Comparison of immunoassays for differentiation of herpes simplex virus type 1 and 2 antibodies

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ABSTRACT

Objectives: To asses the commercial available enzyme-linked immunosorbent assays (ELISA) for differentiation of herpes simplex virus type 1 (HSV-1) and type 2 (HSV-2) antibodies.

Methods: The study was performed between January 1997 to November 2002 in the Division of Virology, Department of Pathological Sciences, Central Manchester Healthcare Trust and University of Manchester, Manchester, United Kingdom. Assays based upon type-specific glycoprotein G-1 (gG-1) for HSV-1, and glycoprotein G-2 (gG-2) from HSV-2 were evaluated to differentiate between HSV-1 and HSV-2 antibodies. Using 5 different ELISA tests, 2 panels of serum samples were tested. Panel one consisted of 88 sera, selected from the serum bank of the Clinical Virology Laboratory, Manchester Royal Infirmary; panel 2 comprised of 90 sera selected from samples collected from Bangladeshi female commercial workers.

Results: The data of this study showed that a high rate of gG-1 based immunoassays ranged from 87.9-100% for sensitivity and 51.5-100% specificity.

Conclusion: Although there are several immunoassays were claimed to differentiate between HSV-1 and HSV-2 antibodies, selection of these assays should be carefully interpreted with the overall clinical framework provided by detailed sexual history and genital examination.

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Genital herpes infection caused either by herpes simplex virus type 1 (HSV-1) or herpes simplex virus type 2 (HSV-2) has become an important public health problem.[1] Detection of antibodies in HSV-infected patients may be readily achieved using a variety of biological or immunological procedures.[2] However, the development of techniques to differentiate HSV-1 and HSV-2 antibodies has proved more difficult. The genomes of HSV-1 and HSV-2 share 47-50% base sequence homology and their genetic maps are largely collinear.[3] In consequence, the viruses exhibit considerable antigenic cross-reactivity. Conventional enzyme-linked immunosorbent assays (ELISA),[4] complement fixation tests,[5] and neutralization tests,[6] have all proved to be unreliable in differentiating and detecting type specific antibody.[7] The most extensively validated method for identifying type-specific antibody is the Western blot assay (WBA).[8] However, standardization of WBAs is difficult, and due to the large number of immunoreactive viral proteins, the WBA pattern obtained is difficult to interpret. In addition, WBAs are less successful in differentiating patients with dual HSV-1 and HSV-2 infections.[9] Immunoassays employing immuno-

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affinity purified glycoprotein G (gG) of HSV-1 (gG-1) and its corresponding HSV-2 glycoprotein, gG-2 or recombinant forms of these proteins have been employed by several workers to detect and differentiate HSV type-specific antibodies.[2,8,10-11] Analysis of the predicted amino-acid sequence of the genes encoding glycoprotein G (gG)-1 and its corresponding HSV-2 glycoprotein gG-2 show the proteins have limited similarity in the N-terminal region, but are clearly homologous in the C-terminal region.[12] The gG-2 protein is approximately 460 amino acids longer than gG-1.[13] Antibody type specific immunoassays, based upon gG, are now available commercially from several companies,[2] and have been evaluated and widely studied.[2,14] Not all assays have undergone performance evaluation to allow Food and Drug Administration approval[2,15] or European in vitro diagnostics CE marking.[16] Using 2 well-characterized panels of sera, we compared several commercially available immunoassays, all with claimed capability to differentiate HSV-1 and HSV-2 antibody. A strip immunoblot assay (Chiron), which has been extensively validated against WBA and other well-characterized 'in-house' HSV-1 and HSV-2 type specific assays, was used as the reference test for this comparison.[17-19]

