ic
INFECTION CONTROL

EDITORIAL

Iodine—Champagne in a Tin Cup

Martin S. Favero, Ph.D.

Dr. Ruth L. Berkelman and colleagues reported recently[1] the recovery of *Pseudomonas cepacia* from blood cultures of 52 patients in four hospitals in New York City over a seven-month period from April through October 1980. Epidemiologic investigations indicated that the positive blood cultures were, in fact, false positives and not indicative of real bacteremia (referred to as "pseudobacteremia"); the source of contamination was a commercially-available 10% povidone-iodine (PI) solution used both as an antiseptic and as a disinfectant. It was shown that *P. cepacia* gained entrance into blood culture tubes from PI left on the skin prior to venipuncture or from PI that was applied to blood culture bottle tops through which blood was inoculated by syringe into culture media. Further, *P. cepacia* was isolated directly from the PI solutions.

This report certainly is not the first one to describe intrinsic microbial contamination of commercially-available germicide solutions. However, Dr. Berkelman and her associates are to be commended for following their epidemiologic leads to "unbelievable results." No microbiologist who has tested iodine solutions for bactericidal efficiency would believe that a gram-negative bacterium like *P. cepacia* could survive for long periods in a 10% povidone-iodine solution containing 1% available iodine —bacterial spores perhaps, but not vegetative bacteria. These investigators believe that the source of the *P. cepacia* most probably was a deionization water treatment system that could have introduced high levels (i.e., 10^5-10^7/ml) of bacteria into the product during manufacture.

Subsequent to this investigation, there was an informal meeting during the Annual Meeting of the American Society for Microbiology in Dallas, Texas, in March 1981, attended by a number of microbiologists and epidemiologists, as well as chemists who are experts in the area of iodine and povidone-iodine chemistry. There were several informal presentations of data and a good deal of discussion. Since that time, I have had occasion to discuss the main points of this meeting with a number of microbiologists in the United States who are considered experts in the use of antiseptics and disinfectants and in environmental control. Much to my chagrin, and that of many of my colleagues, I discovered that some of our ideas and concepts concerning the chemistry and use of iodine and iodophor disinfectants were in error. Further, I have learned that there is little pertinent information in the scientific literature; where there is published information, the sources were usually journals not readily available to the environmental microbiology and infection control communities.

The information in this editorial is based, in part, on the discussions at the informal meetings in Dallas at the time of the American Society for Microbiology meetings, partly on information that has become available in direct discussions with several chemists in the iodine industry and with microbiologists who have performed efficacy testing of iodine solutions, as well as on my own reappraisal of information already in the literature. The purpose of this editorial is to highlight information that, for all practical purposes, has been previously unknown to health professionals and to help correct some of the misconceptions that microbiologists, especially, have had about measuring the bactericidal strength of iodine germicides. This editorial is not intended to halt health professionals' usage of povidone-iodine antiseptics or iodophor-based disinfectants; on the contrary, it is evident that, when manufactured correctly and used according to instructions, they appear to be effective.

Iodine, in the form of either a tincture or an iodophor, has been used for many years by health professionals in infection control and for other broad environmental control purposes. Iodine (I_2) is not very soluble in water and is saturated at about 0.03%, which is 300 ppm free iodine. Free iodine is the chemical species I_2. The term "available iodine" simply means the amount of iodine that can be titrated with sodium thiosulfate. In an aqueous solution, substantially all the available iodine may be free iodine when present in fairly low concentration (i.e., 1-5 ppm). However, in instances where there are higher concentrations of iodine, this is not generally true. For example, in Lugol's solution, iodine is mixed with potassium iodide, and the iodide ion reacts with I_2 to form I_3, which is soluble in water. This permits the amount of I_2 to be increased in solution. In this situation, the following equation applies:

$$I_2 + I_3^- \rightleftharpoons I^- \quad K = 1.4 \times 10^{-3}$$

Despite the fact that Lugol's solution contains 1% dissolved elemental iodine (I_2), the amount of free iodine

https://doi.org/10.1017/S0195941700057076 Published online by Cambridge University Press

cannot exceed 300 ppm.[2] Rather, I_2 is converted to iodide (I_3^-) which acts as a reservoir of iodine (a reservoir that has not been shown to be active against biologic material). Yet, when this solution is titrated with sodium thiosulfate, this reservoir is depleted instantaneously, accounting for the fact that the amount of titratable ("available") iodine would be 1% (10,000 ppm).

