ART
Advanced Renal Technologies

MTN
NEUBRANDENBURG GMBH

aus Verantwortung für die DIALYSE...

CITRASATE®

the citrate-containing concentrate for dialysis

Concentrate from Neubrandenburg

- heparin saving
- improved treatment compatibility
- reduces oxidative stress and inflammation

Product information

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CITRASATE® - The innovative dialysis concentrate

In 2003 Citrasate® was developed and registered as a U.S. patent as a new innovative concentrate for haemodialysis from the company *Advanced Renal Technologies* (ART) U.S.A. In this concentrate the 3 mmol/l of acetic acid were replaced by 0.8 mmol/l of citric acid, resulting in a reduced amount of 0.3 mmol/l of acetate.

It was the aim of this innovation to reduce the possible undesirable side effects of acetate ions and heparin as the anticoagulant. At the same time the positive properties of citrate ions should be used as a natural part of the citric acid cycle inside of the body and to bind free calcium ions in the clotting system forming an chelate-complex.

Citrate ions produce a local anticoagulation in the dialyser capillaries to generate a reduced need for anticoagulants without increasing foreign surface induced clotting events. Within the blood vessel system citrate ions can reduce the oxidative stress via a complex mechanism.

The FDA approved Citrasate® for all dialysis patients and it was also certified in the EU as medical product. In latest clinical studies evidence was given for a significant improvement of compatibility and quality of treatment and a substantial benefit for users.

Advantages of dialysis with Citrasate® for patients

- Reduction of dose of unfractionated or fractionated heparin up to 50% without clotting the inside of the dialyser and extracorporal circuit [1,3,6,7]
- Maintenance of prescribed dialysis dose (spKt/V) despite reduced anticoagulant dosage up to 50% [6-8]
- Strong reduction of postdialytic bleeding times [1]
- Improvement of acid-base status and hemodynamic stability of hypertensive patients [2,5]
- The calcium-phosphate-balance will be maintained in the physiological range [6,7]
- Improvement of treatment quality by reduction of acetate and heparin concentration within the blood [4-8]
- Reduction of oxidative stress and inflammation within the blood[6,8,11] for improvement of treatment quality.

Indications for use of Citrasate®

- pre or post-operative patients
- patients with cholesterol embolism
- patients with gastro-intestinal lesions
- patients with haemorrhagic retinopathies as a result of diabetes
- patients with heparin-induced side effects (e.g. pruritus or osteoporosis)
- patients with acetate-induced side effects (e.g. hypotension or hypoxemia)

Composition of Citrasate® in comparison to standard dialysate*