A Systematic Evidence Review of Trends, Rates, and Burden of Harm Associated With Intravenous Drug Preparation Errors in Healthcare Settings

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Introduction and Objectives

- An intravenous (IV) admixture preparation error (IAPE) — a deviation in the compounding process from specifications (Flynn 1997) — can be considered a preventable event that could lead to inappropriate medication use or patient harm, including death, while a medication is under the control of the healthcare professional, patient, or consumer (nccmerp.org 2015).
- Even simple IV preparation processes can have multiple hidden risk points, such as incorrectly reading and interpreting the physician orders, calculating the volume of solution to withdraw, and choosing the appropriate needle and syringe.
- IV medications such as parenteral nutrition or other critical dose drugs can have multiple ingredients that require mixing and dilution, thus entailing a greater number of potential risk points (Flynn 1997, Cohen 2012).
- IAPE is a safety concern (particularly for drugs with a low therapeutic index, or treatments where errors in preparation might lead to harm or death) but its frequency, risk factors, and associated burden of harm are not well understood.
- Often error rates for oral and IV medications are not reported separately in published studies, preventing the full impact of IV preparation errors from being described (Ghaleb 2010, Benoit 2012).
- Prior research focusing on prescribing or administration has often failed to describe or distinguish between preparation/process errors and errors linked with prescribing or administration (Cousins 2012, Tromp 2009, Abbasinazari 2012, Chua 2009, Prot 2005).
- We conducted a systematic review to determine the occurrence and associated burden of harm from IAPE in healthcare settings.

Methods

- Searches for relevant literature reporting on IAPEs were made across 3 electronic databases, for the period from January 1, 2005–February 6, 2014.
  - Ovid MEDLINE
  - EMBASE
  - International Pharmaceutical Abstracts
- Key search terms are shown in **Table 1**.
- The searches followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) process (Moher 2009):
  - Publications reporting on a randomized controlled trial, prospective cohort study, or observational quality audit were selected for inclusion, as were systematic reviews reporting on these study types.
- For the purposes of this study, IAPE was defined as an error at any step in the preparation process where the drug container was physically handled or manipulated and included reports relating to: wrong drug, wrong dose, wrong concentration, wrong diluent, wrong container, wrong route, contamination, and mislabelling:
  - Errors in prescribing, transcription, administration, and monitoring were not included.
- Data from relevant articles were extracted for further analysis, including: year of publication, country of origin, study period, definition of error, IV preparation location, method of error detection, and error rates.
- The methodological rigor of each study was critically appraised and a composite score was derived based on assessment of the reference contents using the Hawker method (Hawker 2002): good (score 1), fair (score 2), poor (score 3), or very poor (score 4).
- This study was registered with the PROSPERO international database of systematic reviews (CRD42014010418).

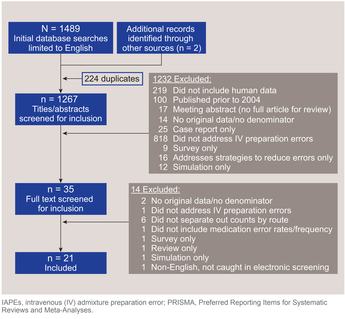
Table 1. Key search terms used in the search for reports of IAPEs across the 3 databases

