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ORIGINAL ARTICLE

Frequently acquired drugs in neonatal intensive care and their physical compatibility

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Abstract

Aim: Incompatibility of intravenous drugs is dangerous and therefore undesirable. The aim of this study was to identify the most commonly acquired intravenous drugs in five neonatal intensive care units and test these for compatibility.

Methods: The most frequently acquired drugs in five key hospitals in the South-Eastern district of Norway for 2019 and 2020 served as a proxy for the prevalence of use. Representatives were selected from the three most prevalent groups based on the Anatomical Therapeutic Chemical classification system. Co-administration of drug pairs was simulated using clinically relevant concentrations and infusion rates representing mixing ratios in the catheter. Particle formation was assessed by particle counting and size measurement, by visual examination using Tyndall beam, by turbidity and by measuring pH of mixed samples.

Results: The most frequently acquired drug groups were anti-infectives, neurological agents and cardiovascular drugs. Compatibility testing revealed that both ampicillin and benzylpenicillin were incompatible with morphine. Flecainide and fluconazole showed no signs of incompatibility with morphine. No information on these combinations in a neonatal-relevant setting is available.

Conclusion: We recommend to abstain from co-administering ampicillin and benzylpenicillin with morphine in neonatal intensive settings. Morphine co-administered with flecainide and fluconazole in neonatal patients were evaluated as safe.

KEYWORDS
children, co-administration, incompatibility, paediatrics, particle formation

1 | INTRODUCTION

Limited venous access in neonates often leads to the need to co-administer intravenous drugs and/or parenteral nutrition via the same catheter.[1] Most neonates only tolerate the insertion of a single or double lumen central venous catheter or peripherally inserted central catheter.[2] Co-administration increases the risk of incompatibility reactions between the infused solutions because of differences in their physicochemical properties.[3] Consequences of incompatibilities may result in precipitation of solid particles or increase in oil-droplet size for emulsions. This can lead to lumen occlusion, embolus formation and organ malfunction.[4–6] Two retrospective studies

reported fatal embolism after infusion of incompatible drugs.[7,8] Compatibility issues are far from uncommon. More than 25% of co-administrations in neonates are incompatible and up to 75% are either incompatible or undocumented.[3,9] Compatibility information can be retrieved from various sources and databases, such Trissel's Handbook on Injectable Drugs, Micromedex IV Compatibility and Stabilis.[10–12] However, the information on specific combinations can be missing or contradicting, and information about which intravenous drugs are compatible during co-administration in small children, in particular neonates, is very scarce.[3,13] Pausing infusions and flushing the intravenous lines prior to and after each intravenous administration is not a realistic solution because small children have extremely low fluid capacity.

Compatibility studies cannot be performed in vivo due to ethical reasons and in vitro studies often performed analyses under predefined, and clinically irrelevant, conditions.[10] One exception was the study by Nilsson et al. that analysed the compatibility of dopamine, morphine and cefotaxime at clinically relevant mixing ratios using a battery of compatibility tests and concluded that they are compatible, both with each other and with a neonatal parenteral nutrition admixture.[14] The same parenteral nutrition was also found to be compatible with fentanyl, paracetamol and vancomycin.[15] Another exception was the study by Staven et al. where two neonatal parenteral nutrition products were reported to precipitate when mixed with ampicillin, fosphenytoin and furosemide.[16,17] Fluconazole, metronidazole and paracetamol were reported to destabilise the preterm all-in-one parenteral nutrition.[17] De Basagoiti et al. investigated the compatibility of alprostadil to neonates with several drugs in 1+1 mixing ratios,[18] whereas Holt et al. studied the compatibility of ibuprofen lysine with several drugs at clinically relevant mixing ratios for preterm infants.[19] No other compatibility studies on intravenous drug co-administration that specifically addressed neonates were found.

Our aim was to identify which intravenous drugs were most commonly used in neonatal intensive care, and which of these were compatible mixing ratios and infusion rates that are clinically relevant for neonates.

Key Notes

- Intravenous drug incompatibility may occur due to limited venous access and poses a risk of particulate precipitate formation.
- Data from five neonatal intensive units showed that anti-infectives, cardiovascular drugs and morphine were prevalent.
- Compatibility tests revealed that morphine combined with ampicillin or benzylpenicillin formed precipitate and must be avoided whereas co-administration of morphine with flecainide or fluconazole is safe in neonates.

