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The effect of nimodipine, fentanyl and remifentanil intravenous products on the stability of propofol emulsions

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Nimodipine is used parenterally to treat ischemic neurological deficits caused by subarachnoid haemorraghe. Infusion of nimodipine should be continued during anaesthesia, surgery or angiography. In this context a simultaneous administration of nimodipine, propofol and fentanyl or remifentanil could be of great advantage. So the aim of this study was to evaluate the physical stability (droplet size) of propofol emulsions in combination with nimodipine and fentanyl/remifentanil. Droplet size of intravenous emulsions is of particular relevance as the administration of larger droplets to patients may cause pulmonary embolism. So the number of oil droplets >10 μm was determined in combinations of propofol emulsion with nimodipine and fentanyl/remifentanil immediately after mixing and after 20 hours by using microscopy. The experiments showed that all combinations of propofol (1 and 2%) with nimodipine infusion solution resulted in coalescence of oil droplets, which finally caused a visible phase separation. Macrogol (polyethylene glycol 400) was identified as the component in nimodipine infusion solution which induced the physicochemical incompatibility with propofol lipid emulsions.

1. Introduction

Nimodipine, a 1,4-dihydropyridine belonging to the group of calcium channel blockers, is used to prevent or treat ischemic neurological deficits caused by cerebral vasospasm following subarachnoid haemorraghe of aneurismal origin. Nimodipine binds to dihydropyridine receptors in the brain and increases the cerebral blood flow selectively without affecting the contraction of systemic arteries to a higher extent. The drug blocks the influx of extracellular calcium into the cell which re-establishes calcium homeostasis and should prevent ischemia (Peroutka and Allen 1983; Katz and Leach 1987).

Subarachnoid haemorrhage (SAH), caused mostly by a ruptured aneurysm, has a case fatality of about 50%, with 30% of the survivors remaining disabled. One reason for the poor outcome of these patients is – besides rebleeding – the occurrence of cerebral arterial spasm. This secondary cerebral ischaemia causes neurological deficits and can lead to further strokes and deaths. For the prevention of vasospasm, a combination of induced mild hypertension, hypervolaemia and the calcium antagonist nimodipine to inhibit the contraction of smooth-muscle cells in the blood vessels of the brain is of proven benefit (Van Gijn and Rinkel 2001). The risk of vasospasm developing is highest between day 3 and 14 after the SAH with duration of 2 to 4 weeks. Therefore, prophylaxis with nimodipine has to commence within 4 days of the haemorrhage and should continue for 3 weeks (Product information Nimotop®).

In most European countries nimodipine is available parenterally (Nimotop® infusion solution). The initial dosage of nimodipine ranges between 0.5 and 1 mg/h; the dose can be increased to 2 mg/h after 2 h of infusion time. The continuous infusion of nimodipine should last for 14 days and should also be continued during anaesthesia, surgery or angiography (Product information Nimotop®). In this context, the simultaneous application with propofol and fentanyl or remifentanil, both of them N-alkyl-substituted piperidines, through the same line of the catheter would be desirable. Propofol is very slightly soluble in water and so is infused in the form of an oil-in-water emulsion.

Mixing or diluting of intravenous emulsions may lead to incompatibilities causing phase separation of the emulsion (Michaels et al. 1996; MacPherson 2001). Droplet size of intravenous emulsions is of particular importance as the administration of larger droplets to a patient may cause pulmonary embolism (Masaki et al. 2003). The size at which this problem arises is widely discussed, but a droplet size of 5 μm in diameter is generally accepted as the upper limit (Han et al. 2001). Droplet size in intravenous emulsions is evaluated mostly by using laser diffraction (LD), dynamic light scattering (DLS), coulter counter methods (CCM) and microscopy (Han et al. 2001; Prankerd and Douglas 1996).

