SCIENTIFIC REPORT

Does use of isotretinoin rule out a career in flying?

S P Mollan, M Woodcock, R Siddiqi, J Huntbach, P Good, R A H Scott

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Aim: To evaluate whether previous isotretinoin use induces permanent, measurable, and clinically significant abnormalities in night vision such that flying is precluded, and whether potential military and civilian commercial aviators should be screened routinely.

Methods: A retrospective, non-interventional, consecutive case series of 47 individuals with a confirmed history of oral isotretinoin use were compared to 20 age and sex matched controls.

Results: 47 individuals (44 males and three females), age range 17–33, underwent Goldmann-Weekers dark adaptation (DA) and standard electroretinogram (ERG) according to ISCEV protocols. 34 patients showed no abnormality in any parameters. Two patients had abnormal DA and ERGs. The mean scotopic ERG b wave amplitude of the isotretinoin group was 496.5 μ V (SD 51.3 μ V) compared with 501.7 μ V (62.3.1 μ V) among the controls. The group mean a:b ratio was 0.55 (0.04) compared to 0.69 (0.08) in the controls.

Conclusion: Previous use of isotretinoin may have caused retinal toxicity in two subjects and laboratory evidence of night blindness in 11 further subjects. One subject had subclinical changes remaining in the ERG 96 months after cessation of isotretinoin. This may justify the directed use of electrophysiological screening in professions that are night vision critical.

Isotretinoin (13-*cis* retinoic acid; Roaccutane, Roche) is a retinoid synthetic vitamin A analogue that is effective in the treatment of severe nodular cystic acne and in prevention of acne scarring.¹ Its ocular side effects include decreased dark adaptation, corneal opacities, dry eye, and benign intracranial hypertension. These side effects generally resolve within 1 month on discontinuation of the drug.^{2–7}

Permanent alterations in dark adaptation (DA) with significant loss of night vision have been described in association with the use of the synthetic retinoids, isotretinoin^{1 5} and etretinate.⁴ Fenretinidine, another synthetic retinoid, showed abnormal rod photoreceptor function that was reversible on cessation of therapy.⁸ Persistent, scotopic electroretinographic changes and significant reduction of DA have been associated with isotretinoin use,^{4 5} but it is unclear if these are clinically significant.^{4 7} Animal studies have demonstrated persistent delays in rhodopsin regeneration and a slow recovery of rod sensitivity after light exposure after administration of isotretinoin.⁹

Severe acne is incompatible with military aircrew personal equipment such as pressure breathing apparatus, and individuals can require oral isotretinoin to make them eligible for selection. The use of isotretinoin can threaten a future career in civilian or military aviation. The US Federal Aviation Authority (FAA) and, until recently, the British Civil Aviation Authority (CAA) and the European Joint Aviation Authorities (JAA) would not award a commercial pilot

medical certificate to bar potential pilots with a history of retinoid use. The UK Armed Forces tests ocular function in such individuals.

The prescription of retinoids for acne vulgaris is increasing; these are increasingly prescribed by non-dermatologists. Further evaluation of potential career limiting side effects will aid proper counselling of patients before treatment. The objective of this study was to evaluate whether previous isotretinoin use induces persistent abnormalities in night vision, electrodiagnostic responses, colour vision, or visual fields compared to an age matched normal control population.

METHODS

This was a retrospective observational study of 47 consecutive military aviator applicants (44 males and three females) who gave a history of oral retinoid use and who underwent ocular electrophysiological testing. They were compared to 20 age and sex matched normal controls (18 males and two females). Statistical comparison of the numerical data was performed using Student's *t* test. Information regarding dose, duration of treatment, and time post-medication to assessment were collated.