Errors	Route of administration	Compounding	Article type
((medication* or drug* or pharmaceutic* or medical or infus*) adj5 error*).mp. OR (adverse adj5 (event* or reaction*)).mp. OR ((medication* or drug* or pharmaceutic*) adj5 (contamina* or safety or incompatib*)).mp. OR (overdos* or over dose*).mp. OR Near miss.mp. OR (incident or incidents or accident*).mp. OR (steril* or unsteril* or septic or sepsis or aseptic or asepsis).mp. OR ((healthcare or health care or hospital or bloodstream or blood stream or cross) adj3 infection*).mp. OR patient safety.mp. OR ((drug or medication* or pharmaceutic*) adj3 (stor* or stability or stable or instability or unstable or expir*)).mp. OR ((wrong* or incorrect* or inappropriate* or error* or inaccura* or deviation*) adj5 (dose* or dosage* or drug* or medication* or pharmaceutic* or concentration* or diluent* or dilution* or strength* or calculat* or volume or label* or product* or quantit*)).mp. OR (missing label* or "no label*" or "not label*").mp. OR Particulate*.mp.	parenteral OR intravenous OR catheter* OR infus* OR iv OR intraocular OR intravitreal OR intramuscular OR subcutaneous OR epidural OR intraosseous OR intraperitoneal OR (ei or im or io or os or ip or iv or pa).fs. use emefd	Compounding OR Compounded OR Reconstitut* OR Admix* OR (prepar* adj5 (pharmacy or pharmacies or pharmacist or pharmaceutic* or drug* or medication* or ward or wards or nurs* or chemotherapy* or antineoplastic* or cytostatic* or nutrition* or mixture* or solution* or compound or compounds)).mp.	(clinical trial or randomized controlled trial or controlled clinical trial or multicenter study or phase 1 clinical trial or phase 2 clinical trial or phase 3 clinical trial or phase 4 clinical trial) (Embase limits) OR (evidence based medicine or consensus development or meta analysis or outcomes research or "systematic review") (Embase limits) OR (clinical trial, all or clinical trial, phase i or clinical trial, phase ii or clinical trial, phase iii or clinical trial, phase iv or clinical trial or comparative study or controlled clinical trial or meta analysis or multicenter study or observational study or randomized controlled trial or systematic reviews) (Medline limits) OR (chart review* or observational or systematic or prospective or cohort or retrospective or controlled study or controlled studies or controlled trial* or cross sectional or evidence based or direct observation* or audit or audits or randomized or blind or blinded or case series).mp. (free text terms)

Results

- Of 1267 studies screened, 21 met the inclusion criteria (**Figure 1**) (**Table 2**).

Figure 1. PRISMA flow diagram for the literature search of IAPEs showing article selection and exclusion



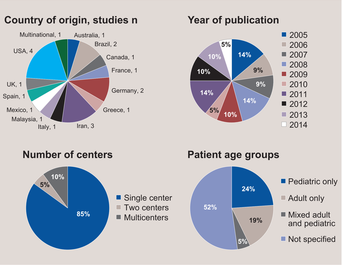
IAPEs, intravenous (IV) admixture preparation error; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

