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Humphrey visual field findings in hydroxychloroquine toxicity

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Learning objectives

Upon completion of this activity, participants will be able to:

- Distinguish the predominant pattern on HVF testing among patients with early HCQ toxicity
- 2. Identify the most valuable type of HVF testing for HCQ toxicity
- 3. Evaluate findings on HVF testing among patients with HCQ toxicity
- Analyze how the diagnosis of HCQ toxicity may be delayed among patients receiving HVF testing

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Humphrey visual field findings in hydroxychloroquine toxicity

Abstract

Purpose To analyze Humphrey visual field (HVF) findings in hydroxychloroquine (HCQ) retinal toxicity.

Methods HVF tests were interpreted retrospectively in this observational case series of 15 patients with HCQ toxicity. Patients seen at Lahey Clinic were identified by diagnosis coding search. Patients with age-related macular degeneration or glaucoma with visual field loss were excluded. HVFs done before the diagnosis were analyzed to see if earlier diagnosis could have been possible.

Results A total of 66 HVFs were reviewed and categorized. Some abnormalities were subtle. Paracentral defects were seen on 10-2 tests whereas 24-2 tests, due to their compressed scale, showed central changes. The abnormalities were often more obvious on pattern deviation rather than the gray scale. Of those patients with prior HVFs available for review, 50% showed HVF abnormalities typical of HCQ toxicity present several months or years before diagnosis. HVF changes preceded fundus changes in nine patients. Conclusion HVF abnormalities indicating HCQ toxicity vary depending on the specific HVF test performed. Clinicians need to be aware of the subtle nature of HVF changes in early toxicity.

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Keywords: hydroxychloroquine toxicity; Plaquenil; toxic maculopathy; Humphrey visual field; retinal toxicity; automated perimetry

Introduction

Misinterpretation of Humphrey visual field (HVF) findings in patients utilizing hydroxychloroquine (HCQ) can lead to delay in

diagnosis of retinal toxicity. Early retinopathy has been defined as an acquired, persistent paracentral scotoma visualized on automated visual field testing without any observable fundus changes.¹ Reports have shown that the visual loss from HCQ toxicity is less likely to be reversible once fundus changes are present.¹⁻³ Although newer testing modalities, such as spectral domain-optical coherence tomography, fundus autofluorescenece, and multifocal electroretinogram, are now recommended as part of screening when available,² automated perimetry remains the most readily available screening test in the majority of practices. Additionally, eye care providers are familiar with interpretation of HVF for glaucoma and other conditions. However, the HVF changes that occur in HCO toxicity are not those seen in glaucoma. Although there have been descriptions in the literature of HVF findings in HCQ toxicity,^{1,4–6} we find that there is confusion in ophthalmology and optometry communities about this topic. HVF findings that may be diagnostic of early HCQ toxicity need to be well understood if clinicians are to be successful at making the diagnosis, particularly when there are no fundus changes to raise suspicion.

The purpose of this study is to review the visual field findings of patients who have been previously diagnosed with HCQ retinal toxicity and to present a summary of HVF patterns seen with this condition, including cases of early toxicity. A secondary goal is to determine if changes could have been recognized earlier in retrospective review of visual field testing done before the time of diagnosis. We will attempt to determine factors that contributed to delay of diagnosis.

Materials and methods

The institutional review board at Lahey Clinic approved this retrospective study. Charts were

reviewed for patients diagnosed with HCQ toxicity at Lahey Clinic. Patients were identified via a diagnosis coding data search for HCQ toxicity. Medical records were requested from outside ophthalmology offices for patients referred to Lahey for evaluation and treatment.

In all, 16 patients were diagnosed with HCQ toxicity between the years 2001 and 2010. One patient was excluded from the study as she did not have any HVF tests for review within 2 years of diagnosis. This patient was diagnosed based on fundus exam. In the remaining 15 patients, diagnosis was based upon reproducible paracentral or central scotoma on automated visual field testing or a single abnormal HVF test combined with typical fundus changes, as per diagnostic criteria of Bernstein.⁷ Patients with significant age-related macular degeneration or severe glaucoma were excluded from the study. Patients with mild glaucoma or drusen without atrophy were not excluded from this study but the co-morbid conditions are noted in the analysis.