So the objective of this study was to evaluate the physical stability of propofol emulsion in combination with nimodipine (Nimotop® infusion solution), fentanyl or remifentanil. The microscopic method was applied for these in-

Table 1: Investigated combinations of propofol (1%, 2%), nimodipine (Nimotop®), fentanyl and remifentanil*

Drug A	Drug B	Results
Propofol 1%	Nimodipine	Strong coalescence/phase separation promptly after mixing
Propofol 2%	Nimodipine	Strong coalescence/phase separation promptly after mixing
Propofol 1%	Fentanyl 10 $\mu g \cdot ml^{-1}$	No change within 20 h
Propofol 1%	Fentanyl 50 $\mu g \cdot ml^{-1}$	No change within 20 h
Propofol 2%	Fentanyl 10 $\mu g \cdot ml^{-1}$	No change within 20 h
Propofol 2%	Fentanyl 50 $\mu g \cdot ml^{-1}$	No change within 20 h
Propofol 1%	Remifentanil 50 $\mu g \cdot ml^{-1}$	Aggregate formation immediately after preparation
Propofol 1%	Remifentanil 100 $\mu g \cdot ml^{-1}$	Aggregate formation immediately after preparation
Propofol 2%	Remifentanil 50 $\mu g \cdot ml^{-1}$	Aggregate formation immediately after preparation
Propofol 2%	Remifentanil 100 $\mu g \cdot ml^{-1}$	Aggregate formation immediately after preparation

*For product characteristics and solvents used see table 1

vestigations as microscopy allows the measurement of enlarged droplets and aggregates as well as the estimation of homogeneity of an emulsion. In contrast to the other methods mentioned, microscopy necessitates no manipulation of the sample such as dilution of emulsions.

2. Investigations and results

Fentanyl, remifentanil and nimodipine (Nimotop® infusion solution) were evaluated microscopically for emulsion stability with propofol 1% and 2% injectable emulsion.
All combinations of propofol (1 and 2%) with nimodipine (Nimotop® infusion solution) resulted in strong coalescence of oil droplets immediately after mixing (Table 1, Fig. 1).
To investigate which of the components in Nimotop® infusion solution is responsible for this incompatibility, mixtures of propofol with 0.9% sodium chloride, citrate-buffer, ethanol and macrogol 400 solution as well as ethanolic nimodipine solution in a ratio of 1 : 1 (v/v) were investigated. The results of these experiments are shown in Table 2. As can be seen in Table 2 and Fig. 2, the cause for phase separation was in any case macrogol, irrespective of the concentration of propofol and the type of applied triglycerides (LCT, long-chain vs. LCT/MCT long-chain/middle-chain).
The combinations of propofol emulsion (1 and 2%) with fentanyl solutions (10 and 50 $\mu g \cdot ml^{-1}$) showed no significant degradation of the emulsion within 20 h (Table 1, Fig. 1).
In the combinations of propofol (1 and 2%) with remifentanil (50 and 100 $\mu g \cdot ml^{-1}$) a prompt formation of aggregates was observed (Fig. 1) (1 and 2%).

3. Discussion

Intravenous emulsions like propofol are dispersed oil-in-water systems and therefore thermodynamically unstable. Combining intravenous emulsions with other intravenous products can induce chemical and physicochemical instability resulting in a change of the drugs and/or of the pharmaceutical formulation. However, in clinical practice, it would be required to administer intravenous emulsions together with other intravenous drugs. To ensure consistent pharmaceutical quality and improved medication safety, it is of particular relevance to investigate the physical stability as well as the chemical stability of such combinations.
Intravenous emulsions have, in general, a narrow droplet size distribution, with a mean size mostly between 100 and 300 nm (Han et al. 2001). Droplet size in parenteral emulsions is of particular importance as the administration

