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CP-068

COMPATIBILITY ANALYSIS OF PROPOFOL - OPTIMIZATION OF DRUG TREATMENT SAFETY

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Background & Objective

Infusion therapy is an essential part in the treatment of intensive care patients. Due to increasingly complex therapy standards a simultaneous application of multiple drugs through a central multi-lumen catheter is unavoidable (Fig. 1). This entails the risk of physicochemical and chemical incompatibility reactions.

One standard sedative used on the intensive care unit is propofol. Because of its physicochemical and optical properties the emulsion poses a special risk in identifying stability problems and incompatibilities (Fig. 2, 3). Additionally, only limited compatibility data are available.

The purpose of this work is the optimization of the drug therapy safety in a cardiovascular intensive care unit in preventing drug incompatibilities of propofol with other analgetic and sedative drugs.

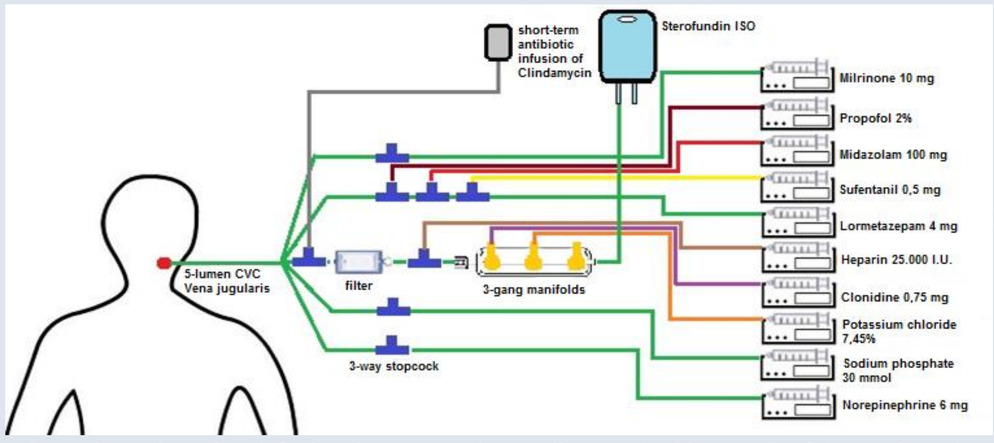

Fig. 1: Snapshot of an infusion therapy on the cardiovascular ICU A1a/b of the UKSH, Kiel

Possible physical incompatibilities and their consequences

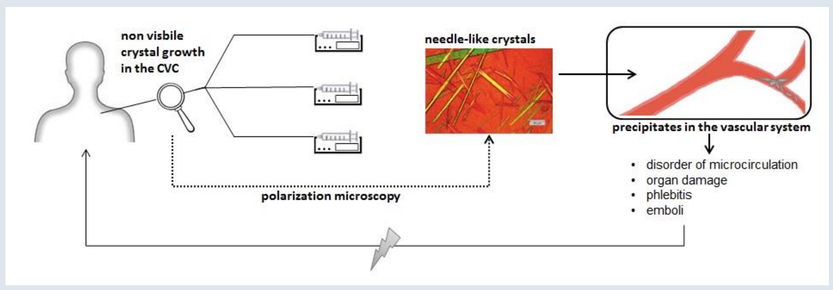

Fig. 2: Formation of precipitates in an incompatible mixture of drugs in the CVC and the possible damage for the patient using the growth of needle-like crystals of propofol (Propofol-®Lipuro 20 mg/ml) in combination with phenytoin (Phenhydan®- Injektionslösung) as an example.

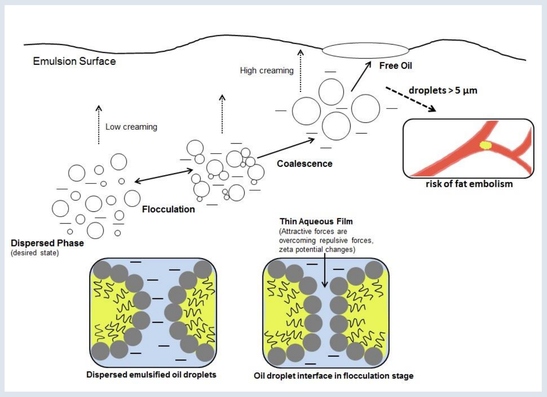

Fig. 3: Schematic of the process of emulsion degradation. The destabilization caused by an incompatibility of propofol with another drug can lead to alterations in the release of propofol *in vivo* and may cause emboli upon emulsion intravenous administration because of presence of enlarged oil droplets.

