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RESEARCH REPORT

Remifentanil and propofol undergo separation and layering when mixed in the same syringe for total intravenous anesthesia

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What is already known

- Multiple anesthetic drugs can be combined to deliver effective TIVA. Sometimes two drugs are mixed in the same syringe for TIVA administration.

What this article adds

- When remifentanil (a solution) and propofol (an emulsion) are mixed in the same syringe, they undergo separation and layering. Concentrations of the component drugs are significantly different in different parts of the mixture.

Keywords
total intravenous anesthesia; propofol; remifentanil; emulsion; mixture

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Summary

Background: Propofol and remifentanil can be combined to deliver total intravenous anesthesia (TIVA). Propofol and remifentanil are sometimes mixed in the same syringe. Since remifentanil is a solution and propofol is an emulsion, we hypothesized that they would separate over time when mixed in the same syringe.

Methods: Nine 60-ml polypropylene syringes were prepared as follows: Group A: 1.25 ml of remifentanil solution (1 $mg \cdot ml^{-1}$) was added to 48.75 ml of propofol (10 $mg \cdot ml^{-1}$) in three syringes. Group B: 2.5 ml of remifentanil (1 $mg \cdot ml^{-1}$) was added to 47.5 ml of propofol (10 $mg \cdot ml^{-1}$) in three syringes. Group C: 5 ml of remifentanil (1 $mg \cdot ml^{-1}$) was added to 45 ml of propofol (10 $mg \cdot ml^{-1}$) in three syringes. The remifentanil lyophilized powder was reconstituted with sterile water and added to the propofol by injection through the port on the bottom of the syringe. The syringe was then inverted five times in succession to mix the drugs. The syringes were mounted in an upright vertical position (plunger on top, port on bottom) with wire on a pegboard. Samples of the mixture were taken from the bottom port (via a 3-way stopcock) and from the top of the syringe (via a stopcock on an 18-gauge needle placed 5 mm through the plunger) at the following time intervals (min) from baseline: T0, T10, T30, T60, T120, T180, T240, T300. Remifentanil and propofol were quantified using specific and validated HPLC/MS/MS assays with automated online sample preparation.

Results: Concentrations of remifentanil were significantly greater at the top than the bottom of the syringes in groups A and B. Concentrations of propofol were significantly greater at the bottom than the top of the syringes in all groups.

Conclusion: Our data indicate that remifentanil solution and propofol emulsion are immiscible: remifentanil separates from propofol and rises to the top. Thus, concentrations of remifentanil and propofol delivered to patients from

the same syringe during TIVA are not those expected and cannot be reliable. Remifentanil and propofol should be administered in separate syringes when used in combination for TIVA.

Introduction

Total intravenous anesthesia (TIVA) is an effective and well accepted anesthetic technique in pediatric anesthesia (1–3). TIVA is commonly composed of combinations of more than one intravenous anesthetic drug, common examples being propofol combined with either remifentanil or ketamine. The drugs are usually administered in separate syringes (4,5), offering the ability to titrate each drug separately. However, sometimes propofol is mixed with another drug in the same syringe to deliver TIVA (6–9). Since propofol is an emulsion and remifentanil is a solution, we hypothesized that their physical differences would lead to separation and layering over time when mixed in the same syringe.

