Visual toxicity of synthetic retinoids

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SUMMARY Twelve patients treated with isotretinoin, a synthetic vitamin A analogue, were assessed before, during, and after therapy. Significant falls occurred in the amplitude of the a waves of the scotopic electroretinogram.

Vitamin A has been used topically and systemically in the treatment of skin disease for some 40 years.¹ Analogues of vitamin A (synthetic retinoids) have been developed which have a better therapeutic ratio than the vitamin, and these analogues are now widely used in dermatological practice. Symptomatic dry eye and blepharitis are well described side effects of these drugs,^{2,4} but recent reports^{5,6} suggest that these synthetic retinoids may interfere with retinal function.

This pilot study was set up to investigate prospectively the effect of synthetic analogues of vitamin A on visual function.

Patients and methods

Seventeen patients about to be treated with a synthetic retinoid preparation (isotretinoin) for a dermatological condition, were referred for a pre-treatment assessment. This assessment included a full ophthalmic history and examination, visual field testing, electroretinography (ERG), electro-oculography (EOG), and dark adaptation (DA) studies. The patients were assessed again at one month and three months after starting treatment. The treatment was a four-month course, and it was intended that any subject showing abnormalities would be reassessed one month after stopping treatment; however, this was not always realised in practice.

One patient treated with another retinoid (etretinate) was included in the study and the results are presented separately.

Results

Of the 17 patients referred two failed to attend and

three attended only once. Twelve patients were included in the study. No abnormality was seen in the EOG or DA assessments of any patient. Abnormalities were found in the a wave of the scotopic ERG to a white stimulus in some patients.

The results of the white scotopic ERG a and b waves are shown in Tables 1 and 2 respectively. The attendance is obviously far from satisfactory. Certain subjects show a drop in ERG amplitude in both a and b waves (for example, patient 9) from the pretreatment values to values found during treatment.

Only seven patients had attended for pretreatment assessment and at three months of treatment. These seven paired results (bold type in Tables 1 and 2) were analysed by the two-tailed paired *t* test. The analysis showed that the a wave results for both the right and left eyes showed a significant fall ($t = -2.60$ and $t = -2.80$ respectively, with 6 degrees of freedom, $p < 0.05$). The b wave changes, however, were not significant ($t = -1.47$ and $t = -1.67$).

Table 1 a Wave ERG values (microvolts)

Patient	Pre-Rx		At 1 month's Rx		At 3 months' Rx		Post-Rx	
	R	L	R	L	R	L	R	L
1			180	180	200	210		
2					240	200	100	170
3	200	180			280	240	260	280
4	260	260	260	240	160	170		
5			325	340	200	220	320	165
6			160	140	180	200	170	130
7	460	460			360	330		
8	240	380	220	200	160	180		
9	340	370	230	250	210	250		
10	300	300	200	200	250	260		
11	220	200	260	280	120	120		
12			200	220	180	180		

Rx=treatment.

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Table 2 *b* Wave ERG values (microvolts)

Patient	Pre-Rx		At 1 month's Rx		At 3 months' Rx		Post-Rx	
	R	L	R	L	R	L	R	L
1			404	400	420	432		
2					460	468	348	460
3	544	484			600	584	620	608
4	408	452	476	436	408	412		
5			492	488	312	236	416	364
6			376	356	380	380	355	290
7	612	596			648	588		
8	472	624	496	412	272	332		
9	496	544	350	332	364	408		
10	656	616	568	520	504	524		
11	464	404	420	468	344	352		
12	360	380	330	306				

Rx=treatment.

The one patient (13) using etretinate showed a large and sustained drop in both a and b waves which has not markedly improved since stopping treatment (Table 3). This fits well with the known pharmacodynamics of this drug.

STATISTICS

The standardisation of electrophysiological tests is not easy, and we have therefore resisted the temptation to compare our results with those from a group of 'normal' patients, despite such a procedure giving larger numbers to work with. By restricting the analysis of data only to those patients who have results for the pretreatment and the three months of treatment assessments it was hoped to reduce some of the variability in these tests.

Discussion

'Retinoid' is a generic term describing naturally occurring compounds with vitamin A activity, and synthetic analogues with or without the biological activity of retinol. Vitamin A is vital to many systems

Table 3 *Patient taking etretinate: a and b wave ERG values (microvolts)*

Patient 13	Pre-Rx	On treatment (4/12 duration)		Post-Rx	
		1/12	3/12	1/12	3/12
a Wave	R	180	160	110	100
	L	160	140	110	120
b Wave	R	320	304	220	260
	R	280	286	214	230

Rx=treatment.

in the body, including the maintenance of epithelia, spermatogenesis, and mucus secretion as well as in vision.⁷

Different metabolites may be involved in different tissues. Certainly it is well known that the conformational change of 11-cis-retinal to the all trans form is an essential step in vision. That different metabolites are involved is supported by the observed differences in side effects of different analogues and by the fact that, when given to retinol deficient animals, retinoic acid can support epithelium, but *not* spermatogenesis or vision.⁸ Many analogues of retinol with a greater or lesser degree of vitamin A activity have been synthesised, and it is not unreasonable therefore to suspect that some of these analogues may interfere with visual function while acting as vitamin A substitutes in other tissues.

Retinol is involved in the functioning of the photoreceptors and so one might expect the primary components of the ERG (early receptor potential and a wave) to be affected more than the later components (b wave). This fits with our data where a wave but not b wave changes occur. Some of our subjects show suggestive changes in the b wave, and with larger numbers there might prove to be significant falls in this component of the ERG. The early receptor potential was not looked at in this study, but changes have been reported with etretinate suggesting disturbance of the primary photochemical process.⁹

While isotretinoin has a fairly short half life, etretinate is stored in fat and has a prolonged effect.¹⁰ The one patient taking etretinate has shown a correspondingly prolonged reduction in his a and b wave amplitudes.

In view of the large number of patients taking these drugs it is impractical to screen them all for visual toxicity. However, until the effects of these synthetic analogues of vitamin A are better understood, we suggest that any patients complaining of difficulties in night vision or with colour vision abnormalities should be reviewed. Certainly patients in those occupations where reduced night vision or colour sensitivity would be a problem, such as the armed forces or merchant seamen, may well require more detailed observation.

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