Information collected included the type(s) of HVF performed, the date of diagnosis, or date that HCQ was discontinued, and the pattern or defect on HVF. Dosages, length of treatment, and results of other screening tests including fundus exam were noted. In this retrospective study, we quote dosages based on actual, self-reported weight recorded in the chart.

Results

In all, 66 HVFs of 15 patients with HCQ toxicity were reviewed. Different HVF strategies had been used for toxicity screening in this cohort of patients referred from a variety of providers. In all, 52 (79%) of the tests were 10-2 test strategies: with slightly over half of these being red target as compared with white target tests. The remaining 14 HVFs were 24-2 and 30-2 tests.

An average of 4.4 HVFs per patient were available for review with a range of 1-16 HVFs per patient. Nine patients showed a significant period of time where there was no HVF performed either because the patient was lost to follow-up for several years (five patients) or the provider did not order the HVF test as part of screening (four patients). In another three patients, we did not have access to any additional HVFs that may have been performed before referral.

Six patients in this series had pigmentary changes noted at the time of diagnosis. Another patient had drusen but normal IVFA at a time when they showed abnormal HVF typical for HCQ toxicity. The remaining eight patients had a normal fundus exam at the time of diagnosis, and therefore would be considered early

Pt #	Age at diagnosis	Systemic disease	Dosage mg/kg/day	Length of treatment (years)	Fundus at time of diagnosis	Color vision ^a	Amsler defect	Visual acuity
1	81	RA	$5.1/2.56^{b}$	19	Normal	Abnormal	No	20/25 20/30
2	60	RA and SLE	8.8	17	Normal	Abnormal	No	20/20 20/200 (amblyopia)
Э	55	Sjogrens	8.8	12	Bull's eye pigmentary changes	Normal	Yes	20/20 OU
4	52	RA	7.4	15	Normal	Normal	No	20/20 20/25
ß	63	RA	6	12	Bull's eye pigmentary changes	Abnormal	Yes	20/25 OU
9	62	SLE	5.9	26	Pigmentary changes	Normal	Yes	20/20 20/25
7	35	Psoriatic arthritis	4.4	сл	Normal	Abnormal	No	20/20 OU
8	55	SLE and Raynauds	6.8	16	Normal	Normal	Yes	20/30 20/20
6	78	RA	7.1	30	Drusen, no pigment	Abnormal	No	20/30 OU
10	51	SLE	6.7	18	Normal	Abnormal	Not tested	20/20 OU
11	85	RA	$7.3/3.8^{\circ}$	6	Bull's eye pigmentary changes	Abnormal	Yes	20/20 OU
12	72	SLE	6.2	20	Bull's eye pigmentary changes	Abnormal	No	20/25 OU
13	70	Sjogrens	5.9	20	Normal	Normal	No	20/20 20/40
14	36	SLE	5.7	20	Subtle pigmentary changes	Abnormal	Yes	20/20 OU
15	55	RA	5.3	15	Normal	Normal	No	20/30 20/25
Abbrevi Test stra	ations: HVF, Humph	rrey visual field; Pt#: pat	ient by number; RA, rh 0-2	neumatoid arthritis; SLE, syste	mic lupus erythematosus.			

 Table 1
 Demographics and ancillary testing for 15 patients with HCQ toxicity

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City University color vision testing (Keeler Ltd, Windsor, England), except for #10, which was by Farsnworth–Munsell desaturation 15 hue.

All dosages are reported based on the patient-reported weight (rather than lean body weight). All patients were on an actual dose of 400 mg/day, except for patient #1 and 11 who started at that dose and then to 200 mg daily as follows: decreased

then decreased to 3.8 mg/kg/day for another 4 years and then decreased to 2.56 mg/kg/day for 1 more year. Patient #1 used 5.1 mg/kg/day for 18 years and Patient #11 used 7.3 mg/kg/day for 5 years and 1 153

toxicity by our criteria. Table 1 shows dosages, length of treatment, fundus findings at time of diagnosis, and results of ancillary testing for each patient. All dosages are reported based on the patient reported weight (rather than lean body weight). All patients were on an actual dose of 400 mg/day, except for patients #1 and 11 who started at that dose and then decreased to 200 mg daily as detailed in the table.

