

Brief communication

Effect of praziquantel and oxamniquine treatment on human isotype responses to *Schistosoma mansoni*: elevated IgE to adult worm

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SUMMARY

Pre- and post-treatment antibody isotype responses to Schistosoma mansoni adult worm and soluble egg antigens were compared in a study population previously used to show that IgE against adult worm correlates negatively with intensity of reinfection following chemotherapeutic cure. IgG subclass responses to adult worm were lower after treatment whereas IgM and IgE were higher. The increase in IgE to adult worm was observed with different preparations of adult worm, including the worm tegument, and with both praziquantel and oxamniquine therapy. No significant difference was observed between pre- and post-treatment isotype responses to egg antigens following either praziquantel or oxamniquine therapy.

Keywords IgE, praziquantel, oxamniquine, schistosomiasis

INTRODUCTION

The understanding of the mechanisms of host immunity against schistosomiasis has been expanded by the use of endemic human population reinfection studies. These studies involve the chemotherapeutic cure of existing infections, monitoring the rate of reinfection, and the identification of immunological correlates with resistance or susceptibility to reinfection (e.g. Dunne *et al.* 1992). Using this methodology, an association between schistosome-specific IgE and low intensities of reinfection following treatment have been shown in studies of *Schistosoma mansoni* (Rihet *et al.* 1991, Dunne *et al.* 1992) and *S. haematobium* (Hagan *et al.* 1991). The peak immune response following chemotherapy occurs five weeks after treatment and is characterized by heightened eosinophilia and total parasite-specific antibody levels (Butterworth *et al.* 1985). Both praziquantel (PZQ) and oxamniquine (OX) have been used to treat schistosomiasis in these population-based studies; PZQ in Africa (Hagan *et al.* 1991) and OX in Brazil (Rihet *et al.* 1991), for example. Although they have different modes of schistosomicidal action, for both drugs a prelude to ultimate worm death and degeneration is damage to the worm tegument exposing the host to a range of parasite antigens (Fallon, Fookes & Wharton, 1996).

We have looked at the effect of drug treatment on parasite-specific antibody isotypes in 68 *S. mansoni*-infected Kenyans. These individuals were from a study population used to demonstrate an association between IgE responses against adult worm antigens and resistance to reinfection (Dunne *et al.* 1992). At that time potential effects of treatment were not addressed. Without any prior selection, 44 subjects were treated with 40 mg/kg PZQ (Bayer Pharmaceuticals) in a single oral dose and 24 with 30 mg/kg OX (Pfizer) in two oral doses on successive days, and all subjects were cured of infection. The mean levels (log_e

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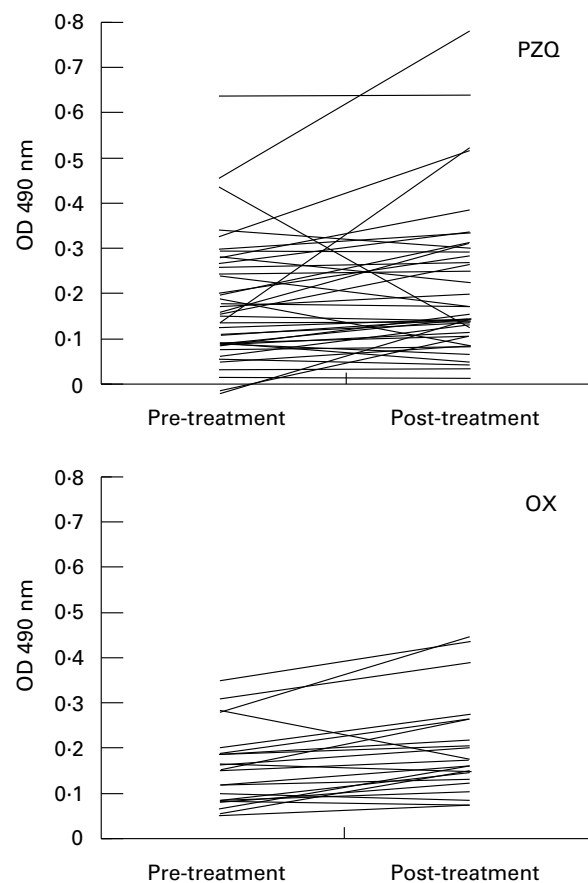
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Table 1 Mean ($\pm 95\%$ confidence interval) antibody isotype responses to *S. mansoni* adult worm preparations before and after chemotherapeutic cure in a population of 68 Kenyan individuals. Level of significance for differences between pre- and post-treatment responses shown

