Eosinophilic pneumonitis induced by aerosol-administered diesel oil and pyrethrum to mice

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ABSTRACT

Objective. *To confirm the episode of eosinophilic pneumonitis that occurred in March 2001 in Manaus, Amazon, northern Brazil, as secondary to home aerosolization with 2% cypermethrin diluted in diesel compared with the more conventional 1% cypermethrin and soybean solution used in prophylaxis of dengue.*

Methods. *Four groups of Swiss mice were kept in polycarbonate cages aerosolized with one of the following solutions: diesel, diesel and cypermethrin, soy oil and cypermethrin, and saline. Three and 6 days after exposure, resistance and compliance of the respiratory system and white cell kinetics in peripheral blood and lung tissue were analyzed.*

Results. *The group exposed to diesel and cypermethrin showed higher respiratory system resistance (*$p < 0.001$*), lower compliance (*$p = 0.03$*), and increased eosinophils in blood (*$p = 0.03$*) and lung tissue (*$p = 0.005$*) compared with the other groups. There was an increase of neutrophils in the blood of all experimental groups on the third day after exposure (*$p < 0.001$*).*

Conclusions. *We concluded that diesel associated with cypermethrin induced lung hyperresponsiveness in this experimental model and was associated with increased polymorphonuclear cells (eosinophils and neutrophils) in blood and lungs. This effect is strongest on the third day after exposure. These results are similar to the episode that occurred in Manaus in 2001 and suggest that diesel plus cypermethrin home aerosolization for arbovirosis prophylaxis should be revised.*

Key words Insecticide, dengue, diesel, eosinophilic pneumonia, Brazil.

Pesticides are widely used throughout the world in agriculture, in homes, and in public health; pyrethroids are among the most frequently used pesticides. The commercially available pyrethroids include permethrin, cypermethrin, cyfluthrin, deltamethrin, and fenvalerate (1). Their indoor bioefficacy using thermal fogging against vector mosquitoes in the tropical environment is widely accepted in the literature; they can be dissolved in water or oily substances or mixed with other active chemicals (1, 2).

Dengue, also called break-bone fever, is an endemic flavivirus that occurs in all tropical countries, especially in the northern and central zones of Brazil, pre-

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senting high morbidity and sometimes mortality. In recent years, this disease has turned from endemic to epidemic, mainly in the southeastern zone, causing dozens of deaths and posing an important challenge to the federal and regional health systems (3).

The disease is controlled through prophylactic elimination of the mosquito by home aerosolization with insecticides in water receptacles used as a larvicide.

Pyrethroid cypermethrin is the drug of choice for indoor aerosolization for larvicide purposes in Brazil. Because of its liposolubility, it is diluted in oily substances. In most cases, the preparation of choice is 1% cypermethrin diluted in soy oil because of the low price and minimum toxicity.

In March 2001, in Manaus in northern Brazil, 2% cypermethrin diluted in diesel was aerosolized by thermonebulization in homes as a prophylaxis against dengue. Several days after exposure, cases of respiratory symptoms were detected presenting interstitial and eosinophilic pneumonia. Women and children who stayed at home were predominantly affected, while men who left home to work and the employers who aerosolized the insecticide seldom presented any symptoms. Forty-eight to 72 hours after aerosolization, 211 suspected cases were detected presenting dyspnea and wheezing, from which 110 were confirmed through clinical exam and laboratory findings as eosinophilic, with interstitial lung infiltration, through X-rays. The presented symptoms were cough (100%), fever (90%), dyspnea (80%), wheezing (36%), blood eosinophilia (100%), and interstitial lung infiltration (100% of hospitalized patients) (4, 5).

The symptoms were progressive and most intense around the third and seventh days after exposure. All cases presented spontaneous regression around the second week of the disease with no aftereffect. Serological tests for influenza and parainfluenza virus, adenovirus and respiratory syncytial virus, *Mycoplasma pneumoniae*, *Legionella pneumophilia*, *Histoplasma capsulatum*, and *Aspergillus fumigatus* were negative (4, 5).

