 mmol/L. With serum TH, bands were visualized faintly at 100 μmol/L and strongly at 1 mmol/L (results not shown).

A number of other bands, the presence of which was not affected by quinine or quinidine, were seen. Those at around 160 Kd (platelet-associated IgG) and 180 Kd have been described by others, while the other fainter bands varied dependent binding of IgG to platelet antigens, incubations of Quinine-dependent IgG binding to these proteins may have been detectable only with membranes and not with whole platelets because of their enrichment in the membrane preparation.

**Drug-dependent IgG binding to platelets with congenital glycoprotein deficiencies.** To confirm the initial diagnosis of the patient with Glanzmann's thrombasthenia, which had been based only on studies of platelet aggregation and fibrinogen content, platelets from this patient were surface labeled. GPIIib and GPIIIa were identified by their mol wts in both reduced and nonreduced states and from previous assignments using this labeling procedure. The pattern of labeling, showing diminished content of GPIIib in comparison with that in normal platelets, was consistent with this initial diagnosis (Fig 3). Quantitation by densitometry showed a GPIIib/Ib ratio of 0.3 with the patient and 0.91 ± 0.13 (n = 4) with normal individuals. GPIIIa was, however, clearly visible on the fluorogram of the reduced sample where it migrates separately from GPIV. The GPIIIa/Ibβ ratio obtained from reduced gels with 0.31 in comparison with 0.15 (n = 3) with normal individuals. Binding of Hu-Pl-M1, specific for the 11b/IIIa complex, to the patient's platelets was 4.5% ± 0.8% of normal (n = 3), and no binding of anti-PlA1 antibodies was seen on immunobots (data not shown), showing that, although constituents of the complex were present, it was antigenically abnormal. A glycoprotein of about 150 Kd was also missing in this patient. Its identity is uncertain at this stage.

When Western blots of platelets from this patient were incubated with serum MS in the presence of quinine, no drug-dependent bands were seen (Fig 3). With serum DH, both the 93- and 140-Kd bands were missing, while those of 174 Kd and 57 Kd were still observed. With serum TH, the 18-Kd band was seen. Some drug-independent IgG binding was also observed.

With platelets from two patients with Bernard-Soulier syndrome, the drug-dependent bands with mol wts of 174 Kd, 18 Kd, and 57 Kd were no longer present, although the 140- and 93-Kd bands were visible. Results from one of these is shown in Fig 3. Significant drug-independent IgG binding was observed only with serum MS to 27-Kd material; the 90-Kd drug-independent band was missing with both sera MS and TH.

**Drug-dependent IgG binding to GPIIIa.** The GPIIib/IIIa complex was purified, and the constituent proteins were shown by SDS-PAGE to have the migration characteristics of GPIIib and GPIIIa (Fig 4A). When GPIIIa was further purified from the complex by preparative SDS-PAGE and subjected to immunoblotting, it reacted with serum containing anti-PlA1 antibodies and with serum DH and MS in the presence of quinine. No drug-dependent IgG binding was observed with serum TH (Fig 4B).
Fig 3. Drug-dependent binding of IgG to proteins in platelets from patients with Glanzmann's thrombasthenia (GT) and Bernard-Soulier syndrome (BSS). (A) Fluorography of surface glycoproteins of GT platelets labeled by the periodate-sodium borohydride method is compared with that of control platelets (Cont) under nonreducing (NR) and reducing (R) conditions. GPIIb and IIa (both shown as IIb) and IIa are indicated. (B and C) Immunoblots of platelets from GT and BSS platelets were prepared as described for Fig 1. Each Q.Ab was incubated in the presence or absence of quinine (1 mmol/L) with nitrocellulose strips containing patient's platelets. The mol wts of standard marker proteins are shown for each experiment, each on a separate gel. Drug-dependent bands are indicated by arrows, and the positions of bands that occurred with strips containing normal platelets are shown by dashed lines. The results are representative of two experiments. (Curved lines toward the bottom of the blot of DH + Q are not bands but the result of a buffer residue on the nitrocellulose.)

pattern occurred when serum DH was absorbed with these platelets in the absence of quinine.

When this absorption was conducted with platelets from a patient with Glanzmann's thrombasthenia, the bands at 174 Kd and 57 Kd were completely removed, while the band at 140 Kd showed the same staining intensity as observed with serum that had been absorbed in the absence of quinine. Thus the specificity of the antibodies reacting with the 140-Kd protein is different from that of antibodies reacting with the 174- and 57-Kd proteins. The 93-Kd band was still visible but less intense. This could result from the presence of GPIIIa (as seen in Fig 3A), which could remove some of the antibodies responsible for the 93-Kd band. Thus the antibodies reactive with the 140-Kd protein also appear to be distinct from those producing the 93-Kd band. This is further supported by results using unabsorbed serum from DH obtained a week after that used for the above experiments.

