Healthcare Workers' Exposure to Antineoplastic (Hazardous) Drugs

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Agenda

- Introduction
- Overview of literature
- Challenges in exposure assessment
- Challenges in controlling exposure
- Policy considerations
- Future studies
- Q + A

Declaration

I do not have any conflicts of interests related to today's presentation.

Introduction

Antineoplastic drugs

- *Definition:* destroying/inhibiting/preventing the growth of neoplasms
  - Also known as hazardous or cytotoxic drugs
  - Primarily used for the treatment of cancer

- According to NIOSH, there are 100+ drugs used in healthcare that are classified "antineoplastic"(http://www.cdc.gov/niosh/docs/2014-138/pdfs/2014-138_v3.pdf)

- Inherently toxic agents; however, to patients, benefits > risks

Exposure

- Main route of occupational exposure is **dermal or skin contact** (Fransman et al., 2004; Fransman et al., 2005)

- *Direct contact*: touching drug or drug vials/IV bags
  - During preparation and administration

- *Indirect contact*: touching drug-contaminated surfaces
  - During receiving, transport, housekeeping

Background

- Occupational exposure concerns initially surfaced in the 1970's
  - Non-selective mode of action – normal cells may also be affected

- Variety of reported health effects from exposed workers

Acute Health Effects

- Review by Connor and McDiarmid (2006)
- Primarily reported in nurses:
  - Hair loss
  - Headaches
  - Acute irritation
  - Hypersensitivity

Chronic Health Effects

- **Reproductive effects**
  - Dranitsaris et al. (2005) – spontaneous abortions *(OR=1.46; 95% CI: 1.11-1.92)*
  - Fransman et al. (2007) – longer to conceive *(adjusted OR=0.8; 95% CI: 0.6–0.9)*
  - Valanis et al. (1999) - exposed workers had a significantly increased risk of spontaneous abortion *(OR=1.5; 95% CI: 1.2 to 1.8)*
  - Valanis et al. (1997) – exposed workers had significantly elevated odds ratio for self-reported infertility *(OR=1.5; CI = 1.1 to 2.0)*

Cancer Risk

- **Breast cancer**
  - Ratner et al. (2010) RR = 1.83; 95% CI = 1.03 - 3.23

- **Cancer risk assessment**
  - Sessink et al. (1994) 1.4 to 10 per million
  - Hon (2012) 1.89 per million

Background

- According to CAREX, there are 75,000 Canadians at risk of exposure
  - Likely an underestimate
- Number of new cancer cases expected to steadily increase as population ages => increased use of antineoplastic drugs
- Also, these drugs are being used outside of acute care settings

Is a concern and will continue to be of concern in the foreseeable future

Exposure limits?

- No exposure limits listed in Ontario or any other Canadian province

- No ACGIH threshold limit values (TLVs®)

- No OSHA permissible exposure limits (PELs)

- Suggested, but not enforceable, exposure thresholds found in the literature

The ALARA Principle applies
(As Low As Reasonably Achievable)

Overview of Literature

Assessing exposure

- No NIOSH or OSHA method available

- Studies have employed:
  - Surface contamination
  - Dermal contamination
  - Urinary contamination
  - Genotoxicity assays

- Good summary by Turci et al.(2003) and Nussbaumer et al. (2011)

Surface contamination

- Collect using a **wipe sample**
  - Analyze via HPLC-MS/MS for one or more drugs

- Use a pre-moistened filter or wipe e.g. Kimwipe

- 10 cm x 10 cm sampling template used where possible

- For other surfaces, area most likely contacted is sampled
  - Dimensions taken and surface area calculated

Surface wipe sampling

- While wearing glove and applying moderate pressure, wipe the surface with a top to bottom motion (vertical) ensuring that the entire template area is wiped *(see figure 1)*

- Then fold the wipe so that the wiped area is on the "inside" of the fold, attempting to not touch the wiped/contaminated portion of the wipe with your glove

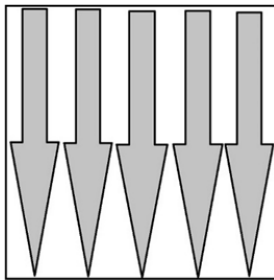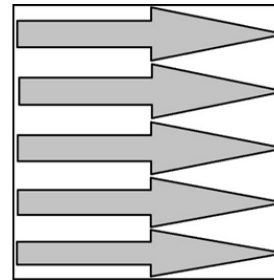- Repeat the wipe sampling in a left to right motion *(horizontal, see figure 2)*

