Ready-to-use gemcitabine

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Incorrect dilution of ready-to-use concentrates of gemcitabine that contain ethanol can result in higher than recommended alcohol concentrations in the final infusion solution, leading to local adverse effects and intoxication.

**Gemcitabine (dFdC, 2',2'-difluorodeoxycytidine)** is a pyrimidine antimetabolite and is a prodrug. Its cytotoxic effect stems from the inhibition of DNA synthesis. It received a marketing authorisation in 1995 for the treatment of a wide range of solid tumours, including non-small cell lung cancer, breast cancer, pancreatic cancer, epithelial ovarian cancer and bladder cancer.

In 2011, the Dutch Pharmacovigilance Centre Lareb received 31 reports of adverse events (AEs) following use of gemcitabine concentrate solution for infusion from five Dutch hospitals. After injection, patients mentioned infusion-related reactions, including pain at the site of injection, diagnosed as thrombophlebitis. Patients also reported drowsiness, dizziness, tingling or a burning sensation. According to the healthcare workers, these side-effects had not been observed previously. After multidisciplinary evaluation of these AEs, a clear time relationship with the introduction of new ready-to-use (RTU) gemcitabine concentrates for infusion was demonstrated. These AEs did not occur with gemcitabine powder solutions for injection.

To date, only two reports have been published on this subject. As far as the authors are aware, these AEs have only been reported in The Netherlands. Remarkably, all reports were related to the use of gemcitabine RTU concentrate from a single manufacturer.

**Formulation**

RTU concentrates have been introduced to reduce the risk of microbiological contamination or preparation errors during the parenteral drug preparation of solutions for infusion. An important limitation of RTU concentrates for infusion is the limited volume available to dissolve the active pharmaceutical ingredient (API); solubility of the API can therefore be a problem. This problem is usually solved by pH adjustment. The pH of the solution is controlled by either the salt form of the drug (hydrochloric acid) or using a buffer (for example, sodium phosphate or sodium acetate). When pH adjustment alone is insufficient to achieve the desired concentration, a combination of an aqueous solution and a water soluble organic solvent (such as ethanol, propylene glycol or macrogol) is often used in parenteral formulations. Many formulations using co-solvents such as these are marketed using high concentrations of organic solvent and are usually (but not always) diluted before injection. Limitations of using co-solvents in parenteral solutions include side-effects, for example, pain, inflammation and haemolysis upon injection.

**Ethanol excipients**

Ethanol (ethyl alcohol or alcohol) is a commonly used excipient in oral and parenteral pharmaceutical formulations worldwide. Ethanol is added to parenteral formulations to enhance or maintain active pharmaceutical ingredient solubility and as an antimicrobial agent. Ethanol in parenteral formulations can cause side-effects. The central nervous system, the cardiovascular system and the lungs are most affected by ethanol. The most common local side-effects of ethanol are pain at the site of injection and haemolysis.

To reduce the risk of these side effects it is recommended that formulations containing ethanol are injected slowly.

**Gemcitabine**

Gemcitabine RTU concentrates registered in Europe are listed in Table 1. Six preparations contain ethanol and one product contains three co-solvents (macrogol, propylene glycol and ethanol). There are four gemcitabine RTU concentrates registered that contain no ethanol.

Regarding the RTU concentrate formulations containing ethanol, the ethanol concentration is approximately 400mg/ml. According to the summary of product characteristics, it is recommended that the total quantity of the gemcitabine 40mg/ml concentrate for solution for infusion should be diluted into at least 500ml of sterile sodium chloride 0.9% solution and administered over 30 minutes. From the report of Lareb, it appears that the preparation was not executed according to the manufacturer’s recommendations in some cases. The gemcitabine RTU concentrate was diluted in 100–500ml, which resulted in a higher ethanol concentration and local AEs. The reported dizziness and drunkenness could be the result of the ethanol used in the RTU formulation. To demonstrate this hypothesis, two typical cases receiving gemcitabine in a 30-minute infusion are evaluated below.

**Case 1**

A 52-year-old male patient, diagnosed with undifferentiated large cell...
**Table 1: Overview of RTU gemcitabine concentrates containing ethanol from different manufacturers in Europe**

<table>
<thead>
<tr>
<th>Manufacturer</th>
<th>Gemcitabine concentration</th>
<th>Ethanol</th>
<th>Propylene glycol</th>
<th>Monosodium phosphate</th>
<th>Hydrochloric acid (HCl)</th>
<th>Sodium hydroxide (NaOH)</th>
<th>Disodium phosphate anhydrous</th>
<th>Water for injection</th>
<th>Concentration ethanol</th>
<th>pH</th>
<th>Shellfish-unrelated</th>
<th>Total ethanol dose per infusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Actavis</td>
<td>40mg/ml</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>395mg/ml</td>
<td>7.0–8.0</td>
<td>36</td>
<td>16,788mg</td>
</tr>
<tr>
<td>Centrafarm</td>
<td>38 g/ml</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>421mg/ml</td>
<td>7.0–9.5</td>
<td>30</td>
<td>18,834mg</td>
<td></td>
</tr>
<tr>
<td>Teva</td>
<td>40mg/ml</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>395mg/ml</td>
<td>Unknown</td>
<td>30</td>
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<td></td>
</tr>
<tr>
<td>Mylan</td>
<td>40mg/ml</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>395mg/ml</td>
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<tr>
<td>Accord</td>
<td>100mg/ml</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>440mg/ml</td>
<td>6.0–7.5</td>
<td>24</td>
<td>7,480mg</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vianex</td>
<td>38mg/ml</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>395mg/ml</td>
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<td>24</td>
<td>17,671mg</td>
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</table>

* All these products are ready-to-use concentrates and contain gemcitabine hydrochloride

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# This is calculated for an average adult (body surface 1.7m²) with a standard dose of gemcitabine (1000 mg/m²)


carcinoma, (body surface 1.79 m², weight 63kg), received gemcitabine treatment (300mg/m²) with a total dose of 537mg. The total amount of ethanol received is 5293mg, which will be administered in 30 minutes. The calculated blood alcohol concentration (BAC) will be 88.6mg/l at the end of the infusion. This concentration is presumed to be safe or unlikely to produce an effect.6

**Case 2**

A 72-year-old male patient diagnosed with non-small lung cell carcinoma, (body surface 2.09m², weight 91kg) is treated with gemcitabine (1125mg/m²) over 60 minutes with a total dose of 2353mg. The total amount of ethanol received is 23,226mg, which will be administered in 30 minutes. The calculated blood alcohol concentration (BAC) will be 88.6mg/l at the end of the infusion. This concentration is presumed to be safe or unlikely to produce an effect.6

**Conclusions**

The Pharmacovigilance Working Party concluded that the AEs reported for gemcitabine concentrate resulted from the insufficient dilution of the concentrate, which led to a higher concentration of alcohol in the final solution. They indicated that the product information for gemcitabine should be updated to emphasise the need to dilute the concentrate correctly before infusion, and the marketing authorization holder should be asked to monitor reports of AEs suggestive of reconstitution errors. Based on the cases presented, the authors believe that a warning for potential effects on driving ability should also be included. Currently, gemcitabine RTU concentrates without ethanol are available on the market. In the case of volume-sparing infusion therapy, low/ethanol-free concentrates or powder for solution for infusion should be administered. Moreover, these AEs emphasise the need for a good implementation strategy when a new product is introduced in the hospital.

**References**