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Original Article

In vitro assessment of isopropanol leakage from antiseptic barrier caps into commonly used needleless connectors

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Abstract

Background: Needleless connectors (NCs) can be disinfected using antiseptic barrier caps (ABCs) to reduce the risk of catheter-related bloodstream infections. However, recent evidence suggests that isopropanol can leak from the ABC into the NC, posing concern about their safe use. We sought to determine in vitro which ABC and NC parameters influence the leakage of isopropanol through the infusion circuit.

Methods: We assessed 13 NCs and 4 ABCs available in the European market. In vitro circuits consisting of an isopropanol cap, a NC, and an 11-cm catheter line were created. The circuits were left in place for 1 to 7 days at room temperature to assess the kinetics of isopropanol leakage. Isopropanol content in ABC and in circuit flushing solutions (5 mL NaCl 0.9%) after exposure to the cap were measured using gas chromatography with a flame ionization detector.

Results: The leakage of isopropanol from the cap to the NC was dependent on the NC, but not the cap. The NC mechanism did not predict the leakage of isopropanol. The Q-Syte NC exhibited the most isopropanol leakage (7.01±1.03 mg and 28.32±2.62 mg at 24 hours and 7 days, respectively), whereas the Caresite NC had the lowest isopropanol leakage at 7 days (1.69±0.01 mg).

Conclusion: The use of isopropanol ABCs can cause isopropanol leakage into the catheter circuit according to NC parameters. Caution should be exercised when using these devices, especially in the pediatric and neonatal population.

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Catheter-related bloodstream infections (CRBSIs) are an important cause of nosocomial infection, with morbidity, mortality, and cost.[1] Pathogens may enter the circulation via an extraluminal route (ie, resulting from migration of microorganism from the skin at the catheter insertion site to the vein) or an intraluminal route.[2–4] In CRBSI related to the intraluminal route, the catheter hub has been identified as a major entry point for microorganisms[5,6] because they can adhere to, migrate to, and colonize the internal lumen of the catheter as well as form a biofilm that allows them to disseminate into the bloodstream.[3,7]

Because these contaminations occur when handling intravascular line connectors during infusion connection, drug injections or blood sampling, needleless connectors (NC) have been introduced into clinical practice to reduce handling of catheter connections and thus reduce the time during which microorganisms can contaminate the ports.[5] Their use has also eliminated the risk of needle-stick injuries, which prevents blood-exposure accidents and limits the use of needles on elastomer injection sites when accessing intravascular catheters.[8] Their effectiveness in reducing infections has been much debated in the literature.[5,9]

To further reduce the risk of CRBSI, catheters can be disinfected by either active or passive disinfection. Active disinfection consists of 15–30 seconds mechanical scrubbing of the hub membrane (or NC) using an alcohol wipe, followed by a drying period before using the catheter.[10] Interestingly, passive disinfection through antiseptic barrier caps (ABCs) have also been proposed to reduce CRBSI.[11–14] These ABCs containing a disinfectant (usually isopropanol 70%) are placed directly on the NC to continuously impregnate and disinfect the catheter access up to 7 days.[15,16] Overall, available evidence suggests that ABCs are effective, safe, easy to use, and cost-effective in reducing CRBSIs compared with isopropanol wipes in adults.[17,18]

To the best of our knowledge, no cases of isopropanol intoxication have been reported with the use of an ABC on a NC. However, in 2 recent studies, isopropanol contained in the ABCs leaked into the NC, raising safety questions about potential isopropanol exposure to patients during routine care, particularly in a pediatric and neonatal intensive care settings.[19,20] To date, no publication has compared a wide range of NCs with respect to the parameters influencing the leakage of isopropanol from ABC to the NC.

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In this study, we characterized the leakage of isopropanol from the ABC to the NC on all the products available on the European market, and we sought to determine which ABC and NC parameters influence the leakage of isopropanol through the infusion circuit.

Material and methods

Materials

We purchased 4 commercially available ABCs from their respective suppliers: 3M Curos (3M, St Paul, MN), DualCap (Catheter Connections, Salt Lake City, UT), BD PureHub (Becton-Dickinson, Franklin Lakes, NJ), Swabcap (B Braun, Melsungen, Germany) (Fig. 1). NC were purchased at the respective manufacturing laboratories, and the associated pictures and product brands are detailed in Figure 2. V-green extension lines (no. 71100.01) were purchased from Vygon (Ecouen, France). Versylène NaCl 0.9% was purchased from Fresenius (Homburg, Germany). Due to the availability of the Swabcap and the MaxPlus NC in our institution, these 2 brands were mainly used in this study.

