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Considering risks to healthcare workers from glutaraldehyde alternatives in high-level disinfection

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Summary Due to concerns over glutaraldehyde's toxicity, two substitutes have recently been introduced; *ortho*-phthalaldehyde (OPA), and a mixture of hydrogen peroxide and peracetic acid. There is limited information about the health effects for employees from these products. This study assesses the current practices regarding the use of high-level disinfectants in British Columbian hospitals and predicts the relative toxicities of each product. Industry practices were compiled using a comprehensive survey of current practices and decision processes in all hospitals in British Columbia. Of 95 hospitals, 64 returned surveys; 80% of these used high-level disinfection. Among user hospitals, 49% used glutaraldehyde alone and 51% had introduced alternatives. Concern about staff health was the most common reason for substituting, but this was frequently not considered when choosing specific alternatives. Hospitals that involved occupational health, infection control or regional staff in high-level disinfectant decisions used glutaraldehyde alternatives less often. In most hospitals, it was difficult to find individuals who were knowledgeable about the use of disinfectants. Potential health effects associated with each type of high-level disinfectant were assessed by review of the published literature and available manufacturers' data along with qualitative structure–activity relationship analysis. Results indicated that although all products irritate the skin and

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respiratory tract, OPA is a potential dermal and respiratory sensitizer but hydrogen peroxide and peracetic acid do not cause allergic reactions. Despite little being known about the risks to employees from glutaraldehyde alternatives, their use is widespread. The potential risks of all high-level disinfectants are serious; thus regulators and users are faced with important risk management decisions before and after they have been introduced into the workplace.

Introduction

High-level disinfection (HLD) is a cleaning process that kills all micro-organisms except bacterial spores.[1] For the past 40 years, glutaraldehyde (in 2–4% solution with water) has been the primary chemical used for HLD. Glutaraldehyde is highly effective but it has been associated with a number of serious health problems among employees, including dermatitis and occupational asthma.[2–5] In 1999 and 2000, two new high-level disinfectants were introduced to the market: Cidex OPA® [0.55% *ortho*-phthalaldehyde (OPA) solution] and Compliance™ (0.23% peracetic acid/7.35% hydrogen peroxide). Both were promoted as safer alternatives to glutaraldehyde even though there was little evidence available to support (or refute) such claims. Although substitution of hazardous chemicals is generally considered to be good practice for reducing risk in the workplace, replacing a known hazard with a chemical with largely unknown toxicity may not be a solution. Basic toxicology data may not be sufficient to determine the potential health effects of new chemicals, and unknown problems may surface later. It is easy to assume that a substance is not hazardous just because it is not known to have serious health effects. A lack of knowledge should be taken as a warning rather than an indication of safety.[6] This project used the example of HLD to examine issues surrounding chemical substitution and employee health, particularly in the acute-care sector of the healthcare industry.

This paper describes the results of a two-part study involving a survey of current practices relating to high-level disinfectant use in hospitals and a review of toxicity data for a range of high-level disinfectant chemicals. As the survey was exploratory in nature, it was not designed to test any preformed hypotheses. The purpose of the survey was to gather information about which chemicals were being used, where they were being used and the decision processes for choosing high-level disinfectant chemicals. The purpose of the toxicity review was to assess all available health information for existing high-level disinfectant products, with particular attention to newer glutaraldehyde alternatives and their relative sensitization potential.

Methods

Survey development and implementation

The survey population included all acute-care hospitals in British Columbia, Canada. A letter explaining the purpose and format of the survey was mailed to the Chief Executive Officers of each Regional Health Board, Community Health Council, Community Health Service Society, and related healthcare unions in British Columbia. A database was created to include the occupational health manager or other personnel responsible for HLD within each hospital.

Product research and key informant interviews with hospital staff from several Vancouver hospitals were used to facilitate development of a mail-out questionnaire. The questionnaire was designed to assess practices related to the use of high-level disinfectants within hospitals. Telephone follow-up was performed to increase the response rate and to gather additional information from respondents.

Data analysis

Survey responses were coded and entered into a data file. Each respondent hospital was assigned to one of three size categories based on the number of admissions per year. Hospitals were also categorized as rural, town or urban according to the population of the municipality in which they were located. Data pertaining to the number of employees working in each hospital were obtained from the Healthcare Benefit Trust, which administers benefit plans to all full-time permanent employees.

