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Original article

Taurolidine-related adverse events in patients on home parenteral nutrition frequently indicate catheter-related problems

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SUMMARY

Background & aims: A catheter-related bloodstream infection (CRBSI) is a serious complication of home parenteral nutrition (HPN) treatment. Despite taurolidine's frequent use as catheter lock solution (CLS) to prevent CRBSIs and its presumed favourable safety profile, data on taurolidine-related adverse events (AEs) and the clinical implications thereof remain merely anecdotal. Aim of this study was to explore taurolidine-related AEs in our large cohort of HPN patients and to develop an algorithm on how to deal with these AEs in clinical practice.

Methods: This retrospective cohort study comprised all adult HPN patients who used taurolidine as a CLS between 2006 and 2021 at our national HPN referral centre. Primary outcome was to identify taurolidine-related AEs. Secondary outcomes were median time to a taurolidine-related AEs and development of a clinical algorithm. A taurolidine-related AE was defined as an event that occurred directly after instillation of taurolidine in the CVAD or at start of fluid/PN infusion.

Results: In total, 470 patients used taurolidine during 700.232 catheter days. In 89 (19%) patients, 103 mild- to severe AEs related to taurolidine were observed. Six patients developed an allergic reaction. Reported AEs compromised vascular access device-related problems (group A) or taurolidine-related problems (group B) in 53 (51%) and 50 (49%), patients, respectively. In groups A and B, 51 (85%) and 21 (18%) patients presented with taurolidine infusion-related pain. Upon rechallenge, 45 (85%) and 16 (32%) patients, respectively, successfully resumed taurolidine locking without residual symptoms.

Conclusion: In this study, use of taurolidine as CLS was generally safe. Most reported AEs were vascular access device-related, and the majority of symptoms concerned pain. Upon rechallenge, a substantial number of patients, especially those in whom pain was the main symptom, could resume CLS locking after addressing the underlying catheter-related problem. Based on these results, we present a clinical algorithm for patients with possible taurolidine-related symptoms.

1. Introduction

Chronic intestinal failure (CIF) patients require long-term parenteral (intravenous) nutrition (PN) and/or fluid supplementation to maintain health and/or growth because of severe gut dysfunction [1]. Home parenteral nutrition (HPN) is a complex and time-consuming treatment that focuses on training patients to self-manage their central venous access device (CVAD) and infusion pump at home [2]. Unfortunately, HPN patients are frequently admitted to the hospital because of potentially life-threatening catheter-related bloodstream infections (CRBSIs). Thus, preventing CRBSIs by maintaining adequate and safe venous access remains key to both patient and technique survival. The most crucial strategy to prevent CRBSIs is strict adherence to antiseptic protocols when managing CVADs [3]. An additional preventive technique is the use of antimicrobial catheter lock solutions (CLSs), such as taurolidine [1].

Taurolidine, a derivate of the amino acid taurine, was first synthesized in the 1970s and used initially as a local treatment for bacterial peritonitis [4,5]. This agent prevents microbial adhesion to catheter surfaces and biofilm formation by engaging an irreversible reaction of its metabolites with bacterial cell components [6–8]. Because of this mode of action, which fundamentally differs from antibiotics, taurolidine displays a very broad spectrum of activity against bacterial as well as fungal pathogens [9–11].

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In line with these notions, clinical studies found taurolidine to be highly effective in preventing CRBSIs when compared to other CLSs [12–14]. From 2006 on, HPN patients in our own tertiary CIF referral centre started using 2% taurolidine as CLS, initially in the context of an open-label randomized trial [15]. Based on the favourable results of this study, in 2008, all of our patients were switched to taurolidine. This has remained our preferred CLS ever since, resulting in CRBSI rates as low as 0.6 events per 1000 catheter days [14]. Over these years, we have obtained a solid body of experience comprising more than 600.000 taurolidine locks.