On the basis of the facts cited above, we hypothesized that the diesel plus cypermethrin solution was responsible for external intoxication. To test this hypothesis, we studied an experimental model to analyze the functional, cytological, and histological respiratory system parameters of mice exposed to cypermethrin diluted in soy oil or diesel and to diesel-only aerosolizations in vivo.

MATERIALS AND METHODS

The Research Committee of the Faculty of Medicine of the University of São Paulo approved this experiment. This study was carried out by the Laboratory of Experimental Air Pollution of the Pathology Department of the Faculty of Medicine of the University of São Paulo.

Animals

We obtained 80 male Swiss mice (20 to 25 g) from the animal care facility of the Faculty of Medicine of the University of São Paulo and divided them into four groups exposed to one of four solutions: diesel only, soy oil and 1% cypermethrin, diesel and 2% cypermethrin, and 0.9% saline.

Animals were kept in four polycarbonate cages (49 × 34 × 16 centimeters (cm)), 20 animals per cage. Previously, each cage was aerosolized with a solution and kept sealed for 2 hours with a paper filter on the grid at the top. After that period, a 10 × 10 cm window was opened in each paper filter to allow for ventilation and then the animals were caged in. Food and water, added only after aerosolization, were provided ad libitum. The cages were kept in a separate room in the animal care facilities on shelves elevated 1.80 meters above the floor and 20 cm from the ventilation system (exhaust), which sends air into the external environment. After 3 days, 10 mice were removed from each cage; after 6 days, the remaining mice were removed, and all mice were subjected to the experimental procedures described below.

Experimental procedures

Mice were anesthetized intraperitoneally with pentobarbital (10 milligrams (mg) per kilogram of body weight), and blood was obtained from the ophthalmic plexus for quantification and differentiation of leukocytes through a lamina smear, stained with Hema 3 in an optic microscope. One hundred cells were counted per animal (× 400).

Respiratory system resistance and compliance were determined with the aid of a flexiVent apparatus (6) in anesthetized and tracheostomized animals. Additional anesthesia was administered during the experiment when needed.

After respiratory mechanical measurements, animals were euthanized by bleeding the aorta. OCT (optimal cutting temperature) was injected via the trachea into the alveoli (3 milliliters (mL)). Lung slices were cut near the carina and peripheral lung tissue, placed in aluminum foil, and kept at –60°C to be cut on a cryostat. Eosinophils were identified through immunohistochemistry (avidin-biotin) with an antibody to eosinophil peroxidase (7). The intensity of eosinophil influx was estimated by determining the number of these cells in a × 1 000 microscopic field. This number was corrected by the density of the alveolar tissue, determined through a standard point counting procedure by a grid of 10^4 square micrometers (μm^2). Values were expressed as cells per 10^4 μm^2 (8).

The concentration of petroleum-derived hydrocarbons inside the cages was estimated by a colorimetric technique, using a Drager gas detection system (Drager Safety AG & Co. KgaA, Germany). Measurements were made twice: at time zero (when animals were introduced into the cage 2 hours after pulverization) and 3 days after exposure. No measurements were made on the sixth day, as no hydrocarbons were detected on the third day in all exposed cages.

Statistical analysis

All data were subjected to an analysis of variance (ANOVA), a statistical method for descriptive and analytical analysis, for determination of cellular predominance in lung and peripheral blood. Parametrical data were analyzed through one-way ANOVA (resistance) and nonparametric results (compliance and eosinophils in lung tissue and blood) were analyzed by Dunn's multiple comparison method and a Mann–Whitney test. Neutrophils in the blood were analyzed by Tukey's multiple comparison tests.

RESULTS

Respiratory mechanics

After 3 days of exposure (3d), animals exposed to diesel and cypermethrin (D+C group) presented higher values of resistance (Rrs) (5.8 ± 0.55 cm of H_2O/mL/s, $p < 0.001$) (Figure 1) and lower compliance (Crs) (0.032 ± 0.006 mL/cm of H_2O, $p = 0.03$) of the respiratory system (Figure 2) than the other groups.

