Electrophysiological Changes Induced by Different Doses of 1-Bromopropane and 2-Bromopropane

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Abstract: Electrophysiological Changes Induced by Different Doses of 1-Bromopropane and 2-Bromopropane: Wenyuan Zhao, et al. —To ascertain the neurotoxicity of 2-bromopropane and 1-bromopropane, three doses of 2-bromopropane (1.1, 3.7 and 11.0 mmol/kg), two doses of 1-bromopropane (3.7 and 11.0 mmol/kg), and a dose of 2,5-hexanediol (2.5-HD) as a positive reference (2.6 mmol/kg) dissolved in olive oil were subcutaneously injected into rats once a day, 5 d/wk for 4 weeks. A control group were injected with olive oil alone. The maximum motor conduction velocity (MCV) and the motor latency (ML) in rat tail nerve, as indexes of the electrophysiological changes, were investigated for 4 weeks. From 2 weeks after the injections, the MCV in the 1-bromopropane and 2-bromopropane-treated groups began to decrease in a dose-dependent fashion. These dose-related decreases continued, and the MCV in the groups injected with 1-bromopropane (11.0 mmol/kg) and 2-bromopropane (3.7 and 11.0 mmol/kg) decreased significantly compared with that in the control group. The ML in the 1-bromopropane and 2-bromopropane-treated groups increased in reverse correlation with the MCV decreases. The changes in ML occurred earlier than the MCV changes in the 1-bromopropane and 2-bromopropane-treated groups. The potency of the peripheral neurotoxic changes induced by 1-bromopropane and 2-bromopropane at the doses used in the present study was weaker than that observed in the positive reference 2,5-HD (2.6 mmol/kg) group. (J Occup Health 1999; 41: 1–7)

Key words: 1-bromopropane, 2-bromopropane, Different doses, Peripheral neurotoxicity, Motor conduction velocity, Motor latency

It has been reported that 2-bromopropane is toxic to reproductive, and hematopoietic organs1-8. As bromopropanes are usually used in a closed system, they have not been considered an occupational health hazard. As such, neither ACGIH, nor NIOSH (National Institute of Occupational Safety and Health, USA) has set on occupational exposure limit. Nevertheless, as a substitute solvent for chlorofluorocarbons, 2-bromopropane was found to be a reproduction and hematopoiesis toxicant in workers in a Korean electronic product factory in 19951-3. Since then, studies have been done to confirm epidemic findings and elucidate the mechanism of toxicity of 2-bromopropane. As an organic solvent, 2-bromopropane should also be examined as to its peripheral neurotoxicity. Some workers in the Korean factory complained of pain or sensation disorders in their hands and legs8. Recently, 1-bromopropane, an isomer of 2-bromopropane, has been introduced into industry as a less toxic nonflammable solvent3. One study has shown that inhalation exposure to 1-bromopropane produced neurotoxicity in rats10. In the present study, to clarify the peripheral neurotoxicity of 2-bromopropane and its structure-related substances, 3 doses of 2-bromopropane and 2 doses of 1-bromopropane were subcutaneously injected into rats for 4 weeks. The electrophysiological changes in the tail nerve were investigated.

Materials and Methods

Animals and treatments: A total of 55 male Wistar rats, weighing 204.9 ± 11.9 g (Mean ± SD) delivered from Seiwa Experimental Animal Institute, Japan, were maintained under a 12 h light/dark cycle (7:00–19:00) in an air-conditioned laboratory (temperature 23 ± 1°C, humidity 50%). The rats were given access to tap water and CE-2 chow (Kurea Company, Japan) ad libitum. After 4 days of adaptation, the rats were divided into seven groups (Table 1). Included in this experiment were one control group injected subcutaneously with olive oil, and a 1-Bro3.7, 1-Bro11, 2-Bro1.1, 2-Bro3.7, 2-Bro11 and 2.5-HD group, given 1-bromopropane at 3.7 and 11.0, 2-bromopropane at a dose of 1.1, 3.7, and 11.0, and 2,5-hexanediol at 2.6 mmol/kg dissolved in olive oil, respectively. The doses 1.1, 3.7, and 11.0 mmol/kg are
supposed to correspond to the exposure levels of 100, 300 and 1000 ppm in inhalation\(^1\). The injection volume for the rats in each group was 2-ml/kg body weight, given once a day, 5 d/wk. The daily walking characteristics were observed, and the daily weight, which was used in calculating the injection volume according to the dosage, was measured before every injection. All chemicals used in this study were purchased from Wako Pure Chemical Industries Ltd., Japan. The purities of 2-Bromopropane, 1-bromopropane, and 2,5-HD were all more than 97.0%.