The reason for the present study is that despite its efficacy in preventing CRBSIs, and while the use of taurolidine locks has generally been found to be safe, there is still limited information on (suspected) taurolidine-related adverse events (AEs) and the implications thereof. To our knowledge, studies are lacking in CIF patients that focused primarily on taurolidine-related AEs. In addition, we wanted to confirm our impression that in a substantial number of cases, patient-reported "side effects" in fact indicate catheter dysfunction, rather than taurolidine-related problems per se (intolerance, allergy, anaphylaxis). Hence, the aim of this study was to evaluate taurolidine-related AEs in our HPN patient cohort who used taurolidine as CLS, and provide an algorithm on taurolidine use for clinical practice.

2. Methods

2.1. Study design and patient selection

This retrospective cohort study was conducted at Radboud University Medical Center, a tertiary referral centre for CIF. Patients were selected from the Nijmegen IF Registry, a web-based Castor EDC database [16]. Patients aged ≥18 years were included if they met the criteria for CIF, received HPN for a minimum of three months, and used taurolidine as CLS between January 2006 and December 2021 [1].

2.2. Data collection

Patient characteristics (sex, age, and underlying disease leading to CIF), CVAD characteristics (type, site of vein insertion, date of insertion, and removal), and HPN characteristics (type of infusion, number of infusions per week, CLS) were collected from the Nijmegen IF registry. For this study we conducted a search in the medical records of all patients and we added data on taurolidine-related AEs to the Nijmegen IF registry.

2.3. Taurolidine management

After each PN or fluid infusion, the CVAD is rinsed with 20 mL 0.9% saline. Subsequently, 5 mL 2% taurolidine (Taurosept, Geistlich Pharma AG Wolhusen, Switzerland) is instilled in the CVAD and remains until the next PN or fluid infusion, when the taurolidine lock is slowly flushed into the patient. Hence, the dwell time of taurolidine differs per patient and depends on the number of infusions per week but usually ranges from 8 h (daily PN) to 72 h (PN twice weekly).

When patients experience a taurolidine-related AE, our strategy is to switch to another taurolidine-containing solution (1.35% taurolidine with 4% citrate; TauroLock, TauroPharm GmbH Waldbüttelbrunn, Germany) or 0.9% saline, depending on the severity of the AE. A rechallenge with 2% taurolidine is conducted if considered safe by a treating physician. In case of doubt, this procedure is performed at the clinical ward.

2.4. Outcomes and definitions

Primary outcome were taurolidine-related AEs in patients with CIF receiving HPN. Secondary outcomes were to identify the cause of the AEs, the median time to a taurolidine-related AE, present the number and location of rechallenges with taurolidine, and to provide an algorithm on how to deal with taurolidine-related AEs in clinical practice. A taurolidine-related AE was defined as an event that occurred directly after instillation of taurolidine in the CVAD or at start of fluid/PN infusion. Patients were categorized into two groups: group A ("vascular access device-related problems") included patients who experienced an AE during a vascular access device-related problem, and group B ("taurolidine-related problems") consisted of patients with most likely taurolidine-related AEs.

2.5. Taurolidine-related adverse events

Taurolidine-related symptoms were independently assessed by two investigators (JK and VG) according to the common terminology criteria for AEs (CTCAE version 5.0) [17]. A third investigator made a final judgement in the absence of consensus (GW). The CTCAE classifies the severity of symptoms into grades from 1 to 5, with a clinical description per grade. In general, grade 1 is mild (asymptomatic or mild symptoms), grade 2 is moderate (minimal, local, or non-invasive intervention indicated), grade 3 is severe

Table 1
Baseline characteristics of both patients and central vascular access devices.

