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Ringer's acetate solution-induced precipitation of remimazolam

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Editor—Certain drug-solvent combinations can result in precipitation. We report formation of a precipitate in an i.v. line induced by combined use of remimazolam and Ringer's acetate solution. In a patient undergoing oral surgery under general anaesthesia, i.v. fluid infusion was started with Ringer's acetate solution containing glucose 1% (Physio140, Otsuka Pharmaceutical, Tokushima, Japan), and general anaesthesia was initiated with administration of remifentanil (0.2 μg kg^{-1} min^{-1}) and fentanyl (0.1 mg) i.v. After 1 min, a bolus of remimazolam (0.2 mg kg^{-1}) was administered, and continuous infusion (1 mg kg^{-1} h^{-1}) was started to maintain anaesthesia, and after administration of rocuronium (40 mg), nasotracheal intubation was carried out uneventfully. I.V. infusion of Ringer's acetate solution was then set to 150 ml h^{-1}. At 20 min after the start of the continuous infusion of remimazolam, the i.v. drip rate was gradually decreased, and finally ceased. We identified a white precipitate that clogged the i.v. line at the joint of the i.v. catheter and drip needle (Fig. 1a), and fluid in the i.v. line had a white turbidity (Fig. 1b). Infusion of remimazolam and surgery was immediately stopped, and a new peripheral i.v. catheter was placed. Desflurane was used as an alternative for maintenance of anaesthesia, and the operation was completed uneventfully. The postoperative course was uneventful.

We tested remimazolam precipitation in our laboratory, examining whether remimazolam concentration, infusion rate of Ringer's acetate solution, or both contribute to the precipitates. We tested formation of the precipitates with three different concentrations of remimazolam (1, 2.5, or 5 mg ml^{-1} dissolved in saline; 13 ml h^{-1}) and three different infusion rates of Ringer's acetate solution (100, 150, or 300 ml h^{-1}). With remimazolam 2.5 and 5 mg ml^{-1} we observed precipitation in the i.v. catheter at slower infusion rates (100 and 150 ml h^{-1}) of Ringer's acetate solution (Fig. 1c). The precipitates began to form ~2 min after the start of remimazolam infusion, and the precipitates gradually increased in the i.v. catheter. At a higher infusion rate of Ringer's acetate solution (300 ml h^{-1}) with continuous infusion of remimazolam (5 mg ml^{-1}), precipitate was not observed in the i.v. line, but was observed around the three-way stopcock. In contrast, a lower concentration of remimazolam (1 mg ml^{-1}) did not produce precipitation in the i.v. catheter at any infusion rate of Ringer's acetate solution.

We conducted experiments to investigate whether the formation of precipitate differs depending on the type of Ringer's solution. When Ringer's lactate solution was infused at slower infusion rates (100 and 150 ml h^{-1}), continuous infusion of the higher concentration of remimazolam (5 mg ml^{-1}; 13 ml h^{-1}) also formed precipitates, which began to form ~5 min after the start of remimazolam infusion (Fig. 1d). The rate of precipitate formation in Ringer's lactate solution was slower than in Ringer's acetate solution. In contrast, lower concentrations of remimazolam (1 and 2.5 mg ml^{-1}) did not form precipitates at any infusion rate of Ringer's lactate solution.

Remimazolam (Anerem® in Japan; ByFavo™ in the USA; Aptimyda™ in the EU) is a novel benzodiazepine that was first approved in Japan as a general anaesthetic.[1,2] Remimazolam is distributed as remimazolam besylate, which is a hydrophilic white powder.[3,4] It is plausible that the white precipitates were formed by the combined use of remimazolam and Ringer's acetate solution. According to the package insert of remimazolam: (i) pH of the remimazolam solution is 2.9–3.9 when one vial (Anerem® 50 mg, ByFavo™ 20 mg) of remimazolam is dissolved into 10 ml of normal saline,[3,4] (ii) remimazolam

