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How Much Effect Does Alcohol Have Against Alcohol-Resistant Norovirus?

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ABSTRACT

Abbreviations: CDC: Center for Disease Control and Prevention; EPA: Environmental Protection Agency; GLP: Good Laboratory Practice; FDA: Food and Drug Administration; OTC: over the counter; MNV: Murine Norovirus; FCV: Feline Calicivirus; SDS: Safety Data Sheet; WHO: World Health Organization

Introduction

Alcohol-resistant microorganisms, such as nonenveloped viruses and bacterial spores, pose a significant threat to human health worldwide. Among these alcohol-resistant microorganisms, infections by human norovirus and *Clostridium difficile* (*C. difficile*) are associated with a large number of illness and heavy economic burdens. According to the US Center for Disease Control and Prevention (CDC), 20% of cases of acute gastroenteritis worldwide are caused by norovirus, with an estimated 685 million cases annually in both low- and high-income countries. About 200 million cases are seen among children under 5 years old, leading to 50,000 to 70,000 child deaths each year. The annual economic burden is estimated to be $60 billion worldwide due to healthcare costs and lost productivity (CDC Norovirus Worldwide). In the United States, norovirus is the leading cause (58%) of foodborne illness. The majority (62%) of norovirus outbreaks were found to occur in long-term care facilities and hospitals, followed by restaurants, schools, and cruise ships [1]. Researchers in academia and industry have developed various products and formulations to combat a wide spectrum of infectious agents. These materials either contain an alcohol (ethanol, isopropanol, etc.) or other ingredients (hypochlorite/bleach, ammonium chloride, hydrogen peroxide, ammonium quaternary compounds, strong base or acids), or a combination of alcohol and other ingredients. The two major categories for use of these virucidal products are for surface disinfection and hand hygiene. In the United States, a surface disinfectant product with norovirus claim is regulated by the Environmental Protection Agency (EPA). These virucidal surface disinfectants must undergo a series of tests in the laboratories in compliance with Good Laboratory Practice (GLP). To be qualified as a virucidal product against norovirus, surface disinfectants must demonstrate >99.9% kill (>3 log10 reduction of viral infectivity) within a short period of time (30 seconds to 5 minutes). However, since many surface disinfectants contain toxic and/or corrosive chemicals, the end users could be exposed to unwanted chemicals or irritants. Therefore, surface disinfectants containing toxic or corrosive ingredients are labeled with specific warnings and instructions for use. For example, according to the EPA, "Sodium

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and calcium hypochlorite are extremely corrosive and can cause severe damage to the eyes and skin. They have been assigned to Toxicity Category I, indicating the highest degree of toxicity, for these acute effects." There are a few active ingredients that can be labeled as "safer". EPA's Design for the Environment's Safer Disinfectant Project is the agency that certifies disinfectants as "safer" for human health and the environment. The current "safer" active ingredient list includes citric acid, hydrogen peroxide, L-lactic acid, ethanol, isopropanol, and peroxyacetic acid. Hand hygiene products are regulated by the US Food and Drug Administration (FDA) as over the counter (OTC) human drug products. As toxic and corrosive ingredients are harmful to the end users, only a few components are allowed to be designated as active ingredients, including alcohols.