Patient characteristics	n = 470
Female - no. (%)	316 (67)
Age - median years (IQR)	63 (21)
Cause of intestinal failure - no. (%)	
Short bowel syndrome	191 (41)
Gastrointestinal motility disorder	167 (36)
Extensive small bowel mucosal disease	23 (5)
Intestinal fistula	29 (6)
Mechanical obstruction	18 (4)
Other	42 (9)
CVAD characteristics	**n = 1.482**
Type of CVAD – no. (%)	
Tunnelled catheter	1.030 (70)
Subcutaneous port system	267 (18)
Nontunneled catheter	62 (4)
Peripherally inserted central catheter	116 (8)
Other or unknown	7 (0)
Site of vein insertion – no. (%)	
Left	550 (37)
Right	877 (59)
Other	2 (0)
Unknown	53 (4)
Type of vein insertion – no. (%)	
Jugular vein	847 (57)
Subclavian vein	287 (19)
Femoral vein	141 (10)
Other	21 (1)
Unknown	186 (13)
Type of infusion - no. (%)	
Nutrition	610 (41)
Fluids	160 (11)
Nutrition and fluids	710 (48)
Other or unknown	2 (0)
Infusion – no. per week (%)	
1	2 (0)
2	32 (2)
3	73 (5)
4	83 (6)
5	84 (6)
6	78 (5)
7	1130 (76)

AE: adverse event, CVAD: central venous access device, IQR: inter-quartile range.

(medically significant, but not immediately life-threatening), grade 4 is life-threatening, and grade 5 is a death related to an AE. A list of the used CTCAE terms can be found in Supplementary files Table 1.

2.6. Statistical methods

Baseline characteristics, primary and secondary outcomes were summarized using descriptive statistics (frequencies, percentages, mean, median and interquartile ranges (IQR). Continuous variables were presented as means with standard deviations or medians and IQR if not normally distributed. Missing data were separately noted in the baseline Table. All statistical analyses were performed using IBM SPSS Statistics for Windows, version 25.0 (IBM Corp. Armonk, NY, USA).

2.7. Ethical approval

This study was approved by the research ethics committee of the Radboudumc in Nijmegen, the Netherlands (reference number 2020-6524) and was reported according to the STROBE guidelines [18].

3. Results

3.1. Demographics

Between 2006 and 2021, a total of 518 patients were under treatment in the Radboud University Medical Center, of whom 470 used taurolidine during 700.232 catheter days. Baseline characteristics of both patients and CVADs are presented in Table 1.

3.2. Taurolidine-related adverse events

In total, 175 symptoms were reported, resulting in 103 taurolidine-related AEs in 89 (19%) patients (Fig. 1). A patient could experience multiple symptoms during one AE. The AE rate was 0.15 per 1000 catheter days. Symptoms ranged from mild to severe, and mostly were pain-related. No life-threatening AEs occurred. Six