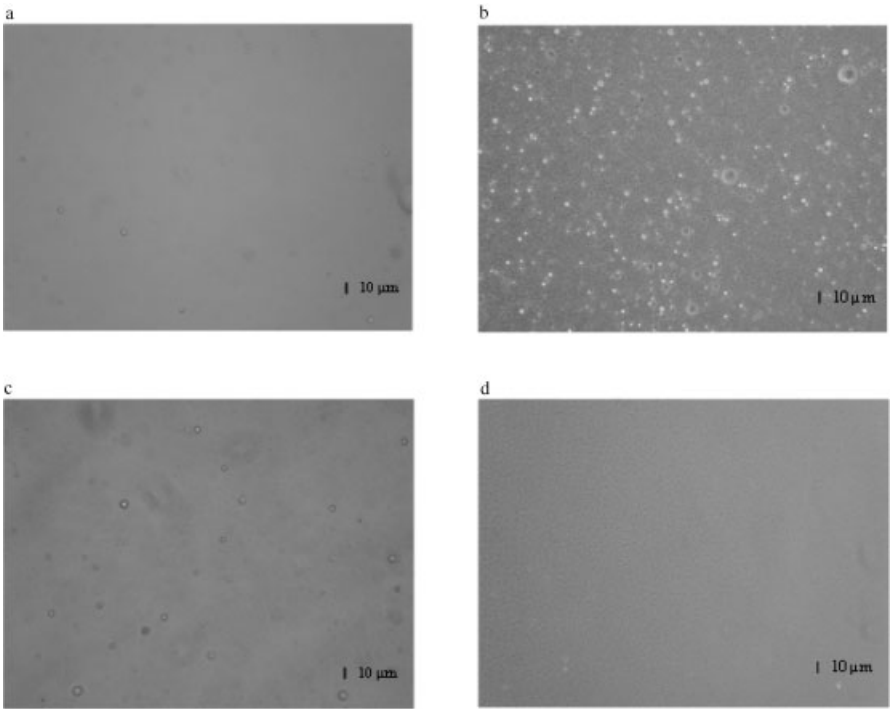

Fig. 1:
Photomicrograph of (a) 1% propofol and of 1% propofol with (b) Nimotop®, (c) Ultiva® and (d) Fentanyl-Torrex® immediately after mixing

Table 2: Investigation of the incompatibility causing component of Nimotop® infusion solution after 20 hours

Drug A	Drug B	Droplets >10 µm · 10 µl^{-1} mean (SD)	Result
Nimodipine[a]	Propofol 1%	65 (5)	No change
Sodium chloride 0.9%	Propofol 1%	139 (8)	Minor change
Ethanol/water[b]	Propofol 1%	23 (3)	No change
Citrate buffer[c]	Propofol 1%	63 (4)	No change
Water f. injection	Propofol 1%	60 (3)	No change
Macrogol 400[d]	Propofol 1%	–	Strong coalescence/ Phase separation
Nimodipine[a]	Propofol 2%	35 (2)	No change
Sodium chloride 0.9%	Propofol 2%	112 (4)	Minor change
Ethanol/water[b]	Propofol 2%	42 (3)	No change
Citrate buffer[c]	Propofol 2%	50 (3)	No change
Water f. injection	Propofol 2%	105 (5)	No change
Macrogol 400[d]	Propofol 2%	–	Strong coalescence/ Phase separation

[a] 10 mg nimodipine ad 50 ml ethanol/water
[b] 10 g ethanol ad 50 ml water
[c] 15 mg citric acid and 100 mg sodium citrate ad 50 ml water
[d] 8.5 g macrogol ad 50 ml water

of larger droplets may pose the risk of pulmonary embolism. It is therefore discussed that the size of particles should not be larger than 5 µm. On the other hand oil droplets are deformable and therefore able to pass pulmonary vessels. The specifications of Ph. Eur. 5 with regard to emulsions for injections are limited to prohibiting any signs of phase separation. According to this description it is the producer's responsibility to fix both the analytical method and the test criteria for parenteral emulsions.