Alcohols are particularly widespread components of hand hygiene products because they are well tolerated on the skin (although not entirely without issue, such as excessive drying). In hand hygiene products, alcohol plays a key role to inactivate common bacteria and enveloped viruses, and alcohol-based hand sanitizers have been an important hand hygiene method during the CIVID-19 pandemic when soap and water is not available. However, the US FDA has not allowed claims of virucidal activity for any hand hygiene products. Accordingly, there is no virucidal hand hygiene product on the US market labeled as such. In general, alcohols are a good, safer choice for disinfectant and hand hygiene products. Enveloped viruses are fairly readily inactivated by alcohols, due to damage to the lipid-based viral envelope. Lacking such an envelope, non-enveloped viruses such as norovirus are much more resistant to inactivation by ethanol, hence their classification as alcohol resistant. However, 'resistant' is not necessarily the same as 'unaffected', raising the possibility that alcohol-based products could have some practical benefit against alcohol-resistant organisms. The question is thus: is an alcohol alone practically effective against norovirus? The definition of "effective" is different among scientific institutions, antiseptic, and pharmaceutical industries. Alcohols can be defined as effective in science if they reduce the infectivity of norovirus by 90% or 99% (1 or 2 log^{10} reduction) in comparison to untreated controls. But this "virucidal activity" by scientific definition only indicates a disqualification for any antiseptic purposes, which requires 99.9% to 99.99% (3 to 4 log^{10} reduction). In addition, an antiseptic product must undergo multiple required tests in GLP-compliant laboratories, using specific methods, equipment, reagents, and controls designated by the regulatory agencies (i.e. EPA, FDA, EU, Health Canada, etc.). That is, a >5 log^{10} reduction of norovirus infectivity in a formulation study from a research institution does not indicate this formulation is effective against norovirus by the antiseptic definition for regulatory purposes until it passed the GLP laboratory tests. For research purposes, scientific studies using formulations containing alcohol have reported significant effects against norovirus or surrogate viruses. Indeed, some researchers have suggested that alcohol alone is effective against norovirus. For example, in 2011, Steinmann's group reported that 60% - 90% ethanol reduced murine norovirus (MNV) S99 (a human norovirus surrogate for hand hygiene product test) by >log 5 in 30 sec [2]. However, this result could not be reproduced by other groups (e.g. [3,4]). Tung, et al demonstrated 50% -90% ethanol has low virucidal activity against feline calicivirus (FCV), two human norovirus strains (<log 1 reduction) and only moderate activity against MNV (<log 2.5 reduction). In another report, Steinmann et al demonstrated unspecified formulations (A, B and C) of alcohol-based hand sanitizer achieved >4 log^{10} reduction of MNV. Formulations A and B contained phosphoric acid, and formulation C contained >90% ethanol [5]. It is known that phosphoric acid can be very hazardous in the case of skin contact, eye contact, and ingestion. It can also cause irritation if aerosol is inhaled. This chemical can cause damage to the skin, eyes, mouth, and respiratory tract. Any norovirus, as well as experimental cells, cannot survive in this strong acid with or without alcohol. Thus, the experimental design was not able to demonstrate the role of alcohol from its results. Another report by Steinmann et al used two WHO hand hygiene formulations with ethanol, glycerol, and hydrogen peroxide (Formula I); or isopropanol, glycerol and hydrogen peroxide (Formula II) against MNV. The results suggested that Formula I reduced MNV infectivity by >5 log^{10} [6]. However, it was later found that neither WHO formulation meets the bacterial efficacy requirements of European Norm 12791 (the basis for approval as a surgical hand preparation), nor do they satisfy European Norm 1500 (the basis for approval as a hygienic hand rub) [7]. In 2013, Steinmann et al tested a modified WHO formula I with increased ethanol content (from 80% to 85%) and decreased glycerol (from 1.45% to 0.725%) against 3 non-enveloped viruses [8]. However, it is not clear if this formulation meets the bactericidal efficacy requirement mentioned by Kampf and Ostermeyereither [7]. In 2008, Belliot et al demonstrated 60% ethanol caused > 4 log^{10} reduction in 30 sec of MNV using plaque assays [9]. A similar method using a Rapid Agar Plate Assay (RAPA) and performed by a different group also generated >4 log^{10} reduction with a regular Purell alcohol-based hand sanitizer [10]. However, the plaque assay is not recommended by any regulatory agencies for efficacy test on hand hygiene or surface disinfectant product. To what extent this discordancy in the effectiveness of alcohols represent methodological differences among laboratories is not clear. But it is clear that these results (>4 log^{10} reductions) were generated from institutional laboratories, and the authors of the above reports did not indicate whether their study results were confirmed by GLP labs according to regulatory guidelines. For surface disinfectants, the US Center for Disease Control and Prevention (CDC) reported in the "Guideline for the Prevention and Control of Norovirus Gastroenteritis Outbreaks in Healthcare Settings" states: Studies of disinfecting non-porous surfaces and hands' evaluations of the efficacy of varying dilutions of ethanol and isopropanol. It was determined that 70-90% ethanol was more efficacious at inactivating FCV compared to isopropanol, but was unable to achieve a reduction of 3 in the log^{10} of the viral titer (99.9%), even after 10 minutes of contact [11]. Consistent with the CDC's guidelines, there is no firm evidence to indicated that alcohol at any concentration is effective against alcohol-resistant norovirus. However, there are commercial surface disinfectant products with norovirus claim, and several do in fact list alcohol as the only active ingredient, suggesting alcohol alone is indeed effective against norovirus. For example, under the List G (products effective against norovirus) from the EPA, a number of products list alcohol as the only active ingredient. Product 84368-1 is formulated with 29.4% ethanol (active ingredient) and 70.6% of undisclosed other ingredients [12]. Product 84150-1 is formulated with 20% ethanol and 80% unknown ingredients (no Safety Data Sheet (SDS) found) [13]. Product 84150-3 is formulated with 29.4% ethanol (active ingredient) and 70.4% of undisclosed ingredients (no SDS found) [14]. Product 84150-4 contains 29.4% ethanol (active ingredient) and 70.6% of undisclosed other ingredients (no SDS found) [15]. With respect to product labeling, designation as an "active ingredient" is a very specific category under EPA regulations, which require no statement about everything contained within the "inactive ingredient" or "inert" category, and which is often not further broken down to components listed on the label or included in the SDS; according to the EPA regulations the manufacturers and distributors of surface disinfectants are not obligated to list "inactive", or "inert" ingredients, and these four products with less than 30% ethanol did not disclose the "inactive ingredients", nor the pH. However, researchers in the disinfectant industry understand that 30% or any percentage of ethanol (or other alcohol) alone in water is not able to inactivate the human norovirus surrogate (feline calicivirus) to the level required by EPA testing. If alcohol alone is effective, it is unnecessary to add toxic and/corrosive ingredients into the products. Therefore, what ingredient in the above-mentioned products inactivates norovirus (either alone or in combination with alcohol) is not known, and whether these undisclosed ingredients are potentially harmful to human cannot be evaluated. For example, unlike the above-mentioned products, another product with norovirus claim discloses all ingredients in the SDS [16], which contains 29.4% ethanol and 1.42% isopropanol as active ingredients, and 0.35% of potassium hydroxide as an inactive ingredient, which gives the pH of the product >12.5.