Mice from the saline group presented no difference on the respiratory system mechanical parameters between the third and sixth days of exposure (Crs, $p = 0.79$; Rrs, $p = 0.422$).

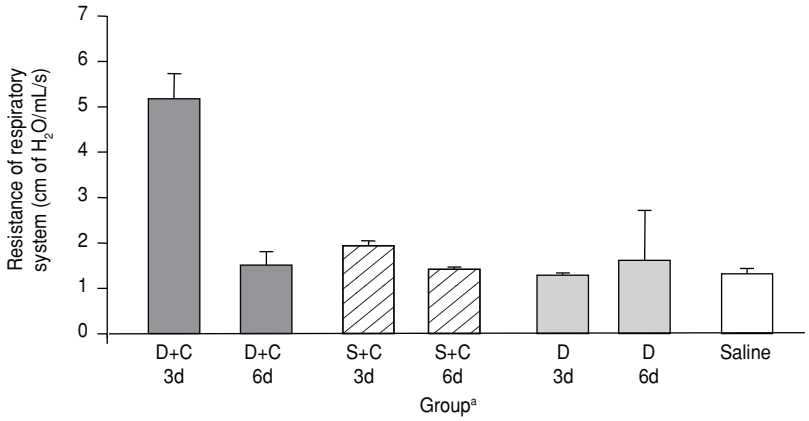
Inflammatory markers

On the third (3d) and sixth (6d) days after exposure, mice in the D+C group had more eosinophils in peripheral blood (20.3% ± 2.9% on 3d and 13.2% ± 1.3% on 6d, $p = 0.01$ and $p = 0.03$, respectively) (Figure 3) as well as in lung tissue (0.05 ± 0.007 cell/10^4 μm^2 at 3d and 0.04 ± 0.006 cell/10^4 μm^2 at 6d, $p = 0.005$ for both periods) (Figure 4) than those in the other groups during the same period. Neutrophils in blood showed an increment in all groups after 3 days of exposure compared with mice on the sixth day of the experiment ($p < 0.001$; Figure 5) except for the saline group, which had no difference in neutrophils during the experiment. Mice exposed to saline presented similar numbers of eosinophils on the third and sixth days of exposure (eosinophils in blood, $p = 0.19$; no eosinophils were found in lung tissue on the third and sixth days of the experiment).

Ambient hydrocarbon levels

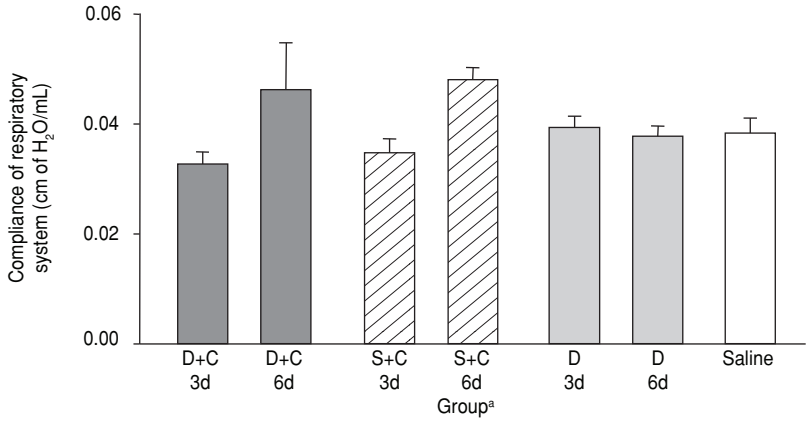
Petroleum-derived hydrocarbons were detected only in cages subjected to aerosolization with diesel (10 mg/L) or diesel and cypermethrin (6 mg/L) at the moment the animals were placed in the cage (2 hours after aerosolization). Measurements made after 3 days of exposure showed hydrocarbon concentrations below the instrument's limits of detection.