Fig 1 Top down

Fig 2 Left to right

Surface Contamination

- Concentration levels generally in units of ng/cm^2

- Numerous surface contamination studies have been performed worldwide
  - "Every published surface contamination study has identified at least one drug present by wipe sample analysis" [Connor et al. (2010)]

- 1 ng/cm^2 has been suggested as a threshold of exposure (USP800)
  - For cyclophosphamide (CP) only

Surface Contamination

- Hon et al. (2013) found contamination throughout the hospital medication circuit
  - Not surprisingly, pharmacy is the most contaminated department

- Also contamination found on floors – can lead to spread

- Positive results found in patient areas – now a possible public health issue

26
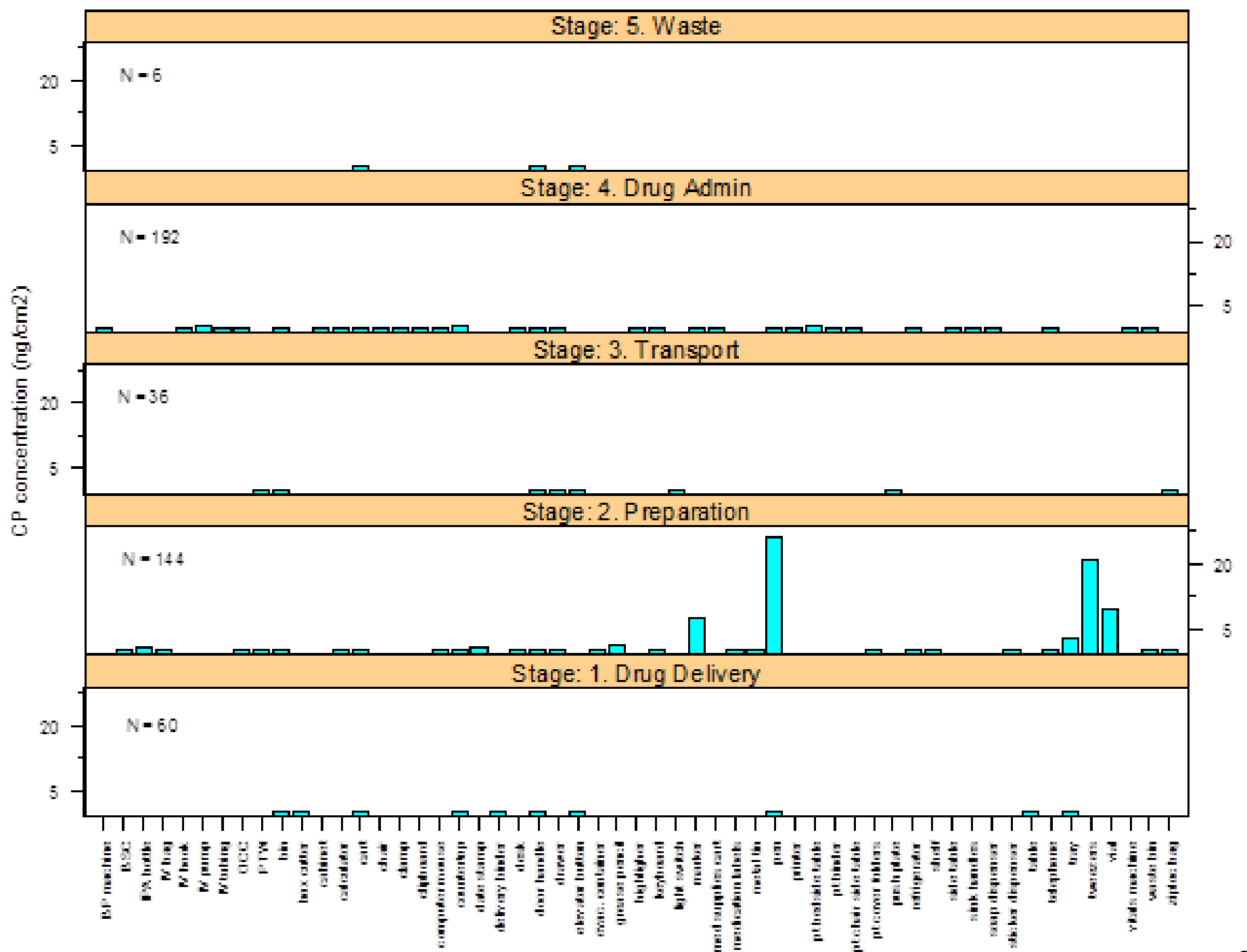
Surface Contamination

- Limitations:
  - Most are capable of detecting only one or two drugs – referred to as "markers"
  - LODs vary depending on the method used
  - Collection efficiency is not well established for different surfaces
  - Only a surrogate of actual exposure

