Transient Retinal Effects of 5,6-Dimethylxanthenone-4-acetic Acid (DMXAA, ASA404), an Antitumor Vascular-Disrupting Agent in Phase I Clinical Trials

Michael B. Jameson, Dianne M. Sharp, Jennifer I. Sissingh, Christopher R. Hogg, Paul I. Thompson, Mark J. McKeage, Mark Jeffery, Susan Waller, Gary Acton, Colin Green, and Bruce C. Baguley

PURPOSE. 5,6-Dimethylxanthenone-4-acetic acid (DMXAA), an anticancer vascular-disrupting agent, has induced transient visual symptoms in some patients. Exploratory investigations were undertaken to characterize the visual disturbances in two consecutive phase I trials.

METHODS. Assessments were made in 21 patients before and immediately after a 20-minute IV infusion of DMXAA, including visual acuity, fundoscopy, color discrimination, pattern electroretinography (PERG), pattern visual-evoked potentials (VEP), and full-field electroretinography (ERG). Evaluation of late effects was undertaken subsequently in 12 patients before and after 6 weeks of IV DMXAA at one dose per week.

RESULTS. Frequency and intensity of transient visual disturbance increased with DMXAA dose, occurring in two thirds of patients at 3000 mg/m^2. Symptoms included blurring, flickering, fragmentation, alteration of colors, and contrast and mild photophobia, starting during the infusion and resolving completely, usually within 60 minutes. Visual acuity was unchanged but color discrimination was perturbed. Dose-dependent increases in PERG P50 implicit time by up to 23 ms returned toward baseline values within 90 minutes. Prominent transient changes on ERG included prolonged scotopic rod and 30-Hz flicker implicit times and reduced 30-Hz flicker amplitude. In the second trial, no clinically significant sustained effects were detected, although an increase in bright flash a-wave implicit time (P = 0.022) was seen on whole-group analysis. In vitro studies showed nonspecific phosphodiesterase inhibition by DMXAA.

CONCLUSIONS. DMXAA induced acute, transient disturbance of retinal activity consistent with phosphodiesterase inhibition. No clinically significant cumulative effects were noted and most effects occurred at doses higher than those used in ongoing clinical trials (ClinicalTrials.gov numbers, NCT00856336, NCT00863733, and NCT00003697). (Invest Ophthalmol Vis Sci. 2009;50: 2553–2559) DOI:10.1167/iovs.08-2068

A novel antitumor agent, 5,6-dimethylxanthenone-4-acetic acid (DMXAA, ASA404; Antisoma, London, UK) acts through acute selective disruption of tumor vasculature by induction of serotonin and cytokines such as tumor necrosis factor (TNF)-α and interferons. It was developed in a program to synthesize active analogues of flavone acetic acid (FAA), an agent with impressive anticancer activity in mice but little in clinical trials. The species specificity of FAA was, in part, attributed to its ability to induce TNF in murine, but not human, monocyte cell lines, whereas DMXAA induced TNF in both. This observation, along with a greater dose potency and effectiveness of DMXAA than FAA in murine tumor models, led Cancer Research UK to advance DMXAA into parallel phase I clinical trials in New Zealand and the United Kingdom.

Patients in both trials reported transient visual disturbance (including disruption of color vision) immediately after infusion of intermediate doses of DMXAA, with increasing prominence as the dose of DMXAA was escalated. Blurring or disturbance of vision had also been reported in the clinical trials of FAA as grade 1 adverse events, commonly in conjunction with shorter infusion times, but no further details were published.

Acute disturbance of color vision due to drugs is rarely reported, and so an evolving series of exploratory investigations was undertaken to characterize the visual disturbance reported by patients with advanced cancer participating in the phase 1 trial conducted at Auckland City Hospital. These assessments focused primarily on the changes occurring immediately after DMXAA infusion, which appeared to resolve within a few hours, but reassessment on later cycles in one patient raised the possibility that there may be cumulative effects on retinal function. Therefore, in a subsequent safety phase Ib trial conducted to identify the optimal dose of DMXAA for further clinical studies, an ophthalmic assessment protocol was used to further characterize the ophthalmic effects of DMXAA, focusing on possible late effects rather than acute changes. We report the findings of both studies regarding the visual disturbance induced by DMXAA.