Table 2. The 21 studies included in the systematic review

1. Abbasinazari M, et al. Evaluating the frequency of errors in preparation and administration of intravenous medications in orthopedic, general surgery and gastroenterology wards of a teaching hospital in Tehran. *Iran J Pharm Res*. 2013;12(1):229-234.
2. Anselmi ML, et al. Errors in the administration of intravenous medication in Brazilian hospitals. *J Clin Nurs*. 2007;16(10):1839-1847.
3. Bertsche, et al. Prioritising the prevention of medication handling errors. *Pharm World Sci*. 2008;30(6):907-915.
4. Castagne V, et al. Cytotoxics compounded sterile preparation control by HPLC during a 16-month assessment in a French university hospital: importance of the mixing bags step. *J Oncol Pharm Pract*. 2011;17(3):191-196.
5. Cousins DH, et al. Medication errors in intravenous drug preparation and administration: a multicentre audit in the UK, Germany and France. *Qual Saf Health Care*. 2005;14(3):190-195.
6. Crill CM, et al. Evaluation of microbial contamination associated with different preparation methods for neonatal intravenous fat emulsion infusion. *Am J Health Syst Pharm*. 2010;67(11):914-918.
7. Dehmel C, et al. Do centrally pre-prepared solutions achieve more reliable drug concentrations than solutions prepared on the ward? *Intensive Care Med*. 2011;37(8):1311-1316.
8. Fahimi F, et al. An observational study of errors related to the preparation and administration of medications given by infusion devices in a teaching hospital. *Iran J Pharm Res*. 2007;6(4):295-299.
9. Fahimi F, et al. Errors in preparation and administration of intravenous medications in the intensive care unit of a teaching hospital: An observational study. *Aust Crit Care*. 2008;21(2):110-116.
10. Hoefel HHK, et al. Errors committed by nursing technicians and assistants in administering antibiotics. *Am J Infect Control*. 2006;34(7):437-442.
11. Macias AE, et al. Nosocomial bacteremia in neonates related to poor standards of care. *Pediatr Infect Dis J*. 2005;24(8):713-716.
12. Mackay MW, et al. Improving Pediatric Outcomes through Intravenous and Oral Medication Standardization. *J Pediatr Pharmacol Ther*. 2009;14(4):226-235.
13. Masini C, et al. Automated preparation of chemotherapy: quality improvement and economic sustainability. *Am J Health Syst Pharm*. 2014;71(7):579-585.
14. Ong WM, et al. Medication errors in intravenous drug preparation and administration. *Med J Malaysia*. 2013;68(1):52-57.
15. Parshuram CS, et al. Occurrence and impact of unanticipated variation in intravenous methotrexate dosing. *Ann Pharmacother*. 2006;40(5):805-811.
16. Rodriguez-Gonzalez CG, et al. Prevalence of medication administration errors in two medical units with automated prescription and dispensing. *J Am Med Inform Assoc*. 2012;19(1):72-78.
17. Sacks GS, et al. Frequency and severity of harm of medication errors related to the parenteral nutrition process in a large university teaching hospital. *Pharmacotherapy*. 2009;29(8):966-974.
18. Seger AC, et al. Impact of robotic antineoplastic preparation on safety, workflow, and costs. *J Oncol Pract*. 2012;8(6):344-349, 1 p following 349.
19. Skouroliakou M, et al. Computer assisted total parenteral nutrition for pre-term and sick term neonates. *Pharm World Sci*. 2005;27(4):305-310.
20. Westbrook JI, et al. Errors in the administration of intravenous medications in hospital and the role of correct procedures and nurse experience. *BMJ Qual Saf*. 2011;20(12):1027-1034.
21. Wheeler DW, et al. Variability in the concentrations of intravenous drug infusions prepared in a critical care unit. *Intensive Care Med*. 2008;34(8):1441-1447.

- **Figure 2** shows the study characteristics:
  - 8 Of the 21 studies (38%) were from Europe[3,4,5,7,13,16,19,21]
  - The majority of references reported on single-center studies (85%).[1,3–4,6–19, 21]

