RESEARCH LETTER

WILEY

Physicochemical compatibility of pentoxifylline injection with high-concentration parenteral medications

S.M.D.K. Ganga Senarathna[1] | Tobias Strunk[2,3,4] | Michael Petrovski[5] | Sarah Woodland[5] | Kevin T. Batty[1,6]

[1]Curtin Medical School, Curtin University, Bentley, Australia
[2]Medical School, University of Western Australia, Crawley, Australia
[3]Neonatal Directorate, King Edward Memorial Hospital, Child and Adolescent Health Service, Subiaco, Australia
[4]Wesfarmers Centre for Vaccines and Infectious Diseases, Telethon Kids Institute, Nedlands, Australia
[5]Pharmacy Department, King Edward Memorial Hospital, Women and Newborn Health Service, Western Australia, Australia
[6]Curtin Health Innovation Research Institute, Curtin University, Bentley, Australia

Correspondence
Kevin T. Batty, Curtin Medical School, Curtin University, GPO Box U1987, Perth, Australia.
Email: Kevin.Batty@curtin.edu.au

Funding source
Women & Infants Research Foundation; Department of Pharmacy at King Edward Memorial Hospital for Women

Received: 16 February 2023; Accepted: 30 May 2023

Pentoxifylline (PTX) is reported to provide beneficial outcomes in the treatment of neonatal sepsis and serious inflammatory conditions.[1,2] In the neonatal intensive care setting, PTX is administered by intravenous (IV) infusion and is routinely co-administered via Y-site with other parenteral medications and/or fluids. Although the physicochemical compatibility of PTX with a range of parenteral drugs, IV fluids, and lipid-free parenteral nutrition solutions has been reported, there is an emerging demand for more PTX compatibility data against previously untested medications (ampicillin, cloxacillin, fentanyl, fluconazole, furosemide, hydrocortisone, and ibuprofen lysine) and high-concentration IV drugs (alprostadil, dopamine, epinephrine, midazolam, milrinone, morphine, and norepinephrine) which may be used in fluid-restricted, vulnerable patients.[3–5] In order to address this requirement for contemporary information, we investigated the physical and chemical compatibility of PTX with a panel of 20 drugs, in 51 PTX-drug combinations.

Pentoxifylline injection (Trental; Sanofi, Italy) was diluted 1 in 4 with 0.9% w/v sodium chloride injection to achieve a clinically relevant test concentration of 5 mg/ml. Parenteral medications were prepared and/or diluted in accordance with the manufacturers' instructions or standard neonatal clinical protocols. Medications that required reconstitution were filtered prior to mixing. An established procedure, including a validated, stability-indicating high-performance liquid chromatography (HPLC) assay was used for evaluating the physical and chemical compatibility of the PTX-drug combinations at room temperature.[3,4,6] Briefly, clear glass vials with impermeable lids were used for each combination of drugs and the respective control solutions:

- PTX solution and the test drug solution were combined 1:1 in each of the four vials;
- PTX solution was diluted 1:1 with 0.9% w/v sodium chloride injection ($n = 4$ vials) as the reference solution for the purposes of visual comparison and HPLC assay, and;

DOI: 10.1002/ped4.12393

- The test drug solution was diluted 1:1 with the applicable diluent ($n = 4$ vials) for the purpose of visual comparison.

All vials were gently mixed and inspected at 5, 15, and 60 min for physical compatibility. Chemical compatibility of all 51 drug mixtures was determined at 60 min on the basis of the PTX concentration ratio of PTX plus test drug to PTX reference solution. Visual observation and chemical compatibility testing also occurred at 2 hours for 10 test drug solutions (22 combinations) at the highest concentration or if prolonged Y-site mixing in the clinical setting was plausible. The ratio of the mean peak areas was determined and the 95% confidence interval (CI) of the ratio was calculated using the confidence limits from a two-sided *t*-test ($\alpha = 0.05$; SigmaPlot v14.5; Systat Software, San Jose, CA). Further details of the method are provided in File S1.

