Physicochemical compatibility and emulsion stability of propofol with commonly used analgesics and sedatives in an intensive care unit

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ABSTRACT

Objectives The purpose of this study was the determination of the physicochemical compatibility and emulsion stability of propofol with other sedatives and analgesics (clonidine hydrochloride, dexmedetomidine, 4-hydroxybutyric acid, (S)-ketamine, lormetazepam, midazolam hydrochloride, piritramide, remifentanyl hydrochloride and sufentanil citrate) that are frequently administered together intravenously.

Methods Drugs were mixed with propofol and stored without light protection at room temperature. Samples were taken at 10 points of time over 7 days. The physical stability and emulsion stability in particular were analysed by visual and microscopical inspection and by measurement of the pH value, zeta potential and globule size distribution. In addition, high-performance liquid chromatography and mass spectrometry were used to identify chemical incompatibilities.

Results 4-Hydroxybutyric acid, midazolam hydrochloride, piritramide and remifentanyl hydrochloride are physically incompatible when mixed with propofol. The reason for this is the development of an increased fraction of oil droplets $>5\ \mu\text{m}$ leading to a higher risk of emboli. Moreover, propofol is chemically incompatible with remifentanyl. The sorption of propofol to the rubber stopper of the syringe was another detectable incompatibility.

Conclusions Propofol should not be administered with 4-hydroxybutyric acid, remifentanyl hydrochloride, midazolam hydrochloride and piritramide through the same intravenous line. Based on the risk of sorption to the rubber material, propofol should be used with caution. A drug loss might occur that leads to an underdosing of the patient requiring a dose adjustment to avoid any adverse consequences. As a result of this study, the drug safety in intensive care units could be optimised.

INTRODUCTION

The incidence of intravenous drug incompatibilities is a recurrent problem, especially in the intensive care medicine, as drugs are almost entirely administered via infusion due to the critical illnesses of the patients.^{1–2} Since analgesics and sedatives are the most commonly used drugs in the intensive care unit (ICU) and often administered simultaneously through the same intravenous line of a central multilumen catheter, the issue of a safe combined infusion is of high importance.^{3–6}

Propofol (2,6-diisopropylphenol) is one of the standard sedatives used in ICUs.⁷ Due to its high lipophilicity, it is formulated as a white opaque oil-in-water injectable emulsion.^{5–8–9} The

physicochemical and optical properties of this formulation pose a special risk in identifying stability and incompatibility problems.⁹ According to the manufacturer, propofol should not be mixed with other therapeutic agents prior to administration.¹⁰ However, in addition to a propofol infusion, patients may receive other drugs simultaneously through the same intravenous access line, leaving possible incompatibilities or instabilities such as drug precipitation and degradation, discolouration and emulsion damage with increased fat globule sizes hardly visible for the human eye.^{5–9} Potential risks of infusing these instable lipid injectable emulsions are catheter occlusion, loss of drug efficacy due to classical physicochemical incompatibilities, hypertriglyceridaemia, oxidative stress, tissue damage to the liver linked to a fat overload syndrome and pulmonary embolism by large-size fat globules ($>5\ \mu\text{m}$).^{11–14}

A detailed literature research on the compatibility of propofol with other medications revealed limited and often contradictory compatibility data obtained from only a small number of investigations. Furthermore, almost exclusively two-drug combinations were analysed. The data were not generated under comparable conditions and left the non-visible incompatibilities and instabilities unexamined. Considering that emulsion stability is a critical parameter, special analytical methods need to be applied.

The aim of the present study was to gain evidence of the emulsion stability in addition to the physical and chemical compatibility of commonly used analgesics and sedatives in combination with Propofol-Lipuro 20 mg/mL to optimise the drug safety of critically ill patients.

An investigation in the 12-bed cardiovascular ICU of the University Hospital Kiel, Germany, showed that clinically significant admixtures were midazolam hydrochloride, sufentanil citrate, clonidine hydrochloride, piritramide and remifentanyl hydrochloride. This demonstrates that the manufacturer's safety advice of a separate propofol infusion cannot always be followed in the daily routine.

Four more drugs were added to the study. Lormetazepam as an alternative and coadministered drug to midazolam hydrochloride in case of reduced effectiveness, especially in children. Dexmedetomidine hydrochloride as a relatively new and more potent α_2 -agonist than clonidine.³ 4-Hydroxybutyric acid and (S)-ketamine hydrochloride were listed as standard drugs in the ICU formulary and included in the observation to complete the group of analgesics and sedatives (table 1).

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Due to the importance of emulsion stability, the following methods were applied: visual and microscopical inspection, pH value and zeta potential (ZP) determination and globule size distribution measurements using light backscattering as well as dynamic light scattering and laser diffraction technique. The chemical compatibility determination was carried out by high-performance liquid chromatography (HPLC) and, for one combination, by mass spectrometry (MS).

METHODS

Drugs studied and sample preparation

The solutions of the selected drugs were prepared as shown in table 1. In case of dilution, 0.9% sodium chloride (NaCl) injection solution was used (Fresenius Kabi, Germany, lot. 19FI07WF, 14GG21, 14HC27, 19HM18WA; B. Braun Melsungen AG, Germany, lot. 124738091; Berlin-Chemie AG, Germany, lot. 133021, 133028). Every compounding was drawn up in 50 mL transparent BD Luer-Lok perfusion syringes (Becton, Dickinson and Company, Ireland, lot. 1408273, 1511209P, 1505244, 1302290). Two-drug mixtures of propofol as well as preparations with 0.9% NaCl injection solution were formulated at a volume ratio of 10:1 (v/v), 1:1 (v/v) and 1:10 (v/v) to cover a wide concentration range and to simulate flow rate variations in the infusion system. The 1:1 (v/v) ratio was chosen according to literature.¹⁵ The multiple-drug mixtures consisting of three drugs were prepared at a 1:1:1 (v/v/v) ratio, and the four-drug combination had a drug ratio of 1:1:1:1 (v/v/v/v). Mixtures were obtained by transferring propofol to the other drug solution-containing syringes using a female/female adapter (B. Braun Melsungen AG). A complete mixing was guaranteed by four back and forth transfers.