2 | MATERIALS AND METHODS

The study was divided into two, each part with a specific set of materials and methods. First, the most frequently used drugs in neonatal intensive care were identified. Next, candidates from the most prevalent groups were selected for physical compatibility testing.

2.1 | Frequently used drugs

Information on drug acquisition by neonatal intensive care units in five member hospitals of the *South-Eastern Norway Regional Health Authority* were collected from the respective hospital pharmacies for years 2019 and 2020. Neonatal intensive care units in the following hospitals were included: Oslo University Hospital, Rikshospitalet and the regional hospitals in Drammen, Kalnes, Kristiansand and Tønsberg. In order to sort and compare the drug classes and turnover, the global World Health Organization (WHO) *Anatomical Therapeutic Chemical* (ATC) classification system was used.[20] The systematic classification of a drug substance in groups and in a hierarchy based on the three descriptors (anatomy, therapy and chemical structure) provides a tool for drug utilisation monitoring and research. The statistics were collected per year, sorted according to ATC group and further by drug product. Since we were interested in potential co-infusion of drugs, all non-parenteral products and drugs not intended for intravenous administration were excluded. Electrolyte solutions were also excluded because of several different suppliers bypassing the hospital pharmacy system. Another WHO tool, defined daily doses,[20] was used to estimate the utilisation of each drug product per neonatal intensive units. Even though defined daily doses are based on doses for adults, similar standards do not exist for children.

The most prevalent ATC groups were identified. Within each ATC group, the drugs with the highest number of defined daily doses were chosen. These were considered to be the most frequently used drugs and therefore likely to encounter the need for co-administration. It is important to keep in mind that this approach does not provide evidence that co-administration did occur. Based on the statistics, five drugs were selected for compatibility studies.

2.2 | Physical compatibility of drugs upon simulated co-administration

An overview of the selected drugs and solutions with their pH information, their manufacturer, excipients, dilution media and final concentration can be found in Table 1. After consulting with clinical pharmacists, we decided to test morphine with each of the other selected drugs because it is common in many co-infusions. Moreover, there are limited compatibility data on morphine hydrochloride used in the Nordic countries in contrast to the more widely used morphine sulphate.

The estimation of potential mixing ratios between drugs in the catheter line has been described earlier.[15,21] Briefly, drug doses and infusion rates are based on national neonatal therapy guidelines and local syringe pump protocols as well as information from Kinderformularium.[22] The estimates cover bodyweights from 0.5 to 10 kg with the aim to cover extreme dose scenarios. The volumetric ratio of morphine to the other drug is determined based on the ratio between the infusion rates. Three mixing ratios of each drug pair were selected for testing including 1 + 1 (Table 2).

Mixed morphine and drug samples and controls were prepared by reconstituting the drug according to manufacturer specification in the summary of product characteristics followed by dilution to the desired clinically relevant concentration. More precisely, ampicillin (STADA) and benzylpenicillin (Panpharma), which were powders, were first reconstituted in water for injection before dilution with the desired volume of glucose (B. Braun) 50 mg/mL (Table 1). Flecainide (MEDA) and morphine (Orion) could be directly diluted with glucose 50 mg/mL to desired concentrations, and fluconazole (B. Braun) was used undiluted. Since dilutions were always made from the specified amount of drug, be it powder or solution of a specific concentration, with a defined volume, the final concentration of the sample was known. Glucose 50 mg/mL was chosen as dilution or infusion medium, although all drugs in this study could also have been diluted and infused with sodium chloride 9 mg/mL.

To prevent particle contamination the separate drug solutions were filtered through a 0.22 µm syringe filter (VWR) into 15 ml sample tubes (Coning). Separate controls of unmixed drug were prepared the same way. All samples and controls were prepared and analysed at ambient temperature.

Samples of morphine and drug combinations were analysed using well-established methods for assessment of potential particle formation.[15,16,21] The mixed samples were analysed immediately after mixing and after 4 h and compared with unmixed controls.

Sub-visual particle content was estimated by light obscuration using the Accusizer Optical Particle Sizer with Syringe Injection Sampler (PSSNICOMP). The total number of particles/mL of particle sizes larger than 0.5, 5, 10 and 25 µm, respectively, was recorded. Samples were deemed compatible if not more than 2000 particles/mL ≥0.5 µm were detected and the large particle limits of the Pharmacopoeia, meaning not more than 25 particles/mL ≥10 µm or not more than 3 particles/mL ≥25 µm, were not exceeded.[21,23] The cut-off for background particles was not more than 100 particles/mL ≥0.5 µm.

