Tolerance to the Ocular and 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 vapor inhalation. Thus, in the present study, GB vapor was generated using an atomization system. Rats were exposed to GB vapor (3.93 $\pm$ 0.18 mg/m^3) for 1 hour on each of 3 consecutive days. The concentration generated was sufficient to depress RBC AChE activity to 45% of control levels (n=6). Miosis was also present in exposed animals, although tolerance to the miotic effect developed after the 2nd exposure (n=15). However, changes in AChE activity in the eye did not parallel the pattern of miosis that was observed, suggesting that the reduction in the miotic potency of GB cannot be attributed to a reduction in the inhibitory effect of GB. Tissue levels of GB were determined following each exposure using a fluoride ion based regeneration assay. The level of GB in the eye was similar following each of the three exposures, suggesting that the miotic tolerance to GB that is observed is not due to a change in the pharmacokinetic properties of GB. The level of GB in heart tissue was 10.3$\pm$2.8 ng/g tissue, which is 20-fold less than levels found in plasma and lung tissue (n=6).

Telemetric transmitters were surgically implanted into rats a week prior to exposure to GB. Blood pressure (BP), heart rate (HR), body temperature, and a lead II electrocardiogram (ECG) were recorded telemetrically (sampling rate = 5000 Hz; filter cutoff = 1250 Hz) pre-, during, and post-exposure (n=3). Time and frequency domain indices of HR variability were calculated 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 following each of the three exposures. The ratio of low frequency power to high frequency power decreased following the first exposure (3.59 $\pm$ 0.48 before vs. 1.88 $\pm$ 0.19 after), suggesting enhanced parasympathetic tone. However, subsequent exposures did not produce the same magnitude of response elicited by the first exposure, suggesting the development of tolerance. 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. These data demonstrate that low-level exposure to GB vapor can produce ocular and 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.