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Medical plastics: compatibility of alfentanil and propofol alone or mixed
Stability of the alfentanil-propofol mixture

E. Levadoux[a,*], V. Sautou[a], J.E. Bazin[b], P. Schoeffler[b], J. Chopineau[a]

[a] *Laboratoire de pharmacie clinique et biotechnique, UFR pharmacie, 28, place Henri Dunant, BP38, 63001 Clermont-Ferrand Cedex, France*

[b] *Service d'Anesthésie-Réanimation, Hopital Gabriel Montpied, 69, Rue Montalembert, BP 69, 63001 Clermont-Ferrand Cedex, France*

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Abstract

This study concerns the respective compatibilities of propofol Diprivan® and alfentanil Rapifen® towards medical plastics during infusion (at different flow rates) and in static models. We also determined this compatibility when the two drugs were administered as a propofol/alfentanil 30/20 (V/V) mixture and we observed the stability of the association. The work was conducted under conditions consistent with the use of the drugs for hospital anesthesia. Propofol and alfentanil were analysed by high performance liquid chromatography (HPLC). Propofol concentration decreased significantly when infused slowly (1 ml/h) for 6 h through PVC tubing. However, at the usual flow rate (10 ml/h), no significant difference was observed. Variations in alfentanil concentration never exceeded 10% (theoretical tolerated limit) at either flow rate of infusion (1 or 10 ml/h). Interrupting infusion for 2 h had no effects on the stability of propofol, and induced no significant loss in alfentanil concentration. The stability was always lower with the propofol/alfentanil mixture than with the two drugs separately.

Keywords: Alfentanil; Propofol; Stability; Compatibility; Plastics; Infusion; Mixture; HPL

Many studies have shown that interactions can occur between certain drugs and medical plastics (Illum and Bungaard, 1982; D'Arcy, 1983; Allwood, 1985; Martens et al., 1990; Arnaud et al., 1991). In the work reported here we assessed the compatibility of propofol and alfentanil towards medical plastics used in infusion sets

Propofol Diprivan®, is a drug widely used as an intravenous general anesthetic. Analgesia additional to anesthesia, can be provided by the administration of a drug such as alfentanil Rapifen®, which has suitable pharmacokinetic properties.

We studied the behavior of these two drugs during a 6-h infusion as performed in hospital. We also studied static models representative of temporary infusion interruptions. As propofol

* Corresponding author.

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Table 1
Analytical conditions used

Drugs to be analysed	Mobile phase	Rate (ml/min)	Injected volume (μl)	Wavelength (nm)	Internal standard
Propofol	75/25 (V/V) mixture of acetonitrile and phosphate buffer (pH 6.8)	0.8	20	270	Thymol (100 μg/ml)
Alfentanil	25/75 (V/V) mixture of acetonitrile and trisodium orthophosphate 0.01 M adjusted to pH 2.6 with orthophosphoric acid 1 M	2	20	195	none

and alfentanil are often used during the same anesthesia, we addressed the stability of a potential mixture of the two drugs. This is particularly relevant since the first is a lipid emulsion, while the second is formulated in aqueous solution. All the studies were done in parallel, assessing the behavior of each drug alone compared with the association of the two. Finally, we determined the influence of infusion flow rate on the compatibility and stability of the two drugs.

To monitor propofol and alfentanil concentrations, we used HPLC methods based on the work of Kumar and Morgan, 1987, Chan and So, 1990 and Guitton et al., 1992.

Propofol Diprivan® and alfentanil Rapifen® are, respectively, marketed by Zeneca Pharma (Cergy, France) and Janssen (Boulogne, France).

The HPLC system, used to analyse them, consisted of successive Merck Hitachi (Darmstadt, Germany) components: an L5000 LC Controller, a 655A-11 pump, a LiChrospher® 100 RP18 (5 μm) precolumn (for alfentanil analysis only), a C18 column Merck 50734 Lichrospher*100, a Rheodyne 7125 injector, and a D2000 chromato integrator.

Analytical conditions used for each active substance tested (mobile phase, rate, injected volume, wavelength and internal standard) are summarized in Table 1.

Calibration scales were plotted for concentrations ranging from 50 to 500 μg/ml (internal standard was at 100 μg/ml) for propofol, and from 25 to 75 μg/ml for alfentanil.

For alfentanil, the standard curve represents peak surface as a function of drug concentration.

Propofol was quantified by taking the ratio of the peak surfaces (propofol peak surface/thymol peak surface) as a function of propofol concentration.