Turbidity was determined with the Turbidimeter 2100Qis (Hach Lange GmbH). Mixed samples were not to exceed 0.3 Formazine Nephelometry Units (FNU) above the values of the unmixed controls.

Measured pH in mixed samples by a Seven Compact pH meter (Mettler Toledo) was compared with pH in unmixed controls. A theoretical evaluation taking pKa value and solubility of each drug into consideration was done.

As support, visual examination with two different Tyndall light sources was implemented. The samples, in flat-bottom tubes, were inspected above a fibreoptic Tyndall beam (Schott KL 1600 LED) and also with a 630–650 nm red laser pen (P 3010 RoHS) shining perpendicularly through it. A Tyndall effect, usually a visible red line from the laser emanating from the laser through the sample, was interpreted as identification of micro-precipitates, even though particles could not be seen with the naked eye. Visual examinations were carried out in a dark room against a black background.[24]

3 | RESULTS AND DISCUSSIONS

3.1 | Frequently used drugs

Oslo University Hospital is by far the largest hospital and serves as the national specialist hospital. The four other hospitals are regional hospitals with neonatal intensive units. Table 3 shows that Oslo

TABLE 1 Overview over studied drugs and solutions with their pH information, excipients, dilution media and final concentrations

Drug (Manufacturer)	Excipients[a]	Dilution	Final concentration
Ampicillin sodium (STADA) pH: not stated[a]	–	Water for injection[b] + glucose 50 mg/mL	100 mg/mL
Benzylpenicillin sodium (Panpharma) pH: not stated[a]	–	Water for injection[c] + glucose 50 mg/mL	100 mg/mL
Flecainide acetate (MEDA) pH: not stated[a]	Sodium acetate, conc. acetic acid, water for injection	Glucose 50 mg/mL[d]	2 mg/mL
Fluconazole (B.Braun) pH:4.0–8.0[a]	Sodium chloride, water for injection	Used undiluted	2 mg/mL
Glucose 50 mg/mL (B. Braun) pH: 3.5–5.5[a]	Glucose monohydrate water for injection	Used as dilution medium	–
Morphine hydrochloride (Orion) pH: 3.0–5.0[a]	Hydrochloric acid, water for injection	Glucose 50 mg/mL[e]	0.2 mg/mL

[a]Summary of Product Characteristics.
[b]1 g in 5 mL water for injection before dilution with glucose 50 mg/mL.
[c]3 g in 10 mL water for injection before dilution with glucose 50 mg/mL.
[d]10 mg/mL injection diluted with glucose 50 mg/mL.
[e]1 mg/mL injection diluted with glucose 50 mg/mL.

TABLE 2 Overview of selected mixing ratios for morphine with another drug

Drug	Morphine + Drug
Ampicillin	2 + 1; 1 + 1; 1 + 67
Benzylpenicillin[a]	100 + 1; 1 + 1; 1 + 10; 1 + 50
Flecainide	5 + 1; 1 + 1; 1 + 53
Fluconazole	1 + 1; 1 + 13; 1 + 50

[a]Extra mixing ratio added based on the results.

TABLE 3 Total number of defined daily doses per neonatal intensive care unit at Oslo University Hospital and four regional hospitals in the South-Eastern Health Region of Norway for the years 2019 and 2020

Neonatal intensive care unit	Defined daily doses
Oslo University Hospital	14 520
Drammen	1075
Kalnes	1160
Kristiansand	1180
Tønsberg	1000

University Hospital had a 10–15 times higher total number of *defined daily doses* in the study period compared to the regional hospitals. The neonatal intensive units in the four regional hospitals had more or less similar total numbers in the period.

The total number of defined daily doses was broken down into ATC groups per unit, and the distribution of classes was clearly different between Oslo University Hospital and the regional hospitals (Figure 1). Oslo University Hospital receives patients who undergo heart surgery, transplantations and other critically ill patients. This may explain the high frequency of drugs in group N, the Nervous system (Figure 1), which includes strong pain medication, sedatives and anaesthetic drugs. It is interesting to notice that there were some similar features in the drug class profiles of the regional hospitals, even though there also were local differences. The main groups were J, the anti-infectives, followed by C, the cardiovascular system drugs, and B, blood and blood-forming agents, which also includes parenteral nutrition. Tønsberg was an exception in that group L, the antineoplastic and immunomodulating drugs came second followed by B and C.