### Statistical analysis

The significance of differences between groups was evaluated by one-way analysis of variance followed by Duncan’s multiple range test with the statistical software SPSS\(^{16}\).

### Results

#### Changes in Body Weight

As shown in Fig. 1 and 2, only body weight values at days 0, 5, 12, 19 and 26 are shown. The control rats had normal weight gain throughout the experiment. The mean of body weight decreased significantly in the 1-Bro11 compared with that in the control group from day 12 to day 26 (Fig. 1). The means in the 1-Bro11 group were also significantly reduced from day 5 to day 26 compared with the 1-Bro3.7 (11.0 vs 3.67 mmol/kg), and from day 12 to day 26 compared with the 2,5-HD group. There was no significant difference between the weight in the 1-Bro3.7 and control groups until day 19, nor between the 2,5-HD and control until day 12 (Fig. 1).

The body weight gain in the 2-Bro11 group was significantly retarded compared with that in the control from day 19 to 26 (Fig. 2). The means of body weight for 2-Bro11, the highest dose 2-bromopropane group, were significantly lower than for 2-Bro3.7, and 2-Bro1.1 from day 12 to 26. Also, the means of body weight in the 2,5-HD group were significantly decreased from day 19 to 26 compared with those in the 2-Bro3.7 and 2-Bro1.1 groups (Fig. 2).

#### Changes in MCV in rat tail nerve

Changes in the MCV in every group are shown in Fig. 3 and 4.

There was no significant difference between the control and the treatment groups in the MCV at the beginning of the experiment (0 week). From 2 weeks after the injections, the MCV in the 1-bromopropane and 2-bromopropane-treated groups began to decrease in a dose-dependent manner compared with the control group. These dose-related decreases continued with significant differences found at 4 weeks after the injections. The MCV in the 1-Bro11, 2-Bro11 and 2-Bro3.7 groups were significantly decreased relative to the control group value, but when the dose of 1-bromopropane was decreased to 3.7 mmol/kg (1-Bro3.7), and 2-bromopropane to 1.1 mmol/kg (2-Bro1.1), the MCV decreases in these groups were not significant relative to the control. The MCV in the 2,5-HD group, the positive control in this study, was the lowest numerically and also significantly different from that in the control group. No significant differences were found between the MCVs in the 1-Bro11, 2-Bro11, 2-Bro3.7 and 2,5-HD groups. The MCVs in the 1-Bro3.7 and 2-Bro1.1 groups were significantly higher than in the 2,5-HD group. It is interesting to note that the MCV in the 2-Bro1.1 group was significantly higher than that in the 2-Bro11 group (Fig. 4).

#### Changes in ML in the tail nerve

Two motor latencies, \(ML_{AB}\) and \(ML_{AC}\), were recorded (Figs. 5–8). Both ML values in the 2,5-HD, 1-Bro11, 2-Bro11 and 2-Bro3.7 groups increased in correlation with the MCV decreases 4 weeks after the injections. In the 1-bromopropane and 2-bromopropane-treated groups, the increases in ML were dose related. Moreover, the \(ML_{AC}\) in the 2,5-HD and 1-Bro11 groups had increased significantly at 2 weeks whereas the MCV decreases at this time were not significant (Figs. 7–8 and Figs. 3–4). Even at 4 weeks, the number of significant differences between the control and treated groups, between the