Setting up in vitro circuits

Circuits consisting of an isopropanol ABC, a NC, an 11-cm polyethylene catheter line (no. 71100.01, batch 211222EH, Vygon) and an obturator (no. 9888.00, batch 241122FD, Vygon) were created (Fig. 3). In all circuits, the catheter line was rinsed and prefilled with NaCl 0.9% before the ABC was placed on the NC. At the end of the application time of the ABC, the circuits were rinsed with 5 mL NaCl 0.9%, which was collected for analysis.

In vitro experiments

The circuits were left in place for 1–7 days to assess the kinetics of isopropanol leakage from the ABC to the NC at room temperature (measured at 20°C). Experiments were carried out with or without a 30-second drying time before rinsing the circuit to evaluate the proportion of isopropanol passing through the Luer tip syringe. The drying time of 30 seconds after removal of the ABC from the NC was used as previously described,[19] although the instructions for the use of these devices do not specify this period.

We used the following methods to evaluate the isopropanol content in the 4 commercially available ABCs. (1) The ABCs were weighed before and after evaporation of their contents in an oven at 37°C for 24 hours, and (2) the ABCs were left in a closed container containing 5 mL NaCl 0.9% for 24 hours to extract isopropanol.

Isopropanol quantitation by headspace gas chromatography with flame ionization detection

We used gas chromatography to simultaneously quantify methanol, acetone, ethanol, and isopropanol (propan-2-ol) using propan-1-ol as the internal standard. Gas chromatography analysis was conducted using a ThermoScientific GC Trace 1300 system (Thermo Fisher Scientific, Waltham, MA) with a flame ionization detector (FID) and a headspace Thermoscientific TriPlus sampler. Chromatographic separation was achieved on a 30-m × 0.25-mm × 0.25-µm DB-WAX fused silica column (Agilent Technologies, Santa Clara, CA) using nitrogen as a carrier gas. SSL Injection port temperature was set to 200°C; the injection volume was 1 mL with split flow; and the oven temperature program was held at 50°C for a 7-minute run time. The FID detector was set at 250°C. Data were recorded and analyzed using Chromeleon 7.2 software (Thermo Fisher Scientific) using peak area ratios of analyte to internal standard with comparison to a 6-point standard curve for quantitative analysis of each analyte.

In a sealed vial, 200 µL internal standard (propan-1-ol) was added to the 10-µL sample and incubated 20 minutes at 80°C before injection. Routine quality-control samples consisted of Medidrug ALC VB 030 and 110 congener alcohols were analyzed before each sample analysis. The lower limit of quantification of isopropanol is 10 mg/L, and this method is linear until 750 mg/L.

Statistical analysis

Data were expressed as the mean ± standard error of the mean (SEM). Intergroup differences as a function of the treatment were probed in a 1-way analysis of variance (ANOVA), with a Tukey post hoc test for group comparisons. All analyses were performed using Prism software (GraphPad Software version 8.0, La Jolla, CA). All tests were 2-sided, and the threshold for statistical significance was set to $P < .05$.

Results

Influence of antiseptic barrier cap parameters on isopropanol leakage through needleless connectors

To investigate the influence of ABC parameters on isopropanol leakage through NCs, we first analyzed the isopropanol contents in the 4 commercially available ABCs (Fig. 4A and B). In the first method, we placed the ABCs in a 37°C oven for 24 hours to evaporate their 70% isopropanol content. The isopropanol contents were significantly different among the ABCs (Fig. 4A). These results were confirmed by infusing the ABCs for 24 hours in 5 mL NaCl 0.9% and assaying for isopropanol in the resulting solution. The BD PureHub ABC contained the most isopropanol (250.8 ± 123.6 mg), followed by the Merit DualCap (181.5 ± 86.45 mg), SwabCap (114.8 ± 14.5 mg), and 3M Curos (72.1 ± 4.3 mg). However, these results did not reach statistical significance. (Fig. 4B).