Dermal Contamination

- Determine dermal contamination by hand wash, cotton pads, destructive testing of gloves or wipe sampling of hands

- Frasman et al. (2005) used all above methods; found pharmacy technicians, oncology nurses and cleaning personnel had dermal exposure during performance of their daily duties

Dermal Contamination

- Most papers which collected dermal samples found positive contamination

- Some studies have demonstrated that permeation of antineoplastic drug through gloves does occur (Connor, 1999; Wallemacq et al., 2006)

- 4 ng/cm^2 has been suggested as a dermal occupational exposure limit (Bos et al., 1998)
  - For cyclophosphamide (CP) only

Dermal contamination results – Hon (2012)

Maximum dermal contamination levels by job title

Job Title	N	Max concentration (ng/wipe)
Pharmacist	40	1.49
Pharmacy receiver	12	1.27
Pharmacy technician	45	9.29
Porter	11	4.55
Nurse (includes LPN)	64	22.8
Transport (shipper/receiver, biopacker, transporter)	8	0.556
Unit clerk	24	2.03
Other workers in admin unit (volunteer, oncologist, ward aide, dietician)	21	22.3

LOD = 0.36 ng/wipe

Dermal Contamination

- Limitations:

    - Cross-sectional – not sure when exposure occurred

    - No standardized method and LODs vary depending on the method used

    - Collection efficiency is not well established

    - Does not factor the amount absorbed

Urinary Contamination

- Collect spot samples or 24-hr samples
  - Spot samples are collected at a specified time during work shift – varied between researchers
  - 24-hr samples can be messy

- $T_{1/2}$ of drugs is a critical factor
  - CP's is estimated to be 6 – 9 hrs; can capture several half-lives over a 24 hr period

- Assesses all possible routes of exposure

- A no-significant risk level (NSRL) of 1,000 ng/day has been suggested for CP (Sargent et al. 2002)

Urinary Contamination

- Burgaz et al. (1999) reported that up to 80% of their samples exceeded the LOD

- Sottani et al. (2010) reported a reduction in the number of positive urine samples over time

- Hon et al. (2015) found every job category in the hospital medication system had detectable levels of CP
  - Includes those who are <u>not</u> tasked with drug preparation or administration

