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Toxic doses of paraoxon alter the respiratory pattern without causing respiratory failure in rats

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Abstract

Respiratory failure, through a combination of muscarinic, nicotinic, and central effects, is the primary cause of death in acute organophosphate poisoning. However, the mechanisms inducing respiratory failure remain unclear. In rats poisoned subcutaneously with paraoxon at doses near the LD_{50}, we studied the pattern of respiration using whole body plethysmography and the occurrence of respiratory failure using arterial blood gases. Subsequently, we studied the effects of atropine on paraoxon-induced modification of ventilation and arterial blood gases. Fifty and 75%, but not 10% of the subcutaneous LD_{50} of paraoxon induced marked and sustained signs and symptoms. At 30 min post-injection and throughout the study, there was a significant decrease in the respiratory frequency (34% (50% versus solvent), and 29% (75% versus solvent)) and a significant increase in the expiratory time (72% (50% versus solvent) and 60% (75% versus solvent)) with no modifications of the inspiratory time. The tidal volume was significantly increased for the 75% but not for the 50% dose. Apnea was never detected. Even at the 75% dose, paraoxon had no effects on PaO_2, $PaCO_2$ or HCO_3^-; however, a significant decrease in arterial pH was observed at 30 min (7.34 ± 0.07 versus 7.51 ± 0.01, $p = 0.03$). Atropine completely reversed the paraoxon-induced respiratory alterations. We conclude that paraoxon, at doses equal to 50 and 75% of the LD_{50}, alters ventilation at rest without inducing respiratory failure during the study period.
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Keywords: Paraoxon; Atropine; Rats; Plethysmography; Arterial blood gases; Respiration

1. Introduction

Organophosphates are used daily throughout the world as pesticides. However, they remain a major health concern due to the large number of annual acute poisonings. Indeed, according to the World Health Organization data, there are more than 3 million organophosphate

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intoxications and more than 220,000 deaths annually (Jeyaratnam, 1990; Segura et al., 1999).

The early and intermediate phases of toxicity of organophosphates are related to the inhibition of cholinesterase activity, resulting in the accumulation of acetylcholine within the synapses throughout the body which induces an overstimulation of the autonomic nervous system. Respiratory failure is considered the primary cause of death (Durham and Hayes, 1962; Lerman and Gutman, 1988; Yamashita et al., 1997). However, its mechanism remains unclear. Organophosphate-induced acute respiratory failure is thought to result from a direct depressant effect on the respiratory center in the brainstem, constriction of and increased secretion by the airways, and paralysis of the respiratory musculature (Bartholomew et al., 1985). Data support the hypothesis that some organophosphates, including paraoxon, can also injure the air-blood membrane (Delaunois et al., 1992).

A number of experimental studies have demonstrated the detrimental effect of organophosphates on ventilation at rest in various species, ranging from rodents to primates. However, the clinical relevancy of these findings remains debatable. Indeed, a large number of experiments were performed using chemical weapons (Aas et al., 1987; Anzueto et al., 1990; Edery and Berman, 1985; Gillis et al., 1988; Johnson and Wilcox, 1975; Lipp, 1976; Rickett et al., 1986; Worek et al., 1995) and the extension of these findings to pesticides remains questionable. A recent prospective study on human self-poisonings resulting from chlorpyrifos, fenthion, and dimethoate ingestion showed that the clinical findings, including the onset of respiratory failure requiring endotracheal intubation as well as the final outcome, were significantly different from each other (Eddleston et al., 2005). Finally, Segura and coworkers provided definitive evidence that paraoxon impaired the mechanics of breathing, although arterial blood gases were not measured (Segura et al., 1999). Surprisingly, in goats receiving intravenous dichlorvos followed by atropine, a significant alteration of the pattern of breathing was observed, without any significant modification of arterial blood gases (Bakima et al., 1989).

Thus, we conducted an experimental study to assess the effects of paraoxon on the pattern of respiration at rest using whole body plethsymography and the effects on arterial blood gases in awake rats. First, we confirmed the LD_{50} of paraoxon administered subcutaneously. Secondly, we studied the effects of three doses, namely 10, 50, and 75% of the LD_{50} of paraoxon, on ventilation at rest and on arterial blood gases in comparison with those induced by the solvent. Finally, we studied the antidotal effects of atropine on paraoxon-induced respiratory effects.

2. Materials and methods

All experiments were carried out within the ethical guidelines established by the National Institutes of Health and the French Minister of Agriculture.

2.1. Animals

Animals employed were Sprague–Dawley male rats (Iffa-Credo, France) weighing between 250 and 350 g at the time of experimentation. They were housed for 8 days before experimentation in a temperature- and light-controlled animal-care unit. They were allowed food and water *ad libitum* until one day prior to experimentation.

2.2. Chemicals and drugs

Paraoxon (diethyl *p*-nitrophenyl phosphate) was obtained from Sigma–Aldrich Chemie Gmbh, Steinheim, Germany. Paraoxon was diluted in sterile distilled water to obtain a stock solution of 3.5 mg/ml. Several dilution of paraoxon were prepared (280, 140 and 28 μg/ml), to inject doses equal to 75, 50 and 10% of the LD_{50}. Solutions of paraoxon were preserved from light and stored at 4 °C during a maximum of 4 weeks.

The stability of these aqueous solutions of paraoxon was verified using high liquid performance chromatography with UV detection at 280 nm, on a Lichrosphere RP18 5 μm column (125 mm × 4 mm, Merck). The mobile phase was composed of water–methanol–acetonitrile (40/50/10%, v/v). Parathion was used as internal standard at concentration of 2 μg/mL. Using a flow gradient (0.4–0.9 ml/min.), the paraoxon was typically eluted at 6 min 36 s and parathion at 9 min 42 s.

Atropine sulfate was supplied by Sigma–Aldrich, Saint-Quentin Fallavier, France. Atropine sulfate was diluted in sterile distilled water in order to obtain a stock solution of 18 mg/ml. One dilution (9 mg/ml) was then prepared to inject doses corresponding to 10 mg/kg. This solution was freshly prepared the day of the experimentation.

Propionylthiocholine, 4,4′-dipyridyl disulfide (Aldrithiol®) dihydrated disodium phosphate, and monopotassium phosphate were obtained from Sigma–Aldrich (St Quentin Fallavier, France). Distilled water (Frésenius FrancePharma, Louviers, France) was used for preparation of the various reagents.

2.3. Study 1: median lethal dose (LD_{50}) of subcutaneous paraoxon in rats

Approximatively 18 h prior to experimentation, the animals were fasted, but allowed free access to water. Following drug administration, animals were placed in individual cages, allowed to eat and drink, and maintained in the laboratory, which was temperature- and light-controlled. Every effort was

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