### Table 1. Grouping and Treatment

<table>
<thead>
<tr>
<th>Group</th>
<th>Number of Rats</th>
<th>Treatment and Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>9</td>
<td>Olive oil</td>
</tr>
<tr>
<td>1-Bro3.7</td>
<td>7</td>
<td>1-Bromopropane 3.7 mmol/kg</td>
</tr>
<tr>
<td>1-Bro11</td>
<td>9</td>
<td>1-Bromopropane 1.1 mmol/kg</td>
</tr>
<tr>
<td>2-Bro1.1</td>
<td>7</td>
<td>2-Bromopropane 1.1 mmol/kg</td>
</tr>
<tr>
<td>2-Bro3.7</td>
<td>7</td>
<td>2-Bromopropane 3.7 mmol/kg</td>
</tr>
<tr>
<td>2-Bro11</td>
<td>9</td>
<td>2-Bromopropane 11 mmol/kg</td>
</tr>
<tr>
<td>2.5-HD</td>
<td>7</td>
<td>2.5-Hexandione 2.6 mmol/kg</td>
</tr>
</tbody>
</table>
Fig. 1. Changes in body weight (mean ± SD) in the 1-Bro3.7, 1-Bro11, 2,5-HD and control groups. The 1-Bro3.7, 1-Bro11, 2,5-HD and control groups comprise the rats injected with 1-bromopropane at 3.7 and 11.0 mmol/kg dissolved in olive oil, with 2,5-hexanediol at 2.6 mmol/kg dissoluted in olive oil, and with the oil alone, respectively.

Fig. 2. Changes in body weight (mean ± SD) in the 2-Bro1.1, 2-Bro3.7, 2-Bro11, 2,5-HD and control groups. The 2-Bro1.1, 2-Bro3.7, 2-Bro11, 2,5-HD and control groups comprise the rats injected with 2-bromopropane at 1.1, 3.7 and 11.0 mmol/kg dissolved in olive oil, with 2,5-hexanediol at 2.6 mmol/kg dissolved in olive oil, and with the oil alone, respectively.

treated groups were more for ML_{AC} than for the MCV.

Discussion

The toxicity of 2-bromopropane and its structurally related bromopropane has been little studied. Since reports of hematopoietic and reproductive disorders due to solvents containing 2-bromopropane among workers in an electronics factory in South Korea^{1-3}, several experimental studies on the effect of 2-bromopropane on the reproductive and hematopoietic systems have been done^{4-9}. 1-Bromopropane and 2-bromopropane are suspected of being peripheral neurotoxical substances,
Fig. 3. Changes in MCV (mean ± SD) in the 1-Bro3.7, 1-Bro11, 2,5-HD and control groups. MCV represents for the maximum motor conduction velocity in the rat tail nerve. The 1-Bro3.7, 1-Bro11, 2,5-HD and control groups represent the rats injected with 1-bromopropane for 3.7 and 11.0 mmol/kg dissolved in olive oil, with 2,5-hexanedione for 2.6 mmol/kg dissolved in olive oil, and with the oil alone, respectively.

Fig. 4. Changes in MCV (mean ± SD) in the 2-Bro1.1, 2-Bro3.7, 2-Bro11, 2,5-HD and control groups. MCV represents the maximum motor conduction velocity in the tail nerve. The 2-Bro1.1, 2-Bro3.7, 2-Bro11, 2,5-HD and control groups comprise the rats injected with 2-bromopropane at 1.1, 3.7 and 11.0 mmol/kg dissolved in olive oil, with 2,5-hexanedione at 2.6 mmol/kg dissolved in olive oil, and with the oil alone, respectively.

but there is no evidence to support this, with the exception of a report by Yu et al. at the 71st Annual Meeting of the Japan Society for Occupational Health. In their study, rats were inhaled 100 or 1,000 ppm 2-bromopropane, or 1,000 ppm 1-bromopropane for 8 h/d, 7 d/wk for 12 weeks.

Yu et al. observed that rat which inhaled 1,000 ppm 1-bromopropane for 4 weeks (8 h/d, 7 d/wk) had a significantly decreased MCV and increased distal latency (DL) in the tail nerve with a significant decrease in body weight. The DL of the rats which inhaled 2-Bromopropane 1,000 ppm began to increase from 8 to 12 weeks of
Fig. 5. Changes in ML_AB (mean ± SD) in the 1-Bro3.7, 1-Bro11, 2,5-HD and control groups. DL_AB represents the distal latency from the proximal to the middle part of the tail nerve. The 1-Bro3.7, 1-Bro11, 2,5-HD and control groups comprise the rats injected with 1-

bromopropane at 3.7 and 11.0 mmol/kg dissolved in olive oil, with 2,5-hexanedione at 2.6 mmol/kg dissolved in olive oil, and with the oil alone, respectively.

