Subclinical impairment of colour vision in patients receiving ethambutol

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1 Colour discrimination was assessed by means of the Farnsworth-Munsell 100-Hue test in 54 patients being treated for tuberculosis with ethambutol and 50 patients who were treated for tuberculosis by drugs other than ethambutol.

2 The ethambutol group showed significantly more errors than controls along the deutan axis.

3 The sub-group of ethambutol treated patients who had been taking the drug for more than 2 months showed significantly more errors along the tritan axis.

4 It is concluded that subclinical colour discrimination impairment is relatively common in patients receiving ethambutol and that a deutan type of defect is an early and a tritan type of defect is a later manifestation of ethambutol toxicity.

Keywords ethambutol colour discrimination ocular toxicity

Introduction

The organ most prominently affected by ethambutol toxicity is the eye. The most serious ocular effect is optic neuritis associated with demyelination of the optic nerve (Schmidt, 1966). The earliest manifestation of eye involvement is a disturbance of colour vision which may be along the protan or deutan axis (Trusciewicz, 1975; Zrenner & Krüger, 1981; Delacoux *et al.*, 1978). Studies in isolated carp retinas have indicated that the drug affects colour opponency reversibly, without changing the sensitivity of the underlying processes (Van Dijk & Spekrijse, 1983). The colour vision disturbances in patients also appear to be reversible (Pahlitzsch & Tiburtius, 1969).

The Farnsworth Munsell 100-Hue test (Farnsworth, 1943) is used to assess colour discrimination in industry, but has also been used to assess the effects of drugs such as digitalis (Aronson & Ford, 1980; Rietbrock & Alken, 1980) and ethambutol (Trusciewicz,

1975; Delacoux *et al.*, 1978) on colour vision.

We wish to report our findings in using this test to ascertain whether we could detect any colour vision disturbances in patients being treated for tuberculosis with ethambutol and who apparently have normal vision.

Methods

The study was conducted at the Ruttonjee hospital on inpatients undergoing chemotherapy for tuberculosis. Patients were on therapy for at least 1 month and had normal vision. Patients with a history of visual disturbances, including colour blindness and any blurring of vision, were excluded from the study. Refraction errors corrected by glasses were not regarded as a reason for exclusion. All patients gave informed verbal consent to visual testing.

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The test population comprised 54 patients receiving ethambutol. The number of patients was determined by the number of patients conforming to our selection criteria during the period of study. A randomly selected group of 50 patients on antituberculous therapy other than ethambutol served as controls.

Patients were tested for colour vision using the Farnsworth Munsell 100-Hue test (Farnsworth, 1943). To avoid the influence of learning, only one test was done per patient. The test is based on arranging a series of 84 coloured caps in sequence according to hue. Caps 1 to 67 range from red to yellow to green to blue to purple and cover the visible light spectrum from 633 m μ to 455 m μ , whereas the remaining caps have a gradual transition back to red. The caps are numbered in sequence on the back and are randomly scrambled before presentation to the subject. Results are expressed on a circular x-axis (colour points 1 to 84) and a radiating y-axis (error scores from 2 to 14). The error score for each cap is determined by adding the differences (irrespective of whether positive or negative) between it and the caps on either side. For instance, a sequence of 28, 31, 29 would score $(31-28) + (31-29) = 5$. A correct sequence would score 2. For determining error scores for a particular area these values are first corrected by subtracting 2 from each and then adding the values.

For persons with normal colour vision errors are scattered randomly around the circular x-axis, whereas in persons with defective colour vision high error scores will be concentrated in a specific area as well as in the complementary area immediately opposite it.

All patients were tested in the same room under fluorescent lighting with exclusion of daylight. Error scores for each colour (red, yellow, green, blue and purple) were determined by adding the score of the midpoint of the particular colour to the three values on either side of it. Similarly, error scores were determined for the areas of transition from one colour to another (yellow to red, green to yellow, blue to green, purple to blue, red to purple).

Individual points on the circular plots were statistically compared for the two groups by the Mann-Whitney test. The individual colour groups were analysed by dividing the test and control populations into two, namely those above and those below a certain error score cut-off point. These results were analysed using Pearson's χ^2 test for error score cut-off values of 10, 15 and 20.

The ethambutol group was further subdivided into those who had taken the drug for up to 2

months and those who had taken it for more than 2 months. These two groups were compared using Pearson's χ^2 test as described for the test and control populations.