The 93-Kd band produced by this serum sample with normal platelets showed a marked decrease in intensity while the other three bands were similar to those in the original serum, suggesting that the amount of one antibody population was decreasing.

Drug-dependent binding of F(ab')2 fragments. Sufficient serum from only two patients (MS and TH) was available to prepare F(ab')2 fragments, and from these there was sufficient F(ab')2 for only one experiment. With serum TH, the 18-Kd band was obtained with both serum and the F(ab')2 preparation (Fig 6), while the 174-Kd band was not visualised. No bands were seen with F(ab')2 from MS (data not shown).

DISCUSSION

In serum from five patients with quinine- and quinidine-induced thrombocytopenia we have observed drug-depen-
dent binding of IgG to platelets both by ELISA and immunoblotting. In the ELISA, drug-specific increases in IgG binding were maximal at different serum dilutions with different patients, as can also be seen in the results of Lerner et al3' for both Q.Ab and Qd.Ab. This is possibly the result of differing affinities of the antibodies and interactions of the drugs with plasma proteins. On immunoblots, drug-dependent IgG binding to a number of different platelet membrane proteins was observed with different sera. These had mol wts of 174, 140, 93, 57, and 18 Kd. Because the 18- and 174-Kd bands were missing from platelets from patients with Bernard-Soulier syndrome, they can be identified in normal platelets as the result of the reaction of drug-dependent antibodies to GPIIX and GPIb. In previous studies, although these two glycoproteins were immunoprecipitated by Qd.Ab from normal platelet lysates and not from lysates of Bernard-Soulier platelets, it was not possible to distinguish whether both or only one of them contained the drug-dependent epitope. We have shown that both GPIb and GPIIX contain drug-dependent epitopes. It is not clear at this stage whether the same epitope occurs on both glycoproteins or whether two distinct epitopes occur.

Platelets from Bernard-Soulier patients also did not show drug-dependent IgG binding to a 57-Kd protein. A deficiency of a protein with this mol wt has not been described in this disorder. A protein of similar molecular weight was immunoprecipitated from platelets treated with the calcium-dependent protease by a Qd.Ab studied by Berndt et al. They interpreted this to represent a proteolytic product of GPIb. Although our platelet preparations were solubilized and electrophoresed in the presence of protease inhibitors, including EDTA and leupeptin, which inhibit the platelet calcium-dependent protease, and the 57-Kd band still occurred in platelets solubilized by boiling for 5 minutes, it is possible that this band results from a cleavage product of GPIb produced by a protease that remained uninhibited. Alternatively, it could represent an additional defect in Bernard-Soulier syndrome.

The mol wts of the 93-Kd and 140-Kd bands agree with those described for GPIIb and GPIIIa. That these bands were a result of drug-dependent IgG binding to these glycoproteins was suggested by their absence from blots of platelets from patients with Glanzmann's thrombasthenia, while...
the bands of 174- and 57-Kd were still observed with serum DH and that of 18-Kd with serum TH. However, although the Glanzmann’s thrombasthenia platelets bound decreased amounts of monoclonal antibody to GPIIb/IIIa in ELISA assays and did not bind anti-PI41 in immunoblots (data not shown), and levels of [3H]-labeled IIB were decreased, the content of [3H]-labeled IIa as determined by quantitative analysis of fluorograms was normal. This suggests that GPIIa in this patient is qualitatively abnormal. That the 93-Kd band on normal platelets was due to drug-dependent binding to GPIIIa was confirmed by studies with the purified glycoprotein. The drug-dependent binding site on GPIIIa is clearly distinct from the PI41 antigen because it was present on PI41-negative platelets. With serum TH, the 174-Kd band was missing on Glanzmann’s thrombasthenia platelets, but it was also often not discernible on normal platelets because of strong staining of platelet-associated IgG.