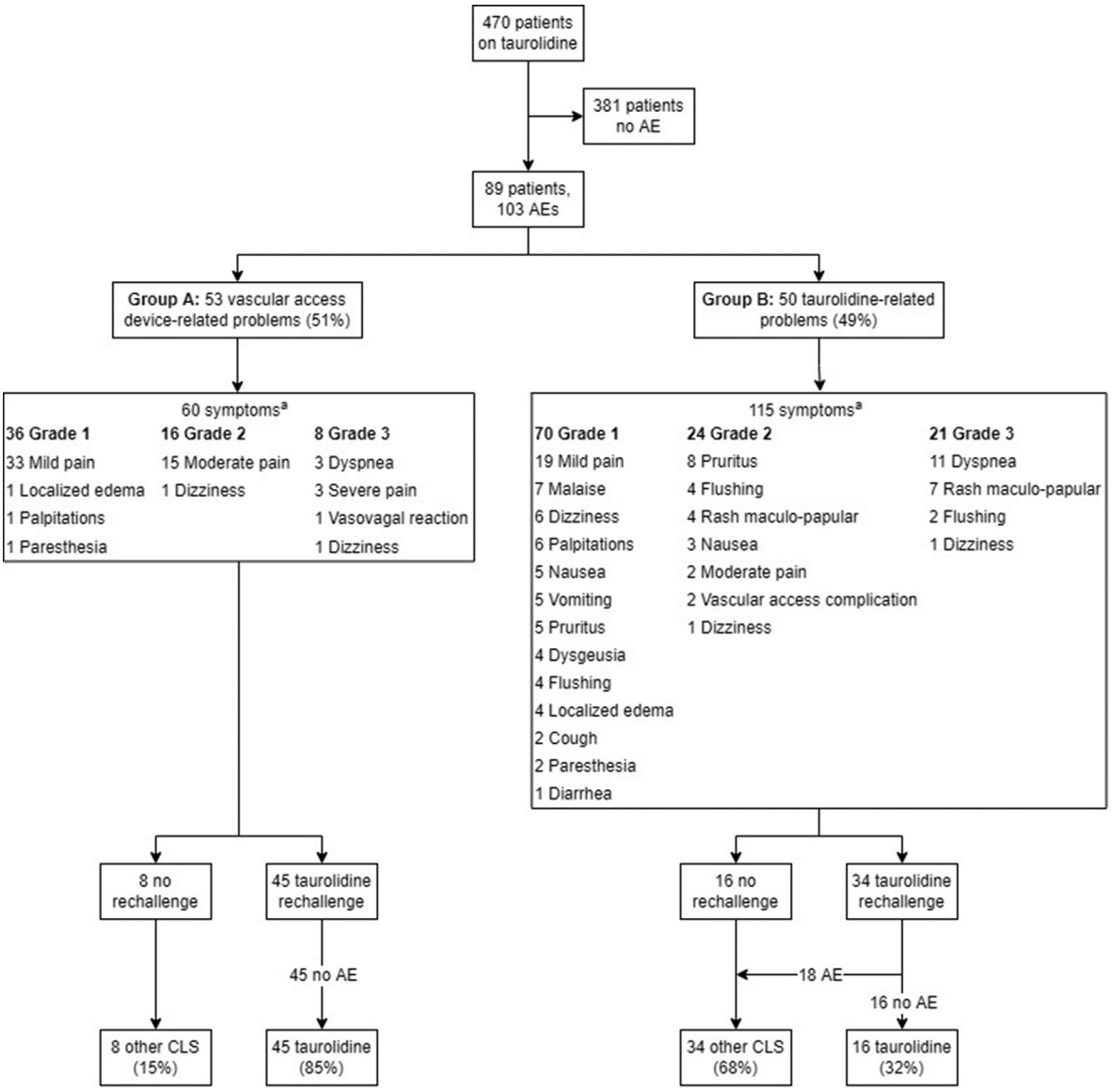

Fig. 1. Flowchart of patient-reported symptoms when using 2% taurolidine, categorized into two groups according to their underlying cause and subsequent rechallenges with taurolidine. CTCAE; common terminology criteria for adverse events, AE; adverse event. CLS; catheter lock solution [a]Patients may have experienced multiple symptoms during one AE. In total, six patients developed an allergic reaction. Grade 1: mild (asymptomatic or mild symptoms), grade 2: moderate (minimal, local, or non-invasive intervention indicated), and grade 3: severe (medically significant, not immediately life-threatening).

patients developed an allergic reaction, all grade 3 reactions. The cause of AEs was considered in 53 (51%) vascular access device-related (group A), while 50 (49%) were taurolidine-related (group B) (Fig. 1).

3.3. Vascular access device-related problems (group A)

In total, 53 AEs in 43 patients were considered vascular access device-related problems. The various symptoms and their severity are shown in Fig. 1. Fifty-one (85%) patients presented with taurolidine infusion-related pain (Fig. 2). Reasons for the symptoms were: 23 thromboses (43%), 14 CVAD malpositions (26%), 7 CRBSIs or local infections (13%), 3 CVAD malfunctions (6%), and 6 unknown (11%). The patients with an unknown cause had no abnormalities on imaging. However, the CVAD was removed because of persistent pain. After treatment or CVAD removal, 45 (85%) patients restarted with taurolidine without recurring AEs (Fig. 1). Thirty-four rechallenges were performed at the clinical ward (not because of severe symptoms but because patients were already admitted), other 11 rechallenges were performed at home due to mild symptoms. Eight patients received no rechallenge with taurolidine since one patient restarted HPN using an arteriovenous fistula (shunt), four patients stopped HPN, two patients did not agree to a rechallenge, and one patient died due to a non-HPN related problem.