METHODS

Full details regarding the eligibility of patients and trial procedures are published elsewhere. In brief, in the first phase I trial, 63 consenting patients with advanced cancer were treated with an IV infusion of DMXAA at a constant dose over 20 minutes every 3 weeks unless...
disease progression occurred or consent was withdrawn. The dose of DMXAA was escalated progressively in cohorts of three to six patients from 6 to 4900 mg \( \cdot \) m\(^{-2} \), to identify the maximum tolerated dose. In the second trial, a crossover design was used to randomly allocate 15 patients to receive six sequential weekly doses of DMXAA (300, 600, 1200, 1800, 2400, and 3000 mg \( \cdot \) m\(^{-2} \)), given as a 20-minute IV infusion. The trials were conducted in accordance with the principles of the Declaration of Helsinki and were approved by the regional ethics committees.

In the first phase I trial, transient visual symptoms were initially assessed by funduscopy and tests of visual acuity and color discrimination before and immediately after DMXAA infusion. These tests were performed at the bedside in daylight conditions as patients were also having intensive pharmacokinetic blood sampling after the first dose. However, patients were evaluated in the Ophthalmic Electrodiagnostic Clinic on second or later cycles with an evolving series of investigations including tests of visual acuity, color discrimination, pattern electroretinography (PERG), pattern visual-evoked potentials (VEPs), and flash electroretinography (ERG). The acute toxicity of DMXAA and the patients’ general condition imposed limitations on testing.

Visual acuity was measured with a Snellen chart. Color discrimination was initially assessed with the Farnsworth-Munsell 100-hue color discrimination test, and then, for more sensitive evaluation, Lanthony’s desaturated 15-hue color discrimination test (D15) was used. The Farnsworth (saturated) 15-hue test was also used in two patients to compare results with those of the desaturated D15 test. The 100-hue test was scored according to the algorithm supplied with the test instructions and plotted on a schematic diagram. The D15 test results were plotted on a schematic diagram and interpreted visually.

Retinal electrophysiological studies were performed immediately before the second DMXAA infusion and then again after its completion as soon as the patients were able to fully cooperate with the procedures (depending on the time taken to recover from other toxicities such as nausea and tremor). These studies were repeated at later time points in selected patients. Electrophysiological studies were performed with an MS60 apparatus (Medelec, Bristol, UK) to record responses and were conducted according to the standards established by the International Society for Clinical Electrophysiology of Vision (ISCEV) for PERG, \(^{12}\) pattern VEP, \(^{13}\) and ERG. \(^{14}\) Normal ranges for these responses in the local population had been determined in the Electrodiagnostic Clinic (Sharp D, Sissingh J, unpublished data, 1995).

In the second trial, an ophthalmic assessment protocol was developed to evaluate the specific areas of retinal function in which changes were noted in the initial phase I trial of DMXAA. Assessments were performed before the first dose and again after the 6-week period of the DMXAA regimen, to assess possible cumulative changes in retinal function. The protocol assessed fundus appearance by funduscopy, intraocular pressure, visual acuity (using the ETDRS chart), contrast sensitivity (using the Pelli-Robson chart), color contrast sensitivity (using Cavity equipment; CH Electronics, London, UK), dark adaptation, PERG, ERG, and on-off bipolar and short wavelength cone (s-cone) responses. Each eye was tested separately and changes in each parameter before and after six doses of DMXAA were calculated for individual eyes. Paired data for each eye were analyzed for all patients with the Wilcoxon matched pairs test (as Gaussian distribution was not assumed).

