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Avoiding crystallization of lorazepam during infusion

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ABSTRACT

Lorazepam is a strong sedative for intensive care patients and a commonly used method of administering it to the patient is by infusion of a freshly prepared lorazepam solution. During lorazepam infusion often unwanted lorazepam crystallization occurs, resulting in line obstruction and reduced lorazepam concentrations. With the aid of solubility measurements a solid–liquid phase diagram for lorazepam in mixtures of a commercially available lorazepam solution and an aqueous glucose solution was determined. This confirmed that the glucose solution acts as an anti-solvent, greatly reducing the lorazepam solubility in the infusion solution. Three approaches are proposed to obtain stable lorazepam solutions upon mixing both solutions and thus to prevent crystallization during infusion: (1) using a high lorazepam concentration, and thus a lower glucose solution volume fraction, in the mixed solution; (2) using an elevated temperature during solution preparation and administration; (3) reducing the lorazepam concentration in the commercial lorazepam solution.

1. Introduction

Lorazepam (Fig. 1) is a powerful sedative drug that is used predominantly at intensive care units (ICUs) in hospitals (Wunsch et al., 2009). In the Netherlands it is the preferred sedative to keep critically ill patients in a prolonged artificial coma. For this, a continuous administration of the right dosage using a safe and reproducible method is important.

According to product labelling, the commercial lorazepam solution should be injected intramuscularly or intravenously. Because the solution is quite viscous, according to approved product labelling in the Netherlands, a 1:1 dilution of the 4 mg/ml commercial lorazepam solution with water, an aqueous NaCl solution or a 5% glucose solution should be prepared shortly before injection. The product labelling differs from country to country: In the United Kingdom, for example, normal saline and water are mentioned as diluents on the labelling, but a 5% glucose solution is not.

Intensive care patients often need to be sedated for prolonged periods of time. Administering the medicine by infusion instead of injection therefore is a logical step (Hoey et al., 1996; Boulatta et al., 1996; Hunfeld et al., 2008). Typically, the infusion solution is freshly prepared by diluting a commercial solution of lorazepam in an organic solvent (polyethylene glycol/propylene glycol with the preservative benzyl alcohol) using an aqueous glucose solution. Upon administering lorazepam in ICUs obstruction of the infusion lines frequently occurs (Hoey et al., 1996). This obstruction is due to the formation of lorazepam crystals in the infusion lines. As it may decrease the lorazepam uptake by patients and create unsafe situations for the patient, the obstruction by lorazepam crystallization is strongly undesired. Usually the mixture is initially clear and transparent and only crystallizes upon infusion. We decided to investigate the crystallization behaviour of Lorazepam in an experimental setting close to conditions in the ICU. We suggest a number of solutions from the viewpoint of crystallization fundamentals which implies that the solutions given here may be outside the approved product labelling given by the producer.

Various attempts were made to find a remedy for the obstruction in the infusion lines due to lorazepam crystallization. It was reported that the solubility of lorazepam was lower when the infusion solution is prepared with a 0.9% NaCl solution (Boulatta et al., 1996). Absorption of lorazepam in PVC bags and PVC infusion lines may result in decreasing lorazepam concentrations (Hoey et al., 1996). When using a volumetric pump for infusion, crystals were mainly observed in the infusion line right after the volumetric pump while the infusion solutions were more stable when using a syringe pump (Hunfeld et al., 2008).

In order for crystallization to occur, a thermodynamic driving force is needed in the solution (Davey and Garside, 2000). This supersaturation is created when the concentration becomes higher than the solubility of the crystalline compound. The solubility 2generally is a function of the solvent or the mixture of solvents used. For instance, the solubility of ortho-amino benzoic acid in

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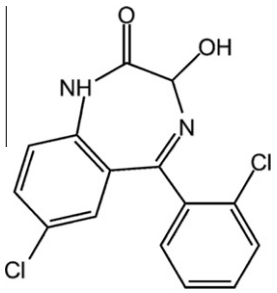

Fig. 1. Molecular structure of lorazepam.

ethanol/water mixtures shows a strong non-linear decrease with increasing water fraction (Jiang et al., 2008). Adding an anti-solvent, such as water in the case of ortho-amino benzoic acid, to a solution will decrease the solubility but at the same time reduce the concentration by dilution. A supersaturation may thus be created by adding an anti-solvent if the solubility decreases more rapidly than the concentration.

Also for lorazepam in a mixture of propylene glycol and water, a decrease of solubility with increasing water volume fraction was observed (Jouyban et al., 2010). Based on solubility measurements this paper reports about the cause of the evident tendency of lorazepam to obstruct the infusion lines and proposes remedies to avoid this. A commercially available lorazepam solution was used for the measurements because the mix of organic solvents it contains has a profound effect on the solubility behaviour of lorazepam.