3.4. Taurolidine-related problems (group B)

In this group, 115 symptoms were reported, resulting in 50 taurolidine-related AEs in 50 patients. The various symptoms and their severity are shown in Fig. 1. Twenty-one (18%) patients presented with taurolidine infusion-related pain (Fig. 2). Sixteen patients received no rechallenge because in 10 patients the attending physician decided that a rechallenge was not appropriate due to the severity of symptoms, two patients restarted HPN via an arteriovenous fistula, two patients did not agree to a rechallenge, one patient stopped HPN and one patient was lost to follow up as care was transferred to another hospital. The other 34 patients received a rechallenge with a taurolidine containing CLS. Twenty-nine rechallenges were performed at home due to mild symptoms, the other 5 were performed at the clinical ward (due to severe symptoms or because these patients had already been admitted). Eighteen patients experienced symptoms again and subsequently switched to 0.9% saline as CLS. Sixteen patients experienced no or mild symptoms. Hence, two continued with taurolock and fourteen with taurosept as CLS (Fig. 1). Four patients immediately experienced symptoms after taurolidine instillation. The median time to an AE in this group was 701 days (IQR 1673).

Notably, 8 patients (16%) experienced a total of 12 mild symptoms due to extra-protocol use of taurolidine. This mostly concerned: a double dosage injection (1 patient) or a too rapid infusion (7 patients). After receiving protocol guidance on how to use taurolidine correctly, all 8 (100%) patients restarted without developing new AEs.

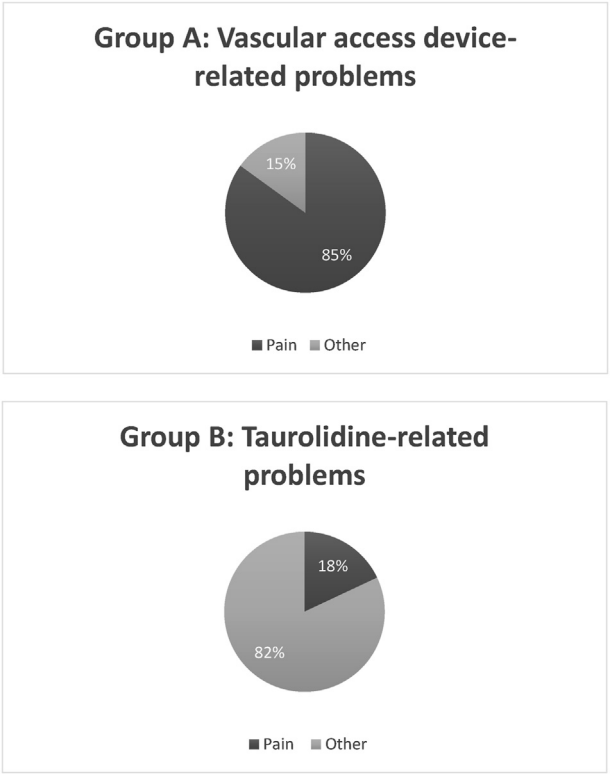

Fig. 2. Proportion of taurolidine infusion-related pain versus "other" symptoms.