All solutions were stored at room temperature for 7 days without light protection, giving account of the circumstances in the ICU. Samples were taken at defined points of time, which will be further explained in the respective method descriptions.

pH determination

The pH was measured with a pH meter (HI 2211 pH/ORP Meter, HANNA Instruments Deutschland GmbH, Germany) for all possible two-drug combinations of propofol and six multiple-drug mixtures (table 2), including the preparations of propofol with NaCl injection 0.9%. The used electrode was especially designed for lipid-containing preparations (HI 1053B, HANNA Instruments Deutschland GmbH). Of each mixture, 3 mL was filled in a 15 mL falcon tube (Sarstedt AG & Co., Germany) directly after mixing and after 0.25, 0.5, 1, 2, 4, 8, 24, 96 and 168 hours. The pH value was read after an equilibration time of 3 min.

Chemical compatibility

High-performance liquid chromatography

The concentrations of 30 propofol-drug combinations and 6 multiple-drug mixtures were determined. Samples were taken directly after mixing and after 0.25, 0.5, 1, 2, 4, 8, 24, 96 and 168 hours. Since the determination of the chemical compatibility of each preparation per HPLC took 75 min, three samples were taken at the previously mentioned points of time, collected in cryo-vials (Carl Roth GmbH+Co. KG, Germany), quick-frozen by dipping the cryo-vial in liquid nitrogen, stored at -80°C and measured immediately after defrosting. Thirty samples per preparation were analysed applying a modified HPLC method used in forensic toxicology.¹⁶

The HPLC system consisted of a Waters W1525 Binary HPLC pump, a Postnova PN 7505 degasser, a Waters W2487 dual wavelength ultraviolet detector and a Waters W717plus

autosampler. Waters Breeze V3.30 was used to acquire and integrate the data. The separation was performed with a Merck LiChroCART LiChrospher 100 RP-8 ($5\text{ }\mu\text{m}$) column ($250\text{ mm}\times 4\text{ mm}$), which was set at 25°C by a column oven (TECHLAB GmbH, Germany). The injection volume was $10\text{ }\mu\text{L}$ and the flow rate was 1.0 mL/min . The detector wavelength was set at 210 nm for the detection of clonidine, dexmedetomidine, lormetazepam, piritramide, remifentanyl and sufentanyl and at 272 nm for the detection of (*S*)-ketamine, midazolam and propofol.¹⁷ The run time of the gradient method was 75 min. The HPLC mobile phase consisted of water with 1% (v/v) triethylamine, adjusted to pH 3.2 using phosphoric acid (phosphate buffer) for one, and of a 60:40 (v/v) solution of the phosphate buffer and acetonitrile for the other hand. The mobile phase was filtered through a $0.45\text{ }\mu\text{m}$ polyamide membrane filter (Whatman GmbH, Germany) and sonicated afterwards.

Calibration was performed by injecting six different concentrations of each drug 3 times. The lowest correlation coefficient was at least 0.9986. The validation of the sample preparation process for the HPLC measurement was carried out by comparing the concentrations of the frozen and defrosted samples with the concentration of the non-frozen samples of all propofol-drug mixtures (1:1 ratio (v/v)). The differences between measured values were less than 3%. The method was considered suitable for the extended procedure of concentration determination. The recovery of propofol in the emulsion formulation was detected with a propofol standard solution of 1.0 mg/mL in methanol (Sigma Aldrich Chemie GmbH, Germany, lot. FN05171101) to a percentage of 98.86%.

Liquid chromatography–mass spectrometry

For the mass spectrometric inspection of the 10:1 mixture of propofol and remifentanyl, samples were taken directly after mixing and after 24 hours. Remifentanyl was additionally inspected at three different pH values (3.26, 6.80, 8.00). The liquid chromatography–mass spectrometry (LC–MS) system consisted of an Agilent 1260 μ -Degasser G1379B, Agilent 1260 Infinity: 12602 HiP ALS G1367E autosampler and an Agilent 1260 Infinity TCC G1316A column oven. The separation was performed with a Zorbax Eclipse C8 ($5\text{ }\mu\text{m}$) column ($150\text{ mm}\times 4\text{ mm}$), which was tempered at 20°C . The mass spectrometers were gained using the ion trap instrument AmaZon SL (Bruker Co., USA) applying the electrospray ionisation in a positive ion mode. The injection volume was 1 and $10\text{ }\mu\text{L}$ and the flow rate was 1.3 mL/min . Bruker Data Analysis 4.0 was used for analysing the obtained data. The run time of the gradient method was 13 min. The mobile phase consisted of 0.1% (v/v) acetic acid and acetonitrile.

Lipid globule size distribution

The United States Pharmacopeia (USP) developed two methods to verify the stability of an emulsion system.¹⁸ As per Method I of USP <729>, the mean droplet size (MDS) must not exceed 500 nm . The determination of the MDS can be accomplished using dynamic light scattering. As Method I is not capable of identifying any particles in the large-diameter tail of the globule population, Method II applies to that: lipid injectable emulsions are considered stable if the percentage of fat globules $>5\text{ }\mu\text{m}$ (PFAT₅) is $<0.05\%$.

Dynamic light backscattering

As required in the USP, the MDS was detected by means of dynamic light backscattering technique, also known as photon

Table 1 Intravenous solutions and concentrations included in the study

Drug	Brand name	Manufacturer	Concentration (mg/mL)	Lot number	pH*
Clonidine hydrochloride†	Clonidin-ratiopharm	Ratiopharm GmbH, Ulm, Germany	0.015	R31039, M33741, 025322, N22041	4.56
Dexmedetomidine hydrochloride†	dexdor	Orion Pharma, Espoo, Finland	0.004, 0.02‡	1515175	4.65
4-Hydroxybutyric acid	SOMSANIT	Köhler Chemie GmbH, Bensheim, Germany	200	1332351, 1317151	7.92
(S)-Ketamine hydrochloride	Ketanest S	Pfizer Pharma GmbH, Berlin, Germany	25	351055, 450064	3.56
Lormetazepam†	SEDALAM	Köhler Chemie GmbH, Bensheim, Germany	0.04, 0.12‡	1406551, 1426751	5.76
Midazolam hydrochloride†	Midazolam-hameln	Hameln pharma plus GmbH, Hameln, Germany	3.6	513067, 306056	3.31
Piritramid†	Dipidolor	JANSSEN-CILAG GmbH, Neuss, Germany	1.0	5005, 2010	3.88
Propofol	Propofol-Lipuro	B. Braun Melsungen AG, Melsungen, Germany	20.0	15056808, 15194808, 15233807, 153828071	7.69
Remifentanyl hydrochloride†	Ultiva	GlaxoSmithKline GmbH & Co. KG, München, Germany	0.05	P035, U281	3.26
Sufentanil citrate†	Sufenta	JANSSEN-CILAG GmbH, Neuss, Germany	0.01, 0.03‡	5001, 2002B	5.69

*Measured value immediately after dilution with NaCl 0.9%, respectively, removal from container.

