De-alcoholization of Paclitaxel Injection for Clinical Application

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Abstract. A generic drug of Taxol® Injection, Paclitaxel Injection NK (PTX injection), cannot be used for patients with severe hypersensitivity or overwhelming intolerance to alcohol because it contains ethanol as a dissolving agent. Therefore, we evaluated the suitability of de-alcoholized PTX injection for clinical application. De-alcoholization was carried out using inactive N2 gas under sterile conditions. The pharmacokinetic properties of the de-alcoholized PTX injection were evaluated in rats after intravenous injection. Finally, the de-alcoholized PTX injection was administered to a patient with alcohol intolerance to evaluate its suitability for clinical application. The ethanol included in the supplied PTX injection was almost completely removed (>99.9%). PTX, the major component of the de-alcoholized PTX injection, was stable with no decomposed compounds or bacterial contamination, although its viscosity was increased by 29-fold compared with untreated PTX injection. No significant differences in the pharmacokinetic parameters of PTX were observed between the de-alcoholized and untreated PTX injections. No drunkenness was observed in the patient with severe alcohol intolerance after injection of de-alcoholized PTX injection. Adverse events such as nausea, muscle pain, joint pain, neuropathy and myelosuppression were observed at similar degrees to those after injection of untreated PTX injection. The plasma concentrations of PTX after injection of the de-alcoholized PTX injection were similar to those after injection of untreated PTX injection. The present findings suggest that almost complete de-alcoholization of PTX can be achieved easily under sterile conditions and that the resulting product can be used safely for patients with severe alcohol intolerance.

The anticancer drug paclitaxel (PTX) is commonly used in the first- and second line treatment of various types of solid cancer, such as breast, non-small cell lung and ovarian cancer. In Japan, the generic drugs of Taxol® Injection (Bristol-Myers Squibb, Tokyo, Japan) are widely used for economic benefits. One of the generic PTX injections, PTX Injection NK (PTX injection; Nippon Kayaku Co. Ltd., Tokyo, Japan), has been reported to be bioequivalent and equally safe in comparison with proprietary injections (1). However, PTX injection includes ethanol as a dissolving agent because the solubility of PTX is very low due to its high hydrophobicity (<30 μg/ml) (2-5). From this reason, PTX injection cannot be used for patients who have severe hypersensitivity or overwhelming intolerance to alcohol, thus other regimens need to be applied. In addition, pharmacists must explain to outpatients receiving chemotherapy with PTX injection that they cannot drive a car. This is also a more serious problem for patients with fewer public transportation facilities who have to come a long way to hospital.

The aim of the present study was to conduct part of the program for the development of guidelines for the safe use of a de-alcoholized PTX injection for patients with severe alcohol intolerance. Firstly, we tried to eliminate ethanol from PTX injection. Secondly, the pharmaceutical and pharmacokinetic characteristics of the de-alcoholized PTX injection were investigated both in vitro and in vivo. Finally, the safety, efficacy and pharmacokinetics of PTX in a patient with severe alcohol intolerance after injection of the de-alcoholized PTX injection were investigated.
Materials and Methods

Materials. Paclitaxel Injection 100 mg/16.7 ml NK was obtained from Nippon Kayaku Co. Ltd. (Tokyo, Japan), Terumo Catheran Needle 23G (0.4x60 mm), Terumo Injection Needle 27G (0.4x25 mm), Terufusion Infusion Line System for Pump and Infusion Pump TE-161S (flow volume control system) were purchased from Terumo Co. Ltd. (Tokyo, Japan), MilliEX GV Filter (0.22 μm) was obtained from Millipore (Billerica, MA, USA). JMS Infusion Line System TI-PJ352PN01 (free drop system) was purchased from JMS Co. Ltd. (Tokyo, Japan). All other chemicals were commercially available and were of the highest purity available.

Pharmaceutical evaluation. For ethanol elimination, the ethanol in PTX injection (100 mg/16.7 ml) was evaporated using a stream of the inactive N₂ gas (300 ml/min) at 70°C. The operation was performed under sterile conditions with a membrane filter with a pore size of 0.22 μm as shown in Figure 1. The residual weight of the vial was measured at desired intervals (just before and at 5, 10, 15, 20, 25, 30, 40, 50 and 60 min after starting the de-alcoholization).