**RESULTS**

**First Phase I Trial**

Visual disturbance was reported by two of three patients at each of the 1375, 1650, 2000, and 2600-mg \( \cdot \) m\(^{-2} \) dose levels and by all patients treated at higher dose levels (3100, 3700 and 4900 mg \( \cdot \) m\(^{-2} \)). The onset of symptoms was toward the end of the 20-minute DMXAA infusion, but resolution was rapid and complete, usually within 30 to 60 minutes. The symptoms, which included blurring, flickering, fragmentation, alteration of colors (often patchy), slight darkening of vision, and mild photosensitivity, intensified with increasing dose but were not usually distressing. The most extreme visual symptoms occurred at the highest dose level, 4900 mg \( \cdot \) m\(^{-2} \), at which a patient initially reported darkening of vision and slight color alteration, evolving over 10 minutes to include greater intensity of red and black, starker contrast, glittering of objects, jittery motion, loss of fine detail, and strobelike effects (pulsating colors). Another patient treated at that dose level noticed a blue hue and reduced color intensity, which pulsed at approximately 1 Hz, and a third described altered, vibrant colors, sharper contrasts, shimmering, glittering, and fluctuation in size of objects. Only one patient, treated at 2600 mg \( \cdot \) m\(^{-2} \), reported visual symptoms at later time points unrelated to the infusion (day and weeks later) comprising occasional, brief pinpricks of light in his visual fields and flickering when his eyes were shut, but no later information is known.

Visual acuity did not change significantly after DMXAA at any dose. Funduscopy was unchanged after DMXAA infusion in two of eight patients and was not performed in others, as transient alterations in retinal function were thought unlikely to be manifested as visible changes. Deterioration in color discrimination on the Farnsworth-Munsell 100-hue test was detected in two of four patients tested at the 1650- and 2000-mg \( \cdot \) m\(^{-2} \) dose levels. The changes seen in one of these patients are depicted in Figure 1. An increase in errors on the desaturated D15 test was observed in five of seven patients after DMXAA infusion of 1650 to 3700 mg \( \cdot \) m\(^{-2} \). The two patients who had both saturated and desaturated D15 tests made more errors on the desaturated test, with the most dramatic changes in both tests being observed in a patient treated with DMXAA at 3700 mg \( \cdot \) m\(^{-2} \) (Fig. 2).

PERG was performed at all dose levels from 1650 to 4900 mg \( \cdot \) m\(^{-2} \) upward, involving 12 patients in total, although assessment of the PERG after infusion was complicated by a transient drug-induced tremor, which gave a noisy recording (Fig. 3), and it was also noted that the P50 wave developed much more slowly after DMXAA. An increase in P50 wave implicit time was observed in all patients, with the greatest increase (23 ms) being recorded in a patient treated at 4900 mg \( \cdot \) m\(^{-2} \), with a significant dose–response correlation (Fig. 4). However, the P50 wave implicit time returned to baseline by 24 hours and, in three patients tested, it remained within normal limits between 1 week and 3 months later.

ERG was performed before and after DMXAA infusion in three patients treated at 3700 mg \( \cdot \) m\(^{-2} \) and in one at 4900 mg \( \cdot \) m\(^{-2} \). Rod responses after DMXAA showed an increase in a- and b-wave implicit times in response to dim blue light (≈1.1 log intensity of standard flash), most marked at the highest dose level (Fig. 5). In contrast, little change in implicit time was seen with the standard flash, and no consistent changes were observed in a- and b-wave amplitude. The sum of the oscillatory potentials decreased in all patients after DMXAA infusion (data not shown). Marked changes were seen in cone responses, particularly reduction in the amplitude of the 30Hz flicker response (by 85% in the most extreme case) and an increase in its implicit time (Fig. 6), with resolution of the changes when retested 24 hours later. Similar, though less prominent, changes in the photopic cone response amplitude were recorded but the effect on a- and b-wave implicit times was inconsistent between patients.