3.5. Clinical algorithm on taurolidine-related adverse events

Based on our experience and the data gathered in this study, we propose a clinical algorithm for patients who develop symptoms following taurolidine use (Fig. 3). In case of symptoms, patients are requested to replace taurolidine with 0.9% saline locking for one week. Depending on the severity of the AE, a rechallenge should be performed either at home or in a controlled hospital setting. The attending physician should always determine whether a rechallenge is justified in case of a severe AE (e.g. anaphylactic reaction). Before rechallenge, protocol guidance on how to use taurolidine correctly should be provided, for example, by extra slowly instilling taurolidine in the CVAD and by flushing taurolidine at least every week. The patient may continue taurolidine treatment in case of no recurrence of symptoms after the rechallenge. Diagnostics to rule out vascular access problems should be performed whenever the patient experiences recurrent symptoms during this rechallenge. Diagnostics usually concern careful inspection of the catheter (exit site) for catheter damage. In addition, fluoroscopy may be performed to detect catheter malpositioning or occlusion. The latter mostly occurs in the form of thrombosis or a fibrin sheath that surrounds the catheter tip and reverses blood flow. In case of a vascular access problem, a rechallenge can be performed after treatment of the underlying problem. The latter mostly implies the use of a fibrinolytic agent to remove a clot or fibrin sheath, but in case of dislocation, catheter removal is required. If diagnostic imaging shows no abnormalities or in case of recurrent symptoms, consider switching to another CLS.

4. Discussion

While taurolidine-containing formulations are becoming increasingly popular as CLS to prevent CRBSIs, data on safety and related AEs are lacking. This study describes the largest body of such data in a single centre HPN cohort available to date and provides an algorithm on how to address possibly taurolidine-related problems. Based on an observation period that spans sixteen years, we demonstrate that taurolidine is generally safe but that in case of lock-related symptoms, suspicion should be raised concerning CVAD dysfunction, especially occlusion or dislocation. More specifically, vascular access-related problems caused 51% of all AEs, 85% of which presented with pain, and almost all resolved by treating the underlying CVAD-related problem.