Looking at the three most prevalent groups, cardiovascular drugs represented between 17% and 22% in all hospitals except, as mentioned above, Tønsberg, where acquisition was much lower. The top drug was adrenaline, representing 50%–77% of the drugs in this group in all hospitals except Oslo University Hospital, where adrenaline accounted for only approximately 30%. There was a broad selection of cardiovascular drugs including flecainide and amiodarone, and diuretic drugs such as furosemide. The nervous systems drugs represented only 1% in three of the regional hospitals, whereas accounted for a significantly higher percentage at Oslo University Hospital at 21% and Drammen at 17%. The most frequent drug in this group was not only fentanyl but also other opioids, such as

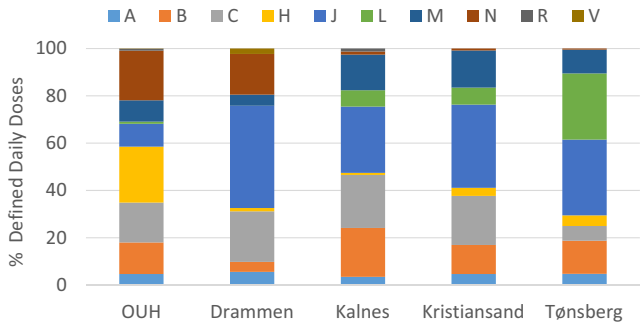

FIGURE 1 Distribution of estimated total drug utilisation based on defined daily doses in groups based to the global World Health Organization code system, the Anatomical Therapeutic Chemical (ATC) classification system, for the neonatal intensive units of Oslo University Hospital (OUH) and four regional hospitals in South-Eastern Norway Health Regional Authority for 2019–2020. A, alimentary tract and metabolism, B, blood and blood forming organs, C, cardiovascular system, H, systemic hormonal preparations, J, anti-infectives for systemic use, L, antineoplastic and immunomodulating agents, M, musculo-skeletal system, N, nervous system, R, respiratory system, V, various. ATC groups not included did not have any defined daily doses during the study period.

morphine were commonly used. For the anti-infectives, the trend was the other way round; this class represented 28%–43% of the total estimated drug utilisation in the regional hospitals compared with only 10% at Oslo University Hospital. This pattern might be explained by patients typically being transferred from Oslo University Hospital to the regional hospitals when they are recovering from the most critical phases, for instance after surgery, where the anti-infective treatment is maintained and completed.

Since anti-infectives were found to be an important group of drugs in all neonatal intensive care units, the statistics was further broken down to the individual drugs to identify which drugs may be relevant for co-infusion. Units seemed to use either ampicillin or benzylpenicillin (Table 4). Therapy guidelines recommend narrow-spectrum antibiotics to limit the development of antibiotic resistance. Data from Tønsberg, which accounted for both types of penicillin, showed a shift from ampicillin in 2019 to benzylpenicillin in 2020 (data not shown). The broad-spectrum antibiotic gentamicin accounted for between 30% and 54% of the drugs. The cephalosporin cefotaxime constituted approximately 10% of drugs in the group at Oslo University Hospital but was less frequently acquired by the regional hospitals. Vancomycin, metronidazole and the antifungal drug fluconazole were represented, but only marginally. Other anti-infective drugs not listed here, constituted 9%–17% in the regional hospitals, but as much as 26% in Oslo University Hospital.

3.2 | Physical compatibility of drugs upon simulated co-administration

From the cardiovascular drugs, flecainide was chosen after consulting with the clinical pharmacists due to frequency of use at

TABLE 4 Overview of frequently occurring anti-infectives in group J of the Anatomical Therapeutic Chemical classification system and their estimated percentage utilisation based on defined daily doses per neonatal intensive care units in Oslo University Hospital (OUH) and the four regional hospitals