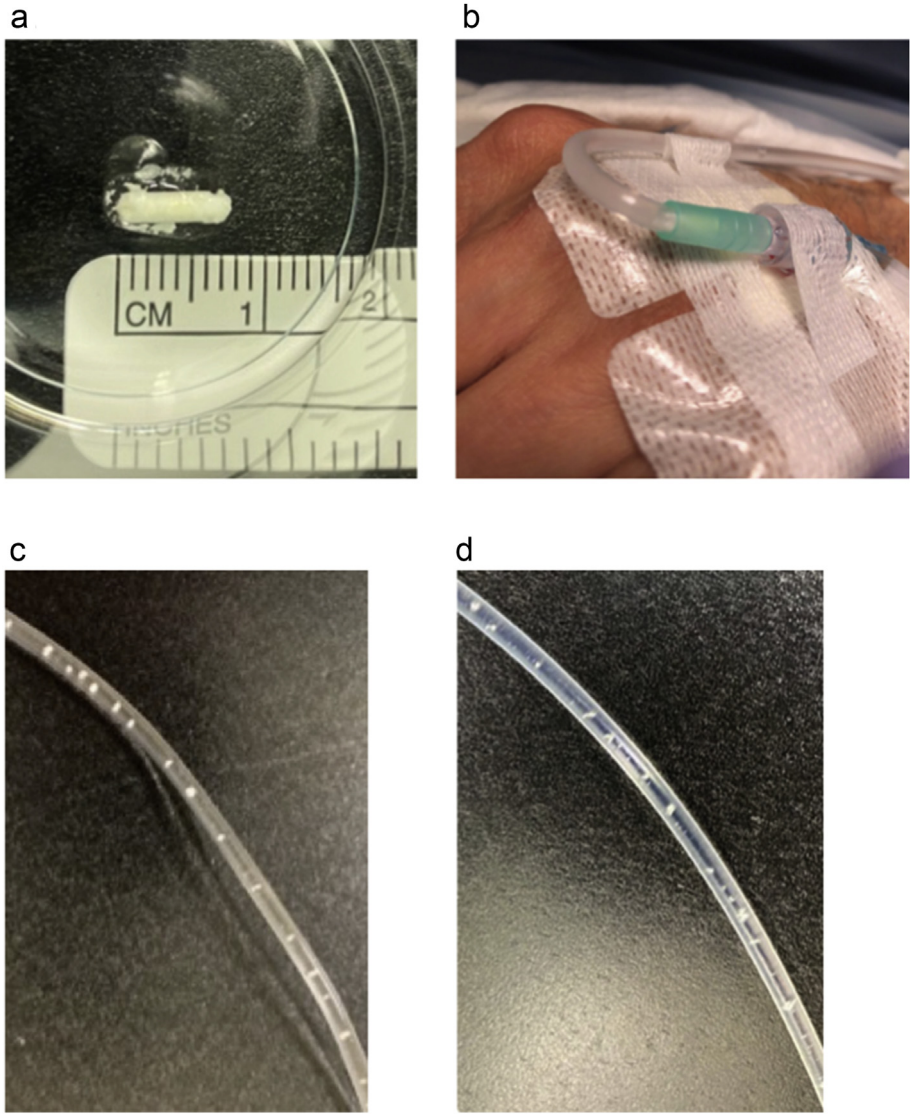

Fig 1. (a) White precipitate in the i.v. line at the union of the i.v. catheter and the drip needle. The entire length of the precipitate was ~0.8 mm. (b) White turbidity of the fluid in the i.v. line. (c) Precipitates in the i.v. line reproduced in the laboratory by combining remimazolam (5 mg ml^{-1}, 13 ml h^{-1}) and Ringer's acetate solution (100 ml h^{-1}). Precipitate formed ~2 min after the start of the infusion of remimazolam. Precipitate carried by the fluid flow aggregated and clogged the union of the i.v. line, and blocked flow. (d) Precipitate in the i.v. line reproduced in the laboratory by combined use of remimazolam (5 mg ml^{-1}, 13 ml h^{-1}) and Ringer's lactate solution (100 ml h^{-1}). Precipitate formed ~5 min after the start of remimazolam infusion.

should not be dissolved in an alkaline solution because its solubility decreases at pH>4,[3] and (iii) Ringer's lactate solution is not recommended as the solvent for remimazolam because it does not completely dissolve and precipitates in this solution.[4] In our case, remimazolam was dissolved in saline, and Ringer's acetate solution was chosen as the infusion solution. Although the pH of Ringer's acetate solution (5.9–6.2) is lower than that of Ringer's lactate solution (6.0–7.5), combined use of remimazolam and Ringer's acetate solution still formed precipitates. However, there have not been recommendations or alerts for selection of the infusion solution yet.[1–5]

Drug concentration and fluid infusion rate contribute to precipitate formation in i.v. line tubing and catheters.[6] Our laboratory findings suggested that higher concentrations of remimazolam and slower infusion rates of Ringer's acetate or lactate solutions (100 or 150 ml h^{-1}) contributed to precipitate formation. It is not surprising that use of the higher concentration of remimazolam (5 mg ml^{-1}) and slower infusion rate

of the Ringer's solution (150 ml h^{-1}) contributed to the precipitates observed. Precipitates collected at the joint between the drip needle and the i.v. line because as the lumen narrows, the infusion flow slows at this site.

As remimazolam forms precipitates in i.v. lines with Ringer's acetate or lactate solution, the combined use of remimazolam and Ringer's solutions should be avoided. If combined use of them is essential, lower concentrations remimazolam, higher infusion rates of Ringer's solution, or both are recommended to avoid precipitate formation.

Declarations of interest

The authors declare that they have no conflicts of interest.

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Prescription for unguided mobile health applications

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Editor—In a recent issue of *British Journal of Anaesthesia*, Li and colleagues[1] discuss the use of digital health for patients with chronic pain during the coronavirus disease 2019 (COVID-19) pandemic. The authors rightly point out that the COVID-19 pandemic has led to isolation and that patients with chronic pain are particularly vulnerable to the negative effects of this pandemic. The authors make a timely suggestion that digital health platforms may offer a solution to patients with chronic pain who lack healthcare access. Their discussion includes specific types of platforms and their drawbacks. They make the case that telehealth requires too much capacity for a health system and is unsustainable. In the case of online health communities, they cite lack of regulatory oversight. They point to chatbots as a possible solution that allows for patient counselling, support, and symptom triage; yet, the cited intervention lacked a significant effect on the outcomes of pain intensity, pain-related impairment, and general well-being[2] when compared with a control condition. Lastly, they mention the important role of psychologists and therapists in the direct care of chronic pain patients.

The authors present a balanced discussion of alternative strategies for care delivery during the pandemic. However, outside of discussion limited to chatbots, we note the relative absence of information about unguided electronic health (eHealth) and mobile health (mHealth) applications, or applications that do not require clinician contact or feedback. These unguided applications avoid some of the drawbacks associated with other digital health interventions in that they do not demand clinician involvement and they have a modest effect on clinically relevant outcomes. We believe the results of our recent meta-analysis that explored unguided eHealth and mHealth applications can add to this discussion.[3] In this meta-analysis, our *a priori* study outcomes were designed based on the Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials criteria for chronic pain clinical trials.[4] Our meta-analysis pooled outcomes from 17 different RCTs of 17 different eHealth and mHealth interventions. We