SUMMARY OF SAFETY PROFILE

KiteLock™ 4% Sterile Catheter Lock Solution

The following discussion demonstrates that the edetate concentration contained in KiteLock™ 4% Sterile Catheter Lock Solution (KiteLock™ 4%) is far too low to have a pharmacological or therapeutic effect on the human body and its elimination if in contact with blood results in an inactive molecule rapidly excreted by the kidneys, thereby also confirming its wide margin of safety.

Composition of KiteLock™ 4% Sterile Catheter Lock Solution

KiteLock™ 4% Sterile Catheter Lock Solution is a clear, colourless, sterile solution with no preservatives, latex, antibiotics and ethanol, and is non-pyrogenic. It is available for single use in 5 mL blow fill seal vials with a 3mL fill. KiteLock™ 4% Sterile Catheter Lock Solution is expressed as equivalent to 4% (w/v) edetate tetrasodium (40 mg/mL containing 2.8% (w/v) edetate (28 mg/mL). It is an alkaline solution with a pH of 10.5.

Clinical Use in Canada Over Last 4 Years

Adult TPN
Paediatric TPN

Assessment of potential risk of systemic chelation

The concentration of edetate found in KiteLock™ 4% Sterile Catheter Lock Solution 3 mL single-use vials is very low (1.2-3.6 mg/kg) compared to therapeutic doses used for chelation therapy for lead poisoning (50-75 mg/kg), hypercalcemia (24 mg/kg) and cardiovascular diseases (43 mg/kg) (Figure 1; Table 1). Consequently, this low concentration of edetate is not expected to act on the body as a chelator even in the unlikely event that a patient's circulatory system is exposed to clinical volumes (3-9mL) of KiteLock™ 4%.

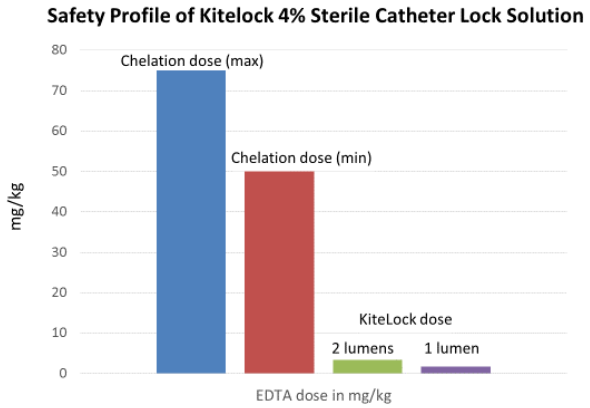

Figure 1. EDTA dose comparison between chelation therapy (maximum and minimum) and the entire administration (flush) of 6 mL (two lumens) and 3 mL (one lumen) of KiteLock™ 4% Sterile Catheter Lock Solution.

As shown in Table 1, the EDTA delivered to the patient under the worse case scenario (the unlikely direct administration of a complete vial to each of three lumens in a triple lumen catheter followed by a failure to aspirate the solution), the dose of EDTA is more than 6x below the lowest therapeutic dose, 20x times lower than the chelation dose, and 200x below the LD_{50} level[1] (Figure 1, Table 1).

Table 1. Comparative doses of EDTA

Treatment	Dose (mg/kg)	Dose (mmol/kg)	Exposure for a 70kg person
KiteLock 3 mL (1 x 3mL vial for single lumen catheter)	1.2	0.004	0.28
KiteLock 6 mL (2 x 3 mL vials for duel lumen catheter)	2.4	0.008	0.56
KiteLock 9 mL (3 x 3 mL vials for triple lumen catheter)	3.6	0.012	0.84
Hypercalcemia therapy[2]	24	0.08	5.6
Chelation therapy for cardiovascular disease treatment[3]	43	0.15	10.5
Chelation therapy for lead poisoning	50-75	0.17-0.25	11.9-17.5

IV administration of 20g	285.7	0.97	68
LD_{50}[1]	500-700	1.7-2.38	119-167

This table thus demonstrates that EDTA concentration contained in KiteLock™ 4% would not be sufficient to act as a chelator systemically.