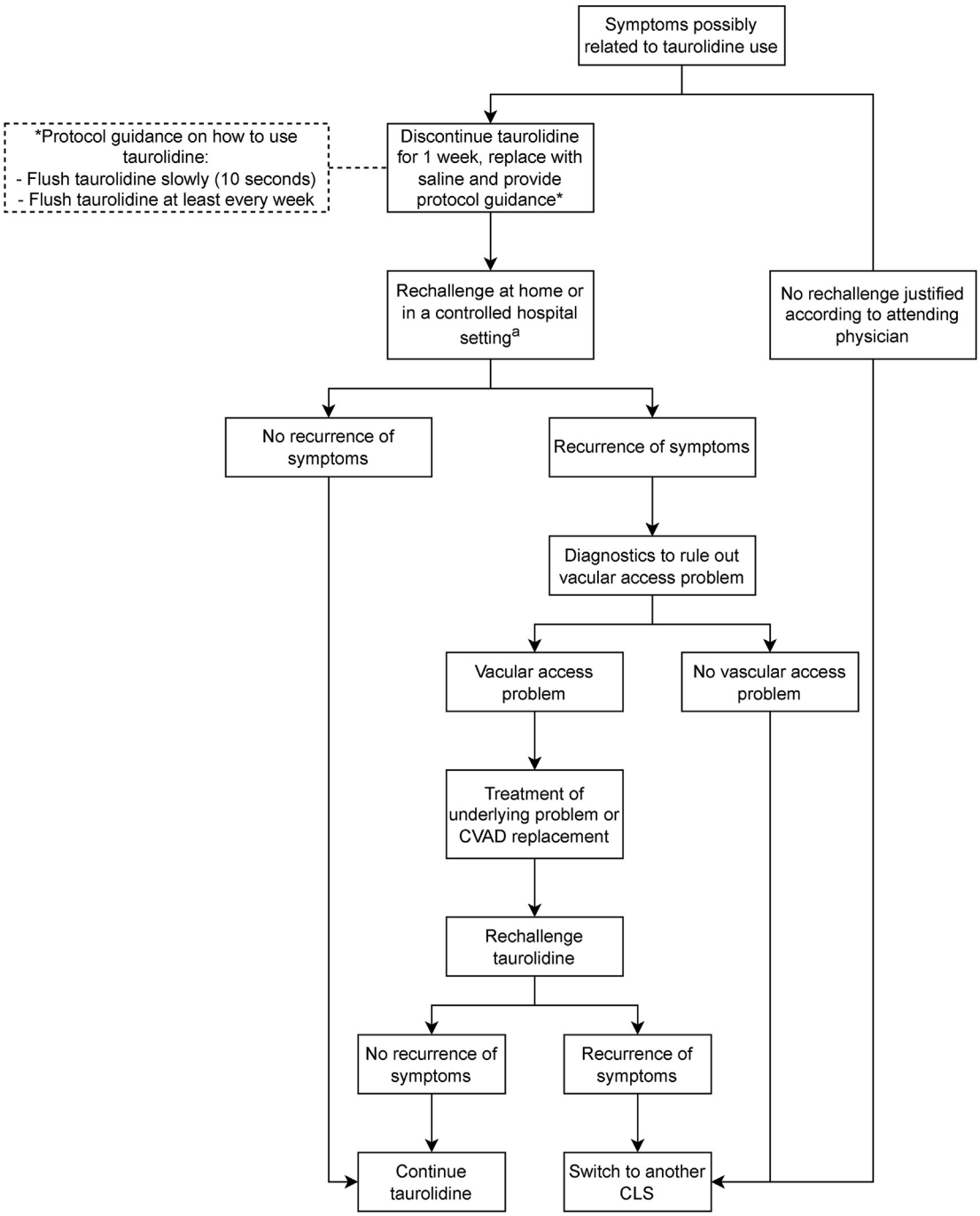

Fig. 3. Algorithm on taurolidine-related adverse events in clinical practice. CLS: catheter lock solution. [a]Left to the discretion of the threating physician.

To date, nine smaller studies on adult HPN patients reported on taurolidine-related AEs. Five (total of 65 patients) found no AEs [15,19–22], while four studies (450 patients) observed 45 patients (10%) with drug-related AEs [12–14,23], mainly pain, taste changes, dyspnea and nausea, vomiting or anorexia. These symptoms corroborate the findings of our study and those reported in oncology and dialysis patients [24,25].

CLSs may be used in two ways, i.e., as a lock solution that is flushed into the patient upon the next PN administration or as a lock that is withdrawn to avoid contact with the systemic circulation. Taurolidine is registered as a medical device, which would preclude intravenous use, however, we choose to flush this lock for several reasons. First, aspiration is not always possible due to obstruction of the catheter tip opening at the level of the vessel wall following suction. Second, since the catheter volume is about 1.5 mL, and assuming that around 5 mL is instilled as a lock, this implies that with each locking of the CVAD, approximately 3.5 mL is flushed into the systemic circulation anyway. Third, by omitting aspiration of taurolidine, we seek to prevent blood from entering the catheter since the latter promotes intraluminal biofilm formation [26]. While the half-life of taurolidine is short, with rapid breakdown into its natural downstream metabolites (i.e., taurine, carbon dioxide, and water [27–29]), concerning toxicity, it has to be realized that intravenous infusions have been reported of up to

20 g/day in the context of treatment of oncological conditions (1000 mL of 2% taurolidine), with an acceptable safety profile [30–32]. Nevertheless, the fact that we flush taurolidine into our patients may have influenced the number and severity of the AEs.

We categorized our cohort into two groups based on the cause of the AE, i.e., vascular access device-related problems (group A) or taurolidine-related problems (group B). In group A, 85% of the patients presented with taurolidine infusion-related pain compared to 18% in group B (Fig. 2). Infusion-related pain is most probably due to congestion and backflow of blood. Moreover, it is known that taurolidine, similar to propofol, reversibly activates the irritant receptor transient receptor potential ankyrin 1 (TRPA1) in calcitonin gene-related peptide (CGRP)-expressing, thus nociceptive, neurons [33]. Transient pain induction and irritation due to neuropeptide release are probably consequences of these properties. A key finding of the present study is that a major subset of patients with vascular access-related problems presents with taurolidine infusion-related pain, which in fact indicates device malfunctioning. Hence, we recommend performing diagnostic imaging, including fluoroscopy or ultrasonography, to rule out vascular problems if the taurolidine-related AE continues after rechallenge. In addition to the previous paragraph, flushing taurolidine into the patient reveals vascular access device-related problems, allowing us to detect and treat this problem earlier.