The drug concentration in a sample was calculated by interpolation from the linear equation $y = ax + b$ of the standard.

Equipment used to realise continuous infusion consisted of an id2s syringe pump system (allegre Biomédical SA, Saint-Etienne, France), 50 ml Plastipack luer-lock polypropylene (PP) syringes (Becton Dickinson, Pont de Claix, France), polyvinyl chloride-polyethylene (PVC/PE) coextruded extention tubes, 150 cm long and 3 mm in diameter (Care LGL, Tarare, France), and Perfupack 3V rampe ABD PVC i.v. sets (Baxter, Maurepas, France).

We set out to reproduce as closely as possible real conditions of administration of propofol and alfentanil for hospital anesthesia, bearing in mind the purposes of the study:

(1) to observe the behavior of propofol alone and alfentanil alone towards the medical plastics of the infusion system;
(2) to determine if this behavior is the same when the two drugs are administered as a propofol/alfentanil 30/20 (V/V) mixture, and to check for interactions between propofol and alfentanil;
(3) to determine the effects of changing infusion flow rate.

For this last purpose, we tested two infusion flow rates: 1 and 10 ml/h (average rate used to maintain general anesthesia).

Samples were carried out using the PP syringe (A), the PE extension tube (B) and the PVC i.v. set (C). These samples provided data allowing the assessment of the compatibility of the drugs towards each medical plastic.

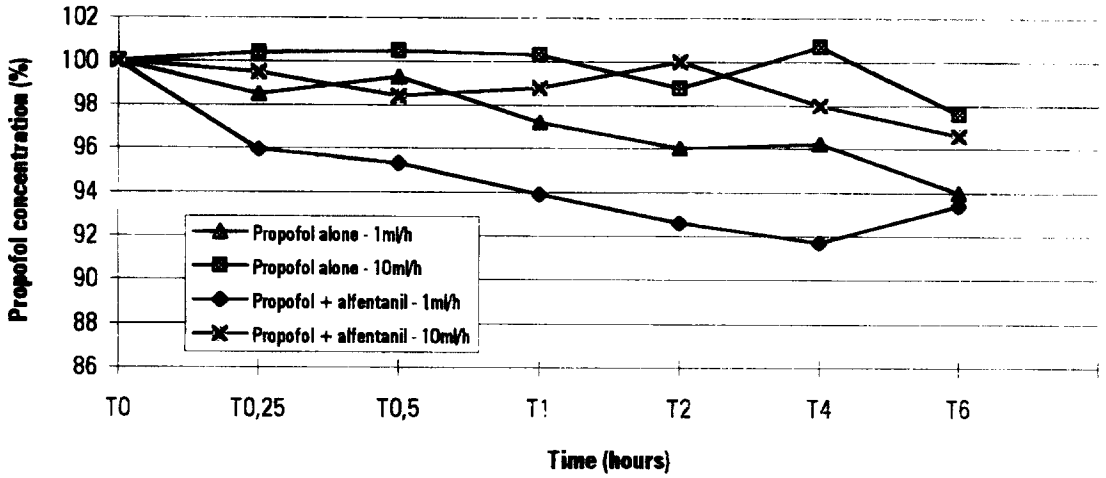

Fig. 1. Stability of propofol alone and mixed with alfentanil towards PVC, during a 6-h infusion at 1 or 10 ml/h.

To comply with clinical practice, we ran an infusion lasting 6 h, with sampling at 0, 15 and 30 min, and 1, 2, 4 and 6 h (T_0 corresponded to sampling before infusion was started, when the tubing was purged).

But, during surgery, the anesthetist often interrupts the infusion to moderate the anesthesia. Accordingly, we also carried out a static study of the stability of the two drugs. We limited the test to 2 h, the maximum duration of interruption of infusion during anesthesia. Sampling times were 0, 5, 10, 15, 30, 60 and 120 min.

For each study, the concentration obtained was an average of five values ($n = 5$), for each sampling time. The results were expressed in percentages of the concentration at T_0, taken as 100%. We considered a substance as stable if the variations observed remained within 10% of the initial concentration.

The method showed high linearity for the concentration range 50–500 μg/ml (for propofol) and 25–75 μg/ml (for alfentanil), with correlation coefficients of 0.9994 and 0.9999, respectively.

The precision of the chromatographic method was correct with coefficient of variation inferior to 3.5 and to 8%, respectively, for intra- and inter-day variabilities.

