ACKNOWLEDGEMENTS

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REFERENCES


IVERMECTIN LEVELS VARY IN TISSUES AND SPECIES

OKONKWO P.O.*, NWOYE I.* AND OGBUOKIRI J.E.*

KEYWORDS: ivermectin, chemotherapy, resistance, bioavailability, filariasis, onchocerciasis.

SUMMARY

Ivermectin (IVM) is high in faeces, not found in urine but low in skin, saliva and breastmilk of man. Plasma levels vary according to species. Binding to plasma proteins varies also. Resistance of some farm animal nematodes to the avermectins has been reported. A small percentage of patients show poor reduction in skin mf after yearly treatment with ivermectin. We suggest that tissue bioavailability of free drug must be ascertained before interpreting animal models and chemotherapy programs.

INTRODUCTION

Ivermectin has achieved much attention in veterinary medicine because of an excellent reputation as an endocitide. There have been reports of resistance of some nematodes in farm animals to ivermectin (Craig, 1993). Interestingly, a small population of individuals do not respond to ivermectin with reduction of dermal microfilariae in mass chemotherapy programs. Filaria worms in rodent models of filariasis (Wanjii, 1992) are also insensitive to ivermectin. There have been no explanations for these phenomena. One possible explanation is variable bioavailability in species and tissues.

In this communication we have measured ivermectin levels in tissues. Variations in the tissue effects of anti-filarial drugs may be related to in situ tissue bioavailability of the drug.

MATERIAL AND METHODS

Ivermectin is measured routinely in our laboratory by an HPLC method (Klotz et al., 1990 ; Krishna and Klotz, 1993). The method can detect 0.5 ng/ml with an interassay and intrassay variability averaging 3.6% and 5.6% respectfully. The assay time is 10 minutes. All human subjects granted informed consent. This study received requisite approval from the Ethical Clearance Committee of the University of Nigeria Teaching Hospital.

RESULTS AND DISCUSSION

Over the last four years we have been distributing ivermectin annually in a community hyperendemic for onchocerciasis (Okonkwo et al., 1991). In this area where the guinea savannah and forest merge, there are typical skin lesions as well as eye lesions.

Table I lists some pharmacokinetic indexes in ten onchocerciasis patients. There are wide individual variations in these parameters. In this small population of patients, there are two pharmacogenetic groups: Early T_{max} (time to reach maximum plasma concentration) – high C_{max} (maximum plasma concentration) group and late T_{max}-low C_{max} group. We are investigating whether the persons with low levels of ivermectin in blood after the normal recommended 150 µg/kg correspond with those who show low reduction in dermal and ocular microfilariae.

<table>
<thead>
<tr>
<th>MEAN</th>
<th>SEM</th>
<th>RANGE</th>
</tr>
</thead>
<tbody>
<tr>
<td>T_{1/2}</td>
<td>56.5</td>
<td>7.5</td>
</tr>
<tr>
<td>CL (ml/min)</td>
<td>142.5</td>
<td>22.6</td>
</tr>
<tr>
<td>V (L/KG)</td>
<td>154.5</td>
<td>190.3</td>
</tr>
<tr>
<td>T_{max}</td>
<td>4.7</td>
<td>0.5</td>
</tr>
<tr>
<td>C_{max}</td>
<td>38.9</td>
<td>5.8</td>
</tr>
</tbody>
</table>

Table I. – Pharmacokinetic parameters of ivermectin in plasma of patients with onchocerciasis.

We have previously shown that ivermectin binds to plasma proteins (Okonkwo et al., 1993). The avidity of binding varies according to species if physiological concentrations are used for in vitro concentrations. On the average human serum albumin binds 95 %, bovine serum albumin 80 %, ovalbumin 75 % and alpha 1 acid glycoprotein < 50 % of total blood ivermectin. Free unbound drug is the only physiologically active entity. Thus levels and types of proteins may largely determine free drug levels. Hypoalbuminemia and raised reactive proteins are often seen in parasitic infections. The T_{1/2} of ivermectin shows wide variability in many species, cattle 1.8, sheep 2.7, dog 1.8, swine 0.5, rabbit 0.8, man 2.3 (days).

In man and some farm animals faeces are the richest source of largely unaffected ivermectin. This is most important in gut dwelling nematodes but of little relevance for filaria worms located in the lymphatic circulation or in skin locations. The drug can be measured in saliva and breastmilk. The levels in milk are low (Figure 1) and we have advocated (Ogbuokiri et al., in press) that the restriction during lactation should be modified to allow the general improvement in well being after ivermectin distribution to extend to babies and their mothers.

Figure 2 is the comparison of the fractional extraction of ivermectin from plasma in saliva, breastmilk and skin. Skin
with a heterogeneity of proteins and lipids should contain low amounts of ivermectin. Our observations are important in interpreting drug effects not only with ivermectin but with other filaricides in all forms of filariasis. The crucial question is whether the drug should impinge on the vital organelles of the worm or are host factors more responsible for drug induced worm killing (Schulz-Key et al., 1993). Is the adult O. volvulus less sensitive because of low ivermectin in the nodule? Are some animal filaria models unsuitable because the particular species show low concentration at the target site? We also have shown that in man there may be a pharmacogenetic basis for handling of ivermectin.

ACKNOWLEDGEMENT

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EFFECT OF REPEATED IVERMECTIN TREATMENT ON THE EVOLUTION AND PROGRESSION OF OCULAR PATHOLOGY IN ONCHOCERCIASIS


KEYWORDS: onchocerciasis, ocular pathology, ivermectin.

In West Africa, control of onchocerciasis by the Onchocerciasis Control Programme (OCP) relies on both vector eradication and chemotherapy (Remme et al., 1990a, 1990b). Ivermectin, the drug of choice, is highly effective against microfilariae of Onchocerca volvulus; a single oral dose achieves a rapid elimination and a long lasting suppression of microfilaridermia (Greene et al., 1985). Such efficacy and the moderate adverse reactions following treat-

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