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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 (ABC) 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. The objective of this study is to determine *in vitro* which ABC and NC parameters influence the leakage of isopropanol through the infusion circuit.

Methods: 13 NCs and 4 ABCs available in the European market were reviewed and assessed. *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 NaCl0.9%) 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 was found to have the most isopropanol leakage (7.01±1.03 mg and 28.32±2.62 mg at 24h and 7 days, respectively), while the Caresite® NC was found to have 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.

KEYWORDS: medical device, isopropanol, antiseptic barrier caps, catheter-related bloodstream infections

1. INTRODUCTION

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

Since 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 enabled to eliminate the risk of needle-stick injuries, to prevent blood exposure accidents and thus limit the use of needles on elastomer injection sites when accessing intravascular catheters ⁸. To date, their effectiveness in reducing infections is 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 in 15-30 seconds mechanical scrubbing of the hub membrane (or NC) using 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 in order to continuously impregnate and disinfect the catheter access up to 7 days ^{15,16}. Overall, available evidence suggests that ABCs are effective, safe, easy in use and cost-effective in reducing CRBSI 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 ABC on NC. However, two studies have recently shown that isopropanol contained in the ABCs can leak into the NC, raising safety questions about potential isopropanol exposure to patients during routine care, particularly in a pediatric or 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.

The objectives of this study are (i) to characterize the leakage of isopropanol from the ABC to the NC on all the products available on the European market and (ii) to determine which ABC and NC parameters influence the leakage of isopropanol through the infusion circuit.

2. MATERIAL AND METHODS

2.1. Materials

Four commercially available ABCs (3M Curoc®, DualCap®, BD PureHub®, Swabcap®) were purchased from their respective suppliers as indicated in Figure 1. NC were purchased at the respective manufacturing laboratories, and the associated pictures and product references are detailed in Figure 2. V-green extension lines (product reference 71100.01) were purchased from Vygon (Ecouen, France). Versylène® NaCl0.9% were purchased from Fresenius (Homburg, Germany). Due to the availability of the Swabcap® and the MaxPlus® NC in our institution, these two product references were mainly used in this study.

2.1. Setting up of *in vitro* circuits

Circuits consisting of an isopropanol ABC, a NC, an 11cm polyethylene catheter line (product reference 71100.01, batch 211222EH, Vygon®) and an obturator (product reference 9888.00, batch 241122FD, Vygon®) were created (Figure 3). In all circuits, the catheter line was rinsed and pre-filled with NaCl0.9% 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 of NaCl0.9% which was collected for analysis.

2.1. *In vitro* experiments

The circuits were left in place for 1 to 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 drying time (30 seconds) before rinsing the circuit in order 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 use of these devices do not specify this data.

To evaluate the isopropanol content in the four commercially available ABCs, they were (i) weighed before and after evaporation of their contents in an oven at 37°C for 24h and (ii) left in a closed container containing 5 mL of NaCl0.9% for 24 hours to extract isopropanol.

2.2. Isopropanol quantitation by HS-GC/FID

This method quantified simultaneously methanol, acetone, ethanol and isopropanol (propan-2-ol) using propan-1-ol as internal standard. Gas chromatography (GC) analysis was conducted using a ThermoScientific GC Trace 1300 system 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) using nitrogen as a carrier gas. SSL Injection port temperature was set to 200°C, injection volume was 1 mL with split flow and the oven temperature program was held at 50°C for a 7 min run time. FID detector was at 250°C. Data were recorded and analyzed using Chromeleon 7.2 software using peak area ratios of analyte to internal standard with comparison to a 6 point standard curve for quantitative analysis of each analyte.

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

2.3. 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 one-way analysis of variance (ANOVA), with a Tukey *post hoc* test for group comparisons. All analyses were performed using Prism software (version 8.0, GraphPad Software, La Jolla, CA, USA). All tests were two-sided, and the threshold for statistical significance was set to $p < 0.05$.