Next, we analyzed isopropanol leakage through a MaxPlus NC for these 4 ABCs left on for 1–7 days. Isopropanol leakage through the NC was not significantly different among the ABCs, either at 24 hours or 7 days (Fig. 4C). Lastly, we showed that a drying time of 30 seconds between ABC removal and rinsing with 5 mL NaCl 0.9% did not change the amount of isopropanol passing through the NC (Fig. 4D). However, rubbing with an isopropanol wipe caused very little isopropanol to pass through the NC. Taken together, these results suggest that isopropanol leakage from the ABC to the NC is not ABC dependent. Because the SwabCap is used in our institution and the drying time has no influence on the isopropanol leakage through the NC, we chose to use this product without drying time for further experimentation.

Influence of needleless connector parameters on isopropanol leakage

To investigate the influence of NC parameters on isopropanol leakage from the ABC to the NC, we left an ABC (SwabCap) on 13 different NCs for 24 hours or 7 days (Fig. 5). Our results showed that isopropanol leakage through the NC changes significantly depending on the NC (Fig. 5). Supplementary Table S1 (online) describes the results of overall difference testing for isopropanol leakage after 24 hours and 7 days. Complete statistical differences

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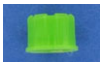
Product reference	Manufacturer	Supplier	Pictures
3M Curos® (REF: CFF1-270R) Batch : 9246521	3M Heath Care 2510 Conway Ave. St Paul, MN 55144 USA	3M France 1 Parvis de l'innovation 95000 Cergy	
DualCap® (REF: 450-LB) Batch : A008160	Merit Medical Systems, Inc. 1600 West Merit Parkway South Jordan, Utah 84095, USA	Merit Medical France Centre d'affaires Parc Lumière 46 Avenue des frères Lumière 78190 Trappes	
BD PureHub® (REF: 306598) Batch : 1288182	BD, Franklin Lakes, NJ, USA	Becton Dickinson France 11 Rue Aristide Berges, 38800 Le Pont-de-Claix	
Swabcap® (REF: EM-SCXT3) Batch : 9534745	ICU Medical 951 Calle Amanecer San Clemente CA 92673 USA	B.Braun Medical 26 Rue Armengaud 92210 Saint Cloud	

Figure 1. Different types of antiseptic barrier cap used in the experiments.

in isopropanol leakage between each NC after 24 hours and 7 days of experiments are described in Supplementary Tables S2 and S3 (online), respectively.

Moreover, 24 hours of ABC attachment to the NC was sufficient to observe differences in isopropanol leakage among the different NCs. The BD Q-Syte, Didactic, and BD MaxPlus NCs were the most permeable to isopropanol in a statistically significant way, passing 7.01 ± 1.03 mg, 6.27 ± 0.87 mg and 4.22 ± 0.65 mg, respectively. All other products did not appear to be significantly different in terms of isopropanol leakage despite the trends observed (Fig. 5A). The Bionector NC (Vygon) emerged as the least isopropanol-leaching NC, with an average of 0.66 ± 0.27 mg isopropanol leaked after 24 hours of use (Fig. 5A).

After 7 days of use, the Caresite NC (B Braun) emerged as the least isopropanol-leaching NC, with an average of 1.69 ± 0.01 mg isopropanol leaked. On the other hand, the Q-Syte NC allowed the most isopropanol to pass through, with an average of 28.32±2.62 mg of isopropanol leaked (Fig. 5B). The trends observed at 24 hours were also found at 7 days and were confirmed by the study of the kinetics of isopropanol leakage through the NC (Fig. 5C).

Discussion

Despite their vital importance, catheters may cause potentially life-threatening complications including CRBSI. To reduce this comorbidity, the most recent clinical evidence supports the use of NCs and ABCs for passive and continuous disinfection of NCs.[18] In this study, we showed that isopropanol can leak from the ABCs to the NC as a function of time, posing concerns about their use. We determined that the brand of NCs used was the most important parameter in this phenomenon.