†Diluted to the standardised concentrations in the ward with NaCl 0.9%.

‡Concentrations used for high-performance liquid chromatography analysis.

correlation spectroscopy (PCS), using the Zetasizer Nano ZS (Malvern Instruments, UK). Samples were taken directly after mixing and after 1, 2, 4, 8, 24 and 168 hours. Before the measurement, viscosity and temperature of the propofol emulsion mixtures were determined, using the Vibro Viscometer SV-10 (A&D Company, Japan) and transferred to the measuring method of the Zetasizer Software 7.03 (Malvern Instruments). Each combination was diluted so that propofol is available in a 1:20 ratio. About 1.3 mL of the samples were filled in polystyrene cuvettes and placed in the instrument. One measuring process consisted of three runs, which for their part were 15 individual measurements. Beside the MDS, the polydispersity index (PDI), displaying the width of the distribution, was calculated.

Laser diffraction

To verify the presence of particles $>5\ \mu\text{m}$, the laser diffraction technique was applied. This method is qualified for a particle range of $0.1\text{--}8750\ \mu\text{m}$.¹⁹ Samples were measured using the laser diffractometer HELOS (Sympatec GmbH, Germany) in the CUVETTE modus. The cuvette had a capacity of 6 mL and was filled with particle-free Aqua bidest. Depending on the mixing

ratio, a preparation volume of $30\text{--}140\ \mu\text{L}$ had to be added to gain the optimal optical concentration of $15\text{--}25\%$. After cautious blending with a spatula, the cuvette was radiated with a helium–neon laser. The data analysis was performed using the software WINDOX 5 (Sympatec GmbH). Samples were analysed directly after mixing and after 24 and 168 hours. To detect the compliance with the particle size measurement specification, silicon carbide (SiC) reference products (Sympatec GmbH, lot. SiC-F1200'17) were tested. The results fully met the required specification.

Turbiscan technology

The Turbiscan Lab (Formulacion, France) was used to analyse the propofol emulsion mixtures by detecting the backscattered light.²⁰ A sample volume of 20 mL was put in special glass cells that were scanned each $40\ \mu\text{m}$ by a pulsed near infrared light source ($\lambda=850\ \text{nm}$) every 15 min within 24 hours. Another scan was performed after 96 and 168 hours. The resulting spectrums show the evolution of backscattered light intensity on the tube height as a function of time. The additional possibility of computing a non-dimensional Turbiscan stability index (TSI) allowed an internal comparison of all propofol–drug mixtures. The

Table 2 Compatibility of examined multiple-drug mixtures

	Drug conc. (%)*	Analgesics		Sedatives		Compatibility
		Drug(s)	Drug conc. (%)*	Drug(s)	Drug conc. (%)*	
Propofol	98.1	+ sufentanil citrate	96.9	+ midazolam hydrochloride	100.0	ct
Propofol	96.9	+ sufentanil citrate	99.5	–‡	–	c
		+ piritramide	100.8			
Propofol	98.1	+ sufentanil citrate	91.4	+ clonidine hydrochloride	101.2	c
Propofol	98.3	+ sufentanil citrate	99.1	+ dexmedetomidine hydrochloride	97.8	c
Propofol	98.5	+ remifentanyl hydrochloride	100.0	+ midazolam hydrochloride	101.7	c
Propofol	94.1	+ sufentanil citrate	99.1	+ midazolam hydrochloride	99.1	c
				+ lormetazepam	96.9	

The variation coefficient was $<3\%$ and is therefore not shown in the table.

*Drug concentration after 24 hours.

†Physically and chemically compatible.

‡No sedative present in combination.

c, compatible; conc., concentration.

measuring accuracy was set with a transmission (silicone oil) and a backscattering (white teflon) standard. The SD was <1%.

Macroscopic and microscopic observations

Visual inspection for discolouration, any enlarged oil droplets or a phase separation of all tested propofol–drug combinations was carried out by the unaided eye against a black background under normal fluorescent laboratory light. Samples were examined simultaneously to the chemical compatibility determination.

Microscopically, all mixtures were analysed for any emulsion destabilisation phenomena like coalescence using the digital video microscope Keyence VHX-500K (Keyence Corp., Japan) at a 800× magnification directly after mixing and after 2, 4, 8 and 24 hours. The resulting images could be seen on the Keyence monitor screen and worked with the VHX-500K Communications Software V1.1 (Keyence Corp).

Zeta potential

ZP measurements were performed by electrophoretic measurements using a Zetasizer Nano ZS (Malvern Instruments). Each mixture was diluted with double-distilled water to a propofol ratio of 1:50 meeting the best quality criteria for the measuring system with the lowest SD. About 720 µL sample volume were filled in disposable folded capillary cells (DTS1070, Malvern Instruments). The electrophoretic mobility was analysed by Laser Doppler Velocimetry and transferred to a ZP by the Henry equation. The dielectric constant of all solutions was assumed to be 78.5 and their viscosity was measured by Vibro Viscometer SV-10 (A&D Company). The respective refractive index was obtained using a refractometer. Every determination was carried out 3 times. Samples were taken directly after mixing, after 24 and 168 hours. To verify the correct operation of the system, the ZP of a transfer standard was measured. The results of the 15 standard measurements were within the ZP range of -42 ± 4.2 mV and the conductivity range of 0.23–0.40 mS/cm.

Particulate matter

To see if there was any crystal growth, all two-drug and multiple-drug mixtures were observed for precipitates after 168 hours. Samples had a volume of 8 mL. They were filtered through a black polycarbonate membrane filter (Isopore Membrane Filters, Merck Millipore, Germany) with a pore size of 0.22 µm and a mean diameter of 47 mm. After filtration, the filters were microscopically examined using the digital video microscope Keyence VHX-500K (Keyence Corp.) with a polarising filter at a 400× magnification.

RESULTS

pH determination

Mixtures were considered compatible with no pH shift >1.0 unit based on the initial pH value over a period of 24 hours.²¹ Measurements showed no changes in pH greater than 1.0 unit over 24 hours and even after 7 days in any of the mixtures. There was no indication of potential incompatibilities. The combinations of propofol with sufentanil (ratio 1:10 (v/v)) and with NaCl 0.9% (ratio 1:10 (v/v)) resulted in the highest pH changes after 24 hours with 0.48 and 0.46 units.