In one patient treated with six cycles of DMXAA at 3700 mg \( \cdot \) m\(^{-2} \), ERG was performed before and after the second and sixth cycles. Comparison of pretreatment recordings revealed ~30% reduction in the amplitude of a- and b-waves of the scotopic and 30Hz flicker responses (Fig. 7), although little
change in photopic, transient cone responses or implicit times was seen. A patient treated at $4900 \text{ mg} \cdot \text{m}^{-2}$ had an ERG performed 3 months after the second cycle and, although no baseline ERG was available for comparison, the ERG was within normal limits for the reference range established in the local population.

FIGURE 1. Farnsworth-Munsell 100-hue test results in a patient before (A) and immediately after (B) treatment with DMXAA at $1650 \text{ mg} \cdot \text{m}^{-2}$. The increase in errors is seen as a shift of the plotted line farther away from the innermost (no error) ring.

FIGURE 2. Saturated and desaturated 15-hue color discrimination tests recorded before (A, B) and immediately after (C, D) DMXAA infusion in a patient treated at $3700 \text{ mg} \cdot \text{m}^{-2}$, showing an increase in the number of errors.
Dose–response relationship of increase in P50 wave implicit time in the PERG after DMXAA infusion.

DISCUSSION

It is clear from these studies that DMXAA induces acute but rapidly reversible changes in retinal function that result in dose-dependent transient visual symptoms. The occurrence of retinal dysfunction in a group of patients with advanced cancer raises the possibility of cancer-associated retinopathy (CAR), a chronic paraneoplastic phenomenon that is thought to be antibody mediated.\textsuperscript{15} However the transient nature of the symptoms and the differing electrophysiological characteristics discount CAR as an explanation of the symptoms. Fluorescein angiography was not performed to evaluate possible transient retinal vascular disruption by DMXAA, because the characteristics of the visual disturbance are not consistent with retinal ischemia. Furthermore, limited preclinical evaluation in mice did not reveal any evidence of retinal vascular activation by DMXAA; indeed the antivascular effects were confined to tumor vessels and the spleen (Wilson WR, personal communication, 2004).

Drug-induced visual disturbance occurs occasionally with vigabatrin and digoxin, but this usually develops slowly, and the electrophotographic changes described\textsuperscript{16,17} do not resemble those seen with DMXAA.

In contrast, sildenafil (Viagra; Pfizer, New York, NY), a drug used for the treatment of erectile dysfunction, can induce visual symptoms\textsuperscript{18,19} that bear striking similarities to those seen with DMXAA. No symptoms with sildenafil is dose-dependent, ranging from 3% of men taking 25 to 50 mg to approximately 50% of those taking 200 mg or more.\textsuperscript{20} Subjects have reported temporary color aberration (usually a bluish tinge or haze), increased light sensitivity, and difficulty seeing in dim light—symptoms that resemble those reported at intermediate doses of DMXAA. No change in visual acuity was seen with either sildenafil\textsuperscript{22} or DMXAA. Dose-dependent impairment of color discrimination changes in rod-mediated responses (remaining within the normal range) identified after the first course of DMXAA had reverted to pretreatment levels.

Statistical analysis of electrophysiological test results across the whole group revealed a significant increase in bright-flash a-wave implicit time ($P = 0.022$) with a trend toward similar changes in the photopic a-wave implicit time ($P = 0.063$). The only statistically significant change in amplitude was an increase in the bipolar on (b-wave) response ($P = 0.047$).

Pattern VEP was performed in five patients at 1650, 2000, and 3700 mg · m$^{-2}$, and whereas an increase in P100 wave implicit time was induced by DMXAA in most of the patients, the number of subjects was too small to determine any dose–response relationship.

