Letter to the Editor

Urethan (Ethyl Carbamate) as a Cosolvent of Drugs Commonly Used Parenterally in Humans

Urethan, a potent teratogenic and carcinogenic agent in experimental animals, has been used in Japan for the past 25 years as a cosolvent of water-insoluble analgesic and sedative drugs. Urethan is used also as a solubilizer and cosolvent for pesticides, fumigants, and cosmetics, because it is a good solvent for various organic materials (6). In the past, urethan was used clinically as an antineoplastic agent and a hypnotic (6). In experimental animals, urethan induces a high incidence of a variety of tumors (7, 13 15), malformations (8, 12), and chromosome aberrations (4). Carcinogenic effects of urethan via placenta (5, 9 11) and via mother’s milk (9) have also been reported. Furthermore, tumors and malformations were transmitted to the next generation of mice subsequent to urethan treatment (11). As shown in Chart 1, small amounts of urethan (10 μg/g body weight) induce lung tumors in mice.

Sixty-three drugs, which are commonly used parenterally in Japan, and 72 cosmetics were analyzed chromatographically. A thin-layer chromatogram (Silica Gel 60 F254, 0.25 mm thick, 20 x 20 cm; E. Merck, Darmstadt, West Germany) was developed in: Solvent System A, acetone:petroleum ether (b.p. 30-60°; 3:7, v/v); Solvent System B, ethanol:benzene:aqueous 50% acetic acid (7:1:1, v/v/v); and Solvent System C, acetone:chloroform:ethyl ether:petroleum ether (1:2:2:5, v/v/v/v). For the detection of carbamates as red spots on chromatograms, p-dimethylamincinnamaldehyde (1 g in 50 ml of 6 s HCI and 50 ml of ethanol) was used (1). As authentic chemicals, methyl carbamate, ethyl carbamate (urethan) (Wako Pure Chemical Ind., Ltd., Osaka, Japan), isopropyl carbamate, n-butyl carbamate (Tokyo Chemical Ind., Co., Ltd., Tokyo, Japan), pyrabital (Grelan Pharmaceutical Co., Ltd., Tokyo, Japan), and aminopyrine (Sumitomo Chemical Ind., Co., Osaka, Japan) were used. Four products for parenteral use showed positive results following these procedures and were chromatographically identical to urethan (Fig. 1). (a) Grelan Injection (pyrabital, 200 mg; and aminopyrine, 100 mg, in 2 ml), (b) Noblon-A Injection (pyrabital, 200 mg; chlorpromazine hydrochloride, 12.5 mg; and diphenhydramine, 20 mg, in 2 ml), (c) Noblon-B Injection (pyrabital, 300 mg; chlorpromazine hydrochloride, 25 mg; and diphenhydramine, 20 mg, in 2 ml), and (d) C-Noblon Injection (pyrabital, 200 mg; surpyrine, 100 mg; chlorpromazine hydrochloride, 15 mg; promethazine hydrochloride, 10 mg; and 8-chlorotheophylline, 25 mg, in 2 ml) contain urethan as a cosolvent, because pyrabital is insoluble in water. These products have been manufactured by Grelan Pharmaceutical Co., Ltd., Tokyo, Japan, and have been sold by Takeda Pharmaceutical Ind., Co., Ltd., Osaka, Japan, since 1950 (a), 1956 (b and c), and 1958 (d).

For the detection of carcinogenicity, a single injection of Grelan Injection (0.002 ml/g body weight) was given to 3-week-old ICR/Jcl mice. Lung tumors were induced in significantly high frequency (Table 1). From the tumor

![Chart 1. Changing urethan dose response of ICR/Jcl mice in relation to tumor induction. Various amounts of urethan (10, 50, 100, 450, and 1000 μg/g body weight) were given s.c. to 3-week-old ICR/Jcl male (○) and female (○) mice. They were maintained on Mouse Diet CA-1 (10) and were sacrificed on the 5th month after treatment. Controls were untreated and were sacrificed 6 months after birth. Pathological lesions were examined especially for tumors. Lung tumors were counted again after fixation in 20% neutral formaldehyde solution (mean ± S.E.). Numbers in parentheses, ratio of tumor-bearing mice to survivors. Application of χ² test with Yates’ correction and t test with approximation of Cochran-Cox yielded p value of 0.001 between 50-, 100-, 450-, and 1000-μg-treated groups and controls, and p value of 0.01 between 10-μg-treated group and controls. Δ, Lung tumor frequency following treatment with Grelan Injection (Table 1). From the tumor frequency, dose of urethan given to mice was estimated to be 150 μg/g body weight. Consequently, concentration of urethan solution in Grelan Injection is 7.5%, because 0.002 ml of this product was given per g body weight.](https://cancerres.aacrjournals.org/article-pdf/35/18/2895/3089267/cancerresearch-35-2895-2899.pdf)
frequency, the concentration of urethan solution in Grelan Injection was estimated to be about 7.5% (Chart 1). Significant embryotoxic and teratogenic effects of Grelan Injection were also detected, but since these were not elicited by urethan only (10), synergism or other combined action with pyrabital and aminopyrine must be considered (Table 2; Fig. 2).