First, we showed that the different types of ABCs did not influence the leakage of isopropanol through the NC, despite different isopropanol content in each ABC. The NC mechanism did not predict isopropanol leakage, as shown with the Q-syte and Safeflow NCs, as well as the Caresite and the MaxPlus NCs, which let through very variable amounts of isopropanol despite common mechanisms (Figs. 2 and 5). Overall, Caresite and Bionector NCs were safer choices when used with isopropanol ABCs, from an isopropanol leakage point of view. The brand and the quality of the NC seal on which the ABC is placed appeared to be the main factors influencing the leakage of isopropanol, as suggested by previous reports.[19,20] Hjalmarsson et al[19] reported isopropanol leakage ranging from 0.154 to 0.405 mg after 24 hours depending on the NC–ABC combination used (ie, Swan-lock or Bionector coupled to SwabCap or Curos).[19] Particularly, the combination of Bionector and SwabCap showed a maximum isopropanol leakage of 0.372 mg after 24 hours, compared to 1.220 mg in our study. The combination Safeflow and Swabcap showed a maximum isopropanol leakage of 1.755 mg after 24 hours, compared to 2.066 mg in our study. Due to the different methodologies used in the literature (which aimed to mimic the real-world conditions[19,20]) and in our study (which aimed to determine how much isopropanol passes from the ABC to downstream of the NC), the comparison of the results is difficult. However, the results in the literature and in our study are of the same order of magnitude: Safeflow leaks more isopropanol than Bionector[19] and Smartsite leaks more isopropanol than Caresite.[20]

Interestingly, the leakage hypotheses are also supported by the findings of Rickard et al,[22] who reported that 2 NCs (Smartsite or MaxPlus, unspecified) became opaque during their study of ABCs, suggesting that isopropanol appears to have seeped between the inner rubber and outer plastic, denaturing the plastic.[22] Similarly, Sauron et al[20] found that the appearance of Smartsite and Caresite NCs was modified after ABC connexion, including loss of transparency and inflation of the NC's fanfold piece.[20] In our experiments, we did not observe such denaturation of the plastic.

Second, toxicokinetic data available in humans indicate that absorption of isopropanol is greater and more rapid through the lungs and gastrointestinal tract and less through the skin. However, no data are available on intravenous isopropanol administrations, raising questions about the safety of such exposure. Although isopropanol has a half-life of 3–7 hours, its metabolite acetone has a half-life of 22 hours, and it is primarily excreted by the kidneys.[23] Toxicological data in the literature are mainly related to intoxication by ingestion with ketosis without acidosis and pseudo-renal failure as hallmarks. Because isopropanol penetrates the central nervous system better than ethanol, isopropanol is more intoxicating than ethanol and can produce sensorium alteration, hypotension, hypothermia, and even cardiopulmonary collapse.[23]

Previous reports mention that isopropanol toxic blood concentrations vary between 250 and 5,200 mg/L.[24–28] Because the smallest weights of newborns can be ~500 g (and the total blood volume of a child is ~75–80 mL/kg), these issues cause greater concern in the pediatric and neonatal population in view of the possibility of substantial isopropanol exposure.[29] Patients may have multiple infusions per day and multiple catheter lines and NC–ABC combinations, thus increasing the risk of isopropanol accumulation. In addition, a reported case of fatal isopropanol poisoning by inhalation in a 1,500-gram male infant suggests that the elimination half-life would be higher in infants than in adults