Fig. 6. Changes in ML (mean ± SD) in the 2-Bro1.1, 2-Bro3.7, 2-Bro11, 2,5-HD and control groups. DL_AB represents the distal latency from the proximal to the middle part of the tail nerve. The 2-Bro1.1, 2-Bro3.7, 2-Bro11, 2,5-HD and control groups comprise the rats injected with 2-
bromopropane at 1.1, 3.7 and 11.0 mmol/kg dissolved in olive oil, with 2,5-hexanedione at 2.6 mmol/kg dissolved in olive oil, and with the oil alone, respectively.

exposure and the body weight began to decrease from the 4th week, but the MCV for these rats decreased significantly only at 8 weeks. Yu et al. also found histopathological changes in tibial nerves in rats exposed to 1-bromopropane (1,000 ppm for 7 weeks), or 2-
bromopropane (100 or 1,000 ppm for 12 weeks).

In the present study, 3.7 or 11.0 mmol/kg 1-
bromopropane or 2-bromopropane was injected subcutaneously for 4 weeks. The body weight in the 1-
Bro11 group decreased significantly from day 12 after
Fig. 8. Changes in MLAC (mean ± SD) in the 2-Bro1.1, 2-Bro3.7, 2-Bro11, 2,5-HD and control groups. MLAC represents the distal latency from the proximal to the distal part of the tail nerve. The 2-Bro1.1, 2-Bro3.7, 2-Bro11, 2,5-HD and control groups comprise the rats injected with 2-bromopropane at 1.1, 3.7 and 11.0 mmol/kg dissolved in olive oil, with 2,5-hexanedione at 2.6 mmol/kg dissolved in olive oil, and with the oil alone, respectively.

the injection of 1-bromopropane (11.0 mmol/kg). The MCV in our 1-Bro11 group had decreased at 4 weeks. These changes at 4 weeks were also reported in Yu et al.'s study. The ML from the proximal to distal part of the tail nerve (MLAC) in the present study increased at 2 weeks. These results show that 1-bromopropane can produce peripheral neurotoxicity after either subcutaneous injection or inhalation. In the present study, the ML from the proximal to distal part of the tail nerve in the 1-Bro3.7 group (Fig. 7) was also significantly increased with a
decrease in the MCV. It can be supposed that the threshold of 1-bromopropane in peripheral nerves with MCV and ML as indexes is lower than 3.7 mmol/kg on subcutaneous exposure.

For 2-bromopropane, the MCV for 2-Bro11 and 2-Bro3.7 had decreased at 4 weeks. It is worth noticing that body weight in the 2-Bro3.7 group showed no change after 4 weeks injection of 2-bromopropane 3.7 mmol/kg while at this time the MCV and ML had changed significantly. These results suggest that change in body weight is not the most sensitive parameter for 2-bromopropane toxicity. As there was no change in body weight, MCV or ML in the 2-Bro1.1 group, the threshold of 2-bromopropane in peripheral nerves with MCV and ML as indexes is higher than 1.1 and lower than 3.7 mmol/kg for subcutaneous injection.

The body weight in 1-Bro3.7 was significantly higher than in 1-Bro11 from day 5. The weights in the 2-Bro1.1 and 2-Bro3.7 group were significantly higher than in the 2-Bro11 group from day 12 (Fig. 2). The MCV and ML (Figs. 4 and 8) in 2-Bro1.1 at 4 weeks were significantly higher than in the 2-Bro11 group. All these changes show that the impairment induced by 1-bromopropane and 2-bromopropane is dose related.

In the Yu et al. study, the same dose of 1-bromopropane (1,000 ppm) had a stronger influence on the MCV and DL in rat tail nerve than that of 2-bromopropane. However, in the present study, the effects of 1-bromopropane and 2-bromopropane (3.7 or 11.0 mmol/kg) on the MCV and ML were similar (data not shown). The reason for the discrepancy between these two studies should be investigated.

2,5-HD was used as a positive reference for the 1-bromopropane and 2-bromopropane treatments. The changes in body weight, MCV, and ML induced by 2.6 mmol/kg 2,5-HD observed in this study are similar to those reported in the past[12–15, 17]. These results prove that the experimental conditions and measurements in the present study are reliable. The impairment of weight, MCV and ML induced by 1-bromopropane and 2-bromopropane (up to 11.0 mmol/kg) was weaker than that observed in the 2,5-HD group (Figs. 1–8). It can be concluded that the peripheral neurotoxicity caused by the doses of 1-bromopropane and 2-bromopropane used in the present study is weaker than that caused by 2,5-HD at a dose of 2.6 mmol/kg.

References