No precipitation, color change, or turbidity was observed in any of the test mixtures, indicating PTX was physically compatible with the test drugs. This finding is consistent with previous reports and in the context of our chemical compatibility data, reflects the importance of determining both the physical and chemical compatibility of IV drug combinations, irrespective of the mode of administration.[3,4]

PTX concentration ratio data are shown in Table 1. Six of the drugs not previously tested (cloxacillin, fentanyl, fluconazole, furosemide, hydrocortisone, and ibuprofen lysine) were shown to be compatible with PTX, although our results indicated it may be preferable to dilute ibuprofen lysine in 5% w/v glucose, rather than 0.9% w/v sodium chloride injection. Eight drugs tested at higher concentrations or in different diluents than previous studies (aciclovir, alprostadil, epinephrine, midazolam, milrinone, norepinephrine, phenobarbitone, and piperacillin/tazobactam) were compatible with PTX.[3,4] Overall, the concentration ratios for all of these combinations were in the range of 99.0%–100.9%, and the 95% CI spanned 100%, indicating there was no difference in PTX concentration between the combination and PTX reference solution.

One notable issue of concern was the incompatibility of the two aminopenicillins with PTX injection (Table 1). Amoxicillin (100 mg/ml) was previously reported to be incompatible with PTX[3]; however, we considered it prudent to compare ampicillin (hitherto untested) and amoxicillin in the present study. We found the PTX concentration was approximately 3% and 4% lower when combined with ampicillin 100 mg/ml and amoxicillin 100 mg/ml, respectively, compared to control, after 1 h. Although further investigation of the cause(s) of this apparent incompatibility was beyond the scope of our study, we recommend avoiding co-administration of PTX with amoxicillin or ampicillin.

Dopamine hydrochloride (1.2 mg/ml in 0.9% w/v sodium chloride injection) was previously shown to be incompatible with PTX and our current findings were similar for dopamine 1.6 mg/ml in 0.9% w/v sodium chloride (Table 1).[3] However, when diluted in 5% w/v glucose injection, dopamine (1.6 mg/ml) was compatible with PTX. At the higher concentration of 7.2 mg/ml, there was no difference between the two diluents, although the 95% CI of the concentration ratios (99.2%) did not span 100% after two hours, thus indicating a statistically significant difference compared to controls. Nevertheless, based on these results, we conclude there is no clinically significant risk when dopamine hydrochloride is diluted in 5% w/v glucose injection and co-administered via Y-site with PTX injection.

Morphine hydrochloride and morphine sulfate 500 μg/ml in 5% w/v glucose, 10% w/v glucose, and 0.9% w/v sodium chloride were compatible with PTX injection, however, results were mixed for morphine hydrochloride and morphine sulfate 200 μg/ml (Table 1). Combined with previous data, we conclude it would be preferable to dilute morphine hydrochloride and morphine sulfate in 5% w/v glucose injection. Dilution in 10% w/v glucose or 0.9% w/v sodium chloride showed modest reductions in concentration ratios (1%–2% compared to control) and most likely presents no clinically significant risk when morphine is co-administered via Y-site with PTX injection for up to 1 h.[3,4]

A confounding result in our current study was the unequivocal compatibility of undiluted calcium gluconate injection (100 mg/ml) with PTX injection (Table 1). Previously, we found that PTX was compatible with diluted calcium gluconate injection (50 mg/ml, a concentration used in the neonatal setting); however, the PTX concentration was approximately 5% lower when mixed with calcium gluconate 100 mg/ml for 1 h.[4] In the present study, we tested the combination on two separate occasions ($n = 10$) and extended the mixture time to two hours, with consistent results evident from the tight 95% CI of the concentration ratio. Whilst we are unable to elucidate the reasons for these conflicting data, we conclude it is reasonable to indicate that PTX is compatible with diluted and undiluted calcium gluconate injection.

Potential limitations of the present study were the modest range of physical compatibility tests we were able to perform and conducting HPLC analysis only for the primary drug (PTX). Turbidity and pH measurements are commonly conducted in physical compatibility studies and have been reported in physicochemical compatibility

TABLE 1 Ratio of pentoxifylline (PTX) concentration when combined with the test drug, compared to PTX standard solution (2.5 mg/ml)