The term "iodophor" refers to the combination of iodine and a solubilizing agent or carrier; the resulting complex or combination acts as a reservoir of iodine which dissociates and liberates small amounts of free iodine in aqueous solution. The number of carriers ranges from quarternary ammonium compounds, detergents, and others to polyvinyl-pyrrolidone ("PVP" or "povidone"). It is the povidone-iodine that is the base for a number of popular antiseptic solutions. Generally, these are formulated so that there is a concentration of 10% povidone-iodine in solution, yielding 1% available iodine. It was evident when talking to the chemists at the Dallas meetings that much of the physical and organic chemistry involved with these iodine complexes is not fully understood. It is well-known, for example, that at a given available iodine concentration, the amount of free iodine in a povidone-iodine solution (or, for that matter, any iodophor solution) is largely determined by the amount of iodide ion present, the counter ion (i.e., K^+, Na^+, Li^+), the solvent, and, especially, the nature of the carriers. In addition, some chemists believe that the amount of water is also critical. They believe that diluting iodophor preparations with water significantly affects the amount of free iodine present. For example, PI antiseptics are usually formulated with 10% povidone-iodine yielding 1% available iodine. These products are antiseptics and are used on skin and tissue in undiluted form. The amount of free iodine in these solutions is approximately 1 ppm.[1,3] Some chemists believe that as this solution is diluted with water, the amount of free iodine increases up to a point. At a 1:10 and 1:100 dilution, the free iodine concentrations would be approximately 7 and 20 ppm, respectively, rather than the 0.1 and 0.01 ppm free iodine that might have been expected. Data were presented at the Dallas meetings to substantiate these concepts.

The assay procedure for determining free iodine in the presence of complexed iodine was one that utilized an organic solvent such as heptane which is layered over a solution. The amount of iodine that comes to equilibrium in the solvent layer proportional to the free iodine in the aqueous phase is then assayed spectrophotometrically. Other chemists pointed out that this indeed may reflect the free iodine level, but a more precise term would be "extractable iodine." Preliminary data were also presented by some microbiologists that showed 1:10 and 1:100 dilutions of povidone-iodine solutions, in point of fact, to be more rapidly microbicidal than undiluted solutions *in vitro*. Chemists favoring the concept of increased free iodine generation as a result of aqueous dilution felt that this was a microbiologic confirmation of their chemical theories, findings and previously reported works that showed first correlation between free iodine and microbicidal performance.[2,4] Chemists agreed that there is no information on the effect of the povidone-iodine complex molecule on microorganisms independent of the presence of free iodine. They explained that these complexes also appear to be affected by water and that the observed increased microbicidal effects at a 1:10 or 1:100 dilution may, in fact, be due to either combined action of free *and* complexed iodine or even complexed iodine alone.

In any case, there was consensus that povidone-iodine antiseptics are formulated specifically to deliver about 1 ppm free iodine in their undiluted forms; this concentration is constant regardless of the organic load because of the extensive iodine reservoir (10,000 ppm available iodine). These products are not meant to be used diluted, since skin reactions may occur from the increased amount of free iodine. It was further pointed out that these germicides are formulated as antiseptics, and it is not the intent of any of the manufacturers that they be employed as disinfectants for use on medical devices, hard surfaces, or environmental surfaces. Further, they pointed out that there are a number of iodophor-based disinfectants formulated specifically for use in environmental situations. However, they acknowledged that the effect of diluting iodophor disinfectants with water appears to be similar to that of povidone-iodine antiseptic preparations (in example, the commercially-available disinfectant, Wescodyne*). It can be readily appreciated that the manufacturer's directions, which call for a 1:213 aqueous dilution of the concentrated product, are designed to give the maximum degree of microbicidal efficiency, which, according to some chemists, correlates to a maximum amount of free iodine present. Consequently, when this material is used undiluted or diluted at only 1:5 or 1:10, there is less free iodine in solution than when the product is diluted 1:213 as directed. Microbiologic data presented at the Dallas meeting supported the notion that the maximum sporicidal efficiency occurred at the 1:213 dilution rather than at lower or higher dilutions.

This information has several practical implications and points up the erroneous views held by many health professionals who use these compounds. For example, a review of the literature concerning the microbicidal capabilities of povidone-iodine solutions reveals that virtually none of the investigators actually knew the amounts of free iodine present in the solutions they tested. Further, many investigators incorrectly assumed that the concentration of available iodine was equivalent to free iodine. (This may be due to equating the term "available iodine" with the term "available chlorine." The latter is defined as the amount of free [Cl_2 and HOCl] and combined chlorine [i.e., chloramines], both of which are microbicidal [free chlorine being more active than combined chlorine].) The term "available" when used with iodine means that amount that is titratable with thiosulfate; available iodine, as such, has not been shown to be microbicidal.

Approximately 75-80% of the reports in the scientific

*Use of commercial names here and elsewhere in this article is for identification only and does not imply endorsement by the Public Health Service or the U.S. Department of Health and Human Services.

literature concerning the microbicidal efficiency of povidone-iodine solutions have been in-use tests involving the degerming of skin and tissues. The results have been impressive, which accounts for the wide use of these types of antiseptics. However, there are very few laboratory-based tests in the literature; the ones that have been reported suffer from the errors noted above in terms of knowing the amount of free iodine present. The problem is further complicated by the fact that many health professionals in the United States tend to use povidone-iodine antiseptics as disinfectants. This may not be good practice. A disinfectant germicide is one that is formulated for use solely on ineminate objects. An antiseptic, on the other hand, is one that is used on skin and living tissue. Some germicides may contain active ingredients that are used for both purposes, but the adequacy for one purpose does not assure adequacy for the other.[5,6] The manufacturers of povidone-iodine antiseptic germicides do not recommend they be used as disinfectants, and this gives credence to the advice to use antiseptics and disinfectants for the separate purposes for which they are intended.