In the taurolidine-related AE group, a broad range of symptoms was observed. It is essential to realize that besides taurolidine, these CLSs also contain other components such as stabilizing agents and sometimes anticoagulants (citrate, heparin, urokinase). It is considered unlikely that the reported AEs were caused by taurolidine itself because, as mentioned before, it is rapidly metabolized into bodily taurine, carbon dioxide, and water. Polyvinylpyrrolidone (povidone, PVP), a synthetic hydrophilic polymer used as a stabilator in taurolidine, could possibly cause AEs since allergy to povidone has been reported in increasing frequency [34,35]. In the taurolidine-related AE group, two patients had a vascular access complication according to the CTCAE classification while using taurolidine. Both patients had a subcutaneous port system and used suppletion of magnesium chloride, which we think may have clogged due to precipitation of magnesium and taurolidine. The median time to an AE in this group was 701 days, which shows that taurolidine-related AEs can occur even after prolonged taurolidine use. Eight patients in this group experienced symptoms when infusion of taurolidine was performed too fast or when a double dosage (10 mL 0.2 g taurolidine) was applied. Concerning the latter, this issue remains uncertain; in a study on 18 healthy men where 5 g of taurolidine were administered by intravenous infusion, all subjects noted discomfort at the infusion site, however, no serious AEs were observed [27]. These notions show that it is crucial to check for protocolar use of taurolidine in case patients present with a suspected taurolidine-related AE.

In our cohort, two patients experienced an AE when taurolidine had remained inside the CVAD for more than two weeks, whereas previously, they had no symptoms with daily flushing of their lock. This implies that alterations in the composition of the CLS may play a role, for instance, due to precipitation after a prolonged instillation period.

An extensive protocol on how to use taurolidine as CLS was lacking in the literature. Based on our experience, we proposed a clinical algorithm to prevent the discontinuation of taurolidine as a tool to prevent CRBSIs (Fig. 3). Since 51% of the possibly taurolidine-related AEs were caused by vascular device-related problems, and 85% of patients restarted taurolidine without any issues in this group, diagnostic imaging is a cornerstone in our algorithm. In addition, given the experienced problems after extra-protocol use of taurolidine and symptoms following the presence of taurolidine inside the CVAD for more than two weeks, we made recommendations for the use of taurolidine as CLS; it is important to flush taurolidine slowly (a minimum of 10 s), and we suggest that taurolidine may stay in the CVAD for a maximum of one week before flushing it.

This study has strengths and limitations. The retrospective nature is a limitation that precludes statements on causality. Underreporting of AEs may have played a role and retrospective assessment, especially grading, of AEs is suboptimal. On the other hand, we collected and analysed the most robust patient cohort from a single centre so far. Another strength is that we not only list these AEs but also point out a frequent underlying cause (catheter malfunction) that should urgently be addressed, and we provide an algorithm on taurolidine use for clinical practice (Fig. 3).

In conclusion, our study shows that not only the use of taurolidine was found to be generally safe, but also it is essential to realize that many reported presumed taurolidine-related AEs signify catheter-related problems rather than an intolerance or allergy to taurolidine. After addressing these issues, based on its proven efficacy to prevent CRBSIs, a rechallenge should be strongly considered.

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Author contributions

Julia Korzilius: Methodology, Formal analysis, Investigation, Writing – original draft Veerle Gillis: Methodology, Formal analysis, Writing – review & editing Yannick Wouters: Writing – review & editing Geert Wanten: Conceptualization, Methodology, Writing – review & editing.

Data share

Data described in the manuscript will be made available upon request pending application and approval by the corresponding author.

Conference presentation

Poster presentation ESPEN September 2022.
Oral presentation WoCoVa October 2022.

Conflict of interest

None.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.clnu.2022.07.025.

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