Drug	Test concentration	Diluent	PTX ratio (%)	95% CI of the ratio
Acyclovir (mg/ml)	5	D5W	99.5	98.9–100.1
Alprostadil (μg/ml)†	10	NS	99.9	99.4–100.5
Alprostadil (μg/ml)†	20	NS	99.9	99.5–100.3
Amoxicillin (mg/ml)	100	WfI	**95.8**	95.0–96.6
Ampicillin (mg/ml)	100	WfI	**96.9**	95.6–98.2
Calcium gluconate (mg/ml)†‡	100	U	99.7	99.3–100.0
Cloxacillin (mg/ml)	100	WfI	100.1	99.1–101.1
Dopamine (mg/ml)	1.6	NS	**97.6**	95.9–99.2
Dopamine (mg/ml)	1.6	D5W	99.3	98.7–100.7
Dopamine (mg/ml)†	7.2	NS	**99.2**	98.7–99.7
Dopamine (mg/ml)†	7	D5W	**99.2**	99.0–99.4
Epinephrine (μg/ml)†	25	D5W	99.8	99.1–100.4
Epinephrine (μg/ml)†	50	D5W	99.5	98.8–100.1
Fentanyl (μg/ml)	5	D5W	100.0	98.7–101.3
Fentanyl (μg/ml)	25	D5W	99.2	97.4–101.0
Fentanyl (μg/ml)	50	U	100.1	99.6–100.6
Fluconazole (mg/ml)‡	2	NS	99.4	98.8–100.1
Furosemide (mg/ml)†	1	NS	100.0	99.7–100.3
Furosemide (mg/ml)†	1	D5W	99.6	99.2–100.0
Hydrocortisone (mg/ml)	2	NS	99.2	97.9–100.5
Ibuprofen lysine (mg/ml)	4	NS	**99.3**	98.9–99.8
Ibuprofen lysine (mg/ml)	4	D5W	100.4	99.1–101.8
Midazolam (μg/ml)	120	D5W	99.4	98.6–100.2
Midazolam (μg/ml)	120	D10	99.1	98.0–100.2
Midazolam (μg/ml)	500	D5W	99.8	99.5–100.1
Midazolam (μg/ml)‡	500	D10	**99.7**	99.5–99.9
Midazolam (mg/ml)†	1	U	99.7	99.4–100.1
Midazolam (mg/ml)†§	1	NS	99.0	97.5–100.5
Midazolam (mg/ml)†§	1	D5W	99.8	99.3–100.4
Milrinone (μg/ml)	200	NS	99.3	98.5–100.1
Milrinone (μg/ml)	200	D5W	100.0	99.0–101.0
Milrinone (μg/ml)†	400	NS	100.2	99.2–101.3
Milrinone (μg/ml)†‡	400	D5W	100.1	99.7–100.5
Morphine hydrochloride (μg/ml)	200	NS	**99.2**	98.8–99.7
Morphine hydrochloride (μg/ml)	200	D10	**97.9**	97.2–98.5
Morphine hydrochloride (μg/ml)†	500	NS	99.9	99.2–100.6
Morphine hydrochloride (μg/ml)†	500	D5W	99.4	98.8–100.0
Morphine hydrochloride (μg/ml)†	500	D10	100.3	99.8–100.7
Morphine sulfate (μg/ml)	200	NS	**98.3**	97.1–99.6
Morphine sulfate (μg/ml)‡	200	D10	100.4	99.8–101.0
Morphine sulfate (μg/ml)†	500	NS	100.3	100.0–100.5
Morphine sulfate (μg/ml)†	500	D5W	100.2	99.8–100.6

(Continues)

TABLE 1 (Continued)

Drug	Test concentration	Diluent	PTX ratio (%)	95% CI of the ratio
Morphine sulfate (μg/ml)†	500	D10	100.9	99.7–102.1
Norepinephrine (μg/ml)‡	12	D5W	99.7	99.1–100.2
Norepinephrine (μg/ml)†	64	D5W	100.1	99.5–100.6
Norepinephrine (μg/ml)	12	NS	99.5	98.3–100.7
Norepinephrine (μg/ml)†	64	NS	99.3	98.7–100.0
Phenobarbitone (mg/ml)	20	NS	99.8	99.2–100.4
Phenobarbitone (mg/ml)	20	D5W	99.9	99.1–100.7
Piperacillin/tazobactam (mg/ml)	80	D5W	100.2	99.9–100.5
Piperacillin/tazobactam (mg/ml)	200	WfI	100.5	99.6–101.5

Results in bold indicate a statistically significant difference, whereby the 95% CI of the ratio did not span 100% (*t*-test).
Abbreviations: CI, confidence interval; D5W, 5% w/v glucose injection; D10, 10% w/v glucose injection; NS, 0.9% w/v sodium chloride injection; PTX, pentoxifylline; U, undiluted; WfI, water for injection.
†Duration of mixture contact time = 2 h (contact time for all other combinations = 1 h).
‡$n \geq 8$ (all other combinations $n = 4$).
§Midazolam 5 mg/ml diluted with NS/D5W; all other combinations were dilutions of midazolam 1 mg/ml injection.
¶Pentoxifylline injection was diluted in 0.9% w/v sodium chloride injection to a final concentration of 5 mg/ml to combine with the test drug solution. Pentoxifylline standard solution (control) for HPLC assay was further diluted to 2.5 mg/ml.