In the therapy of patients with SAH, the simultaneous application of propofol emulsions with nimodipine, fentanyl or remifentanil through the same line of the catheter could

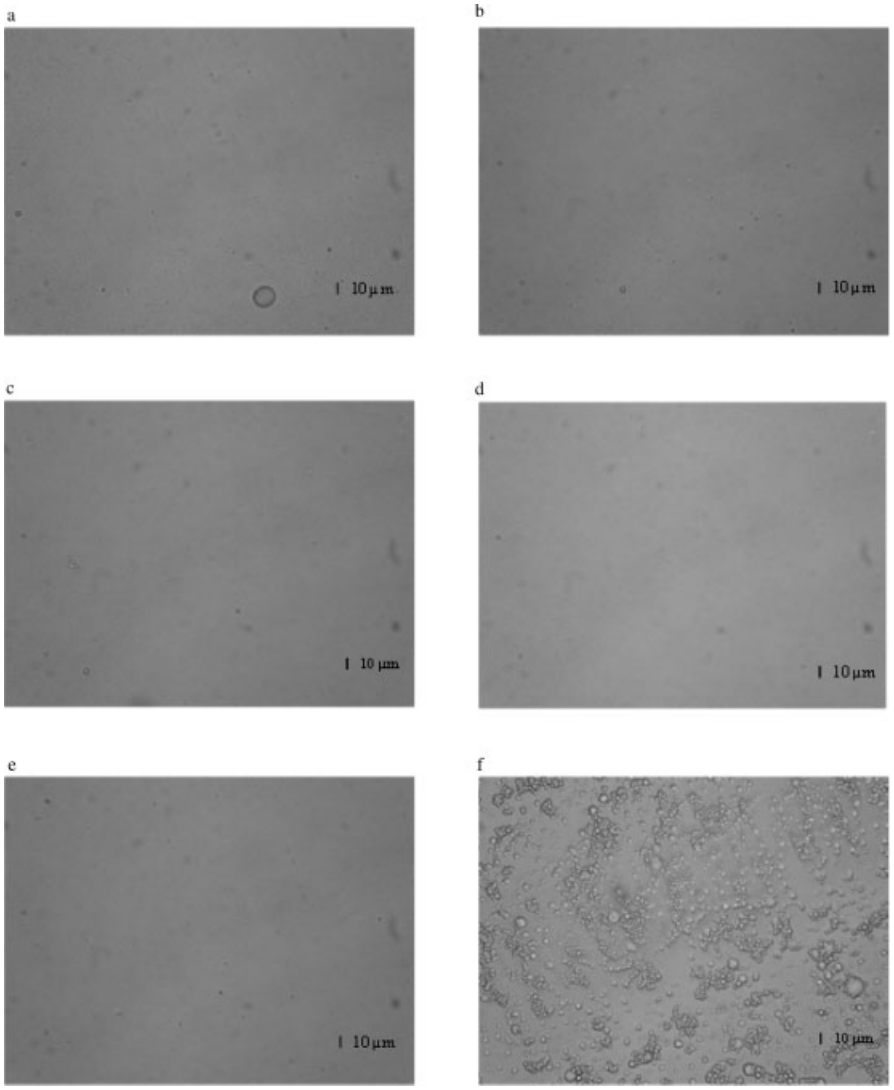

Fig. 2:
Photomicrograph of 1% propofol with (a) nimodipine, (b) sodium chloride, (c) ethanol/water, (d) citrate buffer, (e) water, (f) macrogol 20 h after mixing