Methods. Two panels of serum samples were tested. Panel one consisted 88 sera from 52 patients with proven HSV infection, selected from the serum bank of the Clinical Virology Laboratory, Manchester Royal Infirmary; Panel 2 comprised 90 sera selected from samples collected from Bangladeshi female commercial workers.[20] Ethical permission for the study was obtained from the Local Research Ethics Committees. Several immunoassays were evaluated as follows: immunoblot assay for the Chiron RIBA HSV-1/HSV-2 strip immunoblot assay (Ortho-Clinical Diagnostics, Raritan, NJ, USA) was performed according to the manufacturer's instructions.[17-19] Using enzyme immunoassay, 5 commercial assays were also evaluated; Biokit for Bioelisa HSV-1 and HSV-2 IgG kits (Biokit SA, Barcelona, Spain) utilized plates coated with either purified recombinant HSV-1 gG-1 protein or immuno-affinity purified 'native' HSV-2 gG-2 protein, Gull for Gull HSV Type 1 Specific and HSV Type 2 Specific IgG kits (Gull Laboratories, Salt Lake City, USA) utilized plates coated with either affinity purified 'native' gG-1 antigen or immuno-affinity purified 'native' gG-2 antigens, Centocor for Captia Select HSV2-G kit (Centocor, Malvent, PA, USA) detected only HSV-2 antibody and utilized plates coated with recombinant, gG-2 specific antigen, Clark for HSV-1 and HSV-2 IgG ELISA kits (Clark Laboratories Inc., Jamestown, NY, USA) utilized microtiter plates coated with either purified HSV-1 or purified HSV-2. Differentiation of HSV-1 and HSV-2 antibody was achieved by calculation of a proprietary relative binding ratio (ISR), Biotest for Biotest herpes simplex 1 IgG and Biotest herpes simplex 2 IgG kits (Biotest, Milan, Italy) utilized microtiter plates coated with either purified HSV-1, or purified HSV-2. Differentiation of HSV-1 and HSV-2 antibody was achieved by cross-adsorption of sera with either HSV-1 or HSV-2 purified antigen prior to the addition of test samples to the plate. All assays were performed in accordance with the manufacturers' instructions. Each kit provided a method for determination of a 'cut-off' value to differentiate a positive serum from a negative one. The appropriate manufacturer's 'cut-off' was used for each test.

Results. For comparison of the Chiron Immunoblot assay and Commercial ELISA kits, and based on panel one sera, 3 immunoassays (Biokit, Gull and Centocor) were evaluated. The reference test (Chiron immunoblot) for 88 specimens were: 59 HSV-1 antibody positive, 4 HSV-2 antibody positive, 13 both HSV-1 and HSV-2 antibody positive, and 12 sera negative for both HSV types. These results were in accordance with the results of virus isolation (where appropriate) or clinical evaluation (data not shown). The results of HSV antibody subtyping of these sera are illustrated in **Table 1** (Panel 1). Test and reference test results agreed in 75 of 88 samples with the Biokit test and 68 of 88 with the Gull test. Using the Centocor test all of the 17 sera determined HSV-2 antibody positive or HSV-1 and HSV-2 antibody positive by the Chiron test were found to be HSV-2 antibody positive. However, 2 of the sera found to be negative, and 13 of those found to be HSV-1 were found to be HSV-2 antibody positive by the Centocor assay, indicating very poor agreement between the 2 tests. The sensitivity, specificity, positive and negative predictive values for identifying the correct herpes simplex antibody subtype are shown in **Table 2**. The sensitivity of the tests for HSV-1 antibody was 94.4% with Biokit and 93.1% with Gull. The specificities of HSV-1 antibody subtyping by Biokit or Gull were the same (93.8%). The overall negative and positive predictive values for HSV-1 antibodies were 79% and 98.6% respectively for the Biokit test and 75.0% and 98.5% respectively for the Gull test. The sensitivities for detection of HSV-2 were 94.1% with the Biokit test, 100% with Gull and 100% with Centocor. In contrast, the specificities for subtyping of HSV-2 antibody by Biokit was 88.7%, Gull was 77.5% or Centocor was 77.5%. The positive predictive values

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were low for Biokit (66.7%), Gull (51.5%) and Centocor (51.5%). For the panel 2 which contained a high proportion of HSV-2 antibody positive sera. The overall seroprevalence in the female commercial workers was 94.6%. The 90 sera used in this panel were selected samples collected from a total of 460 women; 23 of the samples were HSV-1 antibody positive, 32 were HSV-2 antibody positive, 34 both HSV-1 and HSV-2 antibody positive and one was HSV antibody negative as determined by the reference test. In assessing Panel 2 sera, 2 further commercial ELISAs (Biotest and Clark) were included in the evaluation. The results of HSV subtyping using these assays are shown in **Table 1**/Panel 2. Four samples were found to be antibody negative using the Gull Test and only 2 samples were found to be negative by Biokit, Biotest and Clark. The Centocor assay gave 23 negative results. Test results agreed for 78 of 90 samples (Biokit), 68 of 90 samples (Gull), 28 of 90 samples (Biotest) and 39 of 90 samples (Clark). Using the Centocor assay, 64 of the 67 sera determined HSV-2, or HSV-1 and HSV-2, antibody positive by the reference test were found to be HSV-2 antibody positive. Two sera found to be HSV-1 antibody positive by the reference test were found to be HSV-2 antibody positive by the Centocor assay **Table 1**/Panel 2. The sensitivity, specificity, positive and negative predictive values for each of the tests in identifying the correct herpes simplex antibody subtype are shown in **Table 3**. The sensitivity of the tests for HSV-1 with Biokit, Gull, Biotest and Clark was high (100%). The overall negative predictive values were also high (100%) for all 4, whilst positive predictive values were 83.8% (Biokit), 78.1% (Gull), 90.5% (Biotest) and 64.1% (Clark). The sensitivities for the detection of IgG antibodies were indicated in **Table 3**. The abilities of these tests to correctly identify the subtype of HSV antibody varied greatly. The assays from Biotest (100%), Biokit (95.8%) and Gull (91.7%) had high specificity for HSV-2. This was much higher than the corresponding specificities for HSV-1. For the Clark Test, the specificity for both HSV-1 and HSV-2 was low. In the Centocor test, one of the 90 tested sera gave an equivocal result. This was excluded from the comparison when sensitivity, specificity, positive and negative predictive values were calculated.