3. RESULTS

3.1 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 four commercially available ABCs (Figure 4A-B). A first method by placing the ABCs in a 37°C oven for 24h to evaporate their 70% isopropanol content allowed us to show that the isopropanol contents were significantly different between the ABCs (Figure 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, showing that the BD PureHub® ABC contains 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 Curoc® (72.1±4.3 mg) (although the results did not reach statistical significance) (Figure 4B).

Next, we analyzed isopropanol leakage through a MaxPlus® NC for these 4 ABCs left on for 1 to 7 days. Our results show that isopropanol leakage through the NC was not significantly different between ABCs, either at 1 and 7 days (Figure 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 (Figure 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. Since the SwabCap® is referenced 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.

3.4 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 a ABC (SwabCap®) on 13 different NCs for 1 to 7 days (Figure 5). Our results showed that isopropanol leakage through the NC changes significantly depending on the NC (Figure 5). Table S1 describes overall difference test for isopropanol leakage after 24h or 7 days of experiment, while complete statistical differences in isopropanol leakage between each NC after 24h or 7 days of experiments are described in Table S2 and S3, respectively (supplementary data).

Twenty-four hours of ABC attachment to the NC was sufficient to observe differences in isopropanol leakage between the different NC. The Q-Syte®, Didactic® and MaxPlus® NCs appear to be 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 product references did not appear to be significantly different in terms of isopropanol leakage despite the trends observed in Figure 5A. The Bionector® NC emerged as the least isopropanol-leaching NC, with an average of 0.66±0.27 mg of isopropanol leaked after 24h of use (Figure 5A).

After 7 days of use, the Caresite® NC emerged as the least isopropanol-leaching NC, with an average of 1.69±0.01 mg of isopropanol leaked. On the other hand, the Q-Syte® NC stands out

as the NC that allows the most isopropanol to pass through with an average of 28.32 ± 2.62 mg of isopropanol leaked (Figure 5B). The trends observed at 24 hours were found at 7 days, and were confirmed by the study of the kinetics of isopropanol leakage through the NC (Figure 5C).

4. DISCUSSION

Despite their vital importance, catheters may cause potentially life-threatening complications including CRBSI. To reduce this comorbidity, the most recent clinical evidence support the use of NCs and ABCs for passive and continuous disinfection of NCs¹⁸. In this study, we showed that isopropanol can leak from the ABCs to the NC as a function of time, posing concerns about their uses. In particular, we determined that the product reference 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 a 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 (Figure 2, Figure 5). Overall, Caresite® and Bionector® NCs appears as the safer choices when using together with isopropanol ABCs, from an isopropanol leakage point of view. The product reference 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. (2020) reported isopropanol leakage ranging from 0.154 to 0.405 mg after 24h depending on the NC/ABC combination used (Swan-lock® or Bionector® coupled to SwabCap® or CuroS®)¹⁹. Particularly, the combination Bionector® + SwabCap® showed a maximum isopropanol leakage of 0.372 mg after 24h, compared to 1.220 mg in our study and the combination Safeflow® + Swabcap® showed a maximum isopropanol leakage of 1.755 mg after 24h, compared to 2.066 mg in our study. Due to the different methodologies used in the literature (which aimed to mimic the true-life conditions^{19,20}) and in our study (which aimed to know how much isopropanol passes from the ABC to downstream of the NC), the comparison of the results is difficult to interpret. However, the results found in the literature and in our study are of the same order of magnitude since 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. (2020), who reported that 2 NCs (Smartsite® or MaxPlus®, unspecified) became opaque during their

study on ABCs thus suggesting that isopropanol appears to have seeped between the inner rubber and outer plastic, denaturing the plastic²². Similarly, Sauron et al. (2015) 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 piece²⁰. In our experiments, we did not observe such denaturation of the plastic.