Considering this and the fact that a maximum of 3 mL of KiteLock™ is used to fill one lumen of a CVAD, therefore only the potential overflow may enter the systemic circulation (≤ 2 mL) at time of locking, and 1.0-1.5 mL may enter the circulation if flushed rather than aspirated and discarded prior to treatment as directed. This minute volume of edetate entering the circulatory system is not expected to cause a chelation effect in the human body, thereby considered a minimal risk of causing clinically significant hypocalcemia. This has been confirmed by the following safety and toxicity studies conducted with KiteLock™ 4%.

Standard toxicological and safety studies as well as published literature (Appendix A) show KiteLock™ 4%'s high margin of safety in patients. No hemolytic (rabbit and human blood) or mutagenic (Ames test) effect was observed nor was there any demonstration of sensitization (Guinea pig maximization test) or skin irritation (rabbit) when KiteLock™ 4% was tested[4].

In addition, a subchronic study in sheep of two administrations of KiteLock™ 4% per day for 35 days did not reveal any biochemical abnormalities (no hypocalcemia)[5]. Systemic toxicity was evaluated as the lock solution was flushed into the body of sheep twice daily as opposed to aspirated and discarded. There were no clinical (physical examination, electrocardiogram), hematological (blood chemistries, coagulation panels and CBC) nor pathological/histopathological abnormalities reported in any animals exposed to KiteLock™ 4% during this study.

Furthermore, there were no safety concerns and in particular there were no episodes of hypocalcemia during the multicentre randomized clinical trial associated with the use of Cathasept (a.k.a. KiteLock™ 4%) for up to 8 months in hemodialysis patients[6].

According to the literature and acute toxicity studies conducted with EDTA, side effects associated with edetate are primarily dependent upon:

a) Dosage
b) Route of administration
c) Rate of administration

The most critical factor being rapid administration of high doses.

a) Dosage:
As previously mentioned, therapeutic dose of EDTA in chelation therapy for hypercalcemia is 50-75 mg/kg (0.17-0.25 mmol/kg). Therefore, for a typical 70 kg person, the therapeutic dose would equal 3.5 to 5.25 g (12.06-18.1 mmol). The dose is delivered intravenously over 3 to 4 hours; not exceeding an injection rate of 20 mg/min (0.069 mmol/min). The therapy is generally administered 1-3 times weekly with symptomatic disease patients requiring a minimum of 20 treatments. LD_{50} dose (median lethal dose) is 500-700 mg/kg of body weight[1]. Therefore, for a typical 70 kg person, the LD_{50} would equal 35-49 g (120.6-181 mmol). The significant difference between therapeutic and LD_{50} supports the low potential for toxic effects from systemic EDTA. This dose correlates well with studies cited in Appendix A (literature review) since all the conducted studies had a much lower dose than the LD_{50}. Acute toxic reactions to EDTA have almost exclusively been associated with administration of EDTA in excess of the recommended therapeutic dose of 50 mg/kg/day and/or administration rates or frequencies outside the current recommendations for chelation therapy.

b) Route of administration:
Intraperitoneal, intramuscular, oral and subcutaneous administration of EDTA results in less rapid changes in the circulating calcium levels when compared with intravenous infusions[7]. As a consequence, the LD_{50} delivered with other routes than IV are higher.

c) Rate of administration:
Rapid intravenous administration of EDTA results in immediate lowering of effective serum calcium levels[7].

As per Rubin's work, the body is capable of replacing serum calcium levels at a rate of 1.25 mmol/min[7].
Total % chelation (highest level) = ((Ca chelation)/(5.5 mmol))x100; since 5.5 mmol is minimum amount of calcium available in serum for chelation.
Total % chelation (lowest level) = ((Ca chelation)/(7.0 mmol))x100; since 7.0 mmol is maximum amount of calcium available in serum for chelation.
The calcium exchange rate between circulating fluid and skeletal tissue = 0.347 mmol/min.

Considering the above, it was thus calculated (Table 2) that it would take eighteen (18) 3 mL vials of KiteLock™ 4% (54 mL) to be flushed entirely, rapidly and simultaneously in one patient to create a lethal effect. This is unlikely to ever happen unless done as a deliberate and malicious act.