Discussion. Purified whole virus antigens are utilized as the basis of several commercial immunoassays (namely the Clark and Biotest assays). The data obtained from these 2 assays confirm numerous other reports that have shown that immunoassays using whole virus antigen preparations cannot properly discriminate virus antibody subtype. Ashley et al[22] showed that in patients with primary genital herpes, seroconversion to the appropriate viral type was shown by 3 indirect ELISAs in only 33%, 55%, or 75% of cases. Also, these immunoassays failed to identify HSV-2 infection in 58-76% of patients with antibodies to both virus subtypes.[4] Field et al[21] reported that indirect ELISA based upon

Table 1 - Comparison of immunoassays.

HSV type	Immunoassay tests					
	Chiron	Biokit	Gull	Centocor	Biotest	Clark
Panel 1						
Negative	12	16	15	55		
HSV-1	59	48	40			
HSV-2	4	3	5	32		
HSV-1 & HSV-2	13	21	28			
Equivocal	0	0	0	1		
Panel 2*						
Negative	1	1	4	23	2	1
HSV-1	23	22	26		78	4
HSV-2	32	21	13	66	0	0
HSV-1 & HSV-2	34	46	47		10	85
Equivocal	0	0	0	1	0	0

*commercial workers, HSV-1 - herpes simplex virus type 1, HSV-2 - herpes simplex virus type 2

Table 2 - Comparison of 3 commercial immunoassays, Panel 1 Sera.

Commercial immunoassay tests	HSV-1 %	HSV-2 %
Biokit		
Sensitivity	94.4	94.1
Specificity	9.38	88.7
Positive predictive value	98.6	66.7
Negative predictive value		
Gull	79	98.4
Sensitivity	93.1	100
Specificity	93.8	77.5
Positive predictive value	98.5	51.5
Negative predictive value		
Centocor	75	100
Sensitivity	ND	100
Specificity	ND	77.5
Positive predictive value	ND	51.5
Negative predictive value	ND	100

*ND - not done, Centocor assay is designed to detect HSV-2 antibody only. HSV-1 - herpes simplex virus type 1, HSV-2 - herpes simplex virus type 2

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whole virus antigens can give false positive HSV-2 antibody results.[21] In particular, these assays should not be relied upon for diagnosis of non-primary, first episode genital herpes (namely first episode of overt genital HSV-2 infection in persons with past HSV-1 infection) since these assays often give misleading or inaccurate results with respect to both virus type and time of acquisition of infection. When the Clark assay was used in the present study, a high degree of cross-reaction between the serum samples of Panel 2 was observed, with 94.4% (85/90) of sera reacting with both HSV-1 and HSV-2 'whole virus' antigen. Although the Clark immunoassay had a high sensitivity (100%) for detection of HSV antibodies, the specificity of the assays was low in subtyping such as sera HSV-1 (3%) or HSV-2 (20.8%) (**Table 3**). With the Biotest assay, the sensitivity of the HSV-1 IgG immunoassay to detect HSV antibodies from the serum samples of Panel 2 was high (100%) and the specificity of the assay was 81.8%. However, the HSV-2 IgG immunoassay had a low sensitivity (15.2%) but with a high specificity (100%) in detecting HSV antibody with the same serum samples. These data suggest that the Biotest assay cannot properly discriminate HSV-2 antibody. Despite the inability of these commercial immunoassays to properly differentiate antibody subtype, their widespread availability is partly explained by the fact that, in many clinical situations, differentiation of antibody subtype is not essential. The high sensitivity of these assays would be of value in serological diagnosis of infection. It is known that the production of antibody to glycoprotein G, detection of which forms the basis of several of the immunoassays evaluated in this study, can be delayed relative to the production of antibody to other immunodominant antibodies, in acute infection.[22] In these circumstances the use of whole virus antigens capable of detecting the full spectrum of the HSV immune response may be advantageous since such assays may be less susceptible to these temporal changes in production of antibody. Until recently, no commercial assays were available for the detection of HSV-1 specific antibodies in human serum. The WBA was the only assay that could discriminate HSV-1 and HSV-2 specific antibodies but due to standardization and test result interpretation, its use in clinical laboratory settings was limited. The availability of HSV-2 specific serological assays offers the opportunity for non-specialist peripheral diagnostic laboratories to perform such serology. The potential use of these 3 HSV-1 and HSV-2 assays was evaluated. There was a high degree of agreement between predictions made using available laboratory and clinical information and HSV antibody subtyping by the Chiron test (data not shown). The latter assay having previously been extensively validated by other workers.[16-19] The advantage of the assay is that with one nitrocellulose strip both HSV-1 and HSV-2 antibodies in serum can be identified. Such RIBA assays are particularly useful for analysis of limited numbers of samples. However for large-scale screening, and for semi-quantitation of virus specific antibody, ELISAs using the type-specific antigen gG-1 for HSV-1 or gG-2 for HSV-2 provide a more appropriate method. Using the Chiron test as a reference test, the sensitivity and specificity of the Biokit, Gull, and Centocor immunoassays were evaluated using 2 panels of sera. The Biokit test showed slightly higher sensitivity in subtyping HSV-1 antibodies (94.4%) when compared to the Gull test (93.1%). Of 4 samples that were negative by the Biokit test and positive for HSV-1 antibodies by the Chiron test, 2 were subtyped as HSV-1, 2 were

