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Evaluation of Possible Toxic Effects of Cyfluthrin during Short-Term, Relevant Community Exposure

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In recent years usage of bed nets (mosquito nets) and other materials impregnated with synthetic pyrethroids have emerged as a new alternative approach against vector-borne diseases (WHO 1989; Majori et al. 1989). Compared with organochlorine, organophosphorus and carbamate insecticides, pyrethroids cause fast knock-down of mosquitoes and other insects on contact at relatively low dosage and short exposures. Among the most tested pyrethroid insecticides on netting are permethrin, deltamethrin and lambdacyhalothrin. It is reported that most water-based formulations of pyrethroids are not absorbed by skin and present a negligible risk to bed net impregnators or users (WHO 1989). Oral lethal dosage of the water-based formulations are very high compared with organophosphorus or carbamate compounds (Babu 1985). In a preliminary study in India lambdacyhalothrin was found safe to bed net impregnators and users (Baskaran et al. 1992).

Recently we conducted a field evaluation of bed nets impregnated with cyfluthrin against malaria transmitted by *Anopheles fluviatilis* in the settlements of two major iron ore mines in the Orissa state, India. Nets were impregnated at 50 mg/m^2 dose every 6 months. Very significant drops were recorded in vector densities, man biting rate, malaria incidence and indoor admissions due to malaria in hospitals (Sharma and Yadav 1995). As perceived by the bed net users, headache, skin irritation, burning sensation in the eyes and lacrimation, nasal irritation, nausea and odour were insignificant and/or transient (Yadav 1995). Although the impregnated bed nets were very well accepted by the community, we considered it pertinent to evaluate possible toxic effects of cyfluthrin during short-term, relevant community exposure. This paper reports results of the evaluation of possible toxic effects of cyfluthrin during short-term exposure of bed net impregnators and users under operational conditions.

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MATERIALS AND METHODS

Five adult male volunteers aged between 18-25 years who had no previous exposure to pyrethroids participated in the tests on impregnators. The study was cleared by the Ispat General Hospital and written consent was obtained from all the participants. Clinical and biochemical examination and chest X-rays, electrocardiogram, pulmonary function tests and nerve conduction studies were performed to exclude presence of any disease as well as to use as pre-exposure baseline data.

The volunteers wore rubber gloves and impregnated 15 nylon bed nets each with cyfluthrin at 50 mg/m^2 dose. Average family size in the area was 5 and it was considered that even if every household used one bed net, each family would need to impregnate up to a maximum of 5 nets each time. Therefore, impregnation of 15 nets by one person was considered as a maximum upper limit for the test. The impregnators were asked to take thorough bath using a common bath soap after impregnation. All above clinical examinations were repeated on days 3 and 5 post-exposure.

Heparinized blood samples of the volunteers were collected in the morning after overnight fast and transported in cold condition to the Ispat General Hospital in Rourkela for analysis. Plasma urea and creatinine were estimated to assess renal status. Bilirubin, alanine amino transferase, alkaline phosphatase, gamma-glutamyl transpeptidase (τ-GT), total protein and albumin were estimated to assess hepatic functions. These tests were done on a Ciba-Corning Express Plus autoanalyzer using Boehringer Manheim (Germany) test kits. Since the local population consumes a local type of brew extensively, volunteers in whom τ-GT was found to be elevated even without any other abnormal liver function tests were excluded from the study. Tests were done before exposure and after third and fifth day of exposure.

Nerve-conduction tests were carried out in the Neurology laboratory of the Ispat General Hospital. The study was done on all impregnators before exposure and after 3 and 5 days of exposure to cyfluthrin. Median and ulnar nerves on both upper limbs were studied using Nicolet Viking-II Electromyogram. The nerve conduction studies included measurement of latency, amplitude and conduction velocity and was performed on both sensory and motor components of median and ulnar nerves. The points of stimulation were at wrist, below the elbow and above the elbow. The patients were examined clinically by one of us (SKS) on all the occasions.