	% per total number of anti-infectives				
Drugs	**OUH**	**Drammen**	**Kalnes**	**Kristiansand**	**Tønsberg**
Ampicillin	25.2	32.8	46.6	1.2	6.8
Benzylpenicillin	0.3	0.7	0.3	39.7	19.0
Cefotaxime	9.9	2.9	6.7	2.8	1.3
Fluconazole	1.3	0	0.6	0.5	0.3
Gentamicin	32.9	48.0	30.7	46.1	54.3
Metronidazole	2.0	0.2	0	0.2	0.6
Vancomycin	2.7	0.7	1.9	0.7	0.6
Others	25.7	14.7	13.1	8.7	17.0

Oslo University Hospital and lack of compatibility data. Since anti-infective drugs was the largest group, three drugs were included from this group. Gentamicin was the top candidate, but this was recently tested in another study (publication in progress). In addition, cefotaxime and vancomycin have recently been studied.[14,15] Therefore, the two penicillins, ampicillin and benzylpenicillin, were selected together with the antifungal drug fluconazole. Finally, the test candidate from group N was morphine. Fentanyl, the top candidate in this group, was recently studied by our group.[15] Even though morphine also has recently been,[14] there are limited compatibility data on morphine hydrochloride. Morphine is a versatile drug that is used in combination with all the selected drugs and was therefore tested in combination with each of the other drugs. A typical scenario would be that morphine is given continuously thus occupying the line, and the other four drugs are administered as intermittent infusions of 30 and up to 60 min. Since this would be too long to stop the administration of the strong opioid, co-administration of morphine with the other drugs are highly relevant. Documented data of their compatibility will contribute to increased patient safety; in case incompatibility is detected, co-administration should be avoided.

The two penicillin types resulted in particle precipitation when in combination with morphine (Table 5). For mixed samples of morphine andampicillin, the 1 + 1 ratio showed strong precipitation of sub-visual particles with an increasing trend with time. At particle counts higher than the detector limit of 9000/mL, the numbers cannot be trusted, but there was no doubt that a massive precipitation took place when mixing equal parts of morphine and ampicillin (1 + 1). This was confirmed by observation of a Tyndall effect with a laser beam. Even though there was massive formation of small particles, no particles exceeded the compendia size limits. Nevertheless, this was a sign of incompatibility between the two drugs. For mixing ratios with either more morphine (2 + 1) or significantly more ampicillin (1 + 67), the sub-visual particle counts were in the range of the controls. None of the combinations showed elevated turbidity measurements as compared to the controls, but the control of unmixed ampicillin already had an inherent turbidity of around 0.5, which was reduced upon dilution in mixed samples. This was confirmed by an inherently weak Tyndall effect. The pH in the mixed samples reflected the high pH of ampicillin (pH 9.0–9.4), which, even though relatively close to the pKa 8.21 of morphine,[25] would promote the unionised form of morphine. Ampicillin, with one acidic pKa of 2.55 and a basic pKa of 7.25,[26] would be ionised on the carboxylic acid moiety but not at the amine and therefore it would be more poorly soluble than below the basic pKa. Since both morphine and ampicillin seemed to be in a pH range where precipitation potentially could happen, it was not surprising that conflicting information can be found in literature.[10,27] Staven et al. found that ampicillin precipitated upon mixing with Numeta G16E (Baxter), a parenteral nutrition admixture intended for term neonates and children up to 2 years.[16] The observed pH of the mixed samples that precipitated was >7.7, that is above basic pKa, whereas that of samples that did not precipitate was measured to 6.2–7.0, below basic the pKa. This supported the findings of the current study except that one might have expected signs of precipitation in all mixing ratios with morphine. Contradicting information is often an issue with the compatibility data from available sources,[10–12] making the clinical situation challenging to manoeuvre. The reason for conflicting information is manifold and complex. Many studies are purely based on visual examinations or a limited number of analytical techniques that may not be able to capture incompatibilities. The mixing ratio in the infusion line might differ from the typical 1 + 1 ratio tested, and the concentration of the drug can deviate. Also, the drug product can be differently formulated and contain other excipients and so on. Therefore, extrapolating information useful in a specific clinical situation is difficult; more experimental data, spanning a broader range of mixing ratios and scrutinised using several methods to reveal incompatibility, is needed.

