

FROM THE LABORATORY TO THE HOME OF THE PATIENT INFECTED WITH *ONCHOCERCA VOLVULUS* (*O. v.*): CLINICAL EXPERIENCE WITH AMOCARZINE (PRELIMINARY RESULTS)

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KEYWORDS : onchocerciasis, chemotherapy, amocarzine.

SUMMARY

If dosed correctly, amocarzine has onchocercicidal effects with acceptable clinical tolerability. Up to now over 1 900 patients were exposed to an initial amocarzine regimen and over 500 have been re-exposed to amocarzine 2 years after initial therapy. Amocarzine is a promising onchocercicidal drug and a potential candidate for onchocerciasis control programmes.

A 3 days postprandial therapy of Amocarzine (= 6 doses) in patients with moderate onchocerciasis had onchocercicidal effects against macro- and microfilariae, because four months post-therapy the majority of adult worms were dead or moribund as evidenced by histological analysis of excised onchocercoma and because skin microfilariae remained reduced for up to two years post-therapy with the best levels at 7-17 % of the initial parasite load. Retreatment schedules with a simplified postprandial dose regimen (= 4 or 2 doses) at the start of the third year post-initial therapy equally showed good clinical tolerability. Single doses with acceptable clinical tolerance produced insufficient efficacy over two years post-therapy, but responded with important reduction of skin microfilariae after retreatment at the 3rd year post-initial therapy.

Amocarzine (CGP 6140) is a 4-nitro-4' - (N-methyl-piperazinylthio-carbonylamido) - diphenylamine and represents a novel compound which is not related to any known anthelmintic. It is a brightly coloured red-orange crystalline powder and was effective in all models for the filariases upon repeated oral administration and similar effects were observed in *in vitro* studies.

Amocarzine was investigated in single oral dose build-up studies in fasting state at the Onchocerciasis Chemotherapy Research Centre in Ghana from 1985-1987. Determination of drug levels in plasma of such doses produced irregular absorption patterns (Lecaillon *et al.*, 1990a) and hence the analysis of efficacy and tolerability became inconclusive. Due to apparent slow action of amocarzine on microfilariae the time for excision of the onchocercoma (= nodulectomy) had to be changed from 60 to 120 days. Because of high dead worm rates in control nodules, the Ghanaian Centre was moved from a vector-controlled area by the Onchocerciasis Control Programme (Tamale, Central Ghana) to a holoendemic region (Hohoe, South-East Ghana). The postprandial administration of amocarzine in patients with *O. v.* was compared to the one in fasting state at the WHO Collaborating Centre in Bamako (Mali). The pharmacokinetic profile showed more homogeneous postprandial drug levels with areas under the curve statistically superior to those in fasting state (Lecaillon *et al.*, 1990b). In

addition fixed-dosing was abandoned for body-weight-adjusted-dosing following reversible neurologic side effects in 1988. Since tolerated single-dosing lacked efficacy, low-dose-repeat-dosing was also investigated from 1986 onwards. Such repeat dose regimens showed encouraging results for efficacy in 1987/1988 in Guatemala. Monitoring of drug absorption by qualitative urine colorimetry, a method developed in the field, was useful. Similarly the monitoring of intranodular changes of onchocercoma by ultrasonography following amocarzine administration was developed in the field as a non-invasive method.

The clinical down-titrating pilot study with postprandial administration was performed at Hohoe in 1988. Combined clinicopharmacokinetic open studies were subsequently conducted in 1989 with a 3 days postprandial drug regimen (6 doses) in Latinamerica (Ecuador, Guatemala) in about 360 adults of both sexes (Poltera *et al.*, 1991 ; Poltera, 1991). The low dose regimen equally produced reliable absorption which therefore fulfills the prerequisite for the therapy of a systemic disease such as onchocerciasis. With this 6 dose amocarzine regimen the majority of patients reported slight dizziness, a condition which was completely reversible, mainly on the 3rd and 4th day post-treatment. Transitory cutaneous rash and pruritus was most noticeable on the 6th day following start of therapy. No alteration was noted in the haematological or biochemical serum values. Nodules surgically excised 4 months after the 3 days regimen showed that 65 % of the adult female worms were dead and further 20 % moribund, 15 % were considered alive. In Ecuador control nodulectomies showed that on the average 81,5 % of the worms were alive while 18,5 % were dead. Dermal microfilariae were reduced to low levels by amocarzine. Ophthalmologically amocarzine was well tolerated. Visual acuity and fields showed no alteration or improved. Microfilariae in the anterior chamber were slowly reduced and by 90 days were negative and remained so. No changes, that could be attributed to the use of amocarzine were noted in the posterior segment. For the future sake of compliance the postprandial amocarzine regimen was subsequently reduced from 6 to 4 doses in about 300 adults/juveniles of both sexes with similar results that is onchocercicidal effects and acceptable or good tolerability (Figure 1).