In all, 11 patients had been using the medication for 15 years or longer. None of our patients had renal disease, which is a risk factor for HCQ toxicity.

Visual field findings

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We reviewed 25 10-2 white tests in 10 of our patients with toxicity. Figure 1 shows a dense, well-defined paracentral ring scotoma in a patient who already had pigmentary fundus changes at the time of referral (patient 3). The remainder of the patients tested with 10-2 white showed more subtle findings. In half of the patients who had 10-2 white tests, the HVF gray scale showed bilateral partial ring defects sparing the central 2 degrees. A complete ring (also sparing the central 2 degrees) was present in the remaining 5 patients who were evaluated by 10-2 white tests. There was no correlation with complete vs partial ring scotoma and presence or absence of fundus changes. Almost all the 10-2 white HVFs showed a defect predictably within the same area: 2-6 degrees from fixation on gray scale, sparing the central 2 degrees. However, two patients showed scattered patches of relative scotoma extending out to 10 degrees, but still sparing the central 2 degrees. Figures 2, 3, and 6 (bottom) show 10-2 white tests from five different patients demonstrating slightly different variations of a paracentral ring defect. In subtle cases, the defect was more obvious when looking at the pattern deviation. In three patients (four tests) the 10-2 white test interpreted as normal by the eye care provider showed a defect suggestive of HCQ toxicity on our retrospective review.

Eight patients had a total of 27 10-2 red tests. Most of the 10-2 red tests showed a complete ring defect bilaterally with a darker gray scale and a wider area affected as compared with the 10-2 white tests (Figure 4). The central sparing was smaller in size and occasionally obliterated. In one of the patients diagnosed by 10-2 red test (patient #10), instead of a ring defect the HVF showed bilateral paracentral scotomas that varied significantly with each test but demonstrated progression over time to a partial ring. In three patients who had 10-2 red tests there were five tests that were read as normal initially but were suggestive of HCQ toxicity on retrospective review.



Figure 1 Late HCQ toxicity: HVF 10-2 white. This visual field (OS of patient #3) shows an easily recognizable paracentral ring scotoma. The patient had pigmentary fundus changes at the time of this HVF.

In the 24-2 and 30-2 testing strategies, because the central area is compressed, one cannot distinguish the central 2-degree field sparing seen on 10-2 tests. Therefore, the HVF pattern on the 24-2 and 30-2 tests showed a small central defect rather than a paracentral ring. Figures 5, 6 (top), and Figure 7 are examples of 24-2 testing in three different patients. We reviewed twelve 24-2 tests and two 30-2 tests in six patients. The central 4 points around fixation are where the scotomas from HCQ toxicity occur on these larger field tests. Tests were felt to be suggestive of toxicity even if there was only one central point scotoma bilaterally of P < 1% probability (represented by a dark gray box on statpac, Zeiss Humphrey, Dublin, CA, USA). It should be noted that a mild, relative defect is seen more easily on deviation plots rather than gray scale. Seven of the twelve 24-2 tests and both of the 30-2 tests reviewed were misinterpreted by the referring eye care provider according to our retrospective review.

Delay of diagnosis

We were able to review HVF scans before diagnosis in 10 patients. Retrospective review showed evidence of HVF abnormality before the diagnosis of HCQ toxicity in five (50%) of those patients who had prior HVF available for review (Table 2). These five patients had 24 total HVF tests reviewed with 14 tests showing findings missed by the clinician. The delay of diagnosis ranged from 11 months to $5\frac{1}{2}$ years. Figures 6 and 7 show examples of



Figure 2 Early HCQ toxicity: HVF 10-2 white. An example typical of early findings on HVF 10-2 white (patient #4, left eye). The defect involves the field from \sim 2 degrees to 6 degrees with central sparing. The right eye test showed very similar findings.

patients who could have been diagnosed earlier based on HVF test results.