All underwent electrodiagnostic testing according to International Society for Clinical Electrophysiology of Vision (ISCEV) standardised protocols.^{10 11} The standard scotopic electroretinogram (ERG) protocol was carried out using a Nicolet Ganzfeld stimulator with a flash intensity of 1 log unit above standard flash (SF) intensity (SF intensity 1.5–3.0 photopic cd.s m⁻²). Pupils were maximally dilated and a Burién-Allan contact lens was used. Peak to peak amplitude and latency of a and b waves were measured to each stimulus paradigm. The a:b wave ratio for the intense scotopic responses was recorded.

Dark adaptometry was performed with a Goldmann-Weekers adaptometer (Haag-Streit, Lieberfeld, Switzerland). After 10 minutes of bleach (1400 asb) in a Ganzfeld, the sensitivity thresholds for cones and rods were determined. Colour vision was evaluated by using a Lanthony 15 hue test.

RESULTS

Forty seven consecutive aviation applicants with a mean age of 22.5 years (range 17–33 years) who had previously taken oral isotretinoin were included and compared to the control group with a mean age 23.6 years (range 17–35 years).

DA testing was within the normal laboratory range ($10^{1.5}$ – $10^{2.5}$) in 45 of the 47 (95.7%) in the isotretinoin group; cases X and Y being abnormal, only reaching thresholds of $10^{3.5}$ and $10^{2.8}$ respectively. There was no significant difference between the mean final thresholds in the isotretinoin group compared to the control group.

Thirty four of the isotretinoin group (72.3%) had normal ERG parameters; 13 had abnormal parameters.

Abbreviations: DA, dark adaptation; ERG, electroretinogram; ISCEV, International Society for Clinical Electrophysiology of Vision; RPE, retinal pigment epithelium; SF, standard flash

Table 1 Summary of results from the abnormal cases X, Y, and Z, with laboratory reference ranges for normal

	Case X	Case Y	Case Z	Laboratory reference ranges (SD)
Dose information	8 week course	12 week course	Unknown	–
Interval between end of dose and assessment	7 months	6 months	Unknown	–
Dark adaptation	10 ^{3.5}	10 ^{2.8}	10 ^{1.9}	10 ^{2.5} –10 ^{1.5}
Scotopic (SF+1 log unit) a wave latency RE	20.7	16	21.6	18.4 (1.6)
Scotopic (SF+1 log unit) a wave latency LE	23.2	16	21.6	18.4 (1.6)
Scotopic(SF+1 log unit) a wave amplitude RE	113.7	220.7	171.3	347 (36.4)
Scotopic (SF+1 log unit) a wave amplitude LE	121.9	177.1	193.7	347 (36.4)
Scotopic (SF+1 log unit) b wave latency RE	42.7	44.6	43.4	48.6 (3.4)
Scotopic (SF+1 log) b wave latency LE	44.8	44.6	43.4	48.6 (3.4)
Scotopic (SF+1 log) b wave amplitude RE	300.4	392.7	412.3	502 (66.1)
Scotopic (SF+1 log) b wave amplitude LE	295.7	406.7	410.2	502 (66.1)
a:b wave ratio RE	0.38	0.56	0.42	0.69 (0.04)
a:b wave ratio LE	0.41	0.44	0.47	0.69 (0.04)

SF, standard flash; RE, right eye; LE, left eye.

had abnormally low a:b wave ratios (lower than control group a:b wave ratio of 0.69 (0.04)). Three further subjects (table 1: cases X, Y, and Z) had reduced a:b wave ratios, with two having abnormal dark adaptation (threshold limit of 10²). Their rod isolated scotopic b waves and intense flash scotopic a waves were below normal amplitude and latency.

Intense flash scotopic a wave amplitude and the intense flash scotopic a:b wave ratio were significantly reduced ($p < 0.005$ and $p < 0.001$ respectively) among the isotretinoin group compared to the control group. Intense flash scotopic b wave amplitudes and latency, single flash photopic and 30 Hz (cone) responses were not significantly different between the two groups (table 2).