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Mechanisms	Product reference	Manufacturer/Supplier	Pictures
Split septum The elastomeric septum has a slit that will be directly crossed either by a plastic trocar or by a male Luer tip, the path of the liquid in the NC is straight and short, in the axis of the NC.	BBRAUN Safeflow® Codan Swanlock (REF 409100H) Batch: 22K07A8171	**Manufacturer**: BBRAUN Melsungen AG, 34209 Melsungen, Germany **Supplier**: B.Braun Medical 26 Rue Armengaud 92210 Saint Cloud	
	BECTON Q-Syte® (REF 385100) Batch: 2118463	**Manufacturer**: BD Infusion Therapy System Inc. Sandy, Utah 84070, USA **Supplier**: Becton Dickinson France 11 Rue Aristide Berges, 38800 Le Pont-de-Claix	
Passage between the elastomer and the shell Compression of a flexible or spring-loaded elastomer element, passage of liquid between the shell and the elastomer element. There is no slit in the elastomer element.	BBRAUN Caresite® Luer Access Device (REF 415122-01) Batch: 0061845377	**Manufacturer**: BBRAUN Medical Inc. Bethlehem, PA, USA **Supplier**: B.Braun Medical 26 Rue Armengaud 92210 Saint Cloud	
	BECTON MaxPlus® (REF : MP1000-C) Batch: 22025313	**Manufacturer** : BD Switzerland Sarl, 1262 Eysins, Switzerland **Supplier**: Becton Dickinson France 11 Rue Aristide Berges, 38800 Le Pont-de-Claix	
	BECTON MaxZero® (REF MZ1000) Batch: 22055429		
Split elastomer Contain an elastomeric element with an accordion-like pleat and a slit at the top. The Luer tip does not pass through the slit but rests against it; the compression of the elastomer element opens the slit, allowing the liquid to pass through. The path of the liquid, always straight, is longer	BECTON Smartsite® (REF 2000E7D) Batch: 1024609		
	VYGON Vadsite® (REF : 898.03) Batch: 111122EC	**Manufacturer** : VYGON, 5 rue Adeline, 95440 Ecouen, France **Supplier** : VYGON, 8 rue de Paris, 95440 Ecouen	
Displacement of a rigid cylinder The connection of the male Luer tip pushes a plastic cylinder, which allows fluid to pass through an orifice, into the inner lumen of the cylinder. When the tip is removed, a spring pushes the cylinder back and closes the NC. O-rings are used to seal the NC.	VYGON Autoflush® (REF: 5897.01) Batch: 051022EK	**Manufacturer** : VYGON, 5 rue Adeline, 95440 Ecouen, France **Supplier** : VYGON, 8 rue de Paris, 95440 Ecouen	
Inverse split septum Compression by the Luer tip of a flexible or spring-loaded elastomer element onto a plastic inner trocar with an end orifice or onto a metal tube. The slot in the elastomer will not be crossed by the Luer tip but by the trocar which will open into the internal lumen of the Luer, passage of the liquid through the orifice, into the internal lumen of the trocar or the metal tube.	ICU Medical MicroClave Clear® (REF : 011-MC100) Batch: 3613805	**Manufacturer**: ICU Medical 951 Calle Amanecer San Clemente CA 92673 USA **Supplier**: ICU Medical Europe 6 place de la Madeleine 75005 PARIS	
	ICU Medical NanoClave® (REF : 011-A1000) Batch: 3651596		
	NEUTRACLEAR® (REF : EL 200) Batch: 22F23-T	**Manufacturer/supplier:** CAIR L.G.L Parc Tertiaire du Bois Dieu, 1 All. des Chevreuils, 69380 LISSIEU - FRANCE	
	DIDACTIC® (REF VALBDDN) Batch: DC161004A	**Manufacturer** : DIDACTIC 76430 Etainhus, France **Supplier** : DIDACTIC, 216 rue Roland Moreno, 76210 Saint-Jean-de-la-Neuville	
	VYGON Bionector® (REF : 896.03) Batch: 271022EU	**Manufacturer:** VYGON, 5 rue Adeline, 95440 Ecouen, France **Supplier** : VYGON, 8 rue de Paris, 95440 Ecouen	

Figure 2. Product references of bidirectional needleless connector used in the experiments. Classification was adapted from bibliographic reference.[21] Note. NC, needleless connector.

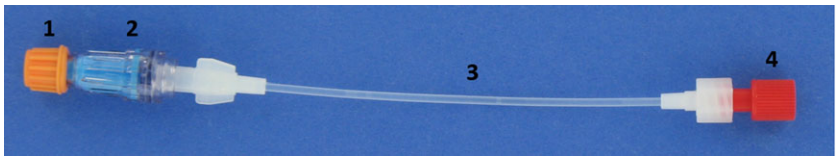

Figure 3. Circuit to connect (1) the isopropanol antiseptic barrier cap, (2) needleless connector, (3) catheter line, and (4) obturator. The example is shown here with a MaxPlus needleless connector and a Swabcap.