For the combination of morphine and benzylpenicillin, precipitation was detected in mixing ratios with higher proportions of benzylpenicillin (Table 5). For the combination 1 + 10, there was clear precipitation immediately after mixing as well as with time. The precipitation was recognised as increased turbidity as well

TABLE 5 Assessment of potential precipitation after mixing morphine 0.2 mg/mL with ampicillin 100 mg/mL, benzylpenicillin 100 mg/mL, flecainide 2 mg/mL and fluconazol 2 mg/mL, respectively (bold font indicate values outside the acceptance criteria) (average ± SD; $n = 3$)

		Particles/mL ≥0.5 µm		Particles/mL ≥5 µm		Particles/mL ≥10 µm		Turbidity (FNU)		pH	
Drug(s)	**Mix ratio**	**0 h**	**4 h**	**0 h**	**4 h**	**0 h**	**4 h**	**0 h**	**4 h**	**0 h**	**4 h**
Ampicillin	Control	380	280	2	4	2	2	0.51	0.55	9.34	9.30
Benzylpenicillin	Control	170	900	2	9	1	5	0.27	0.57	5.95	5.90
Flecainide	Control	20	30	1	0	0	0	0.13	0.15	5.43	5.61
Fluconazole	Control	170	80	3	1	1	0	0.15	0.13	5.80	5.47
Morphine[a]	Control	70 ± 50	70 ± 40	1 ± 1	1 ± 0	0	0	0.18 ± 0.03	0.14 ± 0.02	4.71 ± 0.45	4.70 ± 0.81
Morphine + Ampicillin	2 + 1	180 ± 130	60 ± 340	2 ± 1	2 ± 1	1 ± 0	1 ± 0	0.27 ± 0.02	0.21 ± 0.02	8.97 ± 0.03	8.96 ± 0.02
	1 + 1	**1700 ± 2700**	**>Detector[c]**	2 ± 0	3 ± 4	1 ± 0	1 ± 1	0.36 ± 0.02	0.43 ± 0.23	9.01 ± 0.02	8.98 ± 0.01
	1 + 67	350 ± 450	160 ± 68	5 ± 6	2 ± 1	2 ± 2	2 ± 0	0.40 ± 0.12	0.44 ± 0.12	9.38 ± 0.02	9.31 ± 0.23
Morphine + Benzylpenicillin	100 + 1	110 ± 10	60 ± 9	2 ± 1	2 ± 1	1 ± 0	1 ± 1	0.15 ± 0.02	0.26.0.02	4.79 ± 0.06	4.92 ± 0.10
	1 + 1	460 ± 100	730 ± 180	8 ± 3	4 ± 2	1 ± 1	1 ± 1	0.20 ± 0.02	0.29 ± 0.05	5.75 ± 0.02	5.69 ± 0.04
	1 + 10	**2500 ± 1200**	**4100 ± 2200**	**24 ± 16**	**56 ± 36**	**13 ± 7**	**13 ± 6[b]**	0.39 ± 0.020	**0.54 ± 0.02**	5.88 ± 0.01	5.87 ± 0.01
	1 + 50	220 ± 120	**>detector[c]**	6 ± 3	**28 ± 11**	2 ± 1	**10 ± 5[b]**	0.21 ± 0.04	**0.56 ± 0.18**	5.81 ± 0.01	5.88 ± 0.01
Morphine + Flecainide	5 + 1	180 ± 20	500 ± 380	2 ± 7	7 ± 7	1 ± 0	2 ± 2	0.12 ± 0.01	0.13 ± 0.03	5.47 ± 0.08	5.56 ± 0.03
	1 + 1	230 ± 60	620 ± 270	5 ± 2	8 ± 3	1 ± 1	1 ± 1	0.15 ± 0.04	0.19 ± 0.04	5.48 ± 0.07	5.51 ± 0.04
	1 + 53	340 ± 100	100 ± 70	6 ± 3	2 ± 1	1 ± 1	1 ± 1	0.13 ± 0.03	0.14 ± 0.01	5.56 ± 0.01	5.46 ± 0.02
Morphine + Fluconazole	1 + 1	300 ± 10	120 ± 10	6 ± 3	2 ± 1	2 ± 2	1 ± 1	0.19 ± 0.07	0.13 ± 0.02	5.21 ± 0.02	4.70 ± 0.03
	1 + 13	170 ± 10	80 ± 30	4 ± 0	2 ± 1	1 ± 0	1 ± 1	0.13 ± 0.03	0.15 ± 0.03	5.95 ± 0.09	5.43 ± 0.10
	1 + 50	220 ± 70	120 ± 30	3 ± 0	3 ± 2	1 ± 0	2 ± 2	0.15 ± 0.01	0.14 ± 0.01	6.00 ± 0.04	5.51 ± 0.04

[a]Average of several batches.