Remaining ethanol. The remaining ethanol after 60 min of de-alcoholization was measured by an absolute calibration method utilizing gas chromatography (GC, Agilent 6890N; Agilent Technologies Japan Ltd., Tokyo, Japan) attached to a sample introduction device for head-space (6).

Decomposed materials. The presence or absence of decomposed materials in the de-alcoholized PTX injection was determined by high-performance liquid chromatography (HPLC), and compared with that in the untreated PTX injection. The HPLC method was carried out according to the relative substance detection of PTX in the Pharmacopeia of the United States of America.

Confirmation of bacterial contamination. A mixed solution of the de-alcoholized PTX injection (5 ml) and 5% glucose solution (100 ml) was incubated in Pourmedia Sheep Blood Agar M58 (Eiken Chemical Co., Ltd., Tokyo, Japan) at 37°C for one week. After one-week’s incubation, bacterial contamination was checked and compared with a positive control of Staphylococcus aureus.

Stability. The de-alcoholized PTX injection was preserved at 26±1°C for 1 month, and the crystallization, color changes and the presence of contamination were visually checked.

Stability in liquid. The mixed solution of the de-alcoholized PTX injection (2 ml) and 5% glucose solution (100 ml) was preserved at 37°C for 1 month, and the crystallization, color changes and the presence of contamination were visually checked.

Viscosity. The viscosity of the de-alcoholized PTX injection was measured by digital viscometry (DVL-BII, Tokyo Keiki Inc., Tokyo, Japan) and the commonly used ‘revolution viscometer method’ at 25°C based on the second viscosity measurement of the 15th revised Japan Pharmacopoeia, and was compared with that of the untreated PTX injection.

Animals and pharmacokinetic experiments. Eight-week-old male Sprague-Dawley (SD) rats weighing 265 to 280 g were obtained from Japan SLC (Hamamatsu, Japan). The rats were housed under controlled environmental conditions (temperature: 23±1°C; humidity: 55±5%) with access to a commercial diet and water. Animal experiments were carried out in accordance with the guidelines of Aichi Medical University for the care and use of laboratory animals.

Rats under anesthesia by intraperitoneal injection of sodium pentobarbital (25 mg/kg body weight) were cannulated with polyethylene tubes in the right jugular vein for drug administration and blood collection. After surgical preparation, rats received a single intravenous dose (5 mg/kg) of the de-alcoholized or untreated PTX injection after awakening. The untreated PTX injection (1 ml) was dissolved in 1 ml of saline, whereas the de-alcoholized PTX injection (0.5 ml) was dissolved in 1.5 ml of saline. Blood samples (0.2 ml) were collected at designated time intervals (5, 10, 20, 30, 45, 60, 120, 180 and 240 min after administration). Plasma samples were obtained from the blood samples by centrifugation at 3,000 x g for 10 min at 4°C and stored at −70°C until analysis.

Administration of de-alcoholized PTX injection in a patient. A patient with recurrence of cancer of the uterine corpus after surgery, who had stopped receiving a monthly combination chemotherapy of carboplatin and PTX (m-TC) because of alcohol intolerance despite a good response to this regimen and no response to other regimens, received intravenous administration of the de-alcoholized PTX injection instead of untreated PTX injection. The dose of the de-alcoholized PTX injection was the same as that of the m-TC regimen based on a confirmation of bioequivalence in rats (de-alcoholized PTX injection 180 mg/ml2 plus carboplatin at area under the plasma concentration−time curve 5 (AUC5), every 4 weeks). The alcohol response, efficacy and adverse events were verified. Blood samples (2 ml) were collected at designated intervals (just before and at 12 and 25 h after administration). The clinical application of the de-alcoholized PTX injection was approved by the Institutional Review Board of Aichi Medical University and the patient provided written informed consent to participate in the study.

Drug analysis. The concentration of PTX in the formulation was determined by HPLC. The apparatus used for the HPLC was an LC-10A system (Shimadzu, Kyoto, Japan) equipped with a UV detector (230 nm). The experimental conditions were as follows: column, Cosmocil 5C18 column (4.6 by 150 mm); Nacalai Tesque, Kyoto, Japan); mobile phase, 20 mM potassium dihydrogenphosphate/acetonitrile (1:1 v/v) solution; column temperature, 40°C; flow rate, 1.5 ml/min.

