Cardiovascular Effects of Repeated Low-Level Exposure to Sarin Vapor

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While the acute and chronic effects of exposure to lethal doses of sarin (GB) are well documented, the effects of low-level repeated exposures remain uncertain. Some studies have found effects of low-level exposure of GB that persist after the cessation of exposure. In many of these studies GB liquid was injected parenterally. However, the route of exposure is an important determinant of the effect observed. Arguably, the most relevant route of exposure for GB is inhalation of vapor. Thus, in the present study, GB vapor was generated in a 750-L dynamic airflow chamber using a spray atomization system. Male Sprague-Dawley rats (200-250 g) were surgically implanted with telemetric transmitters (n=3) for the continuous recording of blood pressure (BP), body temperature, and a lead II electrocardiogram (ECG; sampling rate = 5000 Hz; filter cutoff = 1250 Hz). Rats were then exposed to GB vapor (3.93 ± 0.18 mg/m^3) for 1 hour on each of 3 consecutive days. Whole blood and tissues were collected from tissue donor rats at various timepoints post-exposure for the determination tissue GB levels, cholinesterase activity, and blood chemistry.

The concentration of GB vapor generated was sufficient to depress whole blood acetylcholinesterase (AChE) activity to 45% of control levels following the first exposure (n=6). The degree of AChE inhibition was not greater following subsequent exposures (n=6). Whole blood butyrylcholinesterase (BChE) activity was not decreased following any of the three exposures. There were no changes in whole blood [Na^+], [K^+], [glucose], pH, pO_2, pCO_2, or [lactate] following any of the exposures when GB-exposed rats were compared to air-exposed controls. Miosis was also present in exposed animals, although tolerance to the miotic effect developed after the 2nd exposure (n=15). No other overt signs of GB intoxication were present in the exposed rats. Tissue levels of GB were determined following each exposure using a fluoride ion based regeneration assay. The levels of GB in various tissues were as follows: heart tissue = 10.3±2.8 ng GB/g tissue (n=6); plasma = 275±30 ng GB/g tissue; red blood cells = 26±2 ng GB/g tissue. The levels of GB in these tissues were similar following each of the three exposures.

Time and frequency domain indices of heart rate (HR) variability were calculated from telemetrically recorded ECG data using both Fourier and wavelet techniques. BP, HR, and the standard deviation of HR were not significantly altered during or following the exposures. However, the incidence of transient ventricular asystole and ventricular premature beats (VPBs) was increased during and following each of the three exposures.

The ratio of low frequency power to high frequency power, a measure of the balance between sympathetic and parasympathetic tone in the heart, decreased following the first exposure (3.59 ± 0.48 before vs. 1.88 ± 0.19 after). However, subsequent exposures did not produce the same magnitude of response elicited by the first exposure, suggesting the development of tolerance to the disruption in the balance of sympathetic and parasympathetic tone induced by GB vapor. Left ventricular posterior wall thickness and cardiac fractional shortening were assessed using two-dimensional guided M-mode echocardiography. There was no change in these parameters at 1-week or 1-month post-exposure, suggesting that GB vapor exposure does not produce a prolonged alteration in cardiac function or morphology. These data demonstrate that low-level exposure to GB vapor can produce cardiovascular abnormalities and that repeated exposure can result in tolerance to some of these effects. These effects have not been previously reported for inhalation exposures to GB, and may be useful as a basis for military risk management decisions, or as early markers of exposure.