Second, toxicokinetic data available in humans report that absorption of isopropanol is large and rapid through the lungs and gastrointestinal tract and smaller through the skin. However, no data are available on intravenous isopropanol administrations, raising questions about the safety of such exposure. While isopropanol has a half-life of 3 to 7 hours, its metabolite acetone has a half-life of 22 hours and is primarily excreted by the kidneys²³. 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 collapse²³.

Previous reports mention that isopropanol toxic blood concentrations vary between 250 and 5200 mg/L²⁴⁻²⁸. As the smallest weights of newborns can be around 500g (and total blood volume of a child is around 75-80 mL/kg), these issues therefore appear to be of greater concern in a pediatric or neonatal population in view of the possible large dose of isopropanol exposure²⁹. 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 infant than in adults (9.6h versus 3-7h, respectively)^{23,30}. Lastly, cases of transcutaneous alcohol intoxication have been described with isopropanol in adults^{31,32} and ethanol in children³³⁻³⁶, 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 *i.e* synergistic central nervous system depressant effect. The metabolism of isopropanol to acetone could also interfere with the interpretation of biological tests³¹ 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 to date 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

should be taken into account when weighing up the benefits of ABCs in reducing the risk of CRBSI against the risk of isopropanol entering the patient's bloodstream.

Lastly, we showed that the drying time between removal of the isopropanol ABC and injection of solute through the NC did not change the amount of isopropanol to be 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 with regard to the uses of isopropanol-soaked wipes, which therefore constitute a simple solution for reducing patient exposure to intravenous isopropanol as shown in Figure 4¹⁸. 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 wipes¹⁸.

This study must be interpreted according to several limitations. First, this is an *in vitro* study, and it would be interesting to confirm these results on patients exposed to ABCs. In this context, it cannot be excluded that the contact of these devices with the patient's skin leads to an increase in the temperature of these devices (ABCs/NC/catheter), causing an increase in isopropanol leakage as suggested in a previous report²⁰. Second, we were interested in the NCs available on the European market, so further studies are needed to evaluate isopropanol leakage with other product references used outside Europe.

5. CONCLUSIONS

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.

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Not applicable

AVAILABILITY OF DATA AND MATERIALS

All data generated or analysed during this study are included in this published article.

COMPETING INTERESTS

The authors declare that they have no competing interests.

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AUTHOR CONTRIBUTION

Drs Lurton, Le Daré and Boissière had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. Yves Lurton and Brendan Le Daré are co–senior authors.

Study concept and design: Yves Lurton, Brendan Le Daré, Astrid Bacle, Camille Boissière

Acquisition, analysis, or interpretation of data: All authors.

Drafting of the manuscript: Brendan Le Daré, Camille Boissière

Critical revision of the manuscript for important intellectual content: All authors.

Statistical analysis: Brendan Le Daré

Administrative, technical, or material support: Yves Lurton

Study supervision: Yves Lurton and Brendan Le Daré

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FIGURES





Product reference	Manufacturer	Supplier	Pictures
3M Curoso® (REF: CFF1-270R) Batch : 9246521	3M Health 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












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	

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

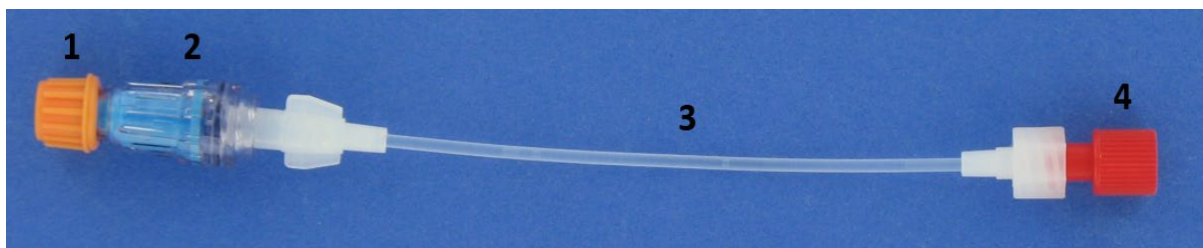


Figure 3: Circuit to connect the isopropanol antiseptic barrier cap (1), needless connector (2), catheter line (3) and obturator (4). The example is shown here with a MaxPlus® needless connector and a Swabcap®.