Results

The test group consisted of 47 males and seven females with a mean age of 52.2 ± 16.8 years (range 22–82). The control group consisted of 36 males and 14 females, mean age 50.6 ± 18.7 years (range 21–78). Due to the higher percentage of females in the control group the sexes were also analysed separately. As the separate analysis did not alter the findings we will only report on the analysis of the total patient population. The patients in the test group were receiving 14.7 ± 4.0 mg kg⁻¹ day⁻¹ of ethambutol for 49 $\pm$ 40 days (range 30–340). The control group had been an antituberculous treatment for 72 ± 57 days (range 30–276).

When comparing individual points on the graph there were significant differences between the test and control groups at two points ($P < 0.05$, Mann-Whitney test), namely at point 13 (yellow) and point 33 (green). In both instances the error was higher in the control than in the test group.

A significantly higher percentage of errors were found in the test population in the yellow area ($P = 0.032$, error cut-off 10) and in the purple-to-blue transition area ($P = 0.049$, error cut-off 20). These findings are shown graphically on a modified recording chart in Figure 1. The circular x-axis represents the colour and transition areas and the radial y-axis the difference in percentage error between test and control population. The latter was determined by adding the three percentages above each cut-off point for the particular colour or transition area for the control population and subtracting it from the same calculation for the test population.

When comparing the two subdivisions of the test group (i.e. those on treatment for up to 2 months and those on treatment for more than 2 months) no significant differences in the areas that differed from the control population (i.e. yellow and purple to blue) were found. There was, however, a significantly higher percentage of errors in the patients on treatment for more than 2 months in the red area ($P = 0.032$ for error cut-off 15, $P = 0.041$ for error cut-off 20) and in the complementary blue to green transition area ($P = 0.025$ for error cut-off 10). These results are shown in Figure 1. These two populations were also assessed in terms of dosage, the less than 2 month group receiving

Figure 1 Representation of the difference in error scores between the control and test population (a) and between the test population on ethambutol for more than 2 months and those on ethambutol for less than 2 months (b).

$15.18 \pm 4.4 \text{ mg kg}^{-1} \text{ day}^{-1}$ of ethambutol (range 8, 1–23, 3) and the more than 2 month group $13.35 \pm 2.6 \text{ mg kg}^{-1} \text{ day}^{-1}$ (range 9, 4–20).

We also compared the subgroup of the test population who had been treated for more than 2 months with controls and found *P* values of 0.341 (error cut-off 10), 0.069 (error cut-off 15) and 0.090 (error cut-off 20) for red and *P* values of 0.041 (error cut-off 10), 0.669 (error cut-off 15) and 0.572 (error cut-off 20) for the blue to green transition area.

Discussion

In looking at individual colour points on the circular plot for the two groups of patients, the two points that showed significant differences were probably chance events, as accepting a *P* value of less than 0.05 as significant one would expect differences occurring by chance in one out of every twenty points. Furthermore, the points are not in complementary colour areas as would be expected if this were due to a particular colour vision defect in the control population. One would also expect that if colour vision defects occurred in the test population they would only affect certain individuals and not the total population. Consequently an analysis of means is probably inappropriate.

In the χ^2 analysis we looked at the relative frequency of errors in the various areas of colour discrimination. When comparing the ethambutol patients with controls, there were significantly

more errors in the former group in the yellow area and the purple to blue transition area. This is somewhere between a protan and a deuteran axis, but appears closer to a deuteran axis. In the yellow area 20% of the test population had error scores above 10 as compared to 6% in the control population. Subtracting the control percentage suggests an incidence of ethambutol induced colour vision change of 14%. No significant changes along the tritan axis were found.

When subdividing the test population into those who had received ethambutol for up to 2 months and those who had been taking the drug for more than 2 months it seemed that duration of therapy in terms of this subdivision did not have an influence on the incidence of deuteran type errors. It was, however, interesting to find that there were significantly more errors along the tritan axis in patients who had taken the drug for more than 2 months.

It is apparent that as there was a relatively small group of hospitalized patients who had been taking the drug for more than 2 months, the influence of this group of people was too small to show up as a significant difference when the test population as a whole was compared to controls. When the more than 2 month group was compared with controls there was in fact a significant difference along the deuteran axis.

Our study found evidence of colour vision defects along the deuteran axis as suggested by other authors (Trusciewicz, 1975; Zrenner & Krüger, 1981; Delacoux *et al.*, 1978). What has not emerged from previous studies is the late

appearance of tritan defects and the dissociation in time as far as the development of these defects is concerned. Our findings suggest that colour vision disturbances in patients receiving ethambutol is relatively common and that deuteran type errors in colour discrimination occur early during ethambutol therapy, whereas errors along the tritan axis develop later.

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