Table 3: Products used for compatibility testing

Drug	Proprietary name/ Manufacturer	Lot Nr.	Other ingredients	Concentration $mg \cdot ml^{-1}$
Propofol 1%	Propofol 1% MCT 20 ml® Fresenius Kabi Austria	F060096	Soy bean oil, MCT, egg lecithin, oleic acid, glycerol, sodium hydroxide	10
Propofol 2%	Propofol 2% 50 ml® Fresenius Kabi Austria	F040114	Soy bean oil, egg lecithin oleic acid, glycerol, sodium hydroxide	20
Nimodipine	Nimotop® Bayer Austria	BXNZ2F1	Ethanol 96%, Macrogol 400, sodium citrate, citric acid	0.2
Remifentanil hydrochloride	Ultiva 5 mg® GlaxoSmithKline	6002	Glycine, hydrochloric acid sodium hydroxide	0.05 0.1
Fentanylcitrate	Fentanyl® 50 µg/ml 10 ml Torrex	F2A752	Sodium chloride	0.01 0.05

be of great advantage. Therefore investigations were carried out concerning droplet size in various mixtures of propofol with nimodipine, fentanyl or remifentanil. Various methods (LD, DLS, CCM, microscopy) are suggested for the analysis of droplet size in propofol mixtures. Microscopy was chosen for the present investigations as this method does not require any manipulation of the samples; it allows the evaluation of the homogeneity of the emulsion as well as the differentiation between oil droplets and solid particles. Microscopy is, however, limited in its detection limit as only oil droplets larger than 1 µm can be determined. Microscopy is also rather time-consuming: oil droplets need to be counted repeatedly in order to obtain reliable data for statistical evaluation.

Macrogol 400 (polyethylene glycol 400) was identified as the component causing a strong coalescence of oil droplets, while only minor or no changes in emulsion stability were observed with all other auxiliary substances. The effect of macrogol 400 on the stability of propofol emulsion is probably caused by volume-exclusion induced aggregation (Lentz 2007). Also, a small change in microscopic appearance could be observed by mixing sodium chloride solution with propofol emulsion probably due to the variation of electrolyte concentration. However we did not detect any noticeable increases in droplet size when adding the other auxiliary substances.

In addition, our microscopic investigations showed no change in emulsion appearance when combining propofol with fentanyl. However an increase of droplet size was detected when remifentanil was added to the propofol emulsion. In this context it should be said that the producer's recommendation is to not mix Ultiva® directly with propofol emulsion (Product information Ultiva®).

The findings derived from our results are only valid for the drugs, products and solvents we tested. The tests did not take into account future possible changes in the pharmaceutical adjuvants or products manufactured by other companies (Kohut et al. 1996).

4. Experimental

The compatibility studies were carried out with propofol solutions (1 and 2%) in combination with remifentanil solutions (50 and 100 $\mu g \cdot ml^{-1}$), fentanyl (10 and 50 $\mu g \cdot ml^{-1}$) and Nimotop® infusion (Table 3). Nimotop® was used undiluted, remifentanil and fentanyl were diluted with 0.9% NaCl solution (Mayrhofer Pharmazeutika G.m.b.H, lot no. 6B1784, Linz, Austria). The auxiliary substances ethanol, citric acid, sodium citrate and macrogol 400 were of pro analysis and/or European pharmacopoeia (Ph. Eur.) grade (Merck, Darmstadt, Germany). Nimodipine was bought from Sigma-Aldrich Handels-GmbH (Vienna, Austria).

Each of the above described intravenous products was combined with other drug solutions in equal ratios, given that the mixing of an intravenous fluid in an administration set with another fluid from a Y injection site occurs according to Allen et al. in a ratio of 1 : 1 (Allen et al. 1977; Allen and Stiles 1981). To determine the quantity of oil droplets (>10 µm), aliquots of 10 µl were used for microscopy. These investigations were carried out with the Axiolab light-optical microscope (Carl Zeiss, AG, Germany) in combination with an Achroplan 10 ×/0.25 Ph1 and an Achroplan 40 ×/0.65 Ph2 objective (Carl Zeiss, AG, Germany). The study was documented with a Sony digital camera Cyber-shot 5.0 DSC-V1.

Six samples of each combination were taken and the counting of oil droplets was carried out immediately after preparation and after 20 h at room temperature.

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Product information Ultiva®

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