Chemical compatibility

High-performance liquid chromatography

The drug combinations were considered chemically compatible if the concentration of each present drug in mixture did not decrease below 90% of the initial value within 24 hours.^{2 21 22} Preliminary studies on the chemical stability of the single-drug

solutions showed no significant decrease in concentration within 24 hours <90%. 4-Hydroxybutyric acid could not be detected using HPLC, and therefore the mixtures were not chemically analysed.

Two-drug combinations

The difference between the three concentration determinations for each point of time in all propofol–drug mixtures was less than 4%. Only three sample points had a variation coefficient between 5% and 6%.

There were no significant changes in drug concentration except for the mixture of propofol and remifentanyl in the ratio 10:1 (9 parts of propofol and 1 part of remifentanyl). This combination turned out to be chemically incompatible. In the time period between 1 and 4 hours, the drug concentration decreased beneath the 90% limit to 74.4% (figure 1A). After 24 hours, only 30.4% of remifentanyl could be detected and after 4 days, no remifentanyl could be found anymore. An additional peak appeared in the HPLC chromatograms with an increasing area in the course of the investigation period. Remifentanyl eluted at 21.8 min and the degradation product at 19.5 min, indicating a higher polarity.

Multiple-drug combinations

There was no loss of drug concentration >10% of propofol and the other six substances within 24 hours (table 2). No additional peaks appeared on the chromatograms during the investigation period. The variation coefficients of the three determinations of each drug in mixture at different sampling time points were less than 3% and could thus be neglected. Only the combination of propofol with sufentanil and midazolam showed a difference in the propofol concentration of 5.33% after 1 hour.

Liquid chromatography–mass spectrometry

Remifentanyl is a drug substance that contains two alkyl esters. One of the ester groups is sterically unhindered and thus susceptible to hydrolysis by aqueous systems and by esterases in blood and tissue, leading to the monocarboxylic acid with no potency.²³ The pH value of the investigated incompatible mixture averaged 6.80, possibly catalysing the hydrolysis due to the more alkaline conditions.²⁴

An investigation into the nature of the decomposition product of the incompatible propofol–remifentanyl combination was performed using the LC–MS technique. It was searched for the molecular ions $[M+H]^+$ of remifentanyl, the corresponding monocarboxylic acid, the dicarboxylic acid and the β -elimination product as a degradation product of remifentanyl under more alkaline conditions.²⁵ Twenty-four hours after mixing, the extracted ion chromatogram of the propofol and remifentanyl combination (ratio 10:1 (v/v)) showed a peak for remifentanyl hydrochloride (6.8 min) and the monocarboxylic acid (6.7 min) (figure 1B). The remifentanyl drug concentration decreased to 77%, showing a decomposition of 23% to the monocarboxylic acid. To further investigate the pH-dependent degradation of remifentanyl, three solutions (0.05 mg/mL) at pH 3.26, 6.80 and 8.00 were analysed. The more alkaline the solution, the higher was the decomposition to the monocarboxylic acid after 24 hours. The sample with a pH of 8.00 showed a high amount of 80.8% of the monocarboxylic acid and even 0.2% of the β -elimination product caused by a ‘retro-Michael reaction’.²⁵ The sample with pH 6.80 showed a monocarboxylic acid amount of 59.5%. The β -elimination product appeared to a percentage of 0.3%. The dicarboxylic acid appeared only after 4 weeks at pH 6.80.

Figure 1 Chemical compatibility results of the propofol–remifentanyl hydrochloride mixture (ratio 10:1 (v/v)) displayed in (A) a high performance liquid chromatography chromatogram showing the concentration of both drugs over a time period of 7 days and (B) an extracted ion chromatogram after 24 hours of mixing obtained by mass spectrometry showing the remifentanyl hydrochloride peak (blue) and the peak of the decomposition product monocarboxylic acid (red) as well as their structural formula. a.u., arbitrary unit (relative unit of measurement to present intensity).

Sorption of propofol

In all of the 1:10 (v/v) propofol–drug mixtures, the HPLC measurements showed an unforeseen incompatibility with the syringe material. The concentration of propofol decreased below 90% of the initial concentration at different time points during the period of 7 days.

Since propofol is highly lipophilic, a sorption to the syringe material was taken into consideration. To prove this hypothesis, 3 50 mL polypropylene perfusion syringes and three glass containers were filled with a propofol–clonidine mixture (ratio 1:10 (v/v)), three more syringes and glass containers were filled with a propofol–NaCl mixture (ratio 1:10 (v/v)), stored at room temperature for 7 days under fluorescent light and analysed directly after mixing, after 2, 4, 6, 8, 24 and 168 hours via HPLC.

After 8 hours, a mean decrease of $4.5 \pm 1.0\%$, after 24 hours of $9.2 \pm 3.0\%$ and after 7 days of $26.7 \pm 6.2\%$ in all six syringes could be detected. The concentration of propofol in the glass containers remained near constant during the investigation period. All six syringes were cut up after termination of the analysis after 7 days and propofol was extracted with methanol by shaking over 7 days. A HPLC analysis showed a mean propofol recovery of $4.6 \pm 0.6\%$ relative to the initial propofol concentration measured directly after mixing in the previous analysis.

To test which of the syringe parts were responsible for the sorption of propofol, the above-mentioned analysis was carried out again. This time only the syringe body and the removable plug on the syringe piston were shaken in methanol separately over 7 days. A HPLC determination of the propofol concentration revealed a $98.3 \pm 0.2\%$ absorption of propofol to the syringe plug and only a $1.7 \pm 0.2\%$ absorption to the syringe body. The amount of absorbed propofol to the syringe plug and body was calculated based on the overall recovery of propofol on both syringe parts.

Lipid globule size distribution

The propofol emulsion mixtures were considered stable if the MDS stayed below 500 nm and the percentage of fat globules $>5 \mu\text{m}$ (PFAT₅) was $<0.05\%$ in a time period of 24 hours.¹⁸

Dynamic light backscattering

None of the analysed mixtures showed a MDS >500 nm and thus they all met the specification of Method I in the USP (table 3). On average, there was no clinical significant increase in MDS. An increase in MDS could be recorded, for example, in the samples of propofol with 4-hydroxybutyric acid from 256.6 to 401.1 nm (ratio 10:1 (v/v)) and with piritramide (ratio 10:1 (v/v)) from 171.7 to 224.6 nm.