Histogram of urinary drug contamination levels – Hon (2012)
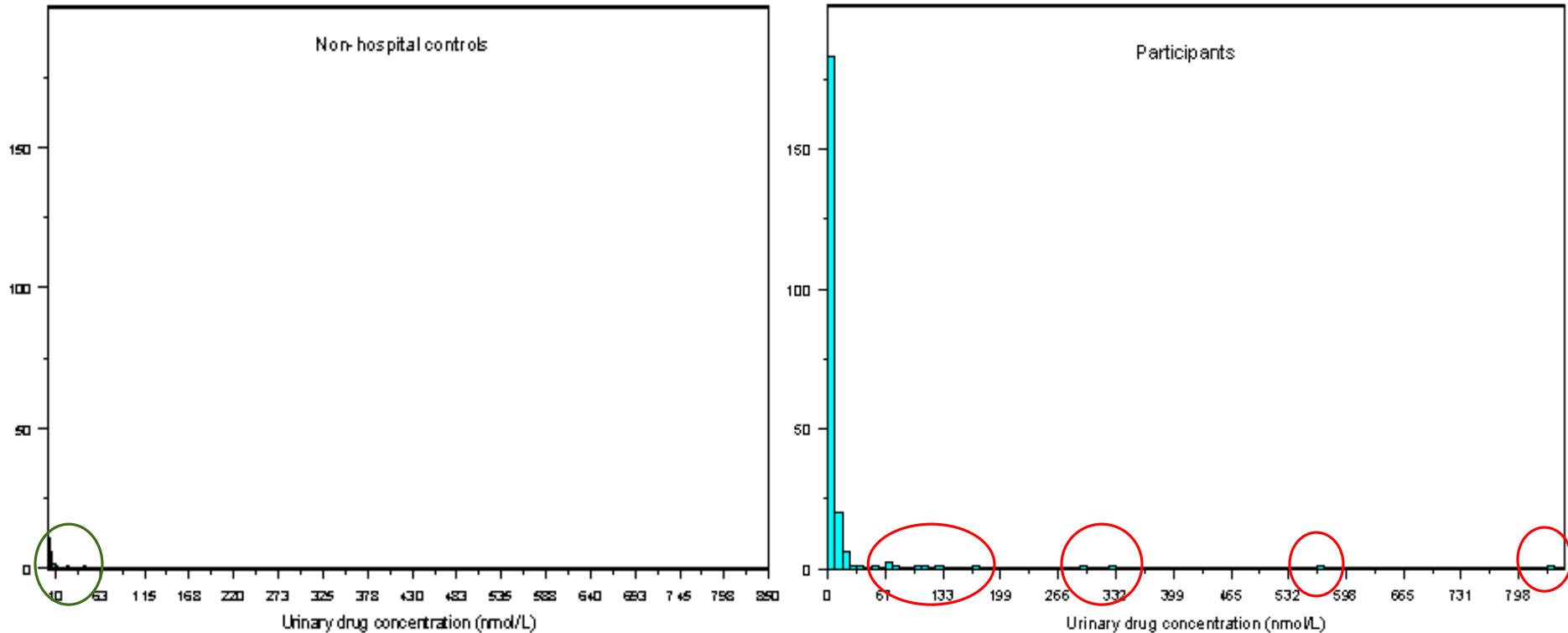
Suggests that workers have opportunities for higher exposure

Urinary Contamination

- Limitations:
  - No standard time to collect (during work shift)
  - No standard method for collecting 24-hr samples
    - Not described in detail
  - Possible degradation during 24-hr sampling collection period?
  - Look at parent product only and/or only a few drugs examined
  - Lot of variability within and between subjects
  - Correlation of results to exposure?

Genotoxicity assays

- Two common tests:
  - *Micronucleus assays* - toxicological screening for potential genotoxic compounds
  - *Comet assays* - technique for the detection of DNA damage

- Rekhadevi et al. (2007) – DNA damage was statistically significant exposed vs. non-exposed

- Burgaz et al. (1999) – micronuclei frequency in lymphocytes were statistically significant in exposed vs. non-exposed

Genotoxicity assays

- Rombaldi et al. (2009) pharmacy and nursing personnel demonstrated **increased DNA damage**

- Ursini et al. (2006) found evidence of **DNA damage** in oncology nurses

- McDiarmid et al. (2010) found **chromosomal abnormalities** in exposed oncology workers

- El-Ebiary et al. (2013) found the numbers of aberrant lymphocytes, as well as chromosomal aberration and micronuclei frequencies, were **significantly increased in exposed personnel** in comparison to matched controls

Challenges in Exposure Assessment

Challenges: Exposure assessment

- Identification of <u>all</u> exposed workers
- No validated sampling method
- Underestimate of exposure
  - Recovery rate unknown
  - Absorption rate for dermal wipe samples?
  - Time dependency issues
- Specificity of genotoxicity assays?
- Determinants of exposure?

Challenges in Controlling Exposure

Challenges: Control of exposure

- Mechanism of spread is unknown
- Minimize exposure of *all* workers at risk
- Difference in control measures between medication circuit stage and/or job categories?
- Cost of control measures e.g. closed system drug transfer devices
- Proper evaluation of controls
- Cleaning protocols
- Appropriateness of ALARA?

Policy Considerations

Policy considerations

- Understand who may be exposed at facility – based the site's hospital medication circuit

- All job categories at-risk should be trained

- Appropriate labelling of these products

- Enforcing use of PPE for all those involved in the medication circuit

- Adoption of best practices

Future Studies

Future studies

- Determine mechanism of spread
- Develop a standard method of assessing exposure
- Establish occupational exposure limits
- Identify determinants of exposure
- Evaluate effectiveness of interventions
- Exposure risks outside of acute care settings
- Epidemiological studies

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