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LOW LEVEL EXPOSURE TO ORGANOPHOSPHATE PESTICIDES IN THE UDA WALAWE AREA AND ITS EFFECTS ON CARDIO-RESPIRATORY AND NEUROLOGICAL FUNCTIONS

by

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Thesis submitted to the University of Sri Jayewardenepura for the award of the Degree of Doctor of Philosophy in Physiology on 'Low level exposure to organophosphate pesticides in the Uda Walawe area and its effects on cardio-respiratory and neurological functions'.

Dedicated to my parents,

my husband, and my sons

Savesh and Rahil

The work described in this thesis was carried out by me under the supervision of Professor A. R. Wickremasinghe, Dr. D. K. Ruberu and Dr. W. van der Hoek and a report on this has not been submitted in whole or part to any University or any other institution for another Degree/ Diploma.

Roshini Peiris-John

29.06.2004

Date

We certify that the above statement made by the candidate is true and that this thesis is suitable for submission to the University for the purpose of evaluation.

Dr A. R. Wickremasinghe — Date 30/8/2003

Dr D. K. Ruberu — Date 4/9/2003

Dr W. van der Hoek — Date 11/9/03

Table of Contents

List of Tables

Page No.

Page No.

Page No.

List of Figures

List of Plates

List of Abbreviations

%N	-	Percent normal
A	-	Acylated/ phosphorylated/ carbamylated AChE
A4/A1	-	Ratio of amplitudes of the fourth to the first action potential
ACh	-	Acetylcholine
AChE	-	Acetylcholinesterase
AcTC	-	Thiocholine esters
AV node	-	Atrio-ventricular node
BMI	-	Body mass index
BuChE	-	Butyrylcholinesterase
C	-	Compound
CAP	-	College of American Pathologists
cAMP	-	Cyclic adenosine monophosphate
ChAT	-	Choline-O-acetyltransferase
CI	-	Confidence interval
CM	-	Colorimetry
CNS	-	Central nervous system
COPIND	-	Chronic organophosphate induced neurological damage
DAG	-	Diacylglycerol
DBP	-	Diastolic blood pressure
DEP	-	Diethyl phosphate
DEPTh	-	Diethyl phosphorothiolate
DETP	-	Diethyl thiophosphate

DMDTP	-	Dimethyl dithiophosphate
DMP	-	dimethyl phosphate
DMTP	-	Dimethyl thiophosphate
DTNB	-	Dithionotrobenzoic acid
ECG	-	Electrocardiograph
EM	-	Electrometry
EMG	-	Electromyograph
ENG	-	Electroneurograph
FAO	-	Food and Agricultural Organisation
FMO	-	Family of enzymes containing flavins
$FEF_{50\%}$	-	Forced mid-expiratory flow rate
FEV1	-	Forced expiratory volume in the first second
FVC	-	Forced vital capacity
GC	-	Gas chromatography
Hb	-	Haemoglobin
HPLC	-	High performance liquid chromatography
IMS	-	Intermediate Syndrome
IP_3	-	Inositoltriphosphate
IPM	-	Integrated Pest Management
LC	-	Liquid chromatography
M1 - M5	-	Muscarinic M1 to M5 receptors
MCV	-	Motor conduction velocity
n	-	Number
NA	-	Noradrenaline

NMJ	-	Neuromuscular junction
Non-IPM	-	Untrained in Integrated Pest Management
NTE	-	Neuropathy target esterase/ neurotoxic esterase
OP	-	Organophosphate
OPIDP	-	Organophosphate Induced Delayed Polyneuropathy
PEFR	-	Peaked expiratory flow rate
Q	-	Quotient
R	-	Alkoxy/ Alkyl group
RBC	-	Red blood cells
SA node	-	Sino-atrial node
SBP	-	Systolic blood pressure
SCV	-	Sensory conduction velocity
SM	-	Spectrophotometry
TNB	-	Thionitrobenzoic acid
TOF	-	Train of four
TOFR	-	Train of four ratio
UNEP	-	United Nations Environmental Health Programme
WHO	-	World Health Organisation
X	-	Leaving group
Yala 1	-	First exposure season studied
Yala 2	-	Second exposure season studied
α1	-	Adrenergic α1 receptor
β1	-	Adrenergic β1 receptor
β2	-	Adrenergic β2 receptor

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Low level exposure to organophosphate pesticides in the Uda Walawe area and its effects on cardio-respiratory and neurological functions

Roshini Janet Peiris-John

ABSTRACT

Over 90% of pesticides used today are insecticides, and approximately half of them are organophosphates (OP). OP compounds are anticholinesterases that inhibit cholinesterase activity resulting in increased availability of acetylcholine (ACh) at its sites of release. ACh influences endocrine and exocrine secretions, cardio-respiratory function, the gut and its secretions, muscle power and functions of the brain. Adverse health effects due to its accumulation are multiple. This study investigated the effects of long term and acute occupational and environmental exposure to OPs on the cardiovascular, respiratory and neurological functions.