[b]Contain particles >25 µm.

[c]Over detector limit >9000 particles/mL.

as a clear Tyndall effect in visual examinations in the case of the total sub-visual particle counts >0.5 μm and also in the case of the specific larger fractions >5, >10 and >25 μm. For the mixing ratio 1 + 50, the immediate measurements were within acceptance limits, but after 4 h massive precipitation was detected in all methods. The pH in the unmixed control was 5.90–5.95 and the pH of the mixed samples mirrored the control for mixing ratios with high amounts of benzylpenicillin. Benzylpenicillin has a pKa at 2.72[26] and would be in its ionised, most soluble form at these values, but morphine becomes less ionised at pH values closer to the pKa of benzylpenicillin. Hence, it is most likely that morphine was the one that precipitates in the mixed samples.

Morphine was found to be compatible with flecainide and fluconazole in all mixing ratios (Table 5). No sign of particle formation was observed in any of the analyses. To the best of our knowledge, there are no other compatibility studies on flecainide and morphine, irrespective of type of morphine salt. The aqueous solubility of the sulphate salt is 1:15.5 and slightly lower than that of the hydrochloride, which is 1:17.5. The pH of both flecainide and fluconazole unmixed controls was around 5.4–5.8, whereas morphine controls were found to have pH values of around 4.7 (Table 5). The mixed samples with morphine were found to have a pH close to the unmixed controls of flecainide and fluconazole, respectively. Since these were well below the pKa of morphine, no precipitation of morphine was to be expected in any of the cases. Earlier reports based on adult conditions have found fluconazole compatible with morphine sulphate in visual compatibility tests.[28,29]

Since ampicillin and benzylpenicillin precipitated in some mixing ratios when mixed with morphine, they should be regarded as incompatible. Flecainide and fluconazole were found to be compatible with morphine and co-administration of these combinations to critically ill neonatal patients should be safe.

In this study, all experiments were performed with isotonic glucose 50 mg/mL as the dilution and infusion solution, although all of the current drugs could equally well be diluted and administered with isotonic sodium chloride 9 mg/mL. Glucose was chosen since most critically ill neonates have fluid restrictions and glucose provides the infant with some energy together with the medication. Moreover, according to product information isotonic glucose has a more acidic pH (Table 1), whereas isotonic sodium chloride should be closer to neutral pH of 4.5–7 (Sodium chloride, Baxter). It was therefore anticipated that a solvent with an acidic pH would have higher potential of interfering with the stability of the drugs upon co-administration and therefore be more relevant to use for compatibility testing than almost neutral sodium chloride. This will of course also depend on the pKa and the solubility of each drug substances, the pH of each drug products as well as the mix. Using isotonic glucose in the current study could have triggered the precipitation for mixed samples of morphine and ampicillin more than the sodium chloride would do, because of the basic pKa of the drugs discussed above. However, from a patient safety perspective, it was considered better to overestimate occurrence of incompatibility and take precautions than to underestimate it.

The results should be interpreted with the following in mind. All samples were prepared, stored and analysed at ambient temperature in this study. However, most neonatal units will have a room temperature above the typical room temperature and medications may dwell in tubing in incubators or under radiant heaters for several hours before reaching the infant's circulation. This could affect the drug negatively; one well-known example being the precipitation of poorly soluble calcium phosphate in parenteral nutrition, which is more prevalent at higher temperatures.[30] Potential effects of increased temperatures are not captured in the current study.

4 | CONCLUSIONS

In this study, frequently used drugs in the neonatal intensive care units were identified using acquisition information from five hospitals in the South-Eastern Norway Regional Health Authority. From the frequently occurring ATC groups J, anti-infectives, N, nervous system and C, cardiovascular system, representative drugs were selected for physical compatibility analyses. Morphine, group N, was studied upon simulated co-administration with flecainide, group C, ampicillin, benzylpenicillin, and fluconazole, group J.

Ampicillin and benzylpenicillin were found to be incompatible with morphine and should not be co-infused with it. Flecainide and fluconazole were compatible with morphine and should be safe to administer in the same catheter line as morphine. These findings contribute to safer and more effective administration of drugs in the neonatal intensive care patient.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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