Methods

Nine 60-ml polypropylene syringes (Bectin Dickinson, Franklin Lakes, NJ, USA) were prepared as follows: Group A: 1.25 ml of remifentanil (Ultiva, Glaxo, Brentford, UK) solution (1 $mg \cdot ml^{-1}$) was added to 48.75 ml of propofol (Diprivan, AstraZeneca, London, UK) (10 $mg \cdot ml^{-1}$) in three syringes, resulting in expected concentrations of 25 $\mu g \cdot ml^{-1}$ remifentanil and 9.75 $mg \cdot ml^{-1}$ propofol. Group B: 2.5 ml of remifentanil (1 $mg \cdot ml^{-1}$) was added to 47.5 ml of propofol (10 $mg \cdot ml^{-1}$) in three syringes, resulting in expected concentrations of 50 $\mu g \cdot ml^{-1}$ remifentanil and 9.5 $mg \cdot ml^{-1}$ propofol. Group C: 5 ml of remifentanil (1 $mg \cdot ml^{-1}$) was added to 45 ml of propofol (10 $mg \cdot ml^{-1}$) in three syringes, resulting in expected concentrations of 100 $\mu g \cdot ml^{-1}$ remifentanil and 9 $mg \cdot ml^{-1}$ propofol. The remifentanil lyophilized powder was reconstituted with sterile water and added to the propofol by injection through the port on the bottom of the syringe. Each syringe was then inverted five times in succession (with a 5-ml air bubble to aid mixing) to simulate clinical practice to mix the drugs. The syringes were mounted in an upright vertical position (plunger on top, port on bottom) with wire on a pegboard. Samples of the mixture (1 ml discarded, followed by 1 ml of sample for analysis) were taken from the bottom port (via a three-way stopcock) and from the top of the syringe (via a stopcock on an 18-gauge needle placed 5 mm through the plunger) (Figure 1) at the following time intervals (min) from baseline: T0, T10, T30, T60, T120, T180, T240, T300.

Remifentanil and propofol concentrations were quantified using HPLC/MS/MS assays with automated online sample preparation. All assays were validated as considered 'fit-for-purpose'. In brief:

Propofol (2,4-Diisopropylphenol) reference material was obtained from Sigma Aldrich (St. Louis, MO, USA) and the internal standard propofol-D18 was from Toronto Research Chemicals (Toronto, ON, Canada). Remifentanil was from Toronto Research Chemicals and its internal standard, sufentanil citrate, from US Pharmacopeia (Rockville, MD, USA).

A 2-dimensional high-performance liquid chromatography–tandem mass spectrometry (LC/LC-MS/MS) system was used. HPLC 1 was used for online sample clean up, desalting, and peak focusing, HPLC 2 for sample analysis. The two HPLC systems consisted of the following components (all series 1100, Agilent Technologies, Palo Alto, CA, USA): HPLC 1: G1312A binary pump, G1379A degasser; HPLC 2: G1312A binary pump, a G1316A column thermostat equipped with a six-port valve Rheodyne, Cotati, CA, USA), and a Leap Technologies (Carborro, NC, USA) autosampler. An

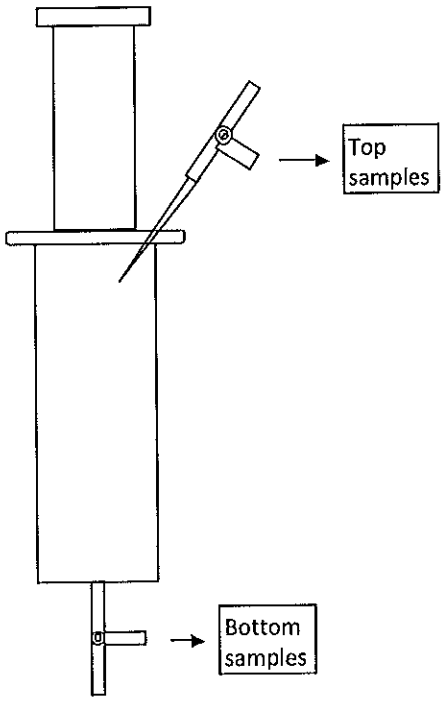

Figure 1 Schematic drawing of sampling sites from vertically mounted syringes.

API 4000 triple-stage quadrupole mass spectrometer was used as detector (AB Sciex, Concord, ON, Canada).

Quantification of propofol

Samples were centrifuged at 13 000 *g* and 4°C for 10 min and then diluted 1 : 5000 using methanol/HPLC-grade water (7/3, volume/volume). About 5 μl of an appropriately diluted internal standard was added to result in a final concentration of 1 $\mu g \cdot ml^{-1}$. The internal standard was used to compensate for potential matrix effects during electrospray ionization.