The concentrations of PTX in plasma were determined by liquid chromatography tandem mass spectrometry (LC/MS/MS) according to the method reported by Zhao and colleagues (7). The LC/MS/MS was an API4000 LC-MS/MS system (AB Sciex) equipped with LC-20AD Prominance HPLC (Shimadzu). PTX was extracted from plasma by liquid-liquid extraction with t-butylmethyl ether. Reversed-phase column-switching chromatography was conducted using an ODS column, and the detection was enabled by electrospray ionization in the positive mode (LC/ESI (+)-SRM).

Pharmacokinetic analysis. The plasma concentration–time data for PTX in each rat after a single administration were analyzed individually using a noncompartmental model. The area under the plasma concentration–time curve (AUC) and the area under the first-moment curve (AUMC) were calculated by the linear
trapezoidal method until the last measurable concentration in plasma and were extrapolated to infinity. The half-life of the terminal phase ($t_{1/2}$) was calculated as $0.693/k$, where $k$ is the elimination rate constant calculated from the terminal linear portion of the log concentration in plasma. The systemic clearance ($CL_{sys}$) was calculated as dose/AUC. The mean residence time (MRT) was calculated as $MRT = AUMC/AUC$. The steady-state volume of distribution ($V_{ss}$) was calculated as $V_{ss} = CL_{sys} \times MRT$.

The primary pharmacokinetic variables used to assess the bioequivalence of de-alcoholized PTX injection were AUC from time zero to the last sampling time point (4 h) and the plasma drug concentration at 5 min after administration ($C_{max}$). The bioequivalence of two formulations (de-alcoholized and untreated PTX injections) was evaluated by analysis of variance (ANOVA). The 90% confidence interval of the ratio of the de-alcoholized PTX injection to untreated PTX injection (test/reference) was calculated using log-transformed data. For the de-alcoholized PTX injection, bioequivalence with the untreated PTX injection was examined to determine if the 90% confidence intervals for the estimated test/reference ratio of AUC and $C_{max}$ were within the standard acceptance range (0.80 to 1.25).

**Validation of infusion rate.** The de-alcoholized (2.5 ml) and untreated (5 ml) PTX injections were dissolved in 50 ml of normal saline separately. The weight of 100 drops was measured in the free-drop infusion line system, with a 0.40×25 mm 27G injection needle, keeping the 100-cm head after priming. Drop count per 1 ml was calculated based on the mean value of five separate measurements. The volume of the drop samples was measured gravimetrically with the specific gravity assumed to be 1.0, because the weight of 1 ml of the de-alcoholized and untreated PTX injections was 1.003 and 1.002 g, respectively. The time required for the finish dropping total volume of solutions was measured at a flow rate of 250 ml/h using the flow volume controlled infusion pump in three samples in each solution.

**Data analysis.** The data are expressed as mean±standard deviation (SD). The ethanol elimination rate constant ($k$) was calculated by the residual method. Statistical analysis was performed with the Statistical Package for Social Science (SPSS) statistical program (SPSS Statistics 17 for Windows; SPSS Japan Inc., Tokyo, Japan). Pearson’s simple regression was applied for the regression analysis of the de-alcoholization, Student’s $t$-test was applied for the ethanol
elimination analysis and plasma PTX concentration analysis. The level of significance was defined at \( p < 0.05 \).

**Results**

*Pharmaceutical evaluation.* The disappearance curve of ethanol from the PTX injection is shown in Figure 2. The vial weight decreased exponentially in the first 30 min after starting the elimination, indicating that ethanol elimination proceeded promptly. Subsequently, the reductions in weight became slow after 30 min. The weight of the original product before elimination was recorded as \( W_0 \), that after the elimination was indicated as \( W_{ss} \) and that after \( t \) min was indicated as \( W_t \). The logarithm of \( \frac{W_t - W_{ss}}{W_0 - W_{ss}} \) was reduced in proportion with the elapse time and was correlated with the line \( y = -0.232 \times t \) (95% confidence interval: \(-0.244\) to \(-0.219\), \( R^2=0.998, p<0.001 \)) until 25 min after starting the elimination. Therefore, the relationship of the weight change with elapsed time was correlated with the function \( y = 6.85 \times e^{-0.232t} + 31.81 \).