Chi-square and logistic regression analyses were conducted using the SAS System for Windows Version 8.01 (SAS Institute, Cary, NC).

Relative toxicity review

A search of the published literature for toxicity data relating to glutaraldehyde, OPA, peracetic acid and hydrogen peroxide was conducted. Requests for unpublished toxicity data were made to manufacturers of glutaraldehyde alternatives and to regulatory agencies in Canada and the USA. Data from all sources were assessed and compared.

Since only limited data were available, a qualitative structure-activity relationship (SAR) analysis was preferred to predict relative respiratory sensitization potential. A list of physical and chemical predictors common to respiratory sensitizers was compiled from published structural analyses of chemicals known to act as respiratory sensitizers. Each of the four active ingredients in currently available high-level disinfectants were compared with this list to estimate relative sensitization potential.

To confirm the findings of the qualitative SAR analysis, the structures of the four high-level disinfectant chemicals were entered into a chemical asthma hazard assessment program (Hazassess), an online quantitative SAR program for low-molecular-weight chemical respiratory sensitizers (http://homepages.ed.ac.uk/jjarvis/research/hazassess/). The Hazassess program uses logistic regression analysis to compare structural fragments of the test chemical with 76 low-molecular-weight (<1000) organic respiratory sensitizers and 303 controls. It produces an odds ratio of the hazard ('hazard index') between 0.00 and 1.00, with 0.00 representing the lowest risk and 1.00 representing the highest risk of respiratory sensitization potential.

Results

Survey response

The questionnaire was mailed to all 95 acute-care hospitals in British Columbia, and responses were received from 64 (67%). Of these, 51 (80%) were using some form of HLD. Approximately half of the hospitals using high-level disinfectants were using glutaraldehyde alone, while half had introduced alternatives either exclusively or in combination with glutaraldehyde. Where alternatives were in use, OPA solutions were used much more frequently than peracetic acid/hydrogen peroxide solutions (Table I).

Table I Chemicals used for high-level disinfection

	N (%)
Hospitals using high-level disinfection	51
Hospitals using glutaraldehyde alone (*N*=25)	
Currently considering alternatives	7 (14%)
Never considered alternatives	11 (21%)
Considered and rejected alternatives	7 (14%)
Hospitals using alternatives (*N*=26)	
Using glutaraldehyde and alternatives	8 (16%)
Using *ortho*-phthalaldehyde alone	15 (29%)
Using peracetic acid/hydrogen peroxide alone	3 (6%)

Use of high-level disinfectants

A variety of departments reported using high-level disinfectants. The most common departments were operating theatres, ultrasound or medical imaging, gastroenterology and sterile processing departments. There were 663 full-time permanent employees working in areas using glutaraldehyde alternatives and 334 employees working in areas using glutaraldehyde alone for HLD. The mean number of potentially exposed employees in each hospital was 20, with more employees working with high-level disinfectants in those hospitals using a combination of glutaraldehyde and alternatives.

Among 25 hospitals that had not introduced any glutaraldehyde alternatives, seven were considering them as a viable option. Five hospitals were planning to use OPA and two were considering peracetic acid/hydrogen peroxide. One of the 26 hospitals that were already using alternatives was planning to discontinue use because of increased costs.

HLD decisions

In general, the decision about which chemical or product to use for HLD involved more than one person or department (Figure 1). Regardless of the product used, the departments that carried out HLD were most frequently involved in the decision. Occupational health, infection control and regional health authorities were also frequently involved in the decision process. Hospitals that had not introduced glutaraldehyde alternatives, however, included these three departments in the decision process more often than hospitals that had introduced glutaraldehyde alternatives. Where