In a rural pilot study for masstherapy with only 2 doses of amocarzine in two Latinamerican Centres there was overall good clinical tolerability. In Ecuador amocarzine was administered to 410 patients after a meal, while in Guatemala amocarzine was swallowed after a fruit juice by 550 patients. In the former a sharp and sustained reduction of the dermal microfilariae was obtained, while in the latter the skin microfilariae were insufficiently reduced. This "non-responsiveness" in the latter Centre prompted a repeat therapy with the same dose after a meal one year after initial therapy. The reduction of skin microfilariae was achieved, therefore corroborating the importance of postprandial administration in the masstherapy (Figure 2). The patients of both Centres will be followed for a second year. It is hoped that a sustained effect will be achieved as in smaller studies with amocarzine retreatments.

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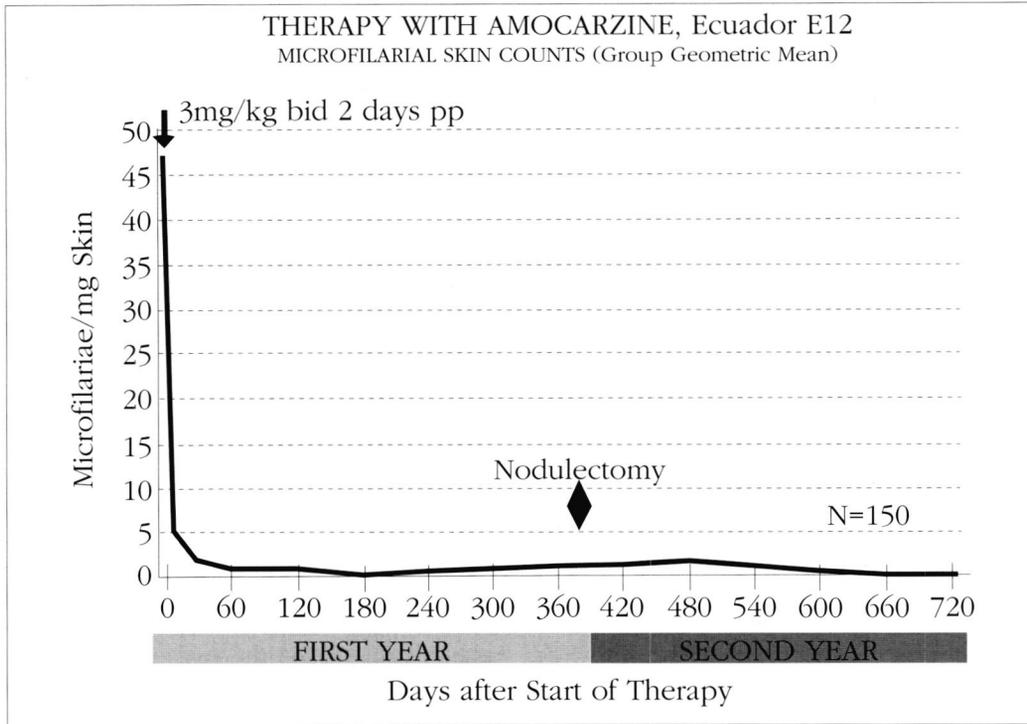


Figure 1. – Clinical trial in Ecuador (E12) in 150 *O.v.* patients of either sex involving adults and juveniles of Amerindian and African origin. Evolution of the microfilarial skin counts over two years after one exposure (to four postprandial doses of amocarzine in 2 days (3 mg/kg each). Nodulectomy was performed one year post-drug.