*Remaining ethanol after elimination, contaminants, stability and viscosity.* The mean amount of ethanol per vial was reduced to only 0.0018 g after the ethanol elimination, whereas the untreated PTX injection included about 6.6 g (8.35 ml \times 0.79 g/ml) of ethanol per vial (Table I). No emerging peak was detected in the HPLC pattern of the de-alcoholized PTX injection, which was very similar to that of the untreated product (Figure 3). This indicates that no decomposed matter was derived by this method. There was no bacterial development after one week of cultivation. The de-alcoholized PTX injection was stable in its appearance for one month. No remarkable change was observed after one week in the 5% glucose solution at 37°C. The viscosity of de-alcoholized PTX injection increased by about 29-fold compared with the untreated product (771 mPas for the de-alcoholized PTX injection and 27 mPas for the untreated PTX injection).

*Plasma concentration–time curves of PTX after the administration of PTX injection.* The comparative disappearance of PTX from plasma after a single intravenous injection of the de-alcoholized and untreated PTX injections in rats was compared. Semilogarithmic plots of the plasma concentration–time data for PTX after a single intravenous injection of the de-alcoholized and untreated PTX injections showed a biphasic elimination pattern (Figure 2). The elimination half-life \( t_{1/2} \) of the de-alcoholized PTX injection was longer than that of the untreated PTX injection. The area under the curve (AUC) of the de-alcoholized PTX injection was smaller than that of the untreated PTX injection.

**Table I. Ethanol content and viscosity before and after ethanol elimination from PTX injection.**

<table>
<thead>
<tr>
<th>Amount of ethanol in vial (g)</th>
<th>Before</th>
<th>After</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vial of PTX injection</td>
<td>6.6a</td>
<td>0.0018±0.0013b</td>
</tr>
<tr>
<td>Viscosity (mPas)</td>
<td>27</td>
<td>771</td>
</tr>
</tbody>
</table>

PTX, Paclitaxel. aThe value was calculated by half volume of PTX injection multiplied by the specific gravity of anhydrous ethanol (0.79). bThe value represents the mean±SD (n=5). The amount of ethanol and viscosity were calculated as described in the Materials and Methods.
injection of the de-alcoholized and untreated PTX injections (5 mg/kg) in rats are shown in Figure 4. There were no significant differences in the plasma concentration–time curves of PTX between the de-alcoholized and untreated PTX injections. The corresponding pharmacokinetic parameters of PTX are summarized in Table II. There were no significant differences in the corresponding pharmacokinetic parameters of PTX between the de-alcoholized and untreated PTX injections.

The 90% confidence intervals for the estimated de-alcoholized PTX injection/untreated PTX injection ratio of logarithm-converted AUC and logarithm-converted Cmax were log 0.883 to log 1.10 and log 0.807 to log 1.03, respectively. Considering that both values were within the range of log 0.80 to log 1.25, the de-alcoholized PTX injection was bioequivalent to the untreated PTX injection in accordance with the guideline of the generic biological equivalence test (8).

Validation of infusion rate. The drop count per 1 ml of PTX injection-saline solution was 28.6 drops/ml, and was the same as that described in the interview form for the PTX injection (9-12). It was 1.5-fold higher than that of normal saline (18.5 drops/ml). The drop count per 1 ml of the de-alcoholized PTX injection-saline solution was 29.1 drops/ml, which was nearly the same as that for the untreated PTX injection-saline solution. The times to finish dropping 50 ml

<table>
<thead>
<tr>
<th>Treatment</th>
<th>AUC (μg h/ml)</th>
<th>CLSYS (l/h/kg)</th>
<th>Vss (l/kg)</th>
<th>t1/2 (h)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Untreated</td>
<td>5.70±0.74</td>
<td>0.89±0.12</td>
<td>0.69±0.12</td>
<td>1.33±0.16</td>
</tr>
<tr>
<td>De-alcoholized</td>
<td>5.75±0.65</td>
<td>0.88±0.09</td>
<td>0.80±0.08</td>
<td>1.36±0.15</td>
</tr>
</tbody>
</table>

PTX (5 mg/kg) was administered intravenously. PTX, Paclitaxel; AUC, area under concentration–time curve from time zero to infinity; CLSYS, systemic clearance; Vss, volume of distribution at steady state; t1/2, terminal half-life. Pharmacokinetic parameters were calculated as described in the Materials and Methods. Each value represents the mean±SD (n=6). No significant differences in any of the parameters of PTX were observed between de-alcoholized and untreated PTX injections.