FIGURE 1. Respiratory system resistance of Swiss mice exposed to diesel and/or cypermethrin



[a] D 3d, diesel 3 days; D 6d, diesel 6 days; S+C 3d, cypermethrin + soy oil 3 days; S+C 6d, cypermethrin + soy oil 6 days; D+C 3d, diesel + cypermethrin 3 days; D+C 6d, diesel + cypermethrin 6 days. $P < 0.001$ D+C 3d compared with other groups. Values are expressed as mean ± standard error of the mean.

FIGURE 2. Respiratory system compliance of Swiss mice exposed to diesel and/or cypermethrin



[a] D 3d, diesel 3 days; D 6d, diesel 6 days; S+C 3d, cypermethrin + soy oil 3 days; S+C 6d, cypermethrin + soy oil 6 days; D+C 3d, diesel + cypermethrin 3 days; D+C 6d, diesel + cypermethrin 6 days. $P = 0.03$ D+C 3d compared with S+C 6d. Values are expressed as mean ± standard error of the mean.

DISCUSSION

This study was designed to determine whether the procedure used to eradicate the dengue mosquito—aerosolization with a solution of 2% cypermethrin diluted in diesel—is able to induce functional and histological alterations in the lungs of mice in order to support the hypothesis of human indoor intoxication by this solution, as exhibited in Manaus in March 2001.

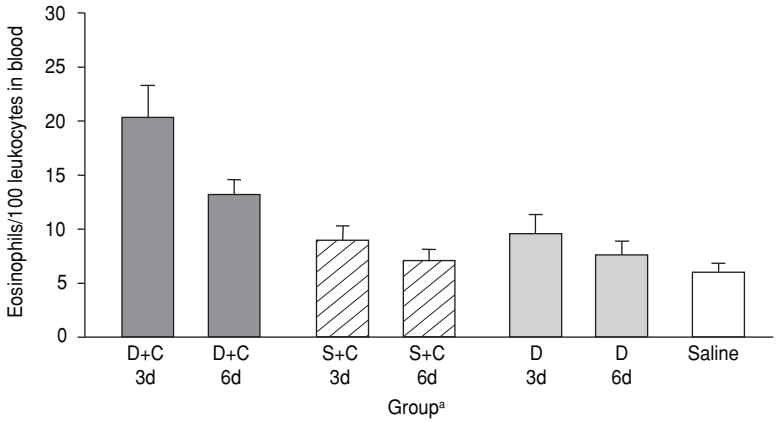
We tried to reproduce the closest situation experienced by these patients by performing an aerosolization in acrylic cages for rodents and keeping them sealed for 2 hours, like the lag time recommended for reoccupation of houses after cypermethrin pulverization. We analyzed lung mechanics, focusing on symptoms of cough, dyspnea, and bronchial spasm; we also measured blood leukocytes and quantified the influx of inflammatory cells in alveolar septa and blood, as eosinophilia in blood and eosinophilic pneumonitis were seen in affected individuals.

Our results indicate that indoor aerosolization of diesel plus 2% cypermethrin induces an acute lung inflammation process, expressed by clinical, functional, and histological tissue alterations, peaking on the third day after exposure and declining by the sixth day. Polymorphonuclear cells in blood exhibited the same time-course pattern, expressing a systemic response.

The acute pneumonitis episode in Manaus pointed out the toxicity to the respiratory system secondary to diesel and cypermethrin home aerosolization or by diesel addition per se in the solution. The literature shows that diesel or cypermethrin can be toxic, depending on the contact route, dosage, and time of exposure. The National Institute of Occupational Safety and Health recommends that people who deal with these substances (applicator workers) use gloves and masks (9–11).