The width of size distribution was calculated as PDI. The values from 0.0 to 0.1 indicate a narrow size distribution and monodispersity, values from 0.1 to 0.4 a broad polydisperse distribution and values >0.4 indicate a very broad polydisperse size distribution. The globule size dispersity after 24 hours varied from near monodispersity with polydispersity indices of 0.08 (1:1:1 mixture (v/v/v) of propofol with sufentanil and midazolam) to a very broad size distribution with indices of 0.35 (10:1 mixture (v/v) of propofol with piritramide). The polydisperse distribution gives an indication of larger-size fat globules.

Laser diffraction

Since larger-size fat globules ($>5 \mu\text{m}$) can be trapped, especially in the lungs,^{8–9 12 14 18} the determination of their amount is highly important. The time-dependent globule size distribution measurements displayed a high amount of fat globules $>5 \mu\text{m}$ in five two-drug mixtures (table 3). After 24 hours, about 60.1% of the fat globules in the sample of propofol and piritramide (ratio 10:1 (v/v)) were $>5 \mu\text{m}$. The propofol combinations with midazolam (ratio 10:1 (v/v)), 4-hydroxybutyric acid (ratio 10:1 (v/v)) and remifentanyl (ratio 1:1 (v/v) and 1:10 (v/v)) were

Table 3 Size distribution of fat globules in all tested propofol emulsion mixtures

	1:1					1:10					10:1					
	PCS			LD		PCS			LD		PCS			LD		
	MDS±SD 0 hours	PDI±SD 0 hours	MDS±SD (nm) 24 hours	PDI±SD 24 hours	PFAT ₃ ±SD (%) 24 hours	MDS±SD (nm) 0 hours	PDI±SD 0 hours	MDS±SD (nm) 24 hours	PDI±SD 24 hours	PFAT ₃ ±SD (%) 24 hours	MDS±SD (nm) 0 hours	PDI±SD 0 hours	MDS±SD (nm) 24 hours	PDI±SD 24 hours	PFAT ₃ ±SD (%) 24 hours	
Two-drug mixtures	Pro	172.8±0.6	0.12±0.02	176.7±0.4	0.09±0.02	0	176.5±2.8	0.08±0.01	178.1±2.5	0.10±0.02	0	174.5±2.7	0.11±0.01	177.4±1.8	0.09±0.01	0
	Clo	179.3±1.9	0.12±0.02	174.6±0.7	0.11±0.02	0	178.0±1.3	0.11±0.02	176.5±2.3	0.11±0.02	0	174.7±2.6	0.10±0.01	176.6±1.4	0.08±0.02	0
	Dex	177.2±1.2	0.15±0.01	175.4±1.0	0.09±0.03	0	181.7±1.2	0.08±0.01	179.7±1.0	0.11±0.01	0	180.2±3.9	0.14±0.02	179.7±4.8	0.11±0.02	0
	Sk	183.5±0.2	0.09±0.00	263.4±11.9	0.24±0.03	0	177.4±1.0	0.08±0.02	207.1±1.2	0.25±0.00	0	256.6±3.6	0.11±0.02	401.1±1.5	0.30±0.04	41.0±10.4
	GHB	177.3±1.2	0.11±0.03	178.1±1.2	0.14±0.01	0	175.3±0.2	0.12±0.01	182.0±1.1	0.14±0.02	0	176.0±1.0	0.08±0.01	182.3±1.4	0.13±0.01	0
	Cor	177.0±2.9	0.16±0.01	176.0±0.9	0.13±0.02	0	175.7±0.6	0.11±0.01	177.0±0.6	0.08±0.01	0	178.4±4.0	0.14±0.03	184.1±1.3	0.14±0.03	37.7±5.6
	Wild	170.9±0.6	0.09±0.04	180.0±2.6	0.13±0.02	0	176.2±1.4	0.13±0.01	174.1±1.5	0.10±0.01	0	171.7±1.0	0.06±0.02	224.6±31.0	0.35±0.12	60.1±15.0
	2ir	175.1±0.5	0.09±0.00	190.8±1.7	0.18±0.01	5.9±1.3	176.0±0.6	0.11±0.02	183.5±1.3	0.15±0.02	20.8±1.5	175.2±2.8	0.12±0.01	177.8±1.4	0.13±0.01	0
	Rem	175.2±1.0	0.10±0.01	184.5±1.1	0.16±0.03	0	176.2±0.2	0.10±0.01	177.3±0.4	0.09±0.02	0	177.9±1.5	0.12±0.01	177.2±1.2	0.11±0.02	0
	Suf	177.4±1.1	0.09±0.02	177.5±2.3	0.12±0.01	0	177.6±1.1	0.12±0.01	176.3±1.7	0.10±0.02	0	176.2±1.7	0.12±0.02	179.8±0.8	0.14±0.02	0
NaCl																
Multiple-drug mixtures	1:1:1/1:1:1						−*					−*				
	PCS					LD					LD					LD
	MDS±SD 0 hours	PDI±SD 0 hours	MDS±SD (nm) 24 hours	PDI±SD 24 hours	PFAT ₃ ±SD (%) 24 hours	MDS±SD (nm) 0 hours	PDI±SD 0 hours	MDS±SD (nm) 24 hours	PDI±SD 24 hours	PFAT ₃ ±SD (%) 24 hours	MDS±SD (nm) 0 hours	PDI±SD 0 hours	MDS±SD (nm) 24 hours	PDI±SD 24 hours	PFAT ₃ ±SD (%) 24 hours	
	Pro	177.2±0.8	0.09±0.03	180.5±2.3	0.08±0.01	0										
	Suf															
	Wild															
	Suf	176.9±1.6	0.11±0.02	179.2±1.8	0.09±0.01	0										
	2ir															
	Suf	177.4±1.3	0.08±0.02	183.5±1.6	0.12±0.02	0										
	Clo															
Multiple-drug mixtures	Suf	176.8±1.5	0.07±0.00	178.3±3.3	0.09±0.04	0										
	Suf															
	Dex															
	Rem	181.4±2.7	0.13±0.03	178.4±0.8	0.09±0.02	0										
	Wild															
	Suf															
	Wild	176.9±1.6	0.11±0.02	170.8±1.3	0.11±0.02	0										
	or															

The values are expressed as mean value and mean±SD (n=3).