Figure 3. Typical HPLC pattern of untreated (a) and de-alcoholized (b) PTX injection.
of normal saline, the untreated PTX injection-saline solution and the de-alcoholized PTX injection-saline solution at the rate of 250 ml/h by the infusion pump were 12 min 28 s, 13 min 20 s and 12 min 55 s, respectively. The observed slight difference corresponded to that of the total volume. These findings indicate that the same adjustment of infusion rate as untreated PTX injection can be applied to de-alcoholized PTX injection.

Administration of the de-alcoholized PTX injection to a patient with alcohol intolerance, and verification of its efficacy, adverse reactions and pharmacokinetics. The patient was a 72-year-old female with cancer of the uterine corpus. She had undergone a modified radical hysterectomy, bilateral salpingo-oophorectomy and pelvic lymphadenectomy in September 2008, and hoped to receive no postoperative chemotherapy. However, a recurrence at the vaginal margin (30×17 mm) was detected. After she was informed and gave informed consent, the chemotherapy was started in June of the next year. Tumor regression from 39×28 mm in June to 20×17 mm in August was observed after only one course of m-TC (PTX 180 mg/m² plus carboplatin AUC5). However, the patient rejected further chemotherapy because of severe alcohol intolerance; somnolence, dizziness, nausea and fatigue were continued for over one week. After tumor growth was observed, a combination chemotherapy of docetaxel and carboplatin was applied in November. Since the disease progressed after two courses, m-TC using de-alcoholized PTX injection was selected as the next chemotherapy.

Table III. Adverse reactions after administration of de-alcoholized and untreated PTX injection to a patient.

<table>
<thead>
<tr>
<th>Adverse reaction</th>
<th>Untreated</th>
<th>De-alcoholized</th>
</tr>
</thead>
<tbody>
<tr>
<td>Somnolence</td>
<td>Grade 2</td>
<td>Grade 0</td>
</tr>
<tr>
<td>Dizziness</td>
<td>Grade 3</td>
<td>Grade 0</td>
</tr>
<tr>
<td>Hot flashes</td>
<td>Grade 2</td>
<td>Grade 1</td>
</tr>
<tr>
<td>Fatigue</td>
<td>Grade 3</td>
<td>Grade 1</td>
</tr>
<tr>
<td>Nausea</td>
<td>Grade 2</td>
<td>Grade 2</td>
</tr>
<tr>
<td>Vomiting</td>
<td>Grade 0</td>
<td>Grade 0</td>
</tr>
<tr>
<td>Anorexia</td>
<td>Grade 2</td>
<td>Grade 2</td>
</tr>
<tr>
<td>Muscle pain</td>
<td>Grade 1</td>
<td>Grade 1</td>
</tr>
<tr>
<td>Joint pain</td>
<td>Grade 1</td>
<td>Grade 1</td>
</tr>
<tr>
<td>Neuropathy</td>
<td>Grade 2</td>
<td>Grade 2</td>
</tr>
<tr>
<td>Leukopenia</td>
<td>Grade 2</td>
<td>Grade 1</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>Grade 1</td>
<td>Grade 0</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>Grade 0</td>
<td>Grade 0</td>
</tr>
<tr>
<td>Anemia</td>
<td>Grade 0</td>
<td>Grade 1</td>
</tr>
</tbody>
</table>

PTX, Paclitaxel. Each grade was estimated on the basis of Common Terminology Criteria for Adverse Events (CTCAE) Version 4 (2010).

The patient was treated by m-TC (de-alcoholized PTX injection 180 mg/m² plus carboplatin AUC5) in January 2010. Adverse reactions after administration of de-alcoholized and untreated PTX injection in a patient are summarized in Table III. After starting infusion of de-alcoholized PTX injection, somnolence and dizziness as symptoms of drunkenness did not occur, although these adverse effects occurred immediately when the first treatment of m-TC using the untreated PTX injection was
started. Hot flashes did not appear on day 1, but did appear on day 2. Fatigue occurred at grade 1, but disappeared within a few days. The degree of hot flash and fatigue were lower in this course due to the PTX injection being de-alcoholized.

The plasma concentration–time curve of PTX corresponded to that of previous report using untreated PTX injection (1, 13) (Figure 5). With no progression of the disease, it was evaluated as stable disease (51×40 mm in January 2010 to 49×38 mm in February 2010).