Our results show that there is not just one quinoline- or quinidine-dependent receptor. The multiplicity of target proteins with which Q.Ab and Qd.Ab react suggests, rather, that these proteins, in the presence of the appropriate drug, form specific epitopes. Although at least some of these epitopes are different, as shown by absorption studies, they share the one common feature of being unstable to reduction, as proposed by Cimo and Gerber. 31 It is not possible to determine whether all Qd.Ab show the same heterogeneity as we have found for Q.Ab because the only Qd.Ab we were able to study reacted with components of the GPIb/GPIX complex as suggested by others. 32,33 Heterogeneity of Q.Ab and Qd.Ab was foreshadowed by observations that antibodies from different patients had different specificities for chemical derivatives of the drugs 10 and by the different reactivities of Bernard-Soulier platelets with Q.Ab and Qd.Ab described by van Leeuwen et al. 9

The failure of Glanzmann’s thrombasthenia platelets to absorb the 140-Kd band produced by serum DH while they partially absorbed the 93-Kd band and completely absorbed the 174- and 57-Kd bands indicates that heterogeneity of Q.Ab exists even within the serum of one patient. The selective decrease in staining of the 93-Kd band of normal platelets by a later sample of unabsorbed serum also supports this contention. These findings also suggest that it is unlikely that binding to Fc receptors is involved, because it could only be explained by a multiplicity of Fc receptors with different specificities. However, drug-dependent binding of F(ab′)_2 from serum TH to GPXI clearly showed that binding to this glycoprotein is independent of Fc. The failure of MS F(ab′)_2 to produce drug-dependent binding at 93 Kd might suggest that GPIIa contains an Fc receptor. However, it could also be that the configuration of the antigen binding site of the Q.Ab MS is only maintained in the presence of the Fc portion or that this antibody may be more susceptible to inactivation during experimental handling. Unfortunately, due to lack of patient sera, it was not possible to examine the binding capacity of F(ab′)_2 to 174-, 140-, and 57-Kd antigens.

Because MS IgG and TH F(ab′)_2 fragments produced drug-dependent IgG binding, it is clear that other plasma proteins are not involved, as shown by others. 33 We previously reported that von Willebrand factor was required for platelet damage by Q.Ab and Qd.Ab, 34 but in subsequent studies, 35 we showed that although PRP from patients with severe von Willebrand’s disease has decreased susceptibility to some Q.Ab and Qd.Ab, the defect was not corrected by purified von Willebrand factor. Devine and Rosse 35 have described a Qd.Ab that required the presence of a protein other than von Willebrand factor for the binding of IgG to platelets. It could be that the heterogeneity of drug-dependent antibodies we have described in this study might extend to the requirements for plasma proteins in epitope formation.

Sera from patients with quinidine-dependent thrombocytopenia have also been reported to contain platelet antibodies that are independent of the drug, 31,36 and GPV has been identified as a target antigen. 36 We found by ELISA two sera that showed, in addition to drug-induced IgG binding, increased IgG binding in the absence of the drug. Some drug-independent IgG binding was also observed on immunoblots, in addition to bands produced by platelet-associated IgG (160 Kd and 180 Kd) as described by others. 27,28 Bands of 90 Kd and 30 Kd were the most pronounced. Because the 90-Kd band was missing on Bernard-Soulier platelets, which lack GPV, it could be a result of binding of an autoantibody to this glycoprotein as described by Stricker and Shuman. 36 However, the drug-dependent 93-Kd band is clearly distinct from GPV, because although it had a similar mol wt, it occurred with Bernard-Soulier platelets. The identity of the drug-independent 28-Kd band with serum MS is unknown. It is of interest that one of the two sera (WB) that showed drug-independent IgG binding by ELISA also showed the most drug-independent bands by immunoblotting. The other (SM), however, produced only faint drug-independent bands. It may be that the antibodies in this serum are directed to antigens not stable to the electrophoretic procedures. The nature of the drug-independent bands, particularly those in normal sera seen faintly in Fig 1, is not clear. Those in the patient sera might be autoantibodies with pathologic significance, or they might all be a result of naturally occurring antibodies similar to those described by others. 37,38

Because different Q.Ab and Qd.Ab are able to distinguish different chemical derivatives of the drugs involved, 16 it is clear that determinants in both drug and platelet surface proteins contribute to epitopes for these antibodies. This is supported by the finding that platelet-bound Q.Ab promoted specific binding of quinine to platelets and inhibited its removal by repeated washing. 39 Therefore, it appears that in thrombocytopenia caused by quinine and quinidine, antibodies can recognize a range of neo-antigens composed either of determinants on both the platelet surface and the drug or of new drug-induced conformations of platelet glycoproteins. It will be of interest to determine whether antibodies to the different glycoproteins are equally able to mediate complement dependent platelet destruction.

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Heterogeneity of drug-dependent platelet antigens and their antibodies in quinine- and quinidine-induced thrombocytopenia: involvement of glycoproteins Ib, IIb, IIIa, and IX

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