Second Phase I Trial

Fifteen patients participated in the trial, of whom 13 were evaluated with the ophthalmic protocol; in three patients, only one eye was tested due to poor vision in the other eye (two patients) or tarsorrhaphy. Visual disturbance was reported with increasing frequency with escalating DMXAA dose (1 report at 300 mg · m$^{-2}$, 3 at 600 mg · m$^{-2}$, 3 at 1200 mg · m$^{-2}$, 7 at 1800 mg · m$^{-2}$, 8 at 2400 mg · m$^{-2}$ and 10 at 3000 mg · m$^{-2}$). Of the 12 patients completing the ophthalmic assessment protocol, four had no discernible changes in any test; in the remainder no consistent abnormality was found after treatment, and any changes were considered mild.

In particular, visual acuity, intraocular pressure, contrast sensitivity, color contrast sensitivity, and dark adaptation were unchanged, except for single instances of a minor change in contrast sensitivity and color contrast sensitivity, which were considered of no clinical significance.

Two patients had prolongation of PERG P50 implicit time by 4 ms: one with preexisting age-related maculopathy, and the other with reduced P50 amplitude and mildly reduced P50 implicit time (without change in amplitude). Two older patients had a change in morphology of the waveform with a broadening of the P50, but the N95 was within normal limits in all patients both before and after treatment, and the N95:P50 ratio was greater than 1.1 in all patients. Most changes on ERG testing remained within the normal range, and no individual patient had deterioration in all parameters of global retinal function. Some of the recordings fell outside of the reference range determined from a group of 10 individuals with normal vision previously tested on the same equipment. None of the patients had electrophysiological findings expected with cancer-associated retinopathy, such as severe global depression of both rod- and cone-mediated responses on the ERG and markedly reduced P50 component of the PERG. One patient completed two six-dose courses of DMXAA, and thus a third set of ophthalmic tests was completed, which revealed that the
These effects were transient and fully reversible.ERGs studying sildenafil in an anesthetized dog model included a loss of a-wave amplitude which may have obscured a small effect, and it is not clear which threshold was used to determine the clinical significance of any changes seen. The ERG changes induced by sildenafil in what threshold was used to determine the clinical significance of any changes seen. The ERG changes induced by sildenafil in an anesthetized dog model included a loss of a-wave amplitude and an increase in both a- and b-wave implicit times, but all these effects were transient and fully reversible. However, the ERG data were examined for differences in group means rather than intraindividual differences, which may have obscured a small effect, and it is not clear what threshold was used to determine the clinical significance of any changes seen. The ERG changes induced by sildenafil in an anesthetized dog model included a loss of a-wave amplitude and an increase in both a- and b-wave implicit times, but all these effects were transient and fully reversible. These changes were greatest at free plasma sildenafil concentrations of 810 nM, with little change until free plasma sildenafil levels reached 71.5 nM, equivalent to those found in humans after a 400-mg dose (four times the maximum recommended dose).

The visual symptoms of sildenafil are ascribed to inhibition of the phosphodiesterase (PDE) isoenzyme type 6 (PDE6), an enzyme found exclusively in the outer retina that is responsible for modulating the transduction cascade of the photoreceptor response to light. In humans the visual symptoms after sildenafil ingestion roughly paralleled the time course of the plasma concentrations and usually resolved within 4 hours. The impact of other PDE inhibitors on in vitro ERG recordings correlated with their potency of PDE6 inhibition. Clinically, other PDE inhibitors used for erectile dysfunction (such as tadalafil and vardenafil) that have little or no activity against PDE6 are not associated with visual side effects.

In vitro studies confirmed that DMXAA is a nonselective inhibitor of PDE but is less dose-potent than sildenafil against PDE 6 (Table 1). However the plasma free DMXAA levels measured in patients who experienced visual symptoms (27–284 μM) approximated or exceeded the estimated IC50 of DMXAA for PDE6 (35 μM) by up to ninefold, whereas the mean plasma-free sildenafil concentrations measured in clinical trials remained below its IC50 for PDE6. This provides important evidence to support the hypothesis that the retinal effects of DMXAA are mediated, at least in part, by inhibition of PDE6 and explains why the visual symptoms and electrophysiologically changes are much more marked with DMXAA than with sildenafil. Other supportive evidence comes from the striking similarities of the symptoms, pattern of changes in color vision, and ERG changes observed with DMXAA, sildenafil, and other inhibitors affecting PDE6.