Discussion

PTX in the conventional PTX injection is formulated in a mixture solution (50:50, v/v) of polyoxyethylene castor oil and absolute ethanol because of its insolubility in water. The melting point of PTX is 213°C, the boiling point of alcohol is 78.3°C and the burning point of polyoxyethylene castor oil is over 300°C. It was expected that only ethanol is eliminated by the present method. After ethanol elimination, the remaining alcohol detected by GC was nearly zero, and no decomposed material was detected by HPLC. The weight change of the vial almost corresponded to the calculated weight of alcohol originally included in the PTX injection. These results indicate that de-alcoholization of PTX injection was successfully completed. No bacterial contamination was detected, this shows aseptic processing was performed throughout the whole process of this method. Although it was of concern whether crystalization of PTX might occur when the alcohol was removed, the crystal did not precipitate. It is also verified from the results that pharmacokinetic parameters were the same for both de-alcoholized and untreated PTX injections. It is thought that the residual PTX in de-alcoholized PTX injection dissolves in polyoxyethylene castor oil by its surfactant activity. De-alcoholized PTX injection was confirmed to exhibit no change in appearance during the one month of the stability test. However, in regard to the low reliability of visual evaluation, it should be used as soon as possible after preparation, and the expiration time for safe use of de-alcoholized PTX injection should be set at 24 h. PTX injection was successfully de-alcoholized easily without loss by the present method. There was no decomposed material or bacterial contamination by use of streaming N₂ gas, and the product was stable, whereas the viscosity was increased by 29-fold. In validation of the infusion rate, although the drop count per unit volume of the de-alcoholized PTX injection-saline solution increased to approximately 1.5 times that of normal saline, it was the same as that of the untreated PTX injection-saline solution. There was not much difference in the infusion times by the flow volume controlled infusion pump, and therefore it is not particularly necessary to adjust the infusion rate of de-alcoholized PTX injection. However, the infusion rate should be adjusted in the same way as that for untreated PTX injection-saline solution for the free-flow infusion system or the drop-count controlled infusion pump. Omura and colleagues (14) reported that the drop count per unit volume of the untreated PTX injection with 5% glucose solution was 1.7 times higher than that of normal saline, and that it depended on the surfactant activity of the polyoxyethylene castor oil. The present study showed that the increase in drop count per unit volume is independent on the existence of alcohol. Our results support their opinion, although we did not use glucose but normal saline in this study. It is also confirmed that the same adjustment of infusion rate as for untreated PTX injection can be applied to de-alcoholized PTX injection.

After the confirmation of the bioequivalence of de-alcoholized PTX injection to that of untreated PTX injection in vivo according to the Guideline for Bioequivalence Studies of Generic Product (6), approved by the institutional Ethical Review Board, it was administered to the patients who had extremely heavy alcohol intolerance. Diphenhydramine hydrochloride and dexamethazone were administered in the premedication to prevent potential risk for allergy to PTX itself and for emesis. Hence, it was necessary to pay attention to the potential for central nervous system side-effects. While no alcoholic reaction was observed, other distinctive adverse effect of PTX did occur. Hot flashes occurred on the second day of treatment with the de-alcoholized PTX injection, although it had occurred immediately when treatment with the untreated PTX injection was started. It is thought that the presence of the remaining castor oil may be related to the delay of hot flashes. Such a patient is really very rare, one who experiences hot flash with a sip of beer, and a few days of nausea, dizziness and somnolence after drinking a half glass of beer. Although treatments with other available agents were not effective, PTX was extremely effective for this patient. In the present study, the de-alcoholized PTX injection had considerable merit for this patient because no alcoholic reaction was induced by the treatment with this formulation, while the treatment with the untreated PTX injection caused alcoholic reaction lasting for over one week.

The use of albumin-bound PTX has been approved by national health insurance in Japan only for breast cancer, whereas its use for endometrial carcinoma is still unapproved. It is reported that the pharmacokinetics of albumin-bound PTX and its therapeutic and side-effects are different from those of conventional PTX (15, 16). In addition, PTX injection is reasonable compared with newly developed albumin-bound PTX formulation in terms of its price. Based on these factors, the de-alcoholized PTX injection was used in this study as an alternative to conventional PTX injection. All of materials used here, except for an aspirator, are available in many general hospitals and the principle is very
simple, although 3 to 4 h will be needed to prepare the de-
alcoholized PTX injection for one treatment.

In conclusion, the present study is the first to suggest that
dealcoholization of PTX injection is very simple and the
method may be applicable for other medicines containing
alcohol, when there is no other choice but to use it for
patients who have severe alcohol intolerance.

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