For online sample clean-up, 100 μl of sample was loaded onto an extraction column (4.6 × 12.5 mm, Eclipse XDB-C8, Agilent, Santa Clara, CA, USA) with 15% HPLC-grade methanol with 0.025% ammonium hydroxide/85% HPLC-grade water + 10 mM ammonium acetate adjusted to pH of 8.0 with ammonium hydroxide. The flow during the sample clean-up step was 5 $ml \cdot min^{-1}$. The switching valve was activated after 0.5 min and the analytes were backflushed onto the analytical column (4.6 × 150 mm, 3.5 μm, Eclipse Zorbax XDB -C8, Agilent). The column was kept at 60°C. A gradient using the same mobile phases as for the sample clean-up started at 15% methanol. After 4.5 min, methanol was 98% and was kept at 98% for the following 2.9 min. The flow rate was 1 $ml \cdot min^{-1}$. The API 4000 triple quadrupole mass spectrometer and HPLC system interfaced with a turbo-ion spray source. The interface was heated to 550°C. Nitrogen (purity: 99.999%) was used as Collision Activated Dissociation (CAD) gas. The mass spectrometer was run in the negative MRM (multiple reaction monitoring) mode. The following ion transitions were monitored: propofol $[M\text{-}H^+]^-$ m/z = 177.1 → 160.8 and propofol-D18 $[M\text{-}D^+]^-$ m/z = 194.2 → 176.1.

Propofol was quantified based on the analyte/internal standard peak area ratios using linear regression with 1/X weighting (Analyst 1.3, AB Sciex, Concord, ON, Canada).The assay was linear from 0.05–10 $\mu g \cdot ml^{-1}$ ($r^2 > 0.99$).

Quantification of remifentanil

After centrifugation and dilution as described for propofol, 5 μl of an appropriately diluted sufentanil internal standard solution was added to result in a final concentration of 5 $ng \cdot ml^{-1}$. About 10 μl of the sample was loaded onto an extraction column (4.6 × 12.5 mm, Eclipse XDB-C8, Agilent). The analytes were cleaned with methanol/0.1% formic acid in HPLC-grade water (2/8, volume/volume, flow: 5 $ml \cdot min^{-1}$) for 1 min. Hereafter the analytes were backflushed onto the analytical column (4.6 ′ 150 mm, 3.5 μm particle size, Eclipse XDB-C8, Agilent). The mobile phase consisted of 0.1% formic acid in water and methanol. The following linear gradient was used: methanol increased from 55% to 98% within 4.0 min and was kept at 98% methanol for 1 min. The flow rate was 1 $ml \cdot min^{-1}$. The column temperature was maintained at 40°C. A turbo-ion spray source was used for ionization, the interface was heated to 480°C and nitrogen (purity: 99.999%) was used as the CAD gas. The mass spectrometer was run in the positive MRM and the following ions were monitored: remifentanil $[M+H]^+$ m/z = 377.4 → 228.4 and the internal standard sufentanil $[M+H]^+$ m/z = 387.5 → 238.4.

Peak area ratios of analyte to internal standard peak area ratios were plotted vs nominal concentrations and calibration curves were constructed using nonweighted linear regression. The assay was linear from 0.1 to 100 $ng \cdot ml^{-1}$ ($r^2 > 0.99$).

For both assays, interbatch accuracy was within 90–110% and interbatch imprecision was <10%. There was no significant matrix interference, matrix effect, or carryover. Autosampler stability at +4°C was at least 24 h.

Statistical analysis

Data were normally distributed, and the one-tailed paired *t*-test was used to compare the concentrations at the top and bottom of the syringes for each drug at each time period. The statistical analysis was carried out using SPSS (version 22.0, IBM, Chicago, IL, USA).

Results

Significant differences in drug concentrations at the top and bottom of the majority of syringes were observed shortly after mixing the two drugs and throughout the duration of the study (Table 1). In groups A and B, concentrations of remifentanil were significantly different at the top and bottom of syringes, with remifentanil having greater concentrations at the top of syringes than at the bottom (Figure 2). In all groups, propofol concentrations were significantly greater at the bottom of the syringes than at the top (Figure 3).