However, PDE6 inhibition may not be the only mechanism by which visual symptoms are induced by DMXAA. Some of the symptoms, such as change in color, size, or motion of objects, suggest that signal processing in the inner retinal layers and/or at more central levels may also be disturbed. Indeed, there is supportive clinical evidence of disrupted central neural processing with the transient confusion and slurred speech seen at the highest dose level administered.

These two clinical studies show no clear evidence of clinically significant persistent retinal toxicity from DMXAA within this dose range; although we acknowledge the limited number of patients evaluated and lack of long-term follow-up. The addition of DMXAA 1200 mg · m−2 to carboplatin and paclitaxel chemotherapy for six cycles in a randomized phase IIb trial in 79 patients with non-small cell lung cancer produced only transient retinal symptoms but improved median survival by 5 months. Repeat-dose toxicity studies in nonhuman primates also suggest that DMXAA does not pose a significant risk to long-term ocular function (Antisoma Research Limited, unpublished data, 2006). At the maximum tolerated dose of DMXAA in this species (~1400–1500 mg · m−2), electrophysiological tests did not reveal any apparent abnormality in the ocular response to light. In addition, microscopic examination...
of the eye did not show any pathologic changes consistent with ocular toxicity.

Clinical and preclinical studies with sildenafil have also allayed concerns about possible chronic retinal toxicity. Despite in vitro studies demonstrating dose-dependent retinal degeneration with prolonged exposure to nonspecific PDE inhibitors, extensive toxicity studies of sildenafil with long-term follow up in humans, dogs, and rats have shown no cause for concern (Zrenner E, et al. J Ophthalmic Inflammation and Degener. 2011;1:21) and this finding is supported by those from extensive postmarketing surveillance. Although long-term electrodiagnostic retinal studies have not been performed in humans or animals, no histologic changes were seen in the retinas of dogs and rats that received sildenafil orally daily at 60 to 150 times (doses were in milligrams per kilogram) the recommended maximum human dose (achieving plasma concentrations that caused marked acute changes in the dog ERG) for 6 to 24 months. Furthermore, patients with preexisting diabetes mellitus did not have an increased risk of adverse visual events with sildenafil, and small trials looking at individuals with age-related macular degeneration, diabetic retinopathy, and glaucoma have not shown any unexpected problems after sildenafil (Grunwald JE, et al. IOVS 1999;40:ARVO Abstract 4048).

No clinical studies have been performed in individuals with retinitis pigmentosa (RP) or those heterozygous for PDE6 mutations but a preclinical model of heterozygous mice (Pdeg<sup>tm1/</sup>) lacking the γ subunit of rod PDE6 showed that sildenafil, at IC<sub>50</sub> doses 10 times the equivalent maximum recommended human dose by weight, caused ERG changes similar to those described in the dog trial, but these were transient and fully reversible. Of note, there were no changes in the ERGs recorded from wild-type mice at the same doses, suggesting that the heterozygous mice were more susceptible to temporary effects of PDE6 inhibition, but without sustained changes.

The evaluation of the retinal effects of DMXAA in these two clinical studies has demonstrated the in vivo clinical and electrophysiological sequelae of potent inhibition of PDE6. On this limited evaluation there was no evidence of clinically significant long-term retinal effects of DMXAA, and none has been demonstrated with another PDE6 inhibitor, sildenafil, although the relevance of its safety data to DMXAA has not been clearly established. However, the lower dose of DMXAA (1800 mg·m<sup>2</sup>) used in an ongoing international, phase III registration trial adds a further safety margin.

### References


### Table 1. Inhibition of PDE Isoenzymes In Vitro by DMXAA

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<th>% Control Activity</th>
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DMXAA is produced by Antisoma Research Limited, London, UK. The origin of the enzymes was either human (h) or bovine (b).