Figure 2. Characteristics of the 21 studies reviewed



- 4 Studies (19%) were in critical care settings and 17 (81%) were in general wards.[7,8,9,21]
- Of studies reporting IV preparation site, 6 reported use of centralized locations with a biological safety cabinet,[4,6,12,13,17,18] 11 reported preparation on the nursing ward,[1,2,3,5,8,9,11,14,16,20,21] and 1 had an even split[7] between these 2 locations:
  - 3 References compared manual versus automated preparation in terms of wrong concentration. In each case, manual preparation had higher error rates (0.3% to 22%) compared with automated preparation (0% to 5%).[7,13,18]
- In 43% of studies, the reported IAPE was detected by direct observation;[1,2,3,8,9,10,14,18,20] in 19% of cases by incident reporting and cross-checking;[12,17,19,21] and in 24% of cases by analysis of final concentrations.[4,7,13,15,18] Error data were collected by pharmacy staff in 38% of studies,[3,4,7,8,9,13,18,21] interdisciplinary team of professionals in 14%,[17,19,20] nurses or nursing students in 10%,[2,10] physicians in 5%[11] and not specified in 33% of studies.[1,5,6,12,14,15,16]
- The types of error and the reported rates for each error varied substantially across researchers (**Table 3**):
  - An incorrect diluent type was reported in 6 references, with wrong diluent type ranging from 0.3% to 49% per dose[1,8,9,14,16,20]
  - An incorrect diluent volume was reported in 6 references, with the wrong dilution volume occurring in between 1% to 54.5% instances per dose[1,5,10,14,16,20]
  - The error of incorrect drug selection was less common, reported in only 4 references, and was 0% in 1 reference, with the highest reported rate of 4.6% per dose[5,8,14,20]
  - 4 References specified "incorrect drug" as a separate error type category with error rates ranging from 0% to 4.6% per dose[5,8,9,10]
  - Labelling errors were reported in 4 references, finding this mistake in 9.3% to 99% of IV preparations[5,8,14,21]
  - Challenges with aseptic technique included failures to disinfect the vial and wrong hand hygiene:
    - 6 References reported inappropriate sterile technique over a range of 3.3% to 100%:[1,3,5,6,11,14]
      - 3 References reported that there was failure to disinfect the vial, with error rates per dose of 4% to 98.7%[1,5,14]
      - Bacterial contamination was reported in 2 references at a rate per dose of 3.3% to 17.7%[6,11]
      - Wrong hand hygiene, of at least 9%, was reported in 4 studies[1,3,5,14]
  - An incorrect final drug concentration was reported in 5 references with error rates per IV dose ranging from 0% to 31%:[4,7,13,15,18]
    - 3 References identified that such error rates ranged from 0% to 5% for automated preparation compared with 0.3% to 22% for manual dose preparation.[7,13,18]
- Higher IAPE rates were reported for ward-based (range: 7.2% to 54.5%) versus centralized (range: <1% to 8.8%) IV preparation.[2,4,7–8,12–14,17,18]
- The only reports of zero IAPE involved computerized dose calculations or the use of automated equipment.[13,18]

Table 3. Summary of the types of IAPEs described, the range of rates of each IAPE per IV drug dose and the number of references supporting observation of such errors

Type of error	Rates per dose	Site of preparation	References
Wrong diluent	0.3% to 49%	All studies ward preparation	1, 5, 9, 14, 16, 20
Wrong dilution	1% to 54.5%	All studies ward preparation	1, 5, 10, 14, 16, 20
Wrong dose	1% to 79%	All studies ward preparation	5, 8–10
Wrong drug	0% to 4.6%	All studies ward preparation	5, 8, 14, 20
Wrong preparation	0.016% to 8.5%	All studies ward preparation	2, 12, 17
Inadequate sterile technique	4% to ~100%*	5 Studies ward prepared; 1 study central pharmacy preparation	1, 3, 5, 6, 11, 14
Failure to disinfect vial	4% to 98.7%	All studies ward preparation	1, 5, 14
Bacterial contamination	3.3% to 17.7%	1 Study central pharmacy prepared; 1 study ward preparation	6, 11
Wrong concentration	0% to 31%	3 Studies compared manual vs automated preparation; 1 study central preparation; 1 study preparation site not specified	4, 7, 13, 15, 18
Wrong label	9.3% to 99%	All studies reported ward preparation	5, 8, 14, 21

*Depending on the technique.

Discussion

- Our systematic review found that IAPEs cause potentially harmful errors, identified that IAPEs are ubiquitous across countries and hospital locations, and that the types of errors are diverse.
- Although the exact rate of IAPEs is unknown, such errors are potentially catastrophic.
- The overall scarcity of studies reporting error rates made it difficult to identify trends.
- Error severity and associated burden of harm were not adequately or sufficiently well documented in the studies to allow an evaluation of the impact on patient care or consequences for healthcare facilities.
- Variability was noted in the type of errors that were reported.

Conclusions

- This systematic review identified few studies reporting data on the frequency or burden of harm of an IAPE as a separate and distinct process category suitable for examination.
- The available evidence suggests that fewer errors occur when drugs are prepared in the pharmacy than on the ward, and when processes are standardized and automated.
- Given the potential burden of harm of IAPEs, there is a need to establish preventative strategies, increase and improve staff training, and build resilience founded on standardized approaches to drug preparation.
- There is a need for further study, and better and more consistent reporting of IAPEs, in order to establish the risk factors for, and burden of harm associated with, these errors.

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