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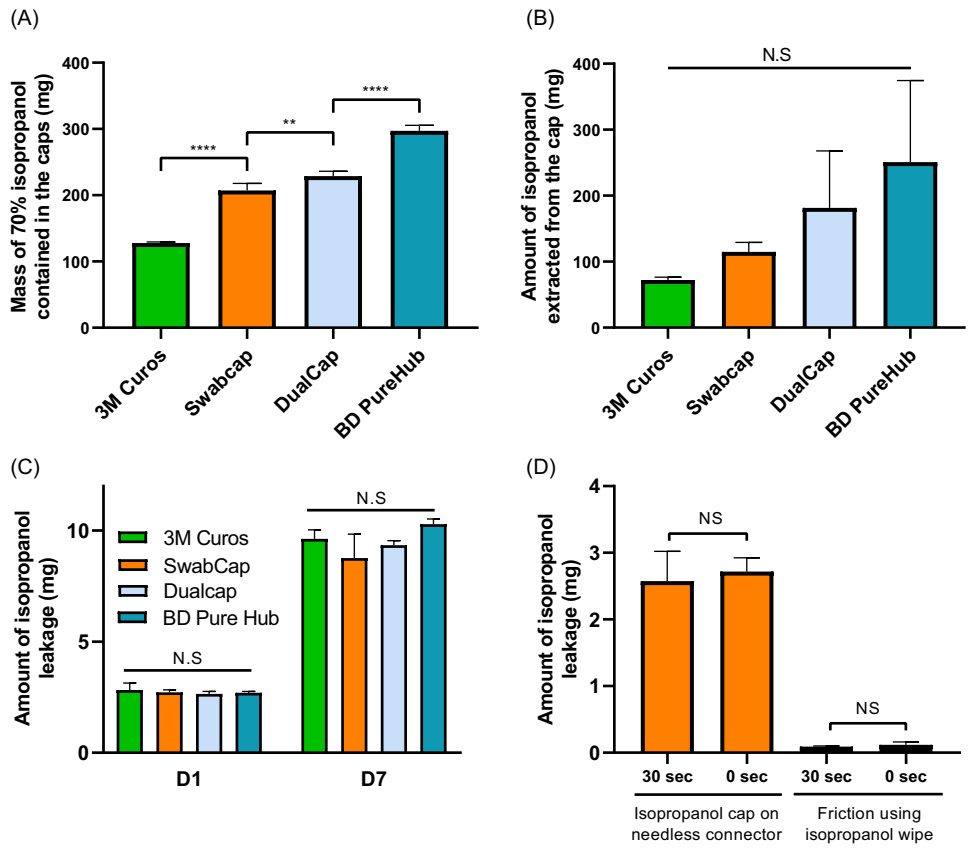

Figure 4. Impact of antiseptic barrier cap parameters on isopropanol leakage through needleless connectors. (A) Difference in mass of antiseptic barrier caps before and after 24 hours in an oven at 37°C and (B) amount of isopropanol extracted during incubation of the antiseptic barrier caps for 24 hours in 5 mL NaCl 0.9%. (C) Influence of antiseptic barrier cap types on isopropanol leakage through needleless connector. The 4 antiseptic barrier caps were placed on a MaxPlus needleless connector for 1–7 days. (D) Influence of the drying time (30 seconds) of isopropanol before rinsing with 5 mL NaCl 0.9%. The SwabCap was placed on the MaxPlus needleless connector for 24 hours. These results are compared with a simple rubbing of an isopropanol wipe for 30 seconds before rinsing with 5 mL NaCl 0.9%. The data are quoted as the mean ± SEM from 3 measurements. **** $P < .0001$; ** $P < .01$. Note. NS, nonsignificant.