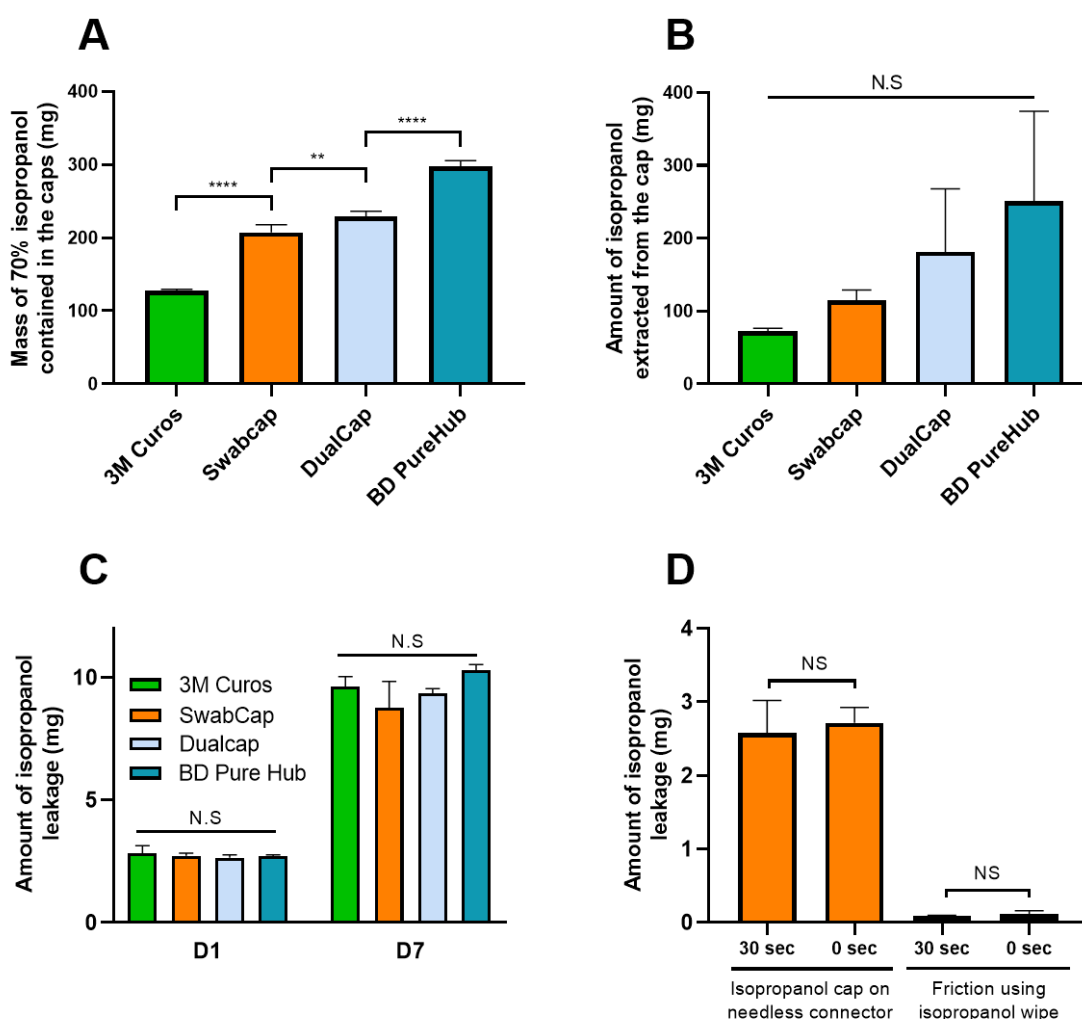


Figure 4: Impact of antiseptic barrier cap parameters on isopropanol leakage through needless connectors. (A) Difference in mass of antiseptic barrier caps before and after 24h in an oven at 37°C and (B) amount of isopropanol extracted during incubation of the antiseptic barrier caps for 24h in 5 mL of NaCl0.9%. (C) Influence of antiseptic barrier cap types on isopropanol leakage through needless connector. The 4 antiseptic barrier caps were placed on a MaxPlus® needless connector for 1-7 days. (D) Influence of the drying time (30 seconds) of isopropanol before rinsing with 5mL of NaCl0.9%. The SwabCap® was placed on the MaxPlus® needless connector for 24 hours. These results are compared