Table 2. Calcium chelation by edetate (MW 288)

Number of injections	Vol (mL)	Mass (mmol)	Ca chelation (1:1)	% Chelation (Lowest level)	% Chelation (Highest level)	Time to replace calcium (minutes)	Time to replace calcium dependent on exchange rate (minutes)
2	6	0.6	0.6	8.6	10.9	0.5	1.7
4	12	1.2	1.2	17.1	21.8	1.0	3.5
6	18	1.8	1.8	25.7	32.7	1.4	5.2
8	24	2.4	2.4	34.3	43.6	1.9	6.9
10	30	3	3	42.9	54.5	2.4	8.6
12	36	3.6	3.6	51.4	65.5	2.9	10.4
14	42	4.2	4.2	60.0	76.4	3.4	12.1
16	48	4.8	4.8	68.6	87.3	3.8	13.8
18	**54**	**5.4**	**5.4**	**77.1**	**98.2**	**4.3**	**15.6**
20	60	6	6	85.7	109.1	4.8	17.3
22	66	6.6	6.6	94.3	120.0	5.3	19.0
23	69	6.9	6.9	98.6	125.5	5.5	19.9
24	72	7.2	7.2	102.9	130.9	5.8	20.7
26	78	7.8	7.8	111.4	141.8	6.2	22.5
27	81	8.1	8.1	115.7	147.3	6.5	23.3
28	84	8.4	8.4	120.0	152.7	6.7	24.2
30	90	9	9	128.6	163.6	7.2	25.9

Furthermore, it is evident from Table 3 below that clinically relevant doses of KiteLock™ 4% are not apt to cause a systemic effect, thereby at low risk of causing clinical hypocalcemia in patients.

Table 3. Safety parameter calculations for 3 mL vials of KiteLock 4%

Number of 3 mL injections	mmol of calcium chelated	% Ca chelated
2 – duel lumen	0.6	10.7
3 – triple lumen	0.9	16.05
4 – 2 catheters with duel lumen	1.2	21.43
6 – 2 catheters with triple lumen	1.8	32.14

Therefore, the proposed device is not anticipated to have any systemic effect on the patient. The above cumulative scientific data demonstrate the lack of clinically relevant chelation effect of KiteLock™ 4% Sterile Catheter Lock Solution at recommended use.

Assessment of potential risk of systemic anticoagulation

Unlike heparin and warfarin, edetate is not used *in vivo* as an effective anticoagulant as it readily binds to circulating calcium at physiological pH and is immediately excreted by kidneys virtually unchanged[8]. There were no coagulation abnormalities reported in sheep[5] or in hemodialysis patients[6] when exposed to EDTA for 35 days and 8 months, respectively.
The above scientific data demonstrates the lack of systemic anticoagulation effect of KiteLock™ 4% Sterile Catheter Lock Solution at recommended use.

Assessment of potential risk of systemic antimicrobial activity

KiteLock™ 4% Sterile Catheter Lock Solution becomes ineffective as an antimicrobial agent *in vivo* as it immediately binds to circulating calcium at physiological pH and excreted by kidneys virtually unchanged[8]. Tri- and tetrasodium EDTA from KiteLock™ 4% will be instantly transformed into the predominant EDTA salt, edetate calcium disodium which has no antimicrobial activity[9]. Furthermore, directions for use of KiteLock™ 4% Sterile Catheter Lock Solution states that the lock should be aspirated and discarded before catheter use[10] for hemodialysis, chemotherapeutic or total parental nutrition therapy.

Therefore, the proposed device will not have any systemic antimicrobial effect on the patient.

Assessment of potential risk of change in blood pH

KiteLock™ 4% Sterile Catheter Lock Solution has a pH of 10.5. This alkaline pH is necessary to ensure that the solution is comprised of a mixture of tri- and tetrasodium EDTA for the most efficient disinfectant activity within the catheter. Normal reference range of pH in human blood is 7.35 – 7.45. Central venous access devices contain < 3 mL of KiteLock™ that could be flushed into the heart blood if not possible to aspirate. A study was conducted to determine the influence of the alkaline pH of KiteLock™ *in vivo*[11]. The results showed that 1 mL release of KiteLock™ 4% would only marginally influence 4 mL of heart blood and have no influence on the pH of 5 mL of blood (Figure 2). Consequently, a 3 mL flush would require dilution by 15 mL of blood in order not to minimally disturb the blood pH.