*No other concentration ratio was analysed.

No. Outer concentration ratio was unity:sec.
ClO, clonidine hydrochloride; Dex, dexametomidine hydrochloride; Esk, (S)-ketamine hydrochloride; GIB, 4-hydroxybutyric acid; LD, laser diffraction; Lor, lorazepam; MDS, mean droplet size; Mid, midazolam hydrochloride; NaCl, sodium chloride; PCS, photon correlation spectroscopy; PDI, polydispersity index; PFAT₅, percentage of fat globules >0.05%; Pir, piraramide; Pro, propofol; Rem, remifentanyl hydrochloride; Suf, sufentanil citrate.

also above the set limit: therefore, they did not meet the specifications of the USP for safe lipid injectable emulsions. The other tested samples had no fat globules $>5\ \mu\text{m}$ leaving these propofol emulsion mixtures stable over 24 hours and safe for infusion.

Turbiscan technology

Another possibility for analysing dispersed systems such as emulsions is the Turbiscan technology. The advantage of this technology is that various products can be studied from low to high concentrations without any sample preparation or dilution.²⁰ Any destabilisation phenomena such as coalescence, flocculation, creaming or sedimentation can be detected. The Turbiscan works using multiple light scattering technique detecting the backscattered and/or transmitted light. Because of the opacity of propofol, only the backscattered light was included in the investigation.

It is possible to generate a dimensionless TSI based on the scan-to-scan difference of the backscattered light of the complete cell height. The instrument noise floor taking into account a TSI of >1.0 indicates a beginning change in emulsion stability. As a general rule, the higher the TSI, the less stable is the emulsion formulation.²⁰ The TSI after 8 hours was used for the stability analysis. Propofol-Lipuro 20 mg/mL served by comparison as stable emulsion formulation. The preparation of propofol with diazepam hydrochloride (ratio 1:1 (v/v)) was used as a negative control. After only a few minutes, the mixture showed signs of phase separation. After 30 min, the TSI was at 5.3 and after 8 hours, there was a complete phase separation with a TSI about 30.

The mixtures of propofol with remifentanyl and 4-hydroxybutyric acid were those with the highest TSI at 3–4 and 4–6, respectively, of the 1:1 (v/v) and 1:10 (v/v) preparations after 8 hours. Propofol-Lipuro 20 mg/mL itself had a TSI of 0.7. The most stable propofol–drug combinations were those with piritramide and sufentanil (ratio 1:1 (v/v)) and with clonidine and piritramide (ratio 1:10 (v/v)) with a TSI lower than 0.7 of propofol. Most of the 10:1 (v/v) samples had a TSI about 1.5 showing a slight destabilisation in comparison with propofol with a TSI of 0.7. Clonidine and sufentanil mixtures with propofol (ratio 10:1) even had a TSI of 0.3–0.5. 4-Hydroxybutyric acid was the least stable mixture with a TSI of 3.4. The results underline the obtained data by lipid globule size measurements. All samples with an increase in globule size as shown in table 3 had higher TSI values than the other samples and Propofol-Lipuro 20 mg/mL. In relation to the two-drug mixtures, the multiple-drug mixtures had only two preparations with a TSI of about 2 and had, in general, a high stability with hardly any additional increase of the TSI even after 7 days.

The TSI changes are also visually displayed as instabilities like creaming and coalescence in the backscattering profiles: a decrease in the backscattering flux at the bottom of the sample (clarification), an increase at the top of the sample (creaming) as well as a decrease in the backscattering over the whole height of the sample (coalescence and flocculation).

Macroscopic and microscopic observations

The visual inspection of the emulsion mixtures revealed five samples that changed their colour from white to a light yellow within 24 hours. This discolouration involved the samples of propofol with 4-hydroxybutyric acid, midazolam, piritramide and remifentanyl in the propofol–drug ratio of 10:1 (v/v). The other sample was the combination of propofol with remifentanyl in a ratio of 1:1 (v/v). In all of the mixtures, the increase in

lipid globule size was visible to the unaided eye. The mixture of propofol with 4-hydroxybutyric acid showed an obvious beginning of phase separation with a great amount of oil deposited at the syringe body. The microscopic observation of all propofol–drug combinations displayed an increase in lipid globule size during the course of investigation due to coalescence in all of the visual instable samples mentioned above (figure 2A–C).

All results underline the findings of the lipid droplet size distribution measurements.

Zeta potential

To gain additional information about the emulsion stability, the ZP of all propofol–drug combinations was determined. The ZP (mV) is the quantified electrostatic charge of emulsion droplets and one of the stability determining factors of colloidal systems. ZP values $\geq \pm 30\ \text{mV}$ indicate a physical long-term stability.²⁶

After 24 hours, most of the 10:1 (v/v) propofol–drug mixtures displayed a ZP of approximately (–) 32–38 mV, except those with piritramide and (S)-ketamine with (–)14–16 mV and with 4-hydroxybutyric acid which showed a ZP of (–)24 mV. The 1:1 (v/v) ratio samples mainly had a ZP of (–)10–15 mV after 24 hours. Only the samples with piritramide, midazolam and (S)-ketamine had values of (+)9–15 mV. The most inhomogeneous ZP distribution could be found among the 1:10 (v/v) ratio combinations. Propofol mixed with remifentanyl resulted in a ZP of (–)4 mV, with clonidine, sufentanil, dexmedetomidine, lormetazepam and NaCl of (–)7–9 mV, with 4-hydroxybutyric acid of (–)0.5 mV and with piritramide, midazolam and (S)-ketamine of (+)25–40 mV.

The multiple-drug preparations had three ZP ranges. The results showed a positive charge of (+)3–6 mV in the ternary mixtures of propofol with sufentanil and midazolam, with remifentanyl and midazolam and also in the fourfold mixture of propofol with lormetazepam, midazolam and sufentanil. The samples of propofol with sufentanil and piritramide were at (+)12 mV. The ones with sufentanil and clonidine and sufentanil citrate and dexmedetomidine had a ZP at (–)12 mV.

On the basis of the obtained results for the 36 mixtures, none of the previously detected destabilisation phenomena in emulsion stability could be explained. Only the low ZP value of (–)4.4 mV after 24 hours of propofol with remifentanyl (ratio 1:10 (v/v)) indicates an instability and thus the risk of coalescence.

Particulate matter

No crystal growth in any of the propofol–drug mixtures could be detected after 7 days under polarised light.