2. Materials and methods

Crystalline lorazepam was obtained from Spruyt–Hillen (IJsselstein, the Netherlands, Lorazepamum Ph.Eur.) as a white powder. For preparing solution mixtures a commercially available lorazepam solution (Temesta injectie 4 mg/ml, lorazepam, RVG 08192, Wyeth pharmaceuticals) and a glucose solution in water (Baxter Viaflo, Glucose 5%) were used.

It should be noted that administration of a diluted lorazepam solution by infusion instead of injection may violate the instructions given by the manufacturer in two ways. Firstly, not all lorazepam solution is administered shortly after dilution because it may take several hours before the last bit of infusion solution is finally administered to the patient. Secondly, the dilutions used for infusion solutions are often not 1:1 as prescribed by the manufacturer. For these reasons administration by infusion instead of injection can lead to crystallization of lorazepam and therefore to dangerous situations for the patients. This article aims to contribute to the discussion about the safe and continuous administration of lorazepam. It is important that practitioners realize that the data given in this article are no replacement for the official information as given by the manufacturer.

2.1. Lorazepam solubility

A known amount of crystalline lorazepam was added into a standard HPLC vial. Known volumes of a commercially available lorazepam solution and a glucose solution in water were added to prepare 1 ml of a lorazepam crystal suspension with known overall composition. The composition was characterized by the volume fraction φ of glucose solution and the mass fraction x of lorazepam.

Saturation temperature measurements were performed using a Crystal16 of Avantium Technologies. In the Crystal16, the transmission of light through a stirred (magnetic stirrer bar) suspension was measured while accurately controlling the temperature. The transmission of light through a crystalline suspension is low because the crystals prevent the light from passing through the sample. Generally, the solubility increases with temperature. Therefore, upon heating (0.3 °C/min) a stirred (1000 rpm) sample containing a suspension with known overall composition, a temperature exists at which the transmission reaches its maximum value, the clear point. This clear point is the temperature at which the suspension becomes a clear liquid. When dissolution kinetics can be neglected, the clear point is a measure of the saturation temperature of the sample with known lorazepam concentration and solvent composition.

By cooling the clear solution sufficiently far below its clear point, recrystallization of the lorazepam occurred and a subsequent saturation temperature could be determined. For every sample two to four saturation temperatures were measured. Before the measurements, the Crystal16 was calibrated to account for a slight difference between the reported temperature by the Crystal16 and the actual temperature in a vial at constant set temperature after 1 h.

The saturation temperature of each sample was measured two to four times. When the temperature during the measurements did not exceed 50 °C these values were within 1 °C of each other. For these samples the arithmetic average of the independent measurements was taken as the saturation temperature. For the samples heated above 50 °C, subsequent saturation temperature measurements resulted in substantially lower saturation temperatures. Lorazepam is known to be prone to substantial degradation at temperatures above 50 °C (Kmetec et al., 1984). Thus, above this temperature of 50 °C degradation of considerable amounts of lorazepam in the sample occurred, lowering the saturation temperature. In these cases, only the saturation temperature of the first measurement run was used in further analyses.

The conversion of mass fraction x to concentration $c = x \times \rho$ was done by using the estimated average solution density ρ. The solution density was estimated by dividing the mass of the mixed clear solution in the vial by the volumes of its constituent solutions which were added using a pipette. It was thereby assumed that the volume effect of mixing was negligibly small. The average solution density was then calculated as the average of all densities of the vials with a certain solvent composition.

2.2. Lorazepam crystallization in syringe and infusion line

Another set of experiments used for investigating the causes of lorazepam crystallization employed a syringe, a syringe pump and an infusion line. In these experiments a lorazepam solution was pumped through a 2 m infusion line into a beaker using a syringe pump. Shortly before each experiment the lorazepam solution was made which, depending on the desired concentration, took between 30 and 90 min. The lorazepam solution was made from the commercially available lorazepam solution and the aqueous glucose solution. No crystalline lorazepam was added to the mixture of these two solutions. The resulting lorazepam solution was pumped through the infusion line at different volumetric flow rates.

All these experiments were performed at a glucose solution volume fraction of $\varphi = 0.92$ and a lorazepam concentration of 0.32 mg/ml. The general calculation procedure for the glucose solution volume fraction is outlined in Table 1.

2.3. Lorazepam crystallization

Experiments to visualize the lorazepam crystals using 3 ml of mixed solutions were carried out in a multiple reactor setup (Crystalline, Avantium Technologies). The setup consisted of eight glass