The reasons for missing the HVF abnormality varied. The HVF strategy most commonly misinterpreted in this study was the larger visual field tests (24-2 and 30-2), accounting for 9 out of 14 total that were incorrectly interpreted. In one patient, the 10-2 test print out in the medical record did not include deviation plots, which in retrospect could have made the paracentral scotoma more readily apparent to the examiner. In one patient the type of HVF strategy used for screening varied several times over a 6-year period of follow-up. Therefore the comparative value of watching for progression over time on a particular test was lacking. Two of our patients had concurrent diagnoses such as drusen (patient #9) and glaucoma (patient #13), which made the interpretation of the HVF difficult according to the recorded evaluation at the time. Lastly, four of these five patients with HVF misinterpretations were also lost to follow-up for 2 years or more between the time when an abnormal HVF test is documented via retrospective review and the time the diagnosis was made by the practitioner. This fact





Figure 3 More examples of early HCQ toxicity: HVF 10-2 white. Three different patients with 10-2 white testing. In each case, the area affected is similar. Top: note that the subtle defect on gray scale is more obvious on pattern deviation. Bottom: this patient had drusen but no pigmentary changes.



Figure 4 Example of HVF 10-2 red in HCQ Toxicity. This paracentral ring with central sparing is classic for HCQ toxicity as seen on red 10-2 testing.





Figure 5 HVF Findings in HCQ Toxicity using 24-2 Test Strategy. On this 24-2 test, the abnormality is shown as a central defect rather than a ring. This is due to the different scale of a 24-2 as compared to the 10-2 test. The defect may be easier to appreciate on total deviation or pattern deviation.

contributed to the length of time the diagnosis was delayed.

Discussion

The patterns seen on HVF in this cohort of patients with HCQ toxicity depended on the type of test used. The 10-2 white test was felt by the authors to be the most reproducible and easiest to interpret. Although visual field defects in HCQ toxicity can be highly variable in terms of the depth of defect, all our patients showed a similar pattern on 10-2 white, with the same areas affected. However, one needs to look carefully for subtle decreases in threshold in the area at risk: 2–6 degrees from center. On 10-2 white HVF even mildly decreased thresholds (4–8 dB) could be recognizable as positive when there was a contiguous pattern of a paracentral ring or partial ring (Figure 2). One also needs to be certain to review the deviation plots,² as this may make subtle defects more obvious. Previous literature has reported that the superior



Figure 6 Delay of diagnosis in a patient with HCQ Toxicity. This series in a single patient shows a delay of diagnosis. Top: The 24-2 from 4/11/03 shows a central defect consistent with HCQ toxicity. Although it is subtle on the gray scale, the abnormality is evident on the pattern deviation. The test was reported as normal. Middle: A 30-2 done 6/19/03 shows a similar result, but again was read as normal. Bottom: After the patient was lost to follow-up for almost 3 years, the diagnosis was made on 3/2/06 with this 10-2 white test. The fundus remained normal.

Table 2	Summary	of HVF	results	for 15	5 patients	with	HCQ	toxicity
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Pt#	Types of HVF reviewed	HVF type at diagnosis	HVF defect at diagnosis	Number of HVF reviewed (number before diagnosis)	Delay of diagnosis	Reasons contributing to delay of diagnosis (see key below)	Type of HVF where the defect was missed
1	10-2 white, 10-2 red, 24-2, 30-2	10-2 white	Ring scotoma	6 (4)	3 years, 11 months	A; B; E	24-2, 30-2, 10-2 white
2	10-2 white, 24-2	10-2 white	Partial ring scotoma	4 (2)			
3	10-2 white	10-2 white ^a	Ring scotoma	3 (0)			
4	10-2 white, 10-2 red	10-2 red	Constricted with central	3 (1)			
			sparing				
5	24-2, 24-2 red	24-2 red ^a	Dense central scotoma	2 (0)			
6	10-2 red	10-2 red ^a	Paracentral scotoma	2 (0)			
7	10-2 white, 10-2 red	10-2 white	Partial ring scotoma	4 (2)	11 months	D; E	10-2 red, 10-2 white
8	10-2 white, 10-2 red	10-2 white	Ring scotoma	5 (2)			
9	10-2 red, 24-2	10-2 red	Ring scotoma	4 (2)	4 years, 3 months	A; B; C	24-2, 10-2 red
10	10-2 red	10-2 red	Partial ring	16 (15)			
11	10-2 white	10-2 white ^a	Partial ring	1 (0)			
12	10-2 white	10-2 white ^a	Partial ring	1 (0)			
13	10-2 white, 10-2	10-2 white	Patchy paracentral ring	7 (6)	5 years, 6 months	A; B; C; D; E; F	24-2, 10-2 white, 10-2 red
	red, 24-2						
14	24-2	24-2 ^a	Central scotoma	3 (2)	3 years, 7 months	A; B	24-2
15	10-2 white	10-2 white	Subtle ring scotoma	5(4)			

Abbreviations: HVF, Humphrey visual field; Pt#, patient number.