Methods

On the cardiovascular intensive care unit documented propofol drug combinations were narrowed down to practice-oriented combinations of propofol (Propofol-®Lipuro 20 mg/ml) with

- clonidine (Clonidin-ratiopharm®),
- midazolam (Midazolam-hameln),
- sufentanil (Sufenta®),
- remifentanil (Ultiva®),
- piritramid (Dipidolor®),
- lormetazepam (Sedalam®),
- γ-hydroxybutyric acid (Somsanit®) and
- dexmedetomidine (dexdor®).

Drugs were diluted with sodium chloride to standardized concentrations used on the ward and mixed with propofol in different ways. Samples were taken at fixed points of time over a period of seven days. The physical and the emulsion stability in particular were determined by pH value, zeta potential and globule size distribution measurements

using light backscattering. Analyses on crystal growth were performed by polarization microscopy and the examination of microbiological growth by the institute of hospital hygiene give additional information about the stability.

The chemical stability determination is carried out by high performance liquid chromatography (HPLC).

Results & Discussion

The light backscattering and zeta potential analyses resulted in three stability groups in which the group with the most destabilization phenomena consisted of γ-hydroxybutyric acid, remifentanil and lormetazepam (Fig. 4). All other mixtures remained stable over a defined period of time.

Tests including the measurement of the globule size distribution are important to determine whether or not the propofol emulsion is stable in combination with the selected analgetic and sedative drugs.

The USP states that oil droplets (> 5 µm) can be trapped in the lungs. The percentage of those globules must not exceed 0,05% otherwise the injectable emulsion is considered instable.

First analyses showed that the mixtures of propofol with γ-hydroxybutyric acid (Fig. 5) and with remifentanil are instable. They resulted in an increase in droplet size diameters > 5 µm which exceeded 0,05%.

So far neither clinically significant pH-shifts nor crystal and bacterial growth could be detected.

The HPLC data indicate a chemical stability of all previously tested propofol drug combinations.

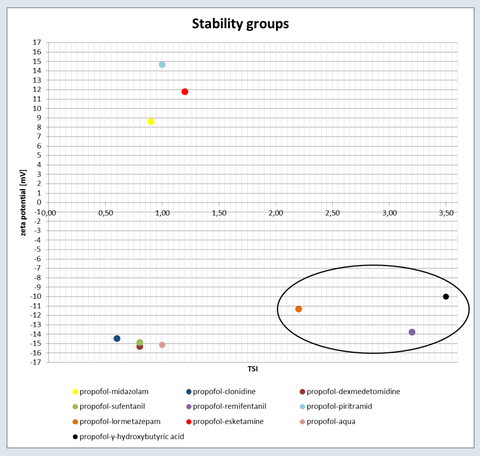

Fig. 4: Combination of the zeta potential and the Turbiscan Stability Index (TSI) after 8 hours.

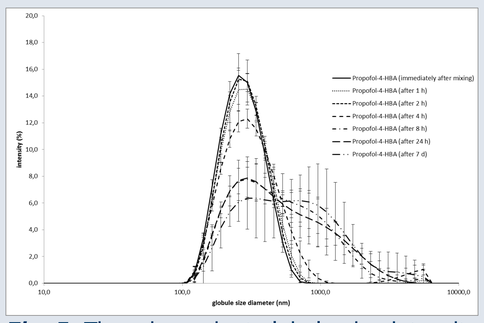

Fig. 5: Time-dependent globule size intensity distribution of the mixture of propofol with 4-HBA (γ-hydroxybutyric acid).

Conclusion

Evidence for incompatibilities and compatibilities of propofol with analgetic and sedative drugs could be obtained. To be able to make a final statement which of the selected propofol-drug-combinations are compatible or incompatible the ongoing analyses considering the emulsion stability as well as the chemical stability need to be completed. As a result the drug treatment safety should be increased in providing safety for the staff working on the ward, in preventing incompatibilities and in improving the patients' safety.

Wissen schafft Gesundheit

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