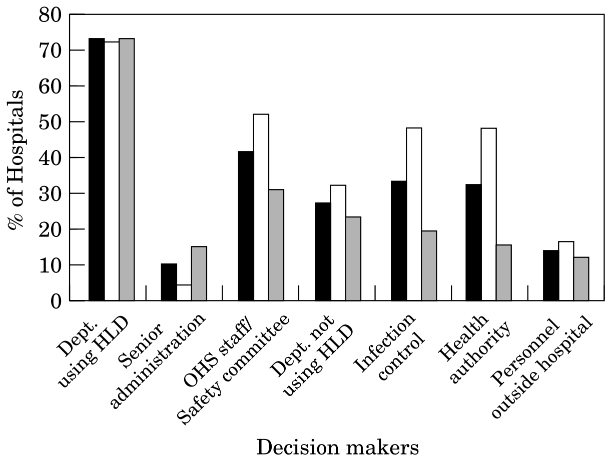

Figure 1 Personnel involved in high-level disinfection (HLD) decisions. Bars indicate the percentage of respondent hospitals in each of three usage categories that included each type of personnel in the decision process for high-level disinfectants. Solid bars, hospitals using any form of HLD, $N=51$; open bars, hospitals using glutaraldehyde alone, $N=25$; hatched bars, hospitals using alternatives, $N=26$.

glutaraldehyde alternatives were being used, protection of employee health was the most common reason for using them (Figure 2). The most frequently reported reasons for not introducing substitutes were technical issues such as damage to existing equipment, staining and lack of apparent benefit from use of the new products (Figure 2).

The relationships between occupational health staff involvement in decisions and the use of any glutaraldehyde alternatives were examined for the 51 hospitals using HLD. Hospitals with on-site occupational health employees used alternatives more frequently than glutaraldehyde ($P<0.05$), but where they were involved in the decision, hospitals introduced alternatives less frequently ($P<0.05$). Among hospitals that used information from sales representatives in choosing products, more had introduced alternatives than among hospitals not using sales information ($P=0.07$).

When all factors that may have influenced high-level disinfectant use were considered together in a multiple regression model, small-sized hospitals and hospitals in which occupational health, infection control or regional health authority personnel were involved in decision making used glutaraldehyde alternatives less frequently (Table II).

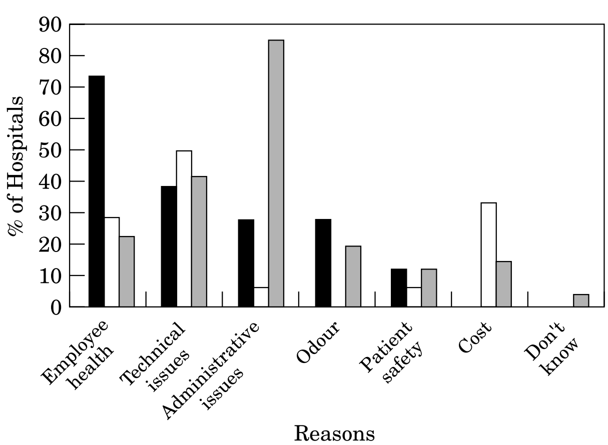

Figure 2 Reasons for introducing and choosing glutaraldehyde alternatives. Bars indicate the percentage of respondent hospitals that reported each given reason for not using glutaraldehyde alternatives ($N=25$), for using glutaraldehyde alternatives ($N=26$) and for choosing one specific alternative over another ($N=26$). Solid bars, reasons for introducing alternatives; open bars, reasons for not introducing alternatives; hatched bars, criteria for choosing alternatives.

Relative toxicity review

The respiratory health effects associated with glutaraldehyde exposure are well described in the literature.[2,3,5,7] Hydrogen peroxide and peracetic acid solutions are known to be skin and respiratory irritants but have not been associated with sensitization. OPA has not been used previously in solution form; information obtained from the manufacturer indicated that the solution has

Table II Multivariable logistic regression model of the relationship between hospital characteristics and the use of glutaraldehyde alternatives

Variable	Odds ratio	95% confidence interval	P
Hospital size: small	0.12	0.10-1.44	0.095
Hospital size: medium	0.36	0.06-2.20	0.269
Vancouver Island Health Authority	5.48	0.40-75.36	0.203
Senior administration involved in HLD decisions	2.70	0.14-53.77	0.515
OHS or safety committee involved in HLD decisions	0.25	0.05-1.28	0.096
Infection control involved in HLD decisions	0.13	0.02-0.75	0.022
Health authority involved in HLD decisions	0.12	0.02-0.77	0.025

HLD, high-level disinfection; OHS, occupational health and safety.