An analytic, follow-up study was conducted among 150 farmers trained in integrated pest management (IPM farmers), 150 untrained farmers (non-IPM farmers) who were occupationally exposed to OPs and 100 freshwater fishermen who were likely to be environmentally exposed to OP, all of whom were resident in the Uda Walawe irrigation scheme in Sri Lanka. They were evaluated at three time points, twice during two cultivation seasons and once during a non-exposure season. Fifty marine fishermen living in Moratuwa, away from agricultural areas were evaluated as a control group. A structured interviewer administered questionnaire was used to obtain information on personal details, occupational history, pesticide handling, past-medical history, social

history and symptom profile. A medical examination was conducted at each time point and included, measurement of blood pressure, handgrip force, and evaluation of vibration sense, two-point discrimination and higher mental function. Haemoglobin corrected red blood cell acetylcholinesterase (AChE) activity was measured and ECG recordings were obtained from all subjects. Electrophysiological, neuromuscular transmission and lung function tests were conducted on a randomly selected subset of 30 farmers, 30 freshwater fishermen and on the 50 marine fishermen. Data were entered in EpiInfo version 6 (CDC, Atlanta) and analysed using SPSS version 10 (Chicago, Illinois) statistical package. Ethical clearance was obtained from the Ethical Review Committee of the Faculty of Medical Sciences, University of Sri Jayewardenepura.

The farmers and freshwater fishermen had, on average, in their lifetime been directly exposed to OP pesticides for 15.5 and 3.86 years, respectively. IPM farmers wore protective clothing during work in the field significantly more than non-IPM farmers ($p<0.05$). Personal protective equipment such as goggles, footwear, gloves or masks were rarely used by both groups of farmers. IPM farmers spent considerably less time per hectare on spraying insecticides as compared to non-IPM farmers ($p<0.001$).

The mean ($\pm$SD) baseline AChE levels (U/ g) during the non-exposure season in the farmers as a single group, in the non-IPM farmers, IPM farmers, in the freshwater fishermen and in the controls were 29.25(4.05), 29.16(3.81), 29.22(3.99), 27.75(3.35) and 32.53(3.97), respectively. AChE inhibition was significant in the farmers and the freshwater fishermen during both exposure seasons studied ($p\leq0.001$). Although IPM

farmers spent less time spraying, and used more protective clothing as compared to non-IPM farmers ($p<0.001$), AChE inhibition was similar in the two groups. AChE inhibition in occupational exposure correlated with adverse effects on sensory and motor systems, but not with nerve conduction studies, cardiovascular or respiratory functions. AChE inhibition in environmental exposure did not correlate with any adverse effect detected. AChE inhibition following a single low level exposure persisted for more than 5 days.

Symptoms associated with CNS effects predominated following long term and acute occupational exposure to OP. Acute environmental exposure to OP pesticides resulted in symptoms suggestive of CNS effects, which were less prevalent following long term environmental exposure.

Handgrip force and vibration sense were significantly weaker in the farmers, following long term and acute occupational exposure as compared to the controls ($p<0.05$). Vibration sense was significantly weaker in the freshwater fishermen following acute exposure to OP as compared to the controls ($p<0.05$). Attention span, short term memory and subtraction skills were weaker in the farmers (both IPM and non-IPM), and freshwater fishermen following long term and acute OP exposure as compared to the controls ($p<0.05$). Sensory conduction velocity (SCV) was significantly faster following long term occupational ($p=0.001$) and environmental ($p<0.001$) exposure, and motor conduction velocity (MCV) was significantly slower ($p<0.05$) following long term occupational exposure, as compared to the controls. Both SCV and MCV decreased following acute occupational and environmental exposure to OP.

Neuromuscular transmission was significantly weaker in the farmers, and the freshwater fishermen, as compared to the controls, following both, long term and acute low level exposure ($p<0.01$).

Diastolic blood pressure was significantly lower following long term and acute, occupational and environmental exposure to OP ($p<0.005$). Systolic blood pressure was significantly lower following acute occupational exposure ($p<0.001$), and long term and acute environmental exposure to OP ($p<0.005$). The PR-interval decreased following long term and acute, occupational and environmental exposure to OP pesticides ($p<0.05$). The QT-interval was significantly shorter during acute occupational exposure to OP ($p<0.001$).

The observed FVC ($p=0.001$), FEV1 ($p=0.003$) and PEF ($p=0.035$) in farmers during the non-exposure season were significantly lower than those in the controls. There were no significant differences in FVC and FEV1 between the freshwater fishermen during both, the exposure and non-exposure seasons, and the controls. Lung function did not correlate with cardiovascular findings following low level OP exposure.

Occupational and environmental exposure to OP pesticides in the Uda Walawe irrigation scheme resulted in adverse effects on the cardiovascular, respiratory and nervous systems. Some effects due to environmental exposure are as severe as those due to occupational exposure. The need for close monitoring of OP use and further studies to minimize the adverse impacts of OPs is strongly recommended.