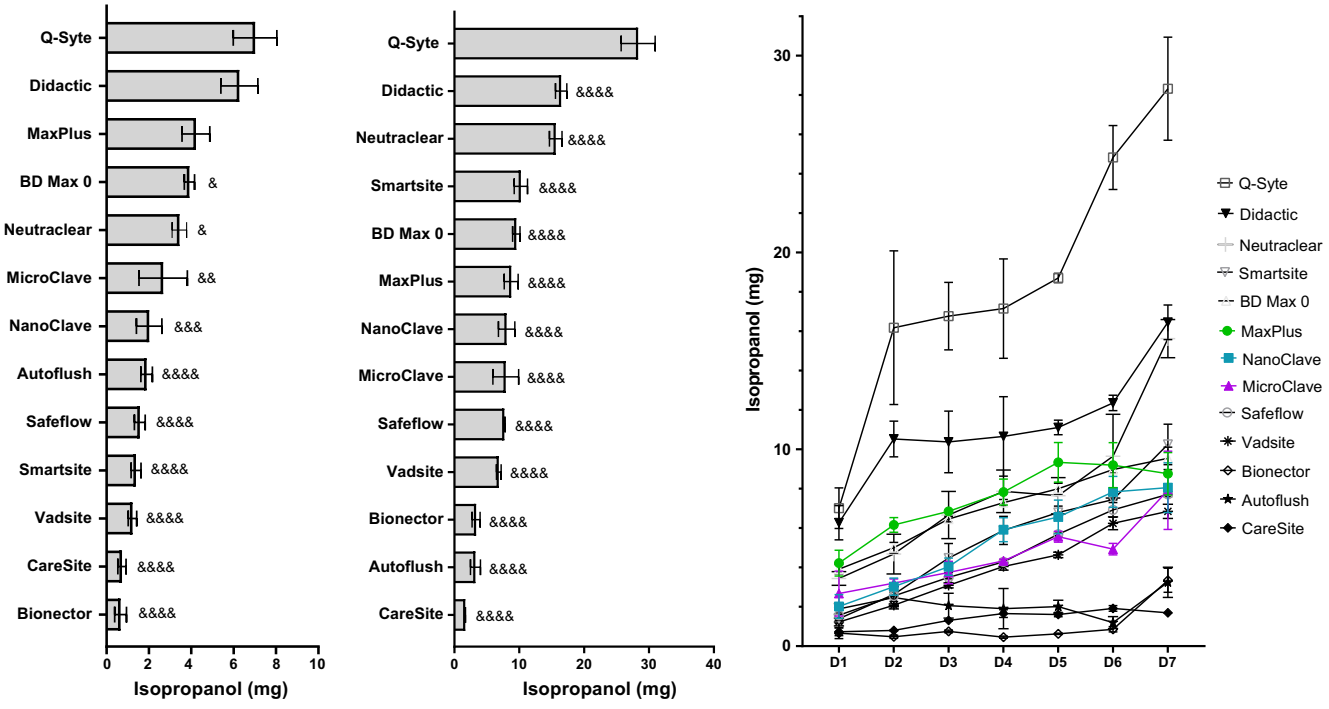

Figure 5. Impact of different needleless connector types on isopropanol leakage. (A) Isopropanol leakage from each antiseptic barrier cap–needleless connector pair was evaluated after 24 hours or (B) 7 days or (C) from 1 to 7 days. The data are quoted as the mean ± SEM from 3 measurements. Compared to Q-syte: & $P < .05$, && $P < .01$, &&& $P < .001$, &&&& $P < .0001$.

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(9.6 hours vs 3–7 hours, respectively).[23,30] Lastly, cases of transcutaneous alcohol intoxication have been described with isopropanol in adults[31,32] and ethanol in children,[33–36] raising the possibility of significant alcohol exposure outside the oral route. Exposure to isopropanol during care requiring the use of central nervous system depressants such as anesthetics could also result in drug interactions (ie, synergistic central nervous system depressant effect). The metabolism of isopropanol to acetone could also interfere with the interpretation of biological tests,[31] and a risk of venous toxicity cannot be excluded. For these reasons, we believe that this issue could be of major concern in neonatal and pediatric intensive care units. To the best of our knowledge, no cases of isopropanol intoxication have been reported following the use of ABCs on NC. However, we believe it is necessary to draw attention to the potential leakage of isopropanol through the NC. This factor should be considered when weighing the benefits of ABCs in reducing the risk of CRBSI against the risk of isopropanol entering the patient's bloodstream.

Lastly, we have shown that the drying time between removal of the isopropanol ABC and injection of solute through the NC did not change the amount of isopropanol passed. These results suggest that the amount of isopropanol present on the NC septum is negligible and is not a major parameter in patient exposure to this alcohol. These results are interesting regarding the uses of isopropanol-soaked wipes, which constitute a simple solution for reducing patient exposure to intravenous isopropanol (Fig. 4).[18] However, the choice of the disinfection method used, whether active or passive, must also take into account the superiority of ABC in terms of reducing the risk of CRBSI compared to isopropanol-soaked wipes.[18]

This study had several limitations. First, this was an in vitro study, and it would be interesting to confirm these results on patients exposed to ABCs. In this context, the contact of these devices with the patient's skin may lead to an increase in the temperature of these devices (ABCs, NC, and catheter), causing an increase in isopropanol leakage, as suggested in a previous report.[20] Second, we were interested in the NCs available on the European market, so further studies are needed to evaluate isopropanol leakage with other product brands used outside Europe.

In conclusion, the use of isopropanol ABCs on NCs can cause isopropanol leakage into the catheter circuit and bloodstream. This leakage is influenced by the NC parameters and not the ABCs. In view of the lack of toxicity data for isopropanol by intravenous administration, caution should be exercised when using these devices, especially in the pediatric and neonatal population. Further studies are needed to assess isopropanol and/or acetone exposure in patients using ABCs on NCs.

Supplementary material. To view supplementary material for this article, please visit https://doi.org/10.1017/ice.2023.285

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