Discussion

The results of this study demonstrate that propofol and remifentanil are immiscible when combined in the same syringe. The physical properties of emulsions and solutions lead to separation and layering when combined. Thus, the concentrations of each drug being delivered to the patient from one end of the syringe may not be those expected, possibly leading to unexpected plasma levels or patient responses during TIVA.

Table 1 Concentrations of remifentanil ($\mu g \cdot ml^{-1}$) and propofol ($mg \cdot ml^{-1}$) at top and bottom of syringes over time

	Expected	T0	T10	T30	T60	T120	T180	T240	T300	Combined
Group A										
Remifentanil TOP	25	20 ± 2	16 ± 3	14 ± 6	21 ± 1	22 ± 4	19 ± 5	17 ± 7	12 ± 3	18 ± 5
Remifentanil BOTTOM	25	9 ± 2	4 ± 2	6 ± 3	5 ± 1	4 ± 1	6 ± 5	4 ± 3	6 ± 1	5 ± 3
Mean difference (95% CI)		−11 (−4, −18)	−12 (−20, −3)	−8 (−21, 5)	−16 (−19, −13)	−18 (−29, −7)	−13 (−20, −6)	−13 (−22, −3)	−6 (−15, 3)	−12 (−14, −10)
P		0.010	0.015	0.057	0.001	0.010	0.008	0.015	0.053	0.0001
Propofol TOP	9.75	6.0 ± 0.5	5.3 ± 0.4	5.5 ± 0.6	6.4 ± 0.8	5.7 ± 1.6	5.0 ± 0.3	7.1 ± 0.6	6.0 ± 0.3	5.9 ± 0.9
Propofol BOTTOM	9.75	10.4 ± 3.7	8.6 ± 2.0	9.2 ± 0.9	11.7 ± 0.4	8.7 ± 0.7	9.8 ± 1.9	8.1 ± 0.2	12.9 ± 6.6	9.9 ± 2.9
Mean difference (95% CI)		4.4 (−5.9, 14.6)	3.3 (−2.6, 9.2)	3.7 (0.3, 7.1)	5.3 (0.6, 8)	3.0 (−1.4, 7.5)	4.9 (0.1, 9.7)	1.0 (−0.8, 2.8)	6.9 (−8.9, 22.8)	(2.8, 5.3)
P		0.105	0.069	0.022	0.007	0.049	0.024	0.073	0.100	0.0001
Group B										
Remifentanil TOP	50	52 ± 15	52 ± 4	58 ± 8	57 ± 7	69 ± 13	56 ± 16	53 ± 10	51 ± 11	56 ± 11
Remifentanil BOTTOM	50	35 ± 7	43 ± 20	46 ± 4	41 ± 4	47 ± 13	47 ± 10	40 ± 10	35 ± 4	42 ± 10
Mean difference (95% CI)		−17 (−32, −1)	−8 (−56, 40)	−12 (−41, 17)	−17 (−41, 7)	−22 (−39, −5)	−9 (−37, 19)	−13 (−63, 38)	−16 (−49, 18)	−14 (−19, −9)
P		0.023	0.267	0.110	0.046	0.015	0.150	0.197	0.090	0.0001
Propofol TOP	9.5	5.7 ± 0.6	4.5 ± 0.3	4.5 ± 0.0	4.4 ± 0.4	4.5 ± 0.5	6.5 ± 1.5	4.5 ± 0.4	5.3 ± 0.6	5.0 ± 0.9
Propofol BOTTOM	9.5	12.2 ± 2.3	11.3 ± 4.4	8.9 ± 1.2	9.9 ± 3.6	7.9 ± 3.1	12.1 ± 1.9	10.8 ± 4.3	8.4 ± 0.6	10.2 ± 3.0
Mean difference (95% CI)		6.5 (−0.5, 13.6)	6.7 (−3.9, 17.4)	4.4 (1.2, 7.6)	5.5 (−4.3, 15.3)	3.3 (−3.1, 9.8)	5.6 (1.8, 9.5)	6.3 (−4.0, 16.6)	3.2 (2.7, 3.6)	5.2 (4.0, 6.4)
P		0.029	0.056	0.014	0.069	0.078	0.012	0.060	0.001	0.0001
Group C										
Remifentanil TOP	100	137 ± 36	134 ± 26	106 ± 9	135 ± 20	136 ± 41	126 ± 26	125 ± 10	127 ± 12	128 ± 23
Remifentanil BOTTOM	100	104 ± 11	107 ± 8	128 ± 13	101 ± 17	138 ± 24	156 ± 30	181 ± 22	122 ± 4	129 ± 31