Isotype	Antigen	Pre-treatment (A) (Mean $A_{490\text{nm}} \pm \text{CI}$)	Post-treatment (B) (Mean $A_{490\text{nm}} \pm \text{CI}$)	Significant differences between Pre-treatment (A) and Post-treatment (B)
IgA		0.069 (± 0.014)	0.064 (± 0.010)	NS
IgG		0.580 (± 0.053)	0.432 (± 0.043)	$P < 0.001$ A > B
IgG ₁		0.219 (± 0.039)	0.154 (± 0.024)	$P < 0.001$ A > B
IgG ₂	detergent-AW	0.120 (± 0.014)	0.107 (± 0.009)	$P = 0.001$ A > B
IgG ₃		0.076 (± 0.015)	0.061 (± 0.011)	NS
IgG ₄		0.340 (± 0.081)	0.233 (± 0.056)	$P < 0.001$ A > B
IgM		0.259 (± 0.035)	0.288 (± 0.034)	$P = 0.022$ B > A
IgE	detergent-AW	0.159 (± 0.028)	0.204 (± 0.034)	$P < 0.001$ B > A
	PBS-teg	0.120 (± 0.022)	0.164 (± 0.028)	$P < 0.001$ B > A
	detergent-teg	0.655 (± 0.032)	0.721 (± 0.027)	$P = 0.004$ B > A
	denuded-AW	0.064 (± 0.019)	0.096 (± 0.022)	$P = 0.004$ B > A

[epg+1]) of infection (PZQ: 5.901; OX: 6.378) and reinfection (PZQ: 3.432; OX: 4.415) were not significantly different between the two treatment groups. The mean age, however, was higher in the PZQ-treated group (PZQ: 24 years; OX: 16 years; $P = 0.033$). We have measured levels of antibody isotypes specifically reactive with detergent solubilised egg and adult worm (detergent-AW) antigens, and also IgE responses to (i) a PBS extract of the adult worm tegument (PBS-teg), (ii) a detergent extract of the adult worm tegument (detergent-teg), and (iii) tegument-stripped adult worm (denuded-AW), by ELISA as described previously (Dunne *et al.* 1992). Isotype responses in sera taken six months after treatment were detected simultaneously with pre-treatment responses and compared by the non-parametric Wilcoxon test for paired data not normally distributed. At six months post-treatment reinfection had not occurred (Dunne *et al.* 1992).

No significant differences were observed between pre- and post-treatment isotype responses to egg antigens. As shown in Table 1, the mean responses of all IgG subclasses to detergent-AW were lower six months after treatment, with total IgG, IgG₁, IgG₂ and IgG₄ being significantly reduced. In contrast, IgE and IgM responses were significantly higher after treatment, and IgE responses to different preparations of the adult worm tegument and the denuded worm body were also significantly elevated following chemotherapeutic cure. In the same population we have found that the changes in IgE and IgG4 responses to detergent-AW (i.e. rise in IgE and decrease in IgG4) occur in both children (5–14 years) and adults (15+ years) (Webster *et al.* 1997). The rise in IgE to adult worm following treatment was very interesting in view of the fact that, in this study population, correlations between isotype responses to *S. mansoni* and

**Figure 1** Individual pre- and post-treatment IgE responses to detergent-AW, detected by ELISA, in *S. mansoni*-infected individuals treated with praziquantel (PZQ) or oxamniquine (OX). Values expressed as mean $A_{490\text{nm}}$ of triplicate assays.

resistance to reinfection were significant for post-treatment levels of adult worm-specific IgE only (Dunne *et al.* 1992).

Numerous studies on the efficacy and tolerance of PZQ and OX in humans have been described (Davis 1993) but there have been limited studies comparing parasite-specific immune responses generated in humans before and after curative treatment of *S. mansoni*. PZQ and OX differ in their rates of drug-induced damage to the worm tegument, as well as the sites and extent of tegumental damage incurred and the rate of antigen exposure (Fallon *et al.* 1996), all of which may affect the specificity of the immune response generated by the host. The cohort studied here were from the same schistosomiasis mansoni-endemic area and had similar genetic backgrounds and degree of exposure to the parasite. This population, therefore, was ideal for comparing the effects of PZQ and OX on IgE responses to *S. mansoni*.

The mean IgE responses to detergent-AW were significantly higher after treatment in subgroups of individuals treated with either OX (means 0.156 [pre-treatment] vs 0.198 [post-treatment]; $P=0.001$) or PZQ (means 0.166 [pre-treatment] vs 0.207 [post-treatment]; $P=0.007$) despite the PZQ-treated group being significantly older. Figure 1, which shows individual pre- and post-treatment IgE responses to detergent-AW for subjects treated with either PZQ or OX, illustrates the rise in IgE levels in most individuals following treatment.

This study, which has shown that IgG subclass responses to *S. mansoni* adult worms decline after chemotherapy whereas adult worm-specific IgE responses are elevated,

indicates that drug treatment has a significant long-term effect on the human immune response. This was shown in a population in which high levels of post-treatment parasite-specific IgE were associated with resistance to reinfection after treatment.

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