At a flow rate of 1 ml/h, propofol was compatible with polyethylene and polypropylene.

In contrast, after 6 h infusion, we observed a significant decrease ($p < 2.5\%$) in the concentration of propofol at the output from the PVC i.v. set, suggesting the drug interacted with the plastic. This is consistent with results obtained by Bailey, 1991.

This effect occurred with both propofol alone and the propofol-alfentanil mixture (Fig. 1), but loss of propofol was greater from the mixture (significant difference with $p < 1\%$). The two drugs thus interact, probably as a result of the lipidic and aqueous natures of their solutions.

At a flow rate of 10 ml/h, unlike the results obtained at a flow rate of 1 ml/h, no significant reduction of propofol concentration at the output from the i.v. set was observed with time.

So, at the output from the PVC i.v. set, there was a significant difference ($p < 1\%$) in propofol concentration according to the flow rate chosen (1 or 10 ml/h). This was the case for propofol both alone and mixed with alfentanil (Fig. 1). At the low flow rate (1 ml/h), the drug interacted with PVC more strongly than at the higher flow rate: 10 ml/h (the commonly used one). The amount of propofol administered to a patient after 6 h will therefore be significantly reduced when the flow rate is low.

The static study revealed no variation in propofol concentration when the infusion was stopped for 2 h, whether the propofol was alone or mixed

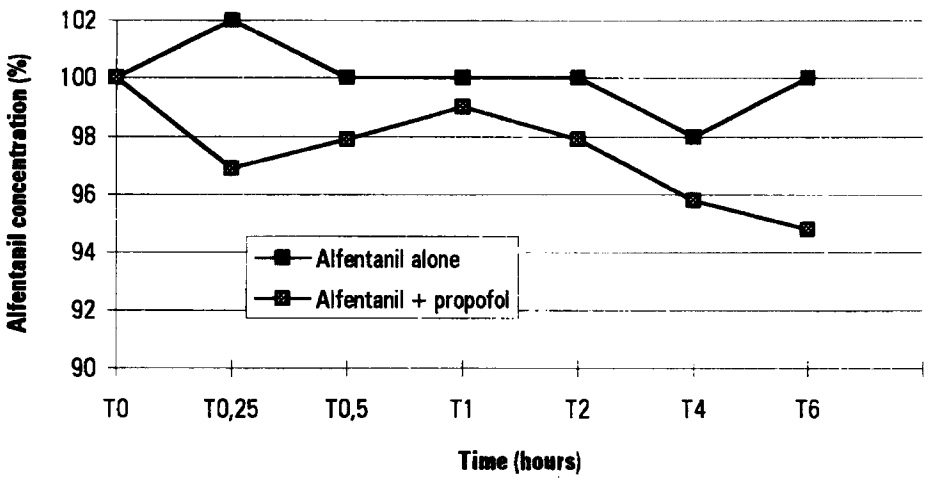

Fig. 2. Stability of alfentanil alone or mixed with propofol during a 6-h infusion at 1 ml/h.

Alone or associated with propofol, we observed no loss of alfentanil greater than 10% of the initial concentration after 6-h infusion at a flow rate of 1 ml/h.

However, we noticed that alfentanil was more stable when administered alone (Fig. 2).

The conclusion stated for a flow rate of 1 ml/h is also valid for a flow rate of 10 ml/h. When alfentanil was used alone, its concentration did not decrease by more than 2% of the initial value. On the other hand, when mixed with propofol, the loss of alfentanil reached up to 7% of the initial value.

This maximum loss was observed 2 h after the start of the infusion; the concentration then reverted to T_{6h}.

These results draw attention to the instability of alfentanil when mixed with propofol, although this instability is still below the theoretically significant 10%.

Previous results suggested that the stability of alfentanil was independent of the infusion flow rate. This was confirmed by an analysis of variance, which revealed no significant difference between the results obtained at a flow rate of 1 ml/h and those obtained at a flow rate of 10 ml/h, with both alfentanil alone and mixed with propofol.

Like the infusion study, the static study revealed a greater instability of alfentanil when mixed with propofol. Loss of alfentanil reached 9% when in association with propofol, against under 2% when used alone.

The greatest loss of alfentanil occurred in polypropylene. Accordingly, we studied the behavior of the drug (alone and in association) in a glass and a polypropylene container, to allow for any alfentanil-polypropylene interaction. Comparable results were obtained for the two materials (Fig. 3). Loss of alfentanil observed when it is mixed with propofol is thus evidently not due to interaction with polypropylene, but to an incompatibility between the two drugs.