Table 1 Continued

	Expected	T0	T10	T30	T60	T120	T180	T240	T300	Combined
Mean difference (95% CI)		−34 (−110, 44)	−27 (−75, 20)	22 (−26, 70)	−34 (−117, 50)	2 (−61, 64)	31 (−31, 92)	57 (8, 106)	−5 (−24, 14)	1 (−14, 17)
P		0.101	0.065	0.905	0.112	0.541	0.917	0.981	0.192	0.571
Propofol TOP	9.0	4.5 ± 0.5	3.7 ± 0.2	4.2 ± 0.1	4.4 ± 0.6	3.9 ± 0.2	4.5 ± 0.6	4.4 ± 0.7	4.6 ± 0.5	4.3 ± 0.5
Propofol BOTTOM	9.0	10.5 ± 0.2	8.9 ± 3.7	12.1 ± 1.7	12.0 ± 1.3	9.4 ± 4.4	4.7 ± 4.2	12.9 ± 2.0	14.1 ± 10.5	10.6 ± 4.8
Mean difference (95% CI)		6.0 (4.4, 7.6)	5.2 (−4.6, 15.0)	7.9 (3.6, 12.2)	7.6 (3.7, 11.5)	5.5 (−5.5, 16.5)	0.1 (−10.5, 10.8)	8.5 (1.9, 15.1)	9.5 (−16.5, 35.5)	6.3 (4.3, 8.3)
P		0.002	0.075	0.008	0.007	0.083	0.482	0.015	0.129	0.0001

Values are expressed as mean ± SD drug concentrations or mean differences (95% CI). $P < 0.05$ was considered statistically significant by one-tailed paired *t*-test.

Although most reports describe the use of separate syringes when drugs are combined for TIVA, mixing propofol and remifentanil in the same syringe for administration to pediatric patients has been reported (6,7). The extent of this practice is unknown, but the results of our study should discourage it. A single syringe mixture of ketamine and propofol (sometimes called 'ketofol') has also been reported for both pediatric (8–10) and adult (11,12) anesthesia and sedation. Since ketamine, like remifentanil, is a solution, we speculate that its

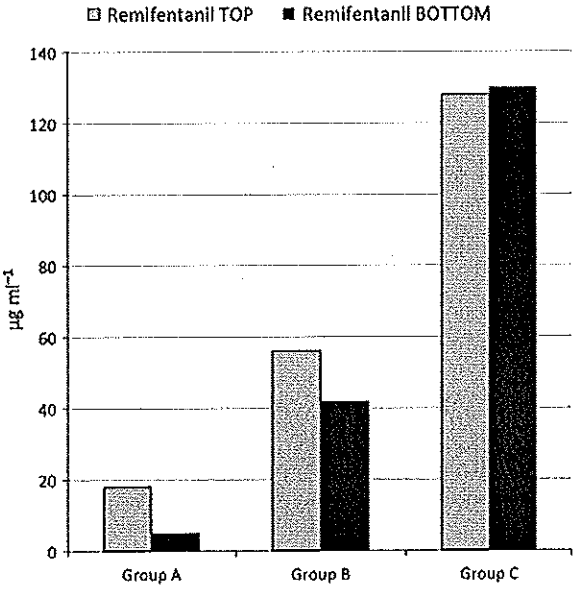

Figure 2 Mean remifentanil concentrations were significantly greater at the tops of syringes in Groups A and B (both $P < 0.0001$ by one-tailed paired *t*-test).