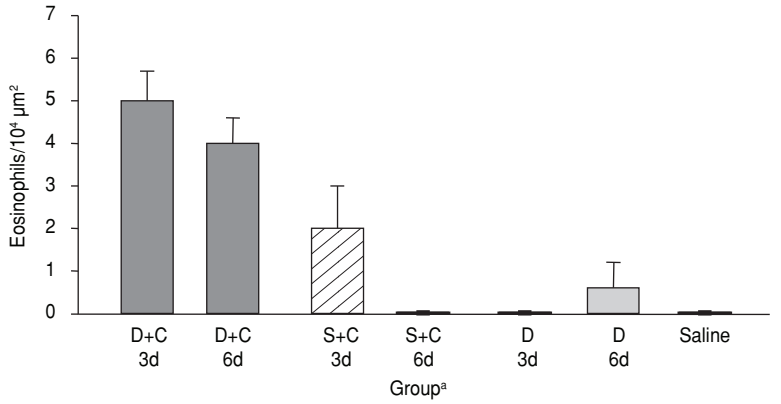
Cypermethrin toxicity depends on the concentration of the solution (12) and on the route of administration—thermonebulization or spatial smoke nebulization (12)—and the location of contact (13), which can induce modulation of the immune system (14), mucocutaneous irritation, bronchial hyperreactivity with clinical signs similar to asthma (1), and potential oncogenesis (10, 15, 16). Concerning pesticide toxicity, previous studies have shown that cypermethrin doses

FIGURE 3. Eosinophils in peripheral blood of Swiss mice exposed to diesel and/or cypermethrin



[a] D 3d, diesel 3 days; D 6d, diesel 6 days; S+C 3d, cypermethrin + soy oil 3 days; S+C 6d, cypermethrin + soy oil 6 days; D+C 3d, diesel + cypermethrin 3 days; D+C 6d, diesel + cypermethrin 6 days. $P = 0.03$ D+C 6d compared with other groups; $P = 0.001$ D+C 3d compared with other groups. Values are expressed as mean ± standard error of the mean.

FIGURE 4. Eosinophils in lung tissue stained with EPO of Swiss mice exposed to diesel and/or cypermethrin



[a] D 3d, diesel 3 days; D 6d, diesel 6 days; S+C 3d, cypermethrin + soy oil 3 days; S+C 6d, cypermethrin + soy oil 6 days; D+C 3d, diesel + cypermethrin 3 days; D+C 6d, diesel + cypermethrin 6 days. $P = 0.05$ D+C 3d and D+C 6d compared with D 3d, D 6d, S+C 3d and saline. Values are expressed as mean ± standard error of the mean.

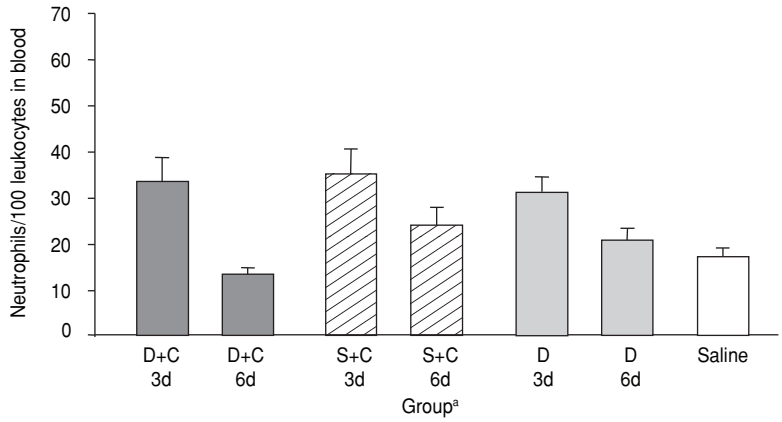
0.5% and higher can exterminate 100% of indoor mosquitoes (12, 17). The World Health Organization suggested a 2% concentration as toxicity level II to humans and efficient in arbovirus prophylaxis, which is still being followed by some countries (18, 19). Chunina et al. showed that high doses of solution are necessary for efficient prophylaxis (20) as insecticide subdoses would not affect the female mosquito in endemic places. This higher dose should be established by taking into account both the toxicity to the mosquito and the effect on human health. Several authors evaluated individual exposure due to occupational application of pyrethroids as a precondition for the assessment of health risks, monitoring pyrethroid levels in blood and urine. They showed that a cypermethrin urinary metabolite is present even though these values were not considerably higher than the acceptable daily intake of pyrethroid set by the World Health Organization (1, 21, 22). In this experiment, we used 1% cypermethrin in soy oil and 2% in diesel solution because we intended to emphasize that the purpose of our study was to mimic the episode that occurred in Manaus in 2001, but in more controlled conditions, through an experimental protocol in rodents. We did not test 2% cypermethrin in soy oil solution as this procedure would contribute to exploration of the toxicity of cypermethrin, which was not the objective of our study.