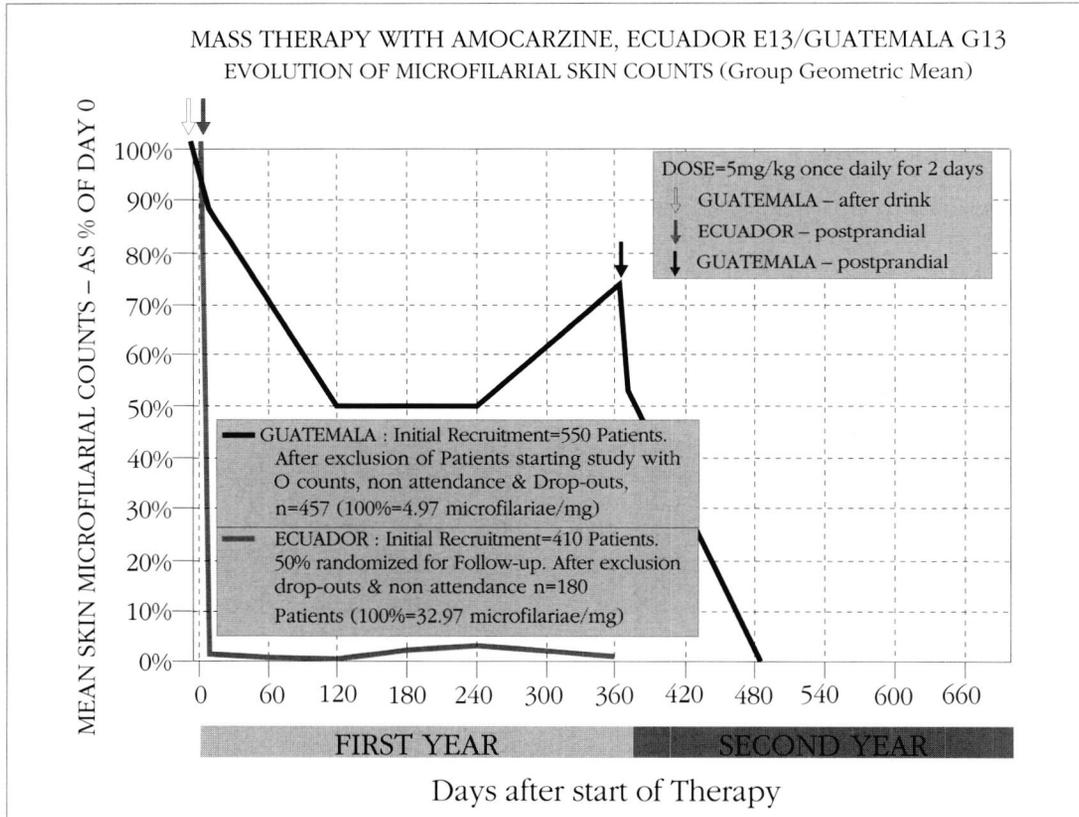


Figure 2. – Rural Pilot Study for Masstherapy with Amocarzine in *O.v.* patients from Ecuador (E 13, n = 180) and Guatemala (G13, n = 457). Evolution of the geometric means of skin microfilariae expressed in % of day 0 = 100 %. In both studies the same dose was administered : in Ecuador after a meal, in Guatemala after a drink. In the latter, retreatment after a meal became mandatory at the beginning of the 2nd year inducing a reduction to zero. Patients will be followed during the 2nd and 3rd year post initial therapy.

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IVERMECTIN LEVELS VARY IN TISSUES AND SPECIES

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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 have 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 endocytide. 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 (Wanji, 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 % respecti-

vely. 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 indices 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 $\mu\text{g}/\text{kg}$ correspond with those who show low reduction in dermal and ocular microfilariae.

	MEAN	SEM	RANGE
$T_{1/2}$	56.5	7.5	29.3-84.9
CL(ml/min)	142.5	22.6	249.2-62.1
V(L/KG)	1545.3	190.3	2418.3-802.7
T_{max}	4.7	0.5	6-3
C_{max}	38.9	5.8	58.6-21.8

Table 1. – 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

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