Table III Summary of dermal and respiratory toxicity data for high-level disinfection chemicals at concentrations approximating in-use conditions (superscript letters refer to type of data; asterisks specify source; numbers indicate references in the citation list)

	Glutaraldehyde	*Ortho*-phthalaldehyde	Hydrogen peroxide	Peracetic acid	Hydrogen peroxide + peracetic acid
In-use concentration	2–4%	0.55%	7.35%	0.23%	7.35% hydrogen peroxide/ 0.23% peracetic acid
Cytoxicity	Cytotoxic (2.5%)[a,8]	Cytotoxic (0.6%)[b,*]	No data	No data	No data
Dermal sensitization	Allergic contact dermatitis/skin sensitization (0.25–5%)[c,d,e,4,9-14,*]	Non-sensitizing (0.56%)[e,*]	Non-sensitizing (3%)[c,16]	Non-sensitizing (0. 15–14%)[e,17,**]	Non-sensitizing (7.35/0.23%)[e,f,18**]
Skin/eye irritation	Skin irritant (1–2%)[c,d,5,7,19,20] Irreversible eye irritant (2.4%)[e,*]	Non-irritating to skin; moderate eye irritant; corrosive[e,*] Skin, eye and mucous membrane irritant; non-allergic dermatitis (0.55–0.56%)[f,21]	Skin and eye irritation (3%)[c,16,22,23]	Non-irritating to skin (0.2%)[d,24] Dermatitis (3%)[d,***] Skin & eye irritation; dermatosis (0.14–0.5%)[g,17]	Severe eye irritant; non-irritating to skin (7.35/0.23%)[e,**] Mild to moderate skin irritant; severe eye irritant (7.35/0.23%)[f,18]
Respiratory sensitization	Respiratory sensitization/ occupational asthma (2%)[c,2,3,15,25]	No known studies of respiratory sensitization	No known studies of respiratory sensitization	No known studies of respiratory sensitization	No known studies of respiratory sensitization
Respiratory irritation	Respiratory irritation (2%)[c,5,7,26]	Respiratory irritation; aggravation of existing respiratory conditions (0.55%)[f,21]	Respiratory irritation (>10%)[c,23]	Respiratory irritation (1%)[d,27]	Mild respiratory irritant (7.35/0.23%)[f,18]

[a] Published in-vitro data.
[b] Unpublished in-vitro data.
[c] Published human studies.
[d] Published animal data.
[e] Unpublished animal data.
[f] MSDS claim.
[g] Unpublished human reports.
* ASP, unpublished data.
** Metrex, unpublished data.
*** National Library of Medicine Hazardous Substances Data Bank http://toxnet.nlm.nih.gov/cgi-bin/sis/htmlgen?HSDB.

never been assessed for respiratory sensitization potential but the crystalline raw material is a dermal sensitizer. All available dermal and respiratory toxicity information related to glutaraldehyde and its alternatives is summarized in Table III.

Qualitative SAR analysis was used to assess the potential for respiratory sensitization among the four high-level disinfectant active ingredients. A large list of predictors of respiratory sensitization was compiled from the published literature.[28–32] Based on this analysis, glutaraldehyde was correctly identified as a typical respiratory sensitizer. It has a molecular weight above 100, is susceptible to Schiff base formation, contains two carbon–oxygen double bonds and is a dialdehyde. OPA, an aromatic dialdehyde, is very similar to glutaraldehyde; it contains the same predictors of respiratory sensitization as glutaraldehyde as well as an aromatic group. Hydrogen peroxide contains one predictor of respiratory sensitization, namely two reactive hydroxyl groups. Peracetic acid contains two reactive groups and a carbon–oxygen bond.

The Hazassess program was used to calculate a respiratory sensitization hazard index for each of the four disinfectants. Glutaraldehyde received a hazard index of 0.8242, and indices for OPA, hydrogen peroxide and peracetic acid were 0.7251, 0.0084 and 0.0261, respectively. These hazard indices suggest that glutaraldehyde and OPA have the potential to act as respiratory sensitizers, while hydrogen peroxide and peracetic acid are highly unlikely to do so.

Discussion

This study suggests that there is a high degree of concern about health among employees who are directly involved in HLD. Despite this concern, there is evidence that the risk management of high-level disinfectants is inadequate. The fact that health was a frequent reason for both introducing and avoiding glutaraldehyde substitutes points to the uncertainty about the potential health effects of these new products. That a high level of concern about employee health was not used as a criterion for choosing substitutes presents an interesting contrast. Factors such as product availability, practices at other hospitals and recommendations from sales representatives appeared to override good intentions for protecting employee health. Some marketing claims for these alternative products are based on lower health risks, and the influence of sales representatives should not be underestimated.