In addition, there are other errors that could be made in devising strategies for environmental control with the use of iodophor disinfectants. Mention has already been made of the potential effects of water dilution on the increase in microbicidal action—making the manufacturers' use-dilution instructions much more critical than with other types of disinfectants. The second error that can occur is the categorical recommendation to use certain concentrations of iodine germicides based on the amount of available iodine. It is not unusual, for example, to see a concentration of 500 ppm available iodine used to designate an intermediate level disinfectant. Depending on the particular concentrated product and the amount of water added prior to its use, it appears that the term "available iodine" is inadequate in terms of bactericidal efficiency; it designates only the extent of the iodine reservoir and may not have anything to do with the amount of free iodine present in a product before or after use-dilution. Consequently, there should be an additional indicator in a set of instructions to enable persons to assess the relative strength of various iodophor germicides.

Although the term, "available iodine," is inadequate, it is not totally meaningless. For example, a microbial population might survive the free iodine demand from a solution containing 1-2 ppm free iodine. The resulting solution would then have 0 ppm I_2 remaining. With an iodophor, the 1-2 ppm I_2 would remain constant and the iodination of microorganisms would continue until there would be no sights left to react with free iodine or when the reservoir of available iodine was exhausted. So, although 1-2 ppm may exist at equilibrium in an iodophor solution, at a given time the microbial population would experience the entire 10,000 ppm of available iodine.

In this context, the chemistry of iodine and iodophors could be briefly summarized as follows: Free iodine is the amount of iodine that exists in solution at equilibrium as I_2. Available iodine is a measure of the potential I_2 that the system can generate when perturbed from the equilibrium state. The addition of iodide forms a chemical species (I_3) which is much more water-soluble than elemental iodine. The free iodine in a solution of I_3 is low, but the available iodine is equal to the I_2 added. Free iodine is microbicidal and the instant I_2 is depleted, it is replaced from the available pool such that any load (i.e., sodium thiosulfate or bacterial cell walls) placed on the system for I_2 will "see" all of the available iodine.

Obviously, a good deal of research is needed to clarify the microbicidal effects of iodine solutions, and there is a need for chemists to arrive at a standardized procedure for determining free iodine in solutions of complexed iodine.

How can vegetative cells of *P. cepacia*, even in large numbers, survive for long periods in povidone-iodine solutions? Berkelman et al[1] proposed that this phenomenon could be due to innate bacterial resistance to iodine or perhaps to protection of the bacteria from iodine by slime or organic materials. It has been documented that certain gram-negative bacteria can acquire extraordinary resistance to free iodine in the concentration of approximately 1-2 ppm free iodine,[7] and it is common knowledge that organic material may afford protection to microorganisms embedded in it. However, this is still a mystery that should be investigated in detail and resolved in the near future. Whether manufacturers of povidone-iodine antiseptics should be concerned about the bacteriologic quality of the water used to prepare their products is debatable. One would have thought that these solutions would be self-sterilizing. However, it was reported at the Dallas meetings (and manufacturers of other types of disinfectants have claimed) that it is common practice to perform bacteriologic quality control on such waters. Whether this practice would be efficacious in controlling contamination and/or be cost effective are subjects that should be considered by manufacturers of germicides.

Martin S. Favero, Ph.D.
*Hepatitis Laboratories Division**
Center for Infectious Diseases
Centers for Disease Control
U.S. Public Health Service
Department of Health and Human Services
Phoenix, Arizona 85014

REFERENCES

1. Berkelman RL, et al. Pseudobacteremia attributed to contamination of povidone-iodine with *Pseudomonas cepacia*. Ann Intern Med 1981; 95(1):32-36.
2. Allawala NA, Riegelman S. The properties of iodine in solutions of surface-active agents. J Am Pharm Assoc 1953; 17(7):396-401.
3. Rodeheaver G, et al. Pharmacokinetics of a new skin wound cleanser. Am J Surg 1976; 132:67-74.
4. Wyss O, Strandskov FB. The germicidal action of iodine. Arch Biochem 1945; 6:261-268.
5. Favero MS. Sterilization, Disinfection, and Antisepsis in the Hospital. In: *Manual of Clinical Microbiology*. 3rd ed., Washington, DC: American Society for Microbiology, 1980, pp 952-959.
6. Spaulding EG, Cundy KR, Turner FJ. Chemical Disinfection of Medical and Surgical Materials. In: SS Block (ed). *Disinfection, Sterilization and Preservation*. Philadelphia: Lea & Febiger, 1977, pp 654-684.
7. Favero MS, Drake CH. Factors influencing the occurrence of high numbers of iodine-resistant bacteria in iodinated swimming pools. Appl Microbiol 1966; 14:627-635.

**World Health Organization Collaborating Centre for Reference and Research on Viral Hepatitis.*