DISCUSSION

In this investigation, the physicochemical and emulsion stability of propofol with commonly used analgesics and sedatives was tested to evaluate the safety of a simultaneous application through the same intravenous line. Analgesic and sedative drugs are the most frequently used drugs for ICU sedation and therefore often combined.^{3–6} So far, only few studies have examined these propofol–drug combinations both in a physicochemical way and using specialised methods for the determination of the emulsion stability.

Three different concentration ratios (10:1 (v/v), 1:1 (v/v) and 1:10 (v/v)) were selected to cover the varying infusion rates in the ICU. If only one concentration ratio of a certain propofol–drug mixture was tested incompatible, it was decided that both drugs should not be administered simultaneously at all.

Figure 2 Time-dependent microscopic globule size distribution images. The figure shows from left to right the photomicrographs after 0, 4 and 24 hours of (A) propofol 2%, (B) of propofol 2% with remifentanyl hydrochloride (ratio 1:1 (v/v)) and (C) of propofol 2% with 4-hydroxybutyric acid (ratio 10:1 (v/v)). Bar: 20 μ m.

Therefore, propofol was incompatible with 4-hydroxybutyric acid, midazolam, piritramide and remifentanyl.

In order to evaluate the compatibility of a propofol–drug mixture, the defined results obtained after 24 hours were used.^{2 21 22} Despite the usual practice in the cardiovascular ICU ward to change propofol syringes every 8 hours to avoid microbiological contamination, longer infusion periods cannot be excluded. We often observed that propofol infusions were not replaced after 8 hours. However, a maximum administration period of 24 hours was not exceeded. By choosing the measurement results after 24 hours to define propofol–drug mixtures as compatible or incompatible, our findings in practice were taken into account. The determinations after 7 days were conducted to simulate ‘worst case’ conditions and to see if there is a tendency of incompatibility in the mixtures at all. The obtained data provide additional evidence for the safety of combined infusions.

In this study, the limit for a tolerable pH change is set at a maximum pH shift of 1 unit based on the initial pH value after mixing.²¹ Most drug incompatibilities are a manifestation of acid–base change so that a pH measurement can be used to detect such incompatibilities.² But mixtures should not be labelled incompatible solely on the basis of pH changes. Therefore, in this investigation, the pH was analysed to predict possible incompatibilities and to explain incompatibilities detected by chemical compatibility analysis using HPLC.

Although the propofol–remifentanyl mixture (ratio 10:1 (v/v)) showed no pH shift indicating no potential incompatibility, the mixture had a more alkaline milieu in comparison to the single-drug solution of remifentanyl, explaining the hydrolysis of the ester group and hence the decomposition of remifentanyl.

The combination of propofol and remifentanyl at a ratio of 10:1 (v/v) was the only chemically incompatible mixture. A previous study analysed the mixture of propofol (10 mg/mL) with remifentanyl hydrochloride (5 μ g/mL) in polypropylene syringes and polyvinylchloride bags, revealing a general instability of remifentanyl caused by a presumed hydrolysis of the ester group of remifentanyl at pH 7–7.5.²⁴ We were able to prove this pH-dependent hypothetical decomposition of remifentanyl in our sample (pH=6.80) by using a mass spectrometric analysis after 24 hours, which showed the β -elimination product as a minor degradation product beside the monocarboxylic acid as the major degradation product. As a result, remifentanyl should not be mixed with any neutral to alkaline drug solution.

Despite the physicochemical stability of the multiple-drug mixture of propofol with remifentanyl and midazolam, a combined infusion should only be made with great caution. The multiple-drug mixtures were only prepared at a 1:1:1 (v/v/v) or 1:1:1:1 (v/v/v/v) ratio, respectively, whereas for each two-drug mixture, we analysed three concentration ratios resembling a broad range of possible drug concentrations. It cannot be excluded that in case of different concentration ratios and

therefore a different pH in the multiple-drug mixture, remifentanyl won't be equally subject to hydrolytic degradation. The same applies to the three-drug combinations of propofol with sufentanil and midazolam, of propofol with sufentanil and piritramide and to the four-drug combinations of propofol with sufentanil, midazolam and lormetazepam. Physical incompatibilities like the increase in oil droplet size $>5\ \mu\text{m}$, which had been observed in the two-drug mixtures of propofol with remifentanyl, midazolam and piritramide could not be detected in the multiple-drug mixtures. Nevertheless, physical incompatibilities cannot be fully excluded for these combinations, as only one of many possible concentration ratios was tested.

To further complement the results of the chemical compatibility analysis, a concentration determination of the propofol samples with 4-hydroxybutyric acid using LC-MS technique should be performed in future.

In 2015, the Food and Drug Administration (FDA) and Becton, Dickinson and Company (Ireland) informed in a safety alert about reduced potency of certain medications when stored in different types of BD syringes. The drug loss is caused by an interaction with the rubber stopper in the syringes. The company and the FDA declared that these syringes should only be filled and used promptly. They are not to be used for storage of compounded pharmaceuticals.²⁷ Through this work, propofol is now another drug on the list that interacts with the rubber stopper. The loss of potency becomes more noticeable in smaller concentrations. The propofol concentration decreased in all tested 1:10 (v/v) mixtures by $>10\%$; in one sample, this already occurred after 4 hours. As no additional peaks could be found in the HPLC chromatograms, the concentration of the admixed drugs remained stable over 7 days, and because of propofol being an unreactive molecule, a chemical incompatibility could be excluded.

Becton, Dickinson and Company provides an opportunity to check whether or not the syringes were produced with the alternate stopper material that is responsible for the drug sorption (the exact composition of the synthetic material is not known). Checking the lot numbers revealed that all syringes used in this study were not produced with this rubber material. Nevertheless, a drug sorption could be detected so that patients may receive subpotent products if these syringes were used on the ward since all medications for continuous infusion are stored for a varying time in syringes in the perfusion system. An exact point of time leading to too much drug loss cannot be predicted as shown in our investigation.

Other studies showed that propofol, as a highly lipophilic drug, is prone to absorb to intravenous administration sets composed of polyvinyl chloride leading to a significant sorptive drug loss.²⁸ Ward staff should always take drug-syringe material incompatibilities into consideration when confronted with decreased drug potency and a required dose adjustment.