Test strategies varied: 10-2 white, 10-2 red, 24-2, or 30-2.

^aDiagnosis based on fundus findings along with HVF pattern.

Reasons contributing to delay of diagnosis: A: failure to recognize abnormality due to 24-2 (or 30-2) strategy used. B: lost to follow-up for a period of time greater than 2 years. C: concurrent diagnosis making interpretation of HVF difficult. D: 10-2 red test suggestive of toxicity but mistakenly interpreted as false positive. E: subtle ring on grey scale on 10-2 white (for patient # 7, the practitioner was lacking the total deviation plot for review). F: changing HVF strategies used on subsequent screening exams, making comparison over time difficult.

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Figure 7 Another example of delayed diagnosis in HCQ toxicity. Top: pattern deviation shows a defect that is difficult to see on gray scale in this 24-2 test from 8/23/05. Middle: the patient was lost to follow-up for $3\frac{1}{2}$ years. The fundus was still normal on 2/21/08. The abnormality is now slightly more evident on gray scale, but was interpreted as normal. Bottom: on 3/10/09 the patient had pigmentary changes and a diagnosis of toxicity was made.

visual field is most likely to be affected first.³ We noted the superior field to be somewhat more affected than inferior field in 7/15 of our patients. The difference was noted in patients with subtle HVF findings as opposed to those with more dense HVF abnormalities. One of the 15 patients showed the inferior field to be slightly more affected than the superior field. In the remaining seven patients, the superior and inferior fields were equally affected.

When evaluating the 24-2 HVF in HCQ screening, one must pay particular attention to the 4 points surrounding fixation on the plot. Unlike in glaucoma, a single point scotoma may be very significant in HCQ toxicity. A lack of understanding of what to expect on 24-2 or 30-2 tests in HCQ toxicity may have contributed to delay of diagnosis in four patients (nine tests) in this cohort. As with 10-2 white tests, we found it was visually easier to detect a subtle abnormality on the pattern deviation than on the gray scale plot on 24-2 tests.

The 10-2 red test has been recommended in the past as the testing strategy of choice for HCQ toxicity due to its sensitivity.^{1,5} Easterbrook¹ reported the 10-2 red test to be 91% sensitive for detection of HCQ toxicity. However, he also reported a low specificity of 57% for this test. For the 10-2 white test he found a lower sensitivity of 78% for detection of HCQ toxicity but better specificity of 84% with the 10-2 white test (Figure 8).

Although our numbers in this series are too small to give any reliable sensitivity or specificity data, the authors feel more comfortable with the 10-2 white test when screening for HCQ toxicity due to the predictability of the defect seen in this cohort. The 10-2 white strategy is also recommended in a recent American Academy of Ophthalmology publication regarding HCQ screening recommendations.² The exception to our use of 10-2 white strategy would be for a patient with concurrent glaucoma. When there are other clinical reasons to perform 24-2 or 30-2 tests, the clinician can use that test for HCQ screening but must be aware of how HCQ toxicity manifests on the larger-scale HVF testing strategies as elucidated above. The 10-2 white testing can then be performed for confirmation. However, it is not recommended to routinely switch between protocols. We believe the lack of consistency of HVF screening strategy used may have



Figure 8 Comparison of red target *vs* white target 10-2 tests. The two tests shown are from a single patient (#13) done 1 day apart. The red target test was felt to be a false positive as it was so dense. Note that the very central 3–4 degrees are relatively less affected, which is typical of HCQ toxicity. The white target test, read as normal, shows decreased threshold in the pericentral region, suggestive of toxicity. Because of misinterpretation, this was a false negative test. In retrospect, both the red target and white target tests should have been seen as supporting the diagnosis of toxicity.

contributed to a significant delay of diagnosis in one of the patients in this cohort.