investigations.[7–11] However, there are resource implications for these tests, not least the requirement for large sample volumes (typically > 10 ml), which is problematic for expensive drugs. Furthermore, the intrinsic value of some physical compatibility tests is unclear and interpretation or specification limits may be inconsistent[12]; for example, in regard to pH unit shift.[9–11] In regard to quantifying only the PTX concentration, we have assumed that physicochemical incompatibility would be the result of interaction between the two drugs and should be detected by the HPLC assay of the primary drug. Although there may be value in quantifying the secondary drug if chemical incompatibility is detected or suspected, a significant impediment to quantifying all of the secondary drugs would be developing and validating HPLC assays for the full range of drugs. A further limitation of the present study was the use of 1:1 mixing ratios, which is a well-established and commonly reported method for simulated Y-site compatibility studies.[7,8,10,13] By comparison, there are reports of both 1:1 and 1:4, or 1:1 and 1:10, mixing ratios of IV drugs, and compatibility studies of parenteral nutrition fluids with IV drugs where 1:1 and a range of mixing ratios (1:2–1:100) have been investigated to simulate extremes of high/low infusion rates of the individual components.[14–18] Although our study was designed to simulate the neonatal setting, where extremes in drug concentrations can be greater than the range of IV infusion rates, there may be clinical scenarios where both the conventional 1:1 mixing ratio of a range of IV drug concentrations and a modest range of mixing ratios is required in Y-site compatibility studies. Notwithstanding the limitations outlined above, by combining conventional visual observation with HPLC analysis for evaluation of chemical compatibility, we consider our study design provides acceptable evidence of physicochemical compatibility in the context of simulated Y-site investigations, and our results will help to address the reported paucity of IV compatibility data.[12,19,20]

In conclusion, our physicochemical compatibility testing of pentoxifylline with 20 parenteral medications used in neonatal care settings showed that ampicillin and amoxicillin should be classified as incompatible. All other drugs may be considered compatible, although glucose 5% w/v was the preferable diluent for dopamine and morphine. Combined with previous studies, the physicochemical compatibility of pentoxifylline has been tested against more than 40 drugs in over 100 combinations of various concentrations and diluents.[3,4]

ETHICAL APPROVAL

Not required.

ACKNOWLEDGMENTS

The authors gratefully acknowledge the assistance of Ms Claire Kendrick, Ms Anna Dao, and Mr Jack Lee (King Edward Memorial Hospital for Women). This work was supported by the Women & Infants Research Foundation and the Department of Pharmacy at King Edward Memorial Hospital for Women.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