Recommended dosage of isotretinoin is 500 µm/kg daily to a maximum of 1 mg/kg, with a maximum cumulative dose of 150 mg/kg per course.¹² Sixty six per cent (31/47) of the isotretinoin group had information recorded regarding the dose received: 83.9% (26/31) had one course, 9.7% (3/31) two courses, and 6.5% (2/31) three courses (duration of courses ranged from 6 weeks to 12 months): 63.8% (30/47) had a documented time interval between medication cessation and electrodiagnostic assessment; mean time interval was 36.7 months, with a range of 3–96 months.

Of the 13 subjects within the isotretinoin group who had any detectable abnormal parameter, eight had information regarding their dose. All had only one course of therapy (range of 6 weeks to 6 months on therapy), and the time interval between cessation and testing ranged 6–96 months (mean 37.6 months).

DISCUSSION

Isotretinoin is the most commonly prescribed oral retinoid² and management of acne vulgaris by non-dermatologists is increasing.³ Knowledge of, and warning of, isotretinoin induced side effects is fundamental in this young population. Recommendations for prescribing¹² do not include the counselling of patients for irreversible loss of dark

adaptation. Reduced night capability has previously been associated with isotretinoin use.^{4–6} A subjective decrease in night vision is not always disclosed by the individual to potential employers and may potentially contribute to dangerous incidents or crashes.

The scotopic ERG and its relation to the level of dark adaptation is well known, as are the effects of vitamin A deficiency on both the ERG a and b wave.¹³ A reduction of the scotopic a wave amplitude in three subjects, and a group mean reduction of the a wave amplitude and a:b wave ratio was noted. The relative proportion of the a wave and b wave is a useful indicator for isolating the photoreceptor response from the postsynaptic retinal response.¹³ It would be expected therefore that a selective reduction in the a wave would confirm photoreceptor (rod) dysfunction and a change in retinal vitamin A metabolism is likely to be the cause of these detectable electrophysical changes in our study.

11-*cis* retinal, a retinoid, is the chromophore residing in rhodopsin and in cone opsins that is responsible for vision. 11-*cis*-retinol dehydrogenase is a microsomal enzyme that is abundant in the retinal pigment epithelial (RPE) cells and essential for the recycling of 11-*cis* retinal. Isotretinoin has been shown in rodents to slow synthesis of 11-*cis*-retinaldehyde and regeneration of rhodopsin by inhibiting 11-*cis*-retinol dehydrogenase in the visual cycle.¹⁰ It is therefore not surprising that ERG findings, in the isotretinoin group, suggest an abnormality within the RPE and photoreceptor outer segments in our series.

Our results are comparable with described literature: Brown *et al*⁴ described a statistically significant fall in the scotopic ERG a wave response to a white stimulus in one subject with isotretinoin. Weleber *et al*⁵ also found one isotretinoin case where ERG abnormalities persisted 25 months after the course. In our group the modifications in DA and ERG parameters were not seen to be fully reversible; one subject had subclinical signs of retinal toxicity 8 years after cessation of isotretinoin. This is contrary to the

Table 2 Isotretinoin group results compared to control group

	Isotretinoin group		Control group		p Value
	Mean	SD	Mean	SD	
A wave amplitude	276.8 µV	22.4	324.2 µV	35.5	<0.005
B wave amplitude	496.5 µV	51.3	501.7 µV	62.3	Not significant
a:b wave ratio	0.55	0.04	0.69	0.08	<0.001

findings of Oner *et al*² who concluded that the side effects of isotretinoin disappear after discontinuation of therapy. Because the interval between discontinuation of drug therapy and electrodiagnostic testing was variable and frequently long, this study cannot fully address the rate at which the retinal toxic effects of isotretinoin disappear.

An encouraging result of this study is that the retinal toxic effects of isotretinoin may be measurable by ERG and DA testing and that, in most people, previous isotretinoin use does not lead to a clinically significant reduction in night vision. We recommend, however, that all prescribing physicians involved in the treatment of acne vulgaris with retinoids be cognisant of the potential consequences of treatment on future career paths.

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