Although HCQ toxicity is indeed uncommon when the appropriate dose is used and when there are no other risk factors (obesity, renal disease, or excessive duration of treatment), toxicity does occur. Recent studies indicate the prevalence may be higher than previously believed,^{2,6,8} ~1% after 5–7 years of use and increasing to 2% for 10–15 years of use according to Wolfe *et al.*⁸ It is important that eye care providers are familiar with the patterns on HVF that indicate toxicity: partial or complete ring defect between 2–6 degrees with central sparing on 10-2 white tests; central scotoma affecting one or more of the 4 points around fixation on 24-2 testing (more evident on deviation plots); or more diffuse central or paracentral defect on 10-2 red visual field testing.

Summary

What was known before

- HCQ toxicity causes HVF defects.
- Prognosis is better with early diagnosis.
- HVF can be useful in diagnosing toxicity. Hydroxychloroquine retinal toxicity is known to cause central or paracentral visual field defects. The prognosis for halting vision loss or reversing visual loss is better if toxicity is diagnosed early, particularly before development of characteristic fundus findings. Although various tests are used for screening for toxicity, HVF is one of the screening tests commonly done.

What this study adds

- Past descriptions of abnormal HVFs in this condition are vague.
- What specifically should we look for on HVF to detect early changes?
- How do the 24-2 HVF findings differ from the 10-2 strategy? The pattern of HVF in this condition has not been well described. This is particularly true of early toxicity. Early diagnosis will be difficult if there is confusion as to what constitutes a suspicious test. This study shows clues for detecting early hydroxychloroquine toxicity based on patterns of HVF tests in patients with toxicity. It also identifies pitfalls for missing a positive test, which could lead to delay of diagnosis.

Conflict of interest

The authors declare no conflict of interest.

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Humphrey visual field findings in hydroxychloroquine toxicity

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 A 50-year-old woman has been using hydroxychloroquine (HCQ) for the treatment of rheumatoid arthritis for the last 3 years. She presents to your clinic for screening for HCQ toxicity.

What is the predominant pattern of early HCQ retinal toxicity on Humphrey visual field (HVF) testing?

- A Arcuate scotoma with fundus changes
- B Temporal sector defects without fundus changes
- C Paracentral scotoma without fundus changes
- D Nasal scotoma with fundus changes
- 2. Which of the following types of HVF testing appears most reliable in identifying patients with HCQ toxicity?
 - A 10-2 white
 - B 10-2 red
 - C 24-2
 - D 30-2
- **3.** As you initiate testing for this patient, what should you consider in regard to HVF findings?
 - A Complete ring scotoma were associated with a higher rate of fundus changes compared with partial ring scotoma
 - B The defects on 10-2 white tests were from 2 to 6 degrees from fixation on gray scale
 - C 10-2 red tests demonstrated a more narrow area affected compared with 10-2 white tests
 - D 24-2 tests were more likely than 10-2 tests to show a paracentral ring

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- 4. You are somewhat surprised to find that the patient has signs of early HCQ toxicity, but this was not noted on previous examinations. What should you consider from the current study in regard to delays in diagnosis of HCQ toxicity?
 - A No patient had HVF abnormalities before the diagnosis of HCQ toxicity
 - B There was no evidence of misinterpretation of 10-2 tests specifically
 - C 24-2 and 30-2 tests appeared to be more easily misinterpreted compared with 10-2 tests
 - D The presence of other ocular diagnoses did not affect any delay in diagnosis of HCQ toxicity

Activity evaluation

1. The activity supported the learning objectives.							
Strongly disagree		Strongly agree					
1 2	3	4	5				
2. The material was organized clearly for learning to occur.							
Strongly disagree		Strongly agree					
1 2	3	4	5				
3. The content learned from	om this activ	ity will impa	ct my practice				
Strongly disagree		Strongly ag	ree				
1 2	3	4	5				
4. The activity was presented objectively and free of commercial							
bias.	-	-					
Strongly disagree		Strongly ag	ree				
1 2	3	4	5				