REFERENCES

1. Pammi M, Haque KN. Pentoxifylline for treatment of sepsis and necrotizing enterocolitis in neonates. *Cochrane Database Syst Rev.* 2015:CD004205. DOI: 10.1002/14651858.CD004205.pub3
2. Kurul S, Taal HR, Flint RB, Mazela J, Reiss I, Allegaert K, et al. Protocol: pentoxifylline optimal dose finding trial in preterm neonates with suspected late onset sepsis (PTX-trial). *BMC Pediatr.* 2021;21:517. DOI: 10.1186/s12887-021-02975-8
3. Senarathna S, Strunk T, Petrovski M, Batty KT. Physical compatibility of pentoxifylline and intravenous medications. *Arch Dis Child.* 2019;104:292-295. DOI: 10.1136/archdischild-2018-315376
4. Campbell AL, Petrovski M, Senarathna SG, Mukadam N, Strunk T, Batty KT. Compatibility of pentoxifylline and parenteral medications. *Arch Dis Child.* 2020;105:395-397. DOI: 10.1136/archdischild-2019-317912
5. Lauterbach R, Strunk T, Patole S, Hurkała J, Pawlik D. Compatibility of intravenous pentoxifylline with other medications infused concurrently in preterm infants with late-onset sepsis. *Acta Paediatr.* 2018;107:1288-1289. DOI: 10.1111/apa.14312
6. Senarathna S, Strunk T, Petrovski M, Batty KT. Stability of pentoxifylline injection: application to neonatal/pediatric care setting. *J Pharm Sci.* 2021;110:3862-3865. DOI: 10.1016/j.xphs.2021.08.035
7. Trissel LA, Ogundele AB. Compatibility of anidulafungin with other drugs during simulated Y-site administration. *Am J Health Syst Pharm.* 2005;62:834-837. DOI: 10.1093/ajhp/62.8.834
8. Veltri MA, Conner KG. Physical compatibility of milrinone lactate injection with intravenous drugs commonly used in the pediatric intensive care unit. *Am J Health Syst Pharm.* 2002;59:452-454. DOI: 10.1093/ajhp/59.5.452
9. De Basagoiti A, Katsumiti A, Abascal S, Bustinza A, López-Giménez LR, Pascual P, et al. Physical compatibility of alprostadil with selected drugs commonly used in the neonatal intensive care units. *Eur J Pediatr.* 2021;180:1169-1176. DOI: 10.1007/s00431-020-03854-7
10. AlSalman F, Howlett M, Breatnach C, Kelly H, O'Brien F. Supporting the use of sildenafil infusions in paediatric and neonatal intensive care - A compatibility study. *Eur J Pharm Biopharm.* 2020;151:153-161. DOI: 10.1016/j.ejpb.2020.04.008
11. Koller AK, Krebs S, Dörje F. Medication safety in intravenous therapy: a compatibility study of clonidine with drugs frequently used in intensive care. *Pharmaceutics.* 2020;13. DOI: 10.3390/pharmaceutics13010021
12. Kanji S, Lam J, Johanson C, Singh A, Goddard R, Fairbairn J, et al. Systematic review of physical and chemical compatibility of commonly used medications administered by continuous infusion in intensive care units. *Crit Care Med.* 2010;38:1890-1898. DOI: 10.1097/CCM.0b013e3181e8adcc
13. Allen LV, Jr, Levinson RS, Phisutsinthop D. Compatibility of various admixtures with secondary additives at Y-injection sites of intravenous administration sets. *Am J Hosp Pharm.* 1977;34:939-943.
14. Humbert-Delaloye V, Berger-Gryllaki M, Voirol P, Testa B, Pannatier A. Screening for physicochemical incompatibilities of intravenous drugs in intensive care units: the case of monobasic potassium phosphate and furosemide. *Eur J Hosp Pharm.* 2015;22:56-58. DOI: 10.1136/ejhpharm-2013-000431
15. Voirol P, Berger-Gryllaki M, Pannatier A, Eggimann P, Sadeghipour F. Visual compatibility of insulin aspart with intravenous drugs frequently used in ICU. *Eur J Hosp Pharm.* 2015;22:123-124. DOI: 10.1136/ejhpharm-2014-000478
16. Knudsen L, Eisend S, Haake N, Kunze T. Physicochemical compatibility of commonly used analgesics and sedatives in the intensive care medicine. *Eur J Hosp Pharm.* 2014;21:161-166. DOI: 10.1136/ejhpharm-2014-000444
17. Tomczak S, Stawny M, Jelińska A. Co-administration of drugs and parenteral nutrition: in vitro compatibility studies of loop diuretics for safer clinical practice. *Pharmaceutics.* 2020;12. DOI: 10.3390/pharmaceutics12111092
18. Staven V, Iqbal H, Wang S, Grønlie I, Tho I. Physical compatibility of total parenteral nutrition and drugs in Y-site administration to children from neonates to adolescents. *J Pharm Pharmacol.* 2017;69:448-462. DOI: 10.1111/jphp.12647
19. Kalikstad B, Skjerdal A, Hansen TW. Compatibility of drug infusions in the NICU. *Arch Dis Child.* 2010;95:745-748. DOI: 10.1136/adc.2009.174268
20. Neininger MP, Buchholz P, Kiess W, Siekmeyer M, Bertsche A, Bertsche T. Incompatibilities in paediatric intensive care - pitfalls in drug information. *Pharmazie.* 2018;73:605-608. DOI: 10.1691/ph.2018.8585

SUPPORTING INFORMATION

Additional Supporting Information may be found online in the supporting information tab for this article.

How to cite this article: Senarathna SMDKG, Strunk T, Petrovski M, Woodland S, Batty KT. Physicochemical compatibility of pentoxifylline injection with high-concentration parenteral medications. *Pediatr Investig*. 2023;7:263–267. https://doi.org/10.1002/ped4.12393