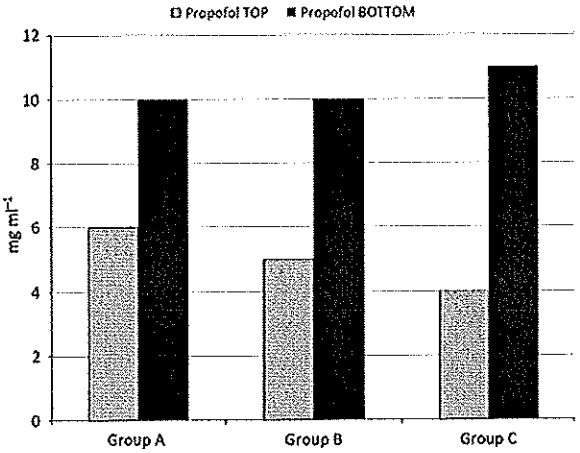

Figure 3 Mean propofol concentrations were significantly greater at the bottoms of syringes in all groups ($P < 0.0001$ by one-tailed paired *t*-test).

mixture with the emulsion propofol would result in similar separation and layering. Thus, imprecise concentrations of both drugs could be delivered to the patient.

The chemical stability of the mixtures of two concentrations of remifentanil with propofol has been described (13). Remifentanil concentrations remained stable in polypropylene syringes and in polyvinylchloride bags when mixed as 50 $\mu g \cdot ml^{-1}$ remifentanil and 10 $mg \cdot ml^{-1}$ propofol. However, in mixtures of 5 $\mu g \cdot ml^{-1}$ remifentanil and 10 $mg \cdot ml^{-1}$ propofol, the remifentanil concentrations decreased over time. The authors speculated that hydrolysis of the ester group of remifentanil caused this decrease. However, storage position, periodic mixing, and sampling ports were not described for either concentration, so it is quite possible that either periodic mixing or passive layering affected the results of that study.

Similarly, a study of ketamine–propofol mixtures in polypropylene syringes reported stable concentrations of both drugs over 3 h (14). However, that study also did not describe the storage, movement, periodic mixing, and sampling methods and was not designed to demonstrate layering, so movement of the syringes prior to sampling may have prevented layering of the drugs. Furthermore, since we sampled the mixture at both the top and bottom of unmoved syringes, our results demonstrate separation and layering rather than deterioration or instability of either drug.

Mixing of some drug solutions with propofol causes coalescence of the oil droplets present in the propofol emulsion, resulting in an increased size of oil globules and leading to the formation of a visible layer over time and a theoretical risk of fat embolism. This has been demonstrated in mixtures of propofol with nimodipine (15), remifentanil (15), and lidocaine (16,17). In citing the latter studies, the statement of the United States Federal Drug Administration (FDA) is that propofol emulsion should not be mixed with other therapeutic agents prior to administration (18).

We measured drug concentrations at the top and bottom of vertically mounted syringes. On some syringe infusion pumps, syringes are mounted in a horizontal position. We believe that separation and layering of drug solutions mixed with propofol would also occur in the horizontal position. In a horizontal position, the drug mixture exits the syringe from the midpoint of the mixture instead of the bottom, and the funneling effect in this position might possibly bring both layers together on leaving the syringe. However, that is speculation and the extent of such mixing would probably be affected by the relative volumes of the two drugs in the syringe, so unplanned drug concentrations might still occur in this position.

We are unable to explain the lack of significant differences in remifentanil concentrations between the top and bottom of syringes in Group C. Perhaps it is related to the larger volume and/or greater concentration of remifentanil solution that was added to propofol in that group or to the decreasing volume of the mixture in the syringes over time, as samples were removed.

This study demonstrates that when the solution remifentanil is mixed with the emulsion propofol in the same syringe, layering of the drugs can occur, resulting in significantly different concentrations of both drugs at the top and bottom of the syringe. Mixing the two drugs in the same syringe prevents individual titration of each drug, presents some potential safety issues due to the coalescence of oil globules in the propofol emulsion, and, as our study demonstrates, can result in delivery of imprecise drug concentrations. TIVA utilizing combinations of anesthetic drugs is an effective and widely used anesthetic technique, but its accuracy should be assured by using separate syringes for each anesthetic drug.

Ethics approval

Ethical approval was not required for this laboratory research study.