Lung function test was performed on bed net impregnators on Vitalograph-Compact II Spirometer at the Occupational Health Centre of the Barsuan Iron Mine Hospital, Tensa. Forced vital capacity (FVC), forced expiratory volume in one second (FEV1) and peak expiratory flow (PEF) were measured for all five bed net impregnators. The tests were carried out before exposure, after 6 hours of impregnation work to see any immediate effect due to vapours etc, if any, and after 4 days of impregnation to see any delayed effect. In performing spirometry at maximum capability, the subjects were instructed to take a full breath in, then close the lips around the mouth pipe and blow out as hard and fast as possible.

Twenty-three bed net users (12 males and 11 females between the age 12-52 years) consented to participate in the evaluation of possible toxic effects on the users of cyfluthrin-impregnated bed nets. Baseline medical tests comprised general clinical examination and liver and kidney function tests as described above. Bed nets impregnated at 50 mg/m^2 were provided to each participant free of charge for use. Special effort was made to ensure regular use of the nets by the participants. Follow-up tests were conducted after 1 month of using bed nets. However, 8 of the 23 bed net users consented for re-examination at the end of 1 month and these were re-examined.

RESULTS AND DISCUSSION

None of the impregnators had any symptom related to allergy or irritation, or developed skin manifestations or any other clinical abnormality. In impregnators the liver and renal function tests remained well within the reference range on days 3 and 5 post-exposure (Table 1). No abnormality was detected by urine and stool tests and X-ray chest screening. Results of nerve conduction on impregnators are given in Table 2. There was no difference in the latency or velocity of nerve conduction of either median or ulnar nerves post-exposure as compared with pre-exposure values.

The spirometry measurements of FVC, FEV1 and PEFR of the 5 subjects were predicted as per the deduction equations of Kamat et al. (1981) as under:

[FVC = 0.037 H – 0.000 7A – 3.187 (Predicted)
FEV1 = 0.274 H – 0.0103A – 1.995 (Predicted)
PEFR = 3.31 H – 1.865 A – 81 (Predicted);

where H = Height in cm; A = Age of the subject in years]

Table 1. Tests on bed net impregnators (n=5).

Tests (Reference values)	Pre-exposure (Mean±SD)	Post-exposure (Mean±SD)	
	Day 0	Day 3	Day 5
Urea (10-35 mg/dL)	15.6± 2.7	19.6± 3.8	16.8± 1.8
Creatinine (0.6-1.5 mg/dL)	1.2± 0.2	1.2± 0.2	1.3± 0.1
Protein (6-8.5 g/dL)	7.6± 0.3	7.8± 0.2	7.5± 0.5
Albumin (3.8-4.4 g/dL)	4.8± 0.2	4.7± 0.2	5.3± 1.2
Bilirubin (<1 mg/dL)	0.6± 0.3	0.7± 0.4	0.7± 0.6
Alk. phosph. (39-117 μg/L)	99.6±27.6	90.2±11.1	96.2±15.5
Ala. am. transf. (<31 μg/L)	29.8±11.7	33.4±19.7	30.6±17.7
τ-gl. transpep. (11-50 μg/L)	26.8± 6.3	21.2± 7.8	23.0± 6.0
Urine sugar	Nil	Nil	Nil
Urine albumin	Nil	Nil	Nil
Urine WBC/RBC/Epi. cells	Nil	Nil	Nil
X-Ray chest	NAD*	NAD	NAD
Stool (occult blood)	Nil	Nil	Nil

*NAD= No abnormality detected

Table 2. Nerve conduction tests on impregnators.