The most important issue that has to be discussed is the stability of lipid injectable emulsions. There is no consensus on the definition for lipid injectable emulsion stability as well as no definite differentiation between the terms 'characterisation' and 'stability' of an injectable emulsion. It should also be taken into consideration that the USP chapter <729> applies to lipid emulsions only and not to admixtures of these emulsions with other medications.²⁹ Nevertheless, it should be kept in mind that the infusion of an instable emulsion could have a negative effect on the health of a critically ill patient. A fat overload syndrome accompanied by oxidative stress and tissue damage to the liver, hypertriglyceridaemia and pulmonary embolism by large-size fat globules ($>5\ \mu\text{m}$) could occur.^{11–14}

Because of the lack of explicit limits to globule size distribution, the USP chapter served as reference point in evaluating the stability of the propofol emulsion mixtures in this study. Instead of the described use of a single particle optical system in Method II for analysing the large diameter tail of the fat globule distribution, the laser diffraction technique was applied. The aim of this study was to detect whether or not there are lipid globules $>5\ \mu\text{m}$ in the samples, but not to provide their exact number. The results of the laser diffraction analysis revealed a high amount of larger-size fat globules $>5\ \mu\text{m}$ in 5 of the 36 mixtures (table 3), by far exceeding the suggested limit of $\leq 0.05\%$ in chapter <729>.¹⁸

The determination of the MDS was conducted as described in Method I in chapter <729> of the USP using PCS.¹⁸ All samples met the USP criteria. However, the suggested MDS limit of $\leq 500\ \text{nm}$ for lipid injectable emulsions is also not supported by scientific evidence.

To further analyse the stability of the propofol-drug mixtures, the ZP and the Turbiscan technique were included in this investigation. Both methods served as an additional source of the evaluation of physical compatibility. The Turbiscan had the great advantage that the samples were not to be diluted. Whereas the data obtained by the Turbiscan technique underline and visualise the results of the lipid globule size measurements, the ZP measurement resulted in an inhomogeneous outcome. Most of the ZPs were not in the range of values $>\pm 30\ \text{mV}$ indicating long-term stability. According to the obtained results, more than the five propofol emulsion mixtures should be physically instable. For example, the mixture of lormetazepam with propofol at a ratio of 1:10 (v/v) led to a potential about $-7\ \text{mV}$, but in no other test an incompatibility was noticed. By the defined long-term stability values of $>\pm 30\ \text{mV}$, the combination of lormetazepam with propofol should not be stable but turned out to be stable for up to 7 days. Even emulsions with values about $-20\ \text{mV}$ are stable for up to a few weeks, and emulsion with approximately $-6\ \text{mV}$ can be found with a limited stability to just a few days. The ZP depends on the charges and on the composition of the outer phase of the emulsion.³⁰ Therefore, the values can be consulted in the explanation for destabilisation phenomena but should not be the only basis for statements about the stability.

The TSI of >1.0 as a limit for a beginning destabilisation was determined due to the lack of a commonly defined value. Taking the instrument noise floor into account as well as the fact that parenteral medications are involved, this limit guaranteed a safe evaluation of the data.

The microscopical and macroscopical observations of the destabilised propofol-drug combinations and the determination of crystal growth in the samples, together with all conducted physical stability testings (figure 3), complement the analysis of propofol emulsion stability.

The results of this research are limited to the applied medications and the used conditions. But since most solutions for injection do not differ significantly in their composition, it has to be assumed that they would show the same incompatibilities and instabilities with the lipid injectable propofol emulsion. Further testing with another propofol-drug product (Propofol 2% (20 mg/1 mL) MCT Fresenius, lot. 16DH0019) and the selected drugs revealed no clinical significant difference in pH, size distribution and emulsion stability to Propofol-Lipuro 20 mg/mL. Both products contain soybean oil, medium chain triglycerides, glycerol, egg lecithin, sodium hydroxide and sodium oleate. The same incompatibilities and instabilities occurred.

		Mixing ratio			
		1:1	1:10	10:1	
propofol (Propofol-Lipuro 20 mg/mL)					clonidine hydrochloride (Clonidin-ratiopharm)
					dexmedetomidine hydrochloride (dexdor)
					4-hydroxybutyric acid (Somsanit)
					(S)-ketamine hydrochloride (Ketanest S)
					lormetazepam (Sedalam)
					midazolam hydrochloride (Midazolam-hameIn)
					piritramide (Dipidolor)
					remifentanyl hydrochloride (Ultiva)
					sufentanil citrate (Sufenta)

physical compatibility
physicochemical compatibility
physical incompatibility
chemical incompatibility

Figure 3 Compatibility of propofol-drug pairs.

CONCLUSION

This study showed that propofol injectable emulsion (Propofol-Lipuro 20 mg/mL) is physically incompatible when mixed with 4-hydroxybutyric acid, midazolam, piritramide and remifentanyl and chemically incompatible with remifentanyl due to a pH-dependent decomposition.

Even though no incompatibilities could be detected in the three-drug mixtures of propofol with remifentanyl and midazolam, of propofol with sufentanil and midazolam, of propofol with sufentanil and piritramide and in the four-drug combinations of propofol with sufentanil, midazolam and lormetazepam, they should not be administered simultaneously out of safety reasons.

The sorption of propofol to the rubber material of the used syringes was a further incompatibility that one should be aware of. In case the patient receives a subpotent medication, a dosage adjustment may be required.

In this investigation, it could also be demonstrated that the analysed propofol injectable emulsion is physicochemically compatible with clonidine, dexmedetomidine, (S)-ketamine, lormetazepam and sufentanil. Even in the multiple-drug mixture with sufentanil and clonidine as well as in combination with sufentanil and dexmedetomidine, propofol is physicochemically compatible, making a combined infusion through the same intravenous line possible.

As a result of this study, the drug treatment safety of critically ill patients in a cardiovascular ICU could be optimised.

What this paper adds

What is already known on this subject

- ▶ There is limited data about the chemical and physical compatibility of propofol in combination with often coadministered analgesics and sedatives through the same infusion system.
- ▶ Few studies have addressed the issue of emulsion stability of propofol in combination with other drugs as this is associated with the risk of emboli and other adverse drug reactions.

What this study adds

- ▶ This study displays the physicochemical and emulsion stability of several clinically relevant two-drug and multiple-drug combinations of propofol with commonly used analgesics and sedatives reducing the lack of compatibility data and optimising the drug safety in intensive care units.
- ▶ Because of a major risk of incompatibilities, propofol should be administered separately from 4-hydroxybutyric acid, midazolam, piritramide and remifentanyl.

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