Our results suggest that inflammation via eosinophils (Figures 3 and 4) is associated with increased respiratory resistance in all animals exposed to cypermethrin and diesel as they expressed higher levels of these cells in blood and tissue and airway resistance on the third day after exposure compared with other groups (Figure 1). These effects were more intense in the group of animals exposed to diesel associated with cypermethrin, where the pyrethroid concentration was double (2%) that in the toxic plus soy oil solution (1%). These data suggest that cypermethrin may be associated with the inflammation observed in experimental animals. Haratym-Maj evaluated a murine model of pyrethroid poisoning and suggested that all pyrethroids, independent of the dose and sex of the animals, caused an increase in the number of leukocytes in peripheral blood (23). They also demonstrated that female mice were more sensitive to hematologic alterations after cypermethrin exposure, when lower doses induced inhibition while higher concentrations resulted in mobilization of leukocytes to blood circulation.

Castranova et al. (24) suggested susceptibility to lung infection after diesel exposure. Mauderly et al. (25) and McClellan et al. (26) showed lung inflammation secondary to inhaled diesel particles. Miyabara et al. (27) demonstrated, in an experimental murine model, allergic airway inflammation and hyperresponsiveness due to diesel exhaust. Our data are also partially in accordance with the literature that points at diesel toxicity as being responsible for alterations in the respiratory system via eosinophils in the lung (Figure 4) and blood (Figure 3) associated with alterations in proximal (resistance) and distal (compliance) pulmonary function (Figures 1 and 2), similar to late hypersensitivity in asthma crises. These alterations were more intense in mice exposed to diesel plus cypermethrin than in those exposed to diesel alone.

The eosinophilic pneumonitis induced by diesel and cypermethrin in this study, similarly to the humans in Manaus, could correspond to the classic late phase of asthma. The process was reversible, mediated acutely by neutrophils as an unspecific response and characterized afterward by eosinophils in blood and lung tissue, inducing bronchial hyperresponsiveness. However, the process lasted for days (3 to 15 days) and the interstitial

FIGURE 5. Neutrophils in peripheral blood of Swiss mice exposed to diesel and/or cypermethrin



[a] D 3d, diesel 3 days; D 6d, diesel 6 days; S+C 3d, cypermethrin + soy oil 3 days; S+C 6d, cypermethrin + soy oil 6 days; D+C 3d, diesel + cypermethrin 3 days; D+C 6d, diesel + cypermethrin 6 days. $P < 0.001$, 3 days compared with 6 days of exposure for all groups. Values are expressed as mean ± standard error of the mean.

pattern of the lung parenchyma would not be expected as a classic sign of asthma disease, which usually lasts hours and predominantly affects the airways. Our data on the respiratory mechanics pointed out both proximal and distal lung effects. The resistance increment (Figure 1) would be connected to wheezes and rhonchi detected in patients from Manaus. The distal alterations of lung tissue, expressed by decreased compliance (Figure 2) and eosinophil influx in the septa, would reflect the interstitial infiltration shown on X-rays of hospitalized patients. In this experimental model, functional data suggest that airway involvement was more severe than that of the distal lung tissue.

The lasting period of increased respiratory resistance and the distal interstitial lung commitment are similar to the toxic oil syndrome described by Kilbourne and colleagues but less toxic. These authors characterized the disease as an epidemic episode of eosinophilia with lung symptoms such as wheezes and rhonchi, dyspnea, fever, and interstitial pulmonary infiltration induced by the ingestion of a mixture of seed oils containing aniline (28, 29).