In conclusion, this study revealed that alfentanil does not interact with medical plastics when infused. In contrast, a significant interaction exists between propofol and PVC tubing when the drug is infused at 1 ml/h. In addition, at this flow rate, the propofol-alfentanil mixture is unstable, presumably because of the conflicting lipophilic and hydrophilic properties of the components. Loss of propofol is greater than that of alfentanil. Given the lower stability of the two drugs in association, it would be wise to avoid administering such a mixture. The infusion flow rate is highly important for the administration of propofol. At the usual flow rate of administration (10 ml/h), no significant interaction with plastics or alfentanil occurs (unlike the flow rate of 1 ml/h). For alfentanil, the flow rate of infusion does not influence the behavior of the drug. Finally, no variation in

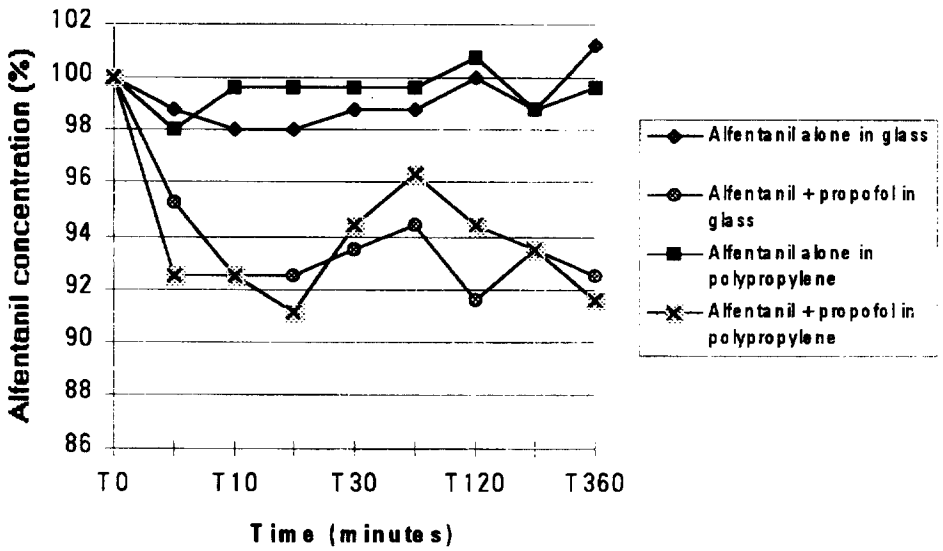

Fig. 3. Stability of alfentanil alone and mixed with propofol towards glass or polypropylene, during a 6-h static study.

the concentration of propofol was observed if the infusion of the drug mixture was stopped for up to 2 h, while we observed an instability of alfentanil under these conditions.

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References

Allwood, M.C., Sorption of drugs to intravenous delivery system. *Pharm. Int.*, 4 (1985) 83–85.

Arnaud, Y., Dauphin, A. and Mignot, A., Interactions matières plastiques/médicaments. In *Les matières plastiques à usage pharmaceutique*, E.M. Inter seconde édition, 1991, pp. 317–345.

Bailey, L., Effect of syringe filter and IV administration set on delivery of propofol emulsion. *Am. J. Hosp. Pharm.*, 48 (1991) 2627–2630.

Chan, K. and So, A.P.C. The measurement of propofol in human blood samples by liquid chromatography. *Methods Find. Exp. Clin. Pharmacol.*, 12(2) (1990) 135–139.

D'Arcy, P.F., Drug interactions with medical plastics. *Drug Intell. Clin. Pharm.*, 17 (1983) 726–731.

Guitton, J., Degoutte, C.S., Durand, D., Rochette, A. and Manchon, M., Dosage du propofol sanguin par HPLC. *J. Pharm. Clin.*, 11 (1992) 221–224.

Illum, J. and Bungaard, H., Sorption of drugs by plastic infusion bags and administration sets. *Int. J. Pharm.*, 10 (1982) 339–351.

Kumar, K. and Morgan, D.J., Determination of fentanyl and alfentanil in plasma by HPLC with ultraviolet detection. *J. Chromatogr.*, 419 (1987) 464–468.

Martens, H.J., De Goede, P.N. and Van Loenen, A.C., Sorption of various drugs in polyvinylchloride, glass and polyethylene lined infusion containers. *Am. J. Hosp. Pharm.*, 47 (1990) 369–373.