with a simple rubbing of an isopropanol wipe for 30 seconds before rinsing with 5 mL of NaCl0.9%. The data are quoted as the mean \pm SEM from three measurements. **** $p < 0.0001$; ** $p < 0.01$. NS: non-significant; D: day; sec: second.

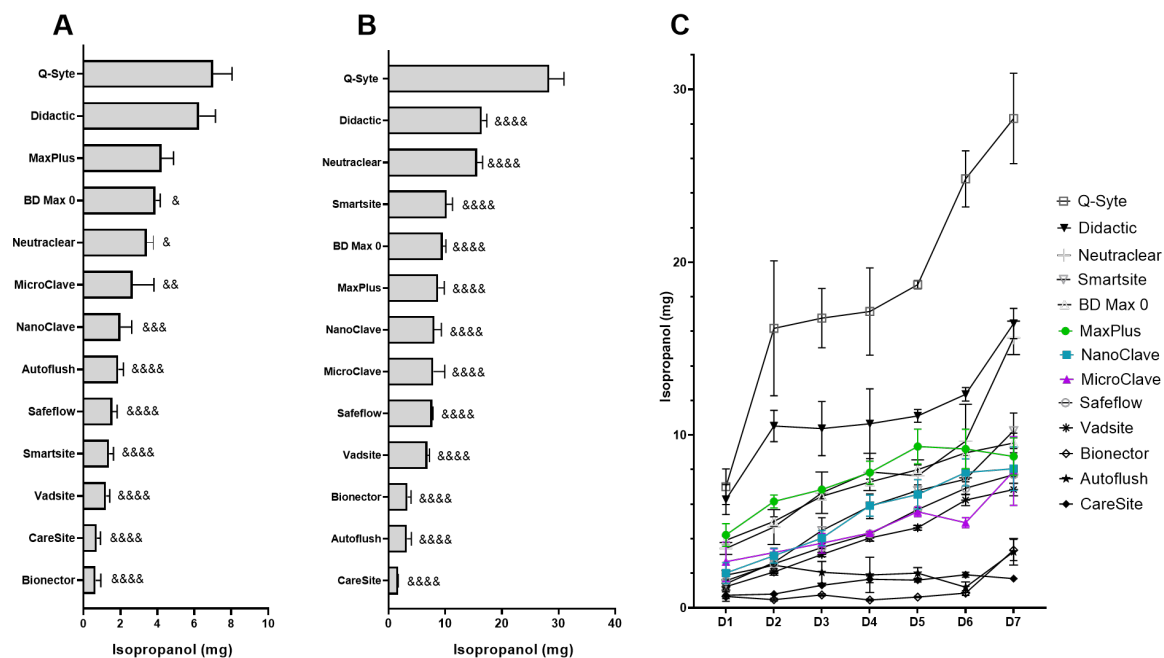


Figure 5: Impact of different needleless connector types on isopropanol leakage. (A) Isopropanol leakage from each antiseptic barrier cap/needleless connector pair was evaluated after 24h or (B) 7 days or (C) from 1 to 7 days. The data are quoted as the mean \pm SEM from three measurements. Compared to Q-syte®: & $p < 0.05$, && $p < 0.01$, &&& $p < 0.001$, &&&& $p < 0.0001$. D: day.