Our work has limitations. Although our data suggest that diesel plus cypermethrin is linked to the pneumonitis eosinophilic episode, an atypical lung disease secondary to other irritant particles or infectious agents other than those checked by serology remains possible. Recently, after the Manaus episode in 2001, cypermethrin in water solution aerosolized by ultra low volume has become the choice in Brazil (4) for arbovirus prophylaxis as suggested by the Pan American Health Organization (30). In fact, some cases of eosinophilic pneumonitis still occur in the north of Brazil after the cessation of use of diesel plus cypermethrin thermonebulization (31), suggesting that other agents could be responsible for this syndrome (32). Another limitation is that cage pulverization and functional and cytological lung alterations in mice are not exactly the same as home pulverization and human respiratory disease, even though we tried to mimic the Manaus episode as closely as possible. The toxicity observed seems to reflect an enhancement of diesel oil toxicity by the pyrethrum compound. Interestingly, mice from the diesel-alone group behaved similarly to the saline and cypermethrin plus soy oil group with regard to mechanical parameters and eosinophils in blood. This finding may suggest that not only is the solvent diesel associated with cypermethrin hazardous but also that precautions should be taken with regard to cypermethrin concentration.

We conclude that 2% cypermethrin diluted in diesel oil produces toxic signs of systemic hypersensitivity predominantly in the lungs, via eosinophils and neutrophils, with maximum clinical manifestation around the third day of exposure, decreasing around the sixth day. The insecticide cypermethrin dissolved in soy oil was shown to be less toxic than the diesel solution, although, as expected, it was more toxic than saline. The clinical and laboratory data of this experimental model allow for the biological plausibility of possible mechanisms implicated in the pneumonitis that occurred in March 2001 after diesel plus cypermethrin home aerosolization for prophylaxis of dengue. As this study is preliminary, we suggest greatly expanded studies on this subject since aerosolized pyrethrum compounds are widely used in household environments throughout the world.

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RESUMEN

Neumonía eosinofílica inducida por aerosol de aceite diésel y piretroide en ratones

Objetivo. Confirmar el episodio de neumonía eosinofílica ocurrido en marzo de 2001 en Manaus, Amazonas, en el norte de Brasil, secundario al uso de aerosol de cipermetrina diluida al 2% en aceite diésel en las viviendas en comparación con la profilaxis más convencional contra el dengue, basada en cipermetrina al 1% con aceite de soya.
Métodos. Se mantuvieron cuatro grupos de ratones suizos en jaulas de policarbonato y se aplicó aerosol con una de las siguientes soluciones: aceite diésel, aceite diésel y cipermetrina, aceite de soya y cipermetrina, y solución salina. Se analizaron la resistencia y el funcionamiento del sistema respiratorio y la cinética de leucocitos en sangre periférica y tejido pulmonar a los tres y seis días después de la exposición.
Resultados. El grupo expuesto a aceite diésel y cipermetrina mostró mayor resistencia del sistema respiratorio ($P < 0{,}001$), peor funcionamiento ($P = 0{,}03$) y más eosinófilos en sangre ($P = 0{,}03$) y tejido pulmonar ($P = 0{,}005$) que los otros grupos. Se observó un aumento de neutrófilos en sangre en todos los grupos experimentales al tercer día después de la exposición ($P < 0{,}001$).
Conclusiones. El aceite diésel con cipermetrina indujo una hiperrespuesta pulmonar en este modelo experimental y se asoció con un aumento en las células polimorfonucleares (eosinófilos y neutrófilos) en sangre y tejido pulmonar. Este efecto es mayor al tercer día después de la exposición. Estos efectos son similares a los observados en el episodio ocurrido en Manaus en 2001 e indican que se debe reevaluar el uso de aerosol de aceite diésel con cipermetrina para la profilaxis de arbovirus en las viviendas.

Palabras clave Insecticidas, dengue, diesel, neutrófilos, neumonía eosinofílica, Brasil.