Quantitative determination of urethan contained in these products was conducted following the microdiffusion method (2) after isolation of urethan by thin-layer chromatography. Doses of urethan used to dissolve pyrabital (average of 6 experiments) were 0.254 g/ampul (2 ml) (12.7%) in Noblon-A Injection, 0.246 g/ampul (12.3%) in Noblon-B Injection, 0.210 g/ampul (10.5%) in C-Noblon Injection, and 0.154 g/ampul (7.7%) in Grelan Injection. It is described in Japanese Pharmacopoeia (Regulations of the Japanese Ministry of Health and Welfare), Ed. 7, that 15% urethan solution can be used to dissolve pyrabital (3). Consequently, the dose commonly used as a single injection in humans [1 to 2 ampuls (0.3 to 0.6 g as pyrabital) to the adult] (3) corresponds to 5 to 10 μg/g body weight as urethan, which is equivalent to the carcinogenic dose of urethan in mice [10 μg/g body weight (Fig. 1)]. The maximum dose of these injections (3 g as pyrabital) in 1 day (3) corresponds to 50 μg of urethan per g body weight. From the clinical experience of the author (surgeon in Osaka University Hospital from 1967 to 1972), these injections have been used commonly as a nonalkaloid analgesic several times at 3- to 5-hr intervals after operation. Consequently, urethan, at up to 5 times the carcinogenic dose in mice, has been used in almost all patients after operation. In Japan, 100 million ampuls of these 4 injections have been

<table>
<thead>
<tr>
<th>Experimental groups</th>
<th>Sex</th>
<th>No. of mice at start</th>
<th>Incidence %</th>
<th>χ² test (p)</th>
<th>Tumors/lung</th>
<th>t test (p)</th>
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<tbody>
<tr>
<td>Grelan Injection</td>
<td>M</td>
<td>31</td>
<td>11/27 40.7</td>
<td>&lt;0.001</td>
<td>0.667 ± 0.177</td>
<td>&lt;0.001</td>
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<td></td>
<td>F</td>
<td>26</td>
<td>15/24 62.5</td>
<td>&lt;0.001</td>
<td>1.250 ± 0.290</td>
<td>&lt;0.001</td>
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<td></td>
<td></td>
<td>57</td>
<td>26/51 51.0</td>
<td>&lt;0.001</td>
<td>0.941 ± 0.169</td>
<td>&lt;0.001</td>
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<td>Controls</td>
<td>M</td>
<td>72</td>
<td>0/72 0.0</td>
<td></td>
<td>0.0</td>
<td></td>
</tr>
<tr>
<td></td>
<td>F</td>
<td>244</td>
<td>2/243 0.8</td>
<td></td>
<td>0.008 ± 0.006</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>316</td>
<td>2/315 0.6</td>
<td></td>
<td>0.006 ± 0.005</td>
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</tbody>
</table>

a Applied with Yates' correction.
b Applied with approximation of Cochran-Cox, because variance ratio was over F value at 1%.
c Mean ± S.E.

<table>
<thead>
<tr>
<th>Experimental groups</th>
<th>Implants</th>
<th>% of implants</th>
<th>χ² test</th>
<th>No.</th>
<th>% of implants</th>
<th>χ² test</th>
<th>No.</th>
<th>% of implants</th>
<th>χ² test</th>
<th>No.</th>
<th>% of implants</th>
<th>χ² test</th>
<th>No.</th>
<th>% of implants</th>
<th>χ² test</th>
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<tbody>
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<td>104</td>
<td>6</td>
<td>5.8</td>
<td>NS*</td>
<td>47</td>
<td>45.2</td>
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<td>51</td>
<td>49.0</td>
<td>&lt;0.001</td>
<td>25</td>
<td>49.0</td>
<td>&lt;0.001</td>
<td>22 O, 9 C, 9 K, 2 P</td>
<td></td>
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<td>Pyrabital</td>
<td>41</td>
<td>0</td>
<td>0.0</td>
<td>NS*</td>
<td>3</td>
<td>7.3</td>
<td>NS</td>
<td>38</td>
<td>92.7</td>
<td>NS</td>
<td>4</td>
<td>10.5</td>
<td>&lt;0.01</td>
<td>4 O, 2 C, 4 K</td>
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<td>Aminopyrine</td>
<td>50</td>
<td>3</td>
<td>6.0</td>
<td>NS*</td>
<td>4</td>
<td>8.0</td>
<td>NS</td>
<td>43</td>
<td>86.0</td>
<td>NS</td>
<td>6</td>
<td>14.0</td>
<td>&lt;0.01</td>
<td>3 O, 2 C, 1 K</td>
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<tr>
<td>Urethan</td>
<td>41</td>
<td>2</td>
<td>4.9</td>
<td>NS*</td>
<td>3</td>
<td>7.3</td>
<td>NS</td>
<td>36</td>
<td>87.8</td>
<td>NS</td>
<td>2</td>
<td>5.5</td>
<td>&lt;0.05</td>
<td>2 K</td>
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<td>5.1</td>
<td>NS*</td>
<td>13</td>
<td>3.7</td>
<td>NS</td>
<td>320</td>
<td>91.2</td>
<td>NS</td>
<td>1</td>
<td>0.3</td>
<td>1 E</td>
<td></td>
<td></td>
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</tbody>
</table>

* Applied with Yates' correction.
* NS, not significant; O, ruptured omphalocele (ventration of the abdominal viscera); C, cleft palate; K, kinky tail; P, polydactyly; E, exencephalus.
* Thirteen of 22 fetuses with omphaloceles had cleft palates or kinky tails.
used for the past 25 years.

This letter was written in order to warn of the possible hazards of using products that contain urethan. Furthermore, it is hoped that all drugs for parenteral use will be examined, because urethan may be (or may have been) used as a cosolvent of water-insoluble drugs in other countries. Long-term follow-up of patients who have been exposed to urethan-containing medicinal preparations is mandatory to ascertain the possible carcinogenic effects of urethan in humans. Such studies are in progress.

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REFERENCES


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