Funding

This study received no external funding.

Conflict of interest

Robert H. Friesen is Chair of the Editorial Board of *Pediatric Anesthesia*. The other authors report no conflicts of interest.

References

1 Lerman J. TIVA, TCI, and pediatrics: where are we and where are we going? *Pediatr Anesth* 2010; **20**: 273–278.

2 Wong GL, Morton NS. Total intravenous anesthesia (TIVA) in pediatric cardiac anesthesia. *Pediatr Anesth* 2011; **21**: 560–566.

3 Lauder GR. Total intravenous anesthesia will supercede inhalational anesthesia in pediatric anesthetic practice. *Pediatr Anesth* 2015; **25**: 52–64.

4 Grundmann U, Uth M, Eichner A *et al.* Total intravenous anaesthesia with propofol and remifentanil in paediatric patients: a comparison with a desflurane-nitrous oxide inhalation anaesthesia. *Acta Anaesthesiol Scand* 1998; **42**: 845–850.

5 Shen X, Hu CB, Ye M *et al.* Propofol-remifentanil intravenous anesthesia and

spontaneous ventilation for airway foreign body removal in children with preoperative respiratory impairment. *Pediatr Anesth* 2012; **22**: 1166–1170.

6 Berkenbosch JW, Graff GR, Stark JM *et al.* Use of a remifentanil-propofol mixture for pediatric flexible fiberoptic bronchoscopy sedation. *Pediatr Anesth* 2004; **14**: 941–946.

7 Tsui BC, Wagner A, Usher AG *et al.* Combined propofol and remifentanil intravenous anesthesia for pediatric patients undergoing magnetic resonance imaging. *Pediatr Anesth* 2005; **15**: 397–401.

8 Weatherall A, Venclovas R. Experience with a propofol-ketamine mixture for sedation during pediatric orthopedic surgery. *Pediatr Anesth* 2010; **20**: 1009–1016.

9 Coulter FL, Hannam JA, Anderson BJ. Ketofol simulations for dosing in pediatric anesthesia. *Pediatr Anesth* 2014; **24**: 806–812.

10 Tosun Z, Esmaoglu A, Coruh A. Propofol-ketamine vs propofol-fentanyl combinations for deep sedation and analgesia in pediatric patients undergoing burn dressing changes. *Pediatr Anesth* 2008; **18**: 43–47.

11 Miner JR, Moore JC, Austad EJ *et al.* Randomized, double-blinded, clinical trial of propofol, 1:1 propofol/ketamine, and 4:1 propofol/ketamine for deep procedural sedation in the emergency department. *Ann Emerg Med* 2015; **65**: 479–488. e2.

12 Grace RF, Tang DW, Namel E. An audit of the haemodynamic and emergence characteristics of single-shot 'ketofol'. *Anesth Intensive Care* 2015; **43**: 503–505.

13 Stewart JT, Warren FW, Maddox FC *et al.* The stability of remifentanil hydrochloride and propofol mixtures in polypropylene syringes and polyvinylchloride bags at 22 degrees-24 degrees C. *Anesth Analg* 2000; **90**: 1450–1451.

14 Donnelly RF, Willman E, Andolfatto G. Stability of ketamine-propofol mixtures for procedural sedation and analgesia in the emergency department. *Can J Hosp Pharm* 2008; **61**: 426–430.

15 Nemec K, Germ E, Schulz-Siegmund M *et al.* The effect of nimodipine, fentanyl and remifentanil intravenous products on the stability of propofol emulsions. *Pharmazie* 2009; **64**: 94–97.

16 Park JW, Park ES, Chi SC *et al.* The effect of lidocaine on the globule size distribution of propofol emulsions. *Anesth Analg* 2003; **97**: 769–771.

17 Masaki Y, Tanaka M, Nishikawa T. Physicochemical compatibility of propofol-lidocaine mixture. *Anesth Analg* 2003; **97**: 1646–1651.

18 United States Federal Drug Administration. http://www.accessdata.fda.gov/drugsatfda_docs/label/2008/019627s046lbl.pdf. (accessed 21 March 2016).