Recommendations from sales representatives were commonly used to choose an alternative product. Despite the lack of information from any source other than manufacturers' representatives, glutaraldehyde alternatives are already widely in use in British Columbia and elsewhere.

When people knowledgeable about occupational health issues were involved in decision making, sales information tended to be used less frequently. However, occupational health professionals were involved in decision making in less than half of the hospitals. Given the potentially serious negative health impacts of high-level disinfectants and the uncertainty about the potential health effects, it would be appropriate to increase the involvement of occupational health professionals in the decision-making process.

The lack of information available impairs informed decision making. Recommendations of sales representatives may be relied upon so heavily because there is no other source of health data about their products. Hydrogen peroxide and, to a lesser extent, peracetic acid have been used as disinfectants and for other purposes for many years, so there is some useful information in the published literature regarding health effects. OPA, on the other hand, has not been used previously in solution form or for disinfection and there is no published information available. Decision makers thus have no independent source of information.

Our toxicity assessment suggests that OPA at least has the potential to cause both dermal and respiratory sensitization. The raw material used for the product is a dermal sensitizer. The qualitative SAR analysis indicated that OPA has similar structural and reactive properties as glutaraldehyde, and shares even more similarities than glutaraldehyde with other chemical respiratory sensitizers. No information was obtained either from the published or unpublished literature or from the SAR analysis to indicate that either hydrogen peroxide or peracetic acid might act as sensitizers.

One of the most important strengths of this survey was that it is the first study to examine issues related to high-level disinfectant use and decision making. This is particularly timely given the recent introduction of new products to the market. It should be emphasized, however, that this was an exploratory analysis only and no a-priori hypotheses were tested. A reasonably high response rate (67%) was achieved but since the number of British Columbian hospitals that use HLD is small, the power to detect significant associations between many of the variables was low.

SAR analysis has a number of methodological limitations. It uses modelling based on empirical data from other chemicals to make predictions, rather than scientific data on the chemical of interest. There is thus room for error; however, in the absence of pre-existing scientific studies, SAR analysis is often used to predict the potential for a chemical to have a specific toxic endpoint.[33] It is a useful first step when other more rigorous studies are not yet available.

An unexpected finding of this work was that it was extremely difficult to locate the person responsible for overseeing HLD in most hospitals. Numerous employees often had to be contacted before the appropriate personnel (or lack thereof) could be identified. When the survey questionnaire was sent directly to the occupational health department, the employees were often unable to fill it out without assistance from other departments. In addition to its importance for patient safety, HLD is a process that has been linked with some very serious occupational health effects. Despite this, there seems to be a lack of general knowledge concerning the use of these disinfectants, and practices often do not appear to be overseen at the hospital level by people educated about occupational health issues.

Both types of glutaraldehyde alternative appear to be safer substitutes. Peracetic acid-hydrogen peroxide solutions may be the safest choice because they are not believed to cause allergic reactions or asthma. This is not to suggest that they are non-toxic, as such solutions are corrosive and highly irritating to the skin, eyes, mucous membranes and respiratory tract. Although OPA appears to have sensitizing potential, both respiratory and dermal, the active ingredient concentration in the currently available OPA-based high-level disinfectant is much lower than that in glutaraldehyde solutions. The solid raw material used to make OPA also has a much lower vapour pressure than glutaraldehyde; 0.0052 mmHg at 21 °C for solid OPA raw material (Advanced Sterilization Products, unpublished report, 2001) compared with 17 mmHg at 20 °C for a 70% stock solution of glutaraldehyde.[34] Thus exposure to OPA should be lower than exposure to glutaraldehyde under normal product use. Sensitization may therefore be less likely to occur.

Although the number of employees potentially exposed to these disinfectants was relatively small given the large number of healthcare workers in British Columbia, HLD should be given priority. When employees are at risk for irreversible chronic health problems such as asthma, utmost precaution should be undertaken to eliminate or reduce that risk. Furthermore, chemical substitution is a common issue elsewhere in health care and other industries with the potential to impact huge numbers of employees. Methods such as SAR analysis can be invaluable to occupational health and safety personnel when faced with choices between known and unknown hazards. Although it has limitations and is not as accurate as empirical data, methods such as SAR analysis would permit decision makers to make evidence-based choices rather than relying on sales-motivated information.

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