The Potential of Triclabendazole in Combination with Praziquantel for the Treatment of *Schistosoma mansoni* Infections

by

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I declare that this thesis is the account of my own research, and contains as its main content work which has not previously been submitted for a degree at any tertiary institution.

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Abstract

Previous work has suggested that triclabendazole (Tcbz), a member of the benzimidazole group of compounds, possessed efficacy against *Schistosoma mansoni* (*S. mansoni*). In view of recent indications in praziquantel (Pzq) treatment failures and loss of sensitivity, it is imperative that new anti-schistosomals are developed as contingent treatment options, while resistance alleles, if any, remain at low frequencies. While recent studies have indicated that Tcbz monotherapy exert weak anti-schistosomal effects, the combined application of Tcbz with Pzq has not been explored. To assess this hypothesis, triclabendazole and its metabolites were initially assessed against the many life-stages of *S. mansoni in vitro*. Combination drug and isobologram analyses against adult *S. mansoni* was also performed, and subsequently assessed against other parasite species to assess the specificity of such effects. Subsequently, the drug combinations were assessed against *S. mansoni in vivo*. A cost-effectiveness model was then developed to predict the feasibility of administering Pzq-Tcbz drug combinations in Senegal. It was concluded that triclabendazole and its metabolites possessed good efficacy against immature schistosomula, although weak efficacy was observed against adult *S. mansoni*. Upon combination with Pzq, however, a strong synergistic effect against adult worms were observed *in vitro*. Praziquantel and Tcbz were also shown to possess unique and independent ovicidal modes of action that can be clinically significant. More importantly, *in vivo* drug trials concluded that the combinations exerted additive effects against *S. mansoni* harbored in mice. Economic modeling and cost-effectiveness analysis further demonstrated the feasibility of this drug combination and showed that the drug combinations may represent a new line of treatment against mansonial schistosomiasis.
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Abbreviations

~ approximately
< less than
> greater than
% percent
°C degree celcius
Abz albendazole
b.w. body weight
Bz benzimidazole
CaCO₃ calcium carbonate
cm centimetres
DDI H₂O double deionised water
DMSO dimethylsulphoxide
DNA deoxyribonucleic acid
EC₅₀ concentration required to cause 50% worm mortality
EC₂₅ concentration required to cause 25% worm mortality
EC₁₀ concentration required to cause 10% worm mortality
EDTA ethylenediaminetetraacetic acid
EGTA ethylene glycol-bis(β-aminoethyl ether) N,N',N'-tetraacetic acid
et al. and others
FCS fetal calf serum
g gram
g unit of gravitational field
G gauge
HCl hydrochloric acid
hr hour
IMF International Monetary Fund
IRR internal rate of return
kg kilogram
L litre
µ (prefix) micro (10 x⁻⁶)
m (prefix) milli (10 x⁻³)
M mole
m    million
x mag  magnification
met  metrifonate
µM  micromoles
mg  milligram
mL  millilitres
mM  millimoles
min  minute
M.W.  molecular weight
n (prefix)  nano (10⁻⁹)
NaOH  sodium hydroxide
NBCS  newborn calf serum
NaCl  sodium chloride
NPV  net present value
Oxm  oxamniquine
PBS  phosphate buffered saline
pH  minus log of hydrogen ion concentration
Pzq  praziquantel
QIMR  Queensland Institute of Medical Research
R&D  research and development
rpm  revolutions per minute
SD  standard deviation
SE  standard error
s  second
Tcbz  triclabendazole
Tcbz-Sx  triclabendazole sulphoxide
Tcbz-Sp  triclabendazole sulphone
US$  United States dollars
WHO  World Health Organization
Wk  week
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