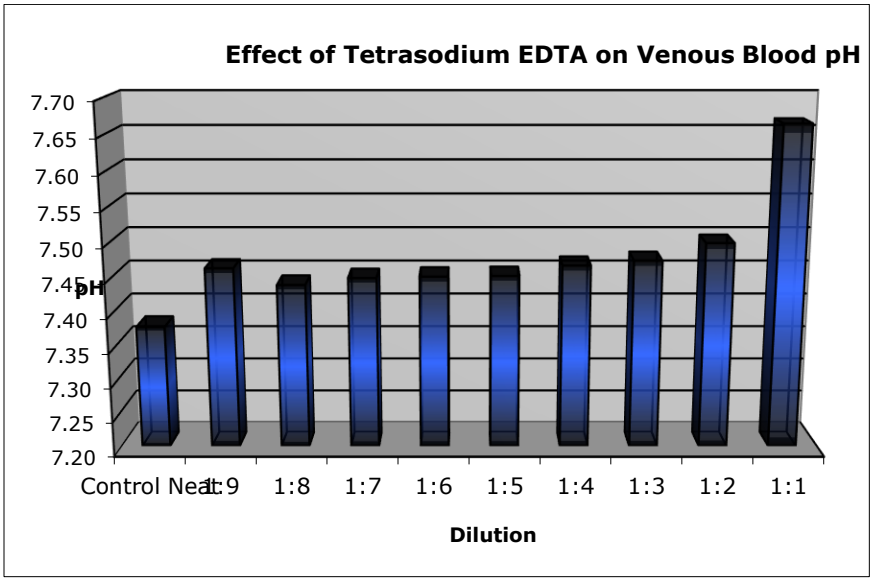

Figure 2. Effect of 4% tetrasodium EDTA on venous blood pH[11]

As at least 90 mL of blood per second is passing through the heart, there is at least a 6-fold margin of safety associated with this scenario. It is unlikely that the 3 mL lock solution could be flushed in as little time as a second therefore this margin would be even greater. No change is thus expected on blood pH with the use of KiteLock™ 4% Sterile Catheter Lock Solution.

Assessment of potential risk of hydraulic effect or gravity causing "leaking or seepage" in circulatory system

The density of the proposed device is 1.02g/mL and human blood density is 1.06g/mL. It is important for a lock solution to closely match the density of blood[12]. A solution with a higher density than blood is less buoyant and may "fall" out of the catheter and into the systemic circulation. A solution with a lower density is more buoyant than blood and may be "pushed" inside of the catheter with little effect. If a patient's catheter tip position changes relative to gravity, matched densities of blood and lock solution are preferred to prevent the lock solution being replaced by blood within the catheter. The osmolarity range of the proposed device is 278-347 mOsm/L which is within the range of human blood osmolarity of 285-310 mOsm/L[13]. Osmolarity is a critical specification tested at time of release for KiteLock™ 4% Sterile Catheter Lock Solution and during stability studies.

Therefore, it is expected that little to no leakage or seepage of the proposed device will occur due to hydraulic effect or gravity.

CONCLUSION

The minute concentration of edetate from KiteLock™ 4% potentially being exposed to the patient's circulatory system is not expected to cause any physiological, pharmacological, therapeutic or adverse effect for the following reasons:

1. The concentration of edetate in each 3mL single-use vial is very low compared to therapeutic levels currently used for chelation therapy, hypercalcemia and cardiovascular diseases.
2. Practically, the minute amount (volume and/or concentration) of edetate which possibly could enter the circulatory system at time of instillation of the lock solution is < 2 mL, i.e. even smaller exposure of edetate than the entire 3 mL vial.
3. Directions For Use (DFU) recommend the aspiration and discard of the lock solution before each treatment. In cases when aspiration is not possible, the amount of edetate possibly entering the circulatory system at time of removal of the lock solution is equal to the internal volume of CVAD which do not exceed 2 mL i.e. an even smaller exposure of edetate than the entire 3 mL vial.
4. At physiological pH, edetate in KiteLock™ 4% readily binds to circulating calcium and is immediately excreted by kidneys virtually unchanged[1] as edetate calcium disodium thereby negating any systemic anticoagulant or antimicrobial activity in the human body.
5. Hypocalcemia is does not occur due to the very low exposure of blood to edetate and rapid homeostasis of calcium within the body[20].
6. The density and osmolarity of KiteLock™ 4% is physiological similar to blood. This specification is important as it decreases the risk of "leakage or seepage" of the solution due to hydraulic effects or gravity while in the catheter.
7. An unlikely flush of an entire 3 mL of KiteLock™ 4% would require dilution by 15 mL of blood not to minimally disturb the blood pH. As at least 90 mL of blood per second is passing through the heart, there is at least a 6-fold margin of safety associated with this scenario.

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APPENDIX A

EDTA Toxicity Overview

The following section provides references to studies conducted to assess the toxic effects of EDTA. None of the mentioned studies resulted in statistically significant toxic effects.

Clinical Literature Review

Table 2: Clinical Literature Review [1].

Citation	Mean or Overall Duration	Total Mean EDTA dose	WCS EDTA Dose	70 kg person Total EDTA Del. –	Total EDTA Del. Mmol	Total del. In 1 hr (mmol)
Abraham et al (2000)	105.7 ± 95.6 hrs	Total dose: 112.62 ± 139.29 µg/kg/min Overall Infusion rate – 40.27 ± 23.28 µg/kg/min	(0.251 mg/kg/min) Infusion rate 0.0635 mg/kg/min	17.57 mg/min Infusion rate – 4.445 mg/min	0.0629 mmol/min	3.77
Barr et al (2000)	74.07±69 hrs	17.39±31.29mg	0.04868 g	48.68 mg	0.017	0.017
Cohen et al (2004)	61.8±50.7 min	13.2±9.6 mg/kg	22.8 mg/kg	1.596 gm	5.7 mmol	5.7
Guldager et al (1992)	5-9 weeks	3 g/3 hr x 20 treatments	2.69 mmol/hr	3g	8.06 mmol	2.69
Herr et al (2000)	41.5±64.7 2 hrs	39.1±92.91 mg	132.01mg/4 1.5hr		0.46 mmol	0.011
Higgins et al (2000)	6 days	127.4 mg Daily dose – 20mg	547.7 mg/day	547.7 mg/day	1.9 mmol/day	0.079
Knudston et al (2006)	2x/week x 15 weeks	40 mg/kg/3hrs	40 mg/kg/3hrs	2800 mg/3 hrs	10 mmol/3hrs	3.33
McDonagh et al (1982)	50 days	3 g/3 hr x 10 infusions	3g	3g	8.06 mmol	2.69
Metzer et al (1961)	12-16 weeks	3g/2.5 hrs x 3 per week	3g	3g	8.06 mmol	3.224
Van Rij et al (1994)	10 weeks	3 g/3 hr	3g	3g	8.06 mmol	2.69
Wahr et al (2000)	302.7±67.5 minutes	21.95±7.103 mg	29.053 mg	29.053 mg	0.103 mmol	0.019
Chatznikolaou et al (2003)	6 months	60mg/week	60 mg	180 mg	0.62 mmol	0.62
Olson (2004) [5]	1 day	**3000 mg/4hrs**	3000 mg/4hr	3000 mg	7.5	1.875
Olson (2004) [6]	1 day	720 mg/35 minutes	720 mg	720 mg	1.8 mmol/35 minutes	13.086
Olson (2004) [7]	35 days	0.3 mmol/minute (3.6 mmol/7 days)	0.6 mmol	3.6 mmol/week	3.6 mmol/week	0.0214

Note: a) WCS – Worst Case Scenario; b) All the above mentioned studies did not result in any statistically significant toxic effects.