Subject	Nerve	Latency (m/sec)			Velocity (m/sec)		
		Day 0	Day 3	Day 5	Day 0	Day 3	Day 5
1. MA	Median	7.2	7.2	7.0	60	61	58
	Ulnar	6.2	6.7	6.4	56	46	54
2. BG	Median	6.1	6.7	7.6	48	56	54
	Ulnar	5.9	5.6	6.3	51	59	58
3. SN	Median	7.5	7.5	6.8	54	59	60
	Ulnar	7.2	6.4	7.0	58	59	50
4. PB	Median	6.6	7.0	6.7	57	55	47
	Ulnar	7.1	7.0	6.4	56	49	55
5. SM	Median	6.3	6.3	6.4	55	67	50
	Ulnar	6.6	5.8	5.6	49	55	55
Mean	Median	6.74	6.94	6.90	54.8	59.6	53.8
±SD		0.59	0.46	0.44	4.4	4.8	5.4
P			0.94	0.34		0.06	0.38
Mean	Ulnar	6.60	6.30	6.34	54.0	53.6	54.4
±SD		0.56	0.59	0.49	3.8	5.9	2.9
P			0.14	0.19		0.46	0.45

Table 3. Results of lung function tests on bed net impregnators.

Subject	FVC (L)			FEV1 (L)			PEFR (L/minute)		
	0 Hr	6 Hr	96 Hr	0 Hr	6 Hr	96 Hr	0 Hr	6 Hr	96 Hr
1. MA	2.8	2.8	2.9	2.7	2.8	2.7	428	415	460
2. BG	3.8	2.8	2.7	2.4	2.1	1.9	420	348	430
3. SN	3.2	3.4	3.2	2.9	2.9	2.8	470	450	440
4. PB	2.7	2.5	2.6	2.2	2.1	1.4	317	381	450
5. SM	2.9	2.8	2.6	2.3	2.4	2.5	500	550	600
Mean	3.1	2.9	2.8	2.5	2.5	2.3	427	429	476
±SD	0.4	0.3	0.3	0.2	0.4	0.6	69	78	70
P		0.18	0.13		0.41	0.14		0.47	0.08

FVC= Forced vital capacity
FEV1= Forced expiratory volume in one second
PEFR= Peak expiratory flow rate

The predicted values of FVC and FEVl were determined. It was found that in all the 5 subjects FVC and FEVl values on all the three occasions were more than 80% of the predicted values as in the case of normal subjects as per Miller prediction quadrants (Miller 1986), thereby showing no evidence of obstructive or restrictive airway disease (Table 3). The PEFR also showed >70% of predicted values for all the 5 subjects on all three occasions. The PEFR is believed to be less effort dependent and merely determined the anatomy and physiology of the flow through the smaller airways. The FVC and FEVl values of 2 subjects were less after 6 hours of exposure to the insecticide than those on day 0, but their PEFR values were well preserved. This may be because the FEVl is thought primarily to reflect the adequacy of the patients' forced expiratory effort whereas the PEFR is less effort dependent. Hence, the tests did not show any adverse effects of cyfluthrin on the lung functions.

In all the 8 bed net users followed successfully there was no symptom related to local or systemic toxicity and no abnormality could be detected clinically. Liver and hepatic functions did not show any statistically significant difference after 1 month exposure in comparison to pre-exposure values (Table 4).

The present study thus showed that short-term exposure with cyfluthrin had no toxic effects on renal, hepatic, pulmonary function and nerve conduction and the nets

Table 4. Renal and liver function tests in bed net users (n = 8).

Diagnostic indices	Pre-exposure (Mean±SD)	1 Month post-exposure (Mean±SD)	*P*
Urea (mg/dL)	15.5±3.0	16.8±6.3	0.55
Creatinine (mg/dL)	0.8±0.1	0.8±0.1	0.52
Bilirubin (mg/dL)	0.6±0.2	0.5±0.2	0.83
Alanine amino transferase (μg/L)	17.7±7.9	18.5±4.8	0.72
Alk. phosphatase (μg/L)	133.8±110.5	141.7±100.8	0.52
Glu. transpeptidase (μg/L)	13.7±6.8	16.1±4.7	0.09

impregnated at 50 mg/m^2 are safe to use. Although pyrethroids have been shown to present negligible risk to human beings at the relevant dosage, it may be mentioned that this is a relatively short-term study. It is possible that long-term exposure could have toxicity, and investigators should remain alert to such possibilities, and further evaluation should be considered in the future.

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