Table 3 - Comparison of 5 Commercial Immunoassays, Panel 2 Sera.

Commercial immunoassay tests	HSV-1 %	HSV-2 %
Biokit		
Sensitivity	100	100
Specificity	66.6	95.8
Positive predictive value	83.8	98.5
Negative predictive value	100	100
Gull		
Sensitivity	100	87.9
Specificity	51.5	91.7
Positive predictive value	78.1	96.7
Negative predictive value	100	73.3
Centocor		
Sensitivity	ND	96.9
Specificity	ND	91.3
Positive predictive value	ND	96.9
Negative predictive value	ND	91.3
Biotest		
Sensitivity	100	15.2
Specificity	81.8	100
Positive predictive value	90.5	100
Negative predictive value	100	30
Clark		
Sensitivity	100	100
Specificity	3	20.8
Positive predictive value	64.1	77.6
Negative predictive value	100	100

ND - not done, Centocor assay is designed to detect HSV-2 antibody only. HSV-1 - herpes simplex virus type 1, HSV-2 - herpes simplex virus type 2

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negative using the Gull test. This possibly reflect the use of both glucoprotein B 1 (gB-1) and gG-1 in the HSV-1 antibody test of Chiron allowing the test to be more sensitive than the Biokit or Gull assays which only use gG-1. On the other hand, the specificities of Biokit and Gull for HSV-1 subtyping were identical (93.8%). When the assays were used to subtype HSV-2 antibodies among the serum samples from Panel 1, the Gull and the Centocor tests were both found to have 100% sensitivity, whilst the Biokit was 94.1% sensitive. However, the specificity of the Biokit test was slightly higher (88.7%) when compared with the Gull and Centocor tests, which both had a specificity of 77.5%. The low specificity for subtyping of HSV-2 antibody, obtained by these immunoassays, suggests that the gG-2 antigen used by Chiron provided a less sensitive test for HSV-2 antibody than the Biokit, Gull or Centocor tests. Using the serum samples from Panel 2, the Biokit and Gull tests showed an identical sensitivity in subtyping HSV-1 antibodies (100%), but the Biokit test specificity was higher than the Gull test (66.6% and 51.5% respectively). On the other hand, the Biokit showed a higher sensitivity and specificity (100% and 95.8%) in subtyping HSV-2 antibodies when compared with the Gull or Centocor (87.9%, 91.7% and 96.9%, 91.3%, respectively). When the Clark test, which utilized whole virus antigen, was compared with immunoassays which used type-specific gG, both were shown to have high sensitivity. However, the ability of the Clark test to correctly identify the subtype of HSV antibody was, in comparison with the type-specific gG immunoassays, very poor (**Table 3**). This study demonstrates the Chiron RIBA, Biokit and Gull assays produce similar results. Assays based upon immuno-affinity purified or recombinant gG can be used for discrimination of HSV-1 and HSV-2 antibodies. Particularly in the context of genitourinary medicine the availability of such assays will enhance clinical management of HSV infected patients and permit appropriate counseling of patients and their partners as to the status of their sexual health. The availability of such assays may also assist clinicians consulting pregnant women during their maternity period and will in future provide the key to the proper evaluation of therapeutic and prophylactic usage of HSV vaccines.[23] The variation on sensitivity and specificity of the assays evaluated in this and other studies[2,24] suggest that testing should be considered only after careful discussion with the patient and, as always, these test results should be interpreted within the overall clinical framework provided by detailed sexual history and genital examination.[7]

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