The product SDS stated that "The following Hazardous Substances are listed under the U.S. Clean Water Act, Section 311, Table 116.4A: Potassium Hydroxide 1310-58-3, 0.35 %". That gives a pH range of 12.6 - 12.9, (24 °C). According to the EPA, "Aqueous wastes with a pH greater than or equal to 12.5, or less than or equal to 2 are corrosive under EPA's rules" [17]. In addition, "if the pH is greater than 12 or 13, the solution attacks skin rapidly enough to be dangerous. Very basic solutions are more corrosive to skin than very acidic solutions [18]". Thus, it is important to know that norovirus or any other microorganisms cannot survive in a >pH 12.5 condition, either with or without alcohol. Thus, where an alcohol (ethanol and isopropanol) is listed as the only active ingredient in surface disinfectant products with norovirus claim, based on the available evidence it is likely not responsible (at least alone) for effective norovirus inactivation, but rather other ingredients in the product (generally listed as inactive) play a key role in the virucidal activity. Thus, it is essential for the end users to be able to evaluate the potential risks from the "inactive ingredients" or "other ingredients", and the pH of an alcohol-containing disinfectant for safety concerns, if they are disclosed in the SDS. For hand hygiene products, the current CDC guidelines for hand hygiene on a cruise ship (where norovirus outbreaks are all-too common) is hand wash with warm water and soap. If soap and water is not available, use alcohol-based sanitizer with >60% alcohol [19]. Consistent with the CDC, the FDA does not agree that current alcohol-based hand sanitizers are effective against norovirus. Scientists are still searching for other options to improve the virucidal activity against norovirus by increasing the concentration of alcohol, alteration of the pH, addition of new ingredients in hand hygiene formulations, and developing alcohol-free virucidal products, with encouraging progress.

In conclusion, both the FDA and CDC suggest that currently available alcohol-based hand hygiene products are not effective against norovirus. "Effective" hand hygiene formulations, with alcohol alone against norovirus, in academic publications are with discrepancies in methodology, testing conditions, and compliance with regulatory requirements. With respect to surface disinfectants, the antiseptic industry recognizes there is no effective surface disinfectant product using alcohol alone against norovirus. Chemicals other than alcohol are used in the products against norovirus as inactive ingredients not required for disclosure on the labels. Toxic and/or corrosive chemicals could be the major contributors to the virucidal activity against norovirus. The good news is that alcohol-based virucidal surface disinfectant products with ingredients found from popular beverages are on the horizon. Consumers and end users are encouraged to identify potential health risks from toxic and/or corrosive ingredients in surface disinfectant products, and follow the instructions and cautions provided by the manufacturers.

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