Technical Note

Estimation of trisodium citrate (Citra-Lock™) remaining in central venous catheters after the interdialytic interval

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Introduction

Infection of central venous catheters used for haemodialysis remains an important cause of morbidity and mortality [1]. Patency of the catheters can be maintained between dialyses by a heparin lock, but this has no antibacterial activity. Sodium citrate, especially at higher concentrations, is an anticoagulant with intrinsic antibacterial activity [2]. However, citrate inadvertently entering the circulation of the patient will chelate calcium ions and depress the ionized calcium level. This may prolong the QT interval [3], which may lead to ventricular dysrhythmias and torsade de pointes.

We investigated the amount of citrate remaining in dialysis catheters after the interdialytic interval in order to assess the risk of this amount entering the circulation.

Patients and methods

Eight incidental patients with a central venous dialysis catheter were examined. They had an Ash Split (Medcomp, Harleysville, PA, USA) (n = 5, of whom one patient was studied twice), or 15 cm single (n = 1) or double (n = 2) lumen jugular catheter (Medcomp), resulting in a total of 17 lumina studied. At the end of dialysis, after flushing of the catheter lumen with 10 ml of 0.9% NaCl, a lock of 0.9–2.1 ml citrate per lumen was slowly infused according to the instructions of the manufacturer of the catheters and of the Citra-Lock™ (Dirinco, Rosmalen, The Netherlands). The protocol specified that the infusion be stopped immediately if the patient reported a ‘metallic’ taste, but this did not occur during the study. At the start of the following dialysis 10 ml of blood, including citrate, was aspirated in tubes placed on ice. For validation, similar samples were also taken postdialysis immediately after locking. Thus, in a total of 34 samples the citrate concentration was determined after dilution 1:100 using an enzymatic method (Instruchemie, Delfzijl, The Netherlands). Haematocrit was also determined and the amount of remaining citrate was calculated as: (1 – haematocrit) × 10 ml × citrate concentration. This takes into consideration the fact that citrate does not enter erythrocytes resulting in a distribution volume equal to the plasma volume.

Because a citrate assay is not always routinely available, we also measured the sodium concentration in 12 samples to examine the relation between the sodium and the citrate concentrations. We used an indirect potentiometric method with an ion selective electrode (Hitachi 917, Roche Diagnostics, Germany) which automatically repeats the determination in a diluted sample if the result lies outside the linear range.

Results

The citrate concentrations in the aspirate ranged from 33 to 400, median 215 mmol/l. After correction for the haematocrit this corresponds to a volume of Citra-Lock™ of 0.1 to 1.9, median 1.0 ml. The highest recovery was found in the samples taken postdialysis immediately after locking: 1.0 to 1.9, median 1.7 ml for the Ash Split or 51 to 96% of the administered dose and 0.3 to 0.9, median 0.4 ml or 28 to 77% for the jugular catheters. The recovery after the interdialytic interval was substantially lower: 0.6 to 1.6, median 0.9 ml for the Ash Split and only 0.1 to 0.8, median 0.2 ml for the jugular catheters. This is equal to 30 to 81% and 12 to 68% of the administered dose and 37 to 86%
and 43 to 88% of the immediate recovery, for the Ash Split and the jugular catheters, respectively.

The sodium concentration measured in 12 samples ranged from 448 to 991 mmol/l and showed a strong linear correlation with citrate: \( \text{citrate} = 0.47 \times \text{sodium} - 73 \), \( r = 0.99, P < 0.001 \). However, these very high citrate concentrations in plasma showed a negative interference with the ion selective electrode, which is very probably dependent on the type of electrode and instrument. Therefore, an instrument-specific calibration and regression line, as shown in Figure 1, may be necessary.

### Discussion

Little is known about the fate of solutions used to lock central venous dialysis catheters in vivo. Leakage of these substances out of the catheter may result in clotting which would compromise the adequacy of subsequent dialysis. If the solution has antimicrobial activity, this loss would also increase the risk of infection. Furthermore, entrance of these substances into the circulation may cause untoward reactions in the patient. In vitro studies demonstrated significant early and late leakage from a catheter lock [4]. In patient studies it was reported, that clinically relevant amounts of a heparin lock may enter the systemic circulation, resulting in prolongation of the activated partial thromboplastin time [5]. This might contribute to minor or major bleeding [4,6].

Trisodium citrate is increasingly used as a catheter lock because of its antimicrobial activity in addition to the anticoagulation. However, following the report of a fatal accident, concerns have been raised about the safety of concentrated citrate [7,8].

In addition to accidental administration of an overdose and to diffusion, several factors may contribute to the entrance of locking solution into the circulation. The locking solution will mix with the fluid in the catheter lumen during instillation. Injection of the catheter volume in vitro was found to result in spillage of up to 15% [9]. This will reduce the effective concentration at the catheter tip. The injection volume may be increased to 120% for achieving the full strength at the tip, but this results in even more spillage. A blood clot in the catheter lumen will reduce the effective volume, resulting in an additional amount similar to the clot volume entering the circulation. Intermittent compression of the catheter due to movement of the patient will force locking solution out of the catheter and its replacement by an equal volume of blood. Gravity will drag solution out of the catheter when a locking solution is employed with a density higher than blood and when the catheter holes face downward. Increased viscosity may only temporarily delay this process [10]. If the catheter has multiple holes, blood will enter and exit and flush out the locking solution. When the tip of the catheter is occluded by clot, it may not be possible to aspirate the remaining locking solution. Administration of a fibrinolytic agent for subsequent attempted thrombolysis will force the locking solution into the circulation.

To assess the risk of citrate entering the circulation during attempted fibrinolysis, we measured the amount of citrate remaining in the catheter after the interdialytic interval. For validation, we also measured the amount that could be recovered postdialysis immediately after locking. We found a recovery of immediately aspirated citrate of less than 100%, notably for the jugular catheters. Nevertheless, a substantial amount of citrate remains in the catheter, particularly the Ash Split, apparently sufficient for prevention of clotting and infection [6].

Theoretically rapid bolus injection of 1 ml of Citra-Lock\textsuperscript{TM} in 1 or 2 s may result in unsafe ionized calcium concentrations, but based on an extrapolation of animal tests, this would only be expected to cause a brief depression of blood pressure in a 70 kg patient [8]. The slow administration of this amount seems therefore not to be very dangerous. The safety of trisodium citrate was confirmed in a large clinical trial, where no serious adverse events were encountered [6].

As Citra-Lock\textsuperscript{TM} consists of trisodium citrate, it contains three sodium ions for each citrate ion. When the first blood aspirated from a catheter locked with citrate is inadvertently sent to the laboratory, severe hypernatraemia may be reported due to contamination with trisodium citrate [11]. We measured sodium in 12 samples and found a very good linear correlation with the citrate concentrations. Measurement of citrate is not routinely available in most hospital laboratories. Our results show that a sodium determination can be used as a simple and accurate measure of the citrate content in the aspirate. However, an instrument-specific calibration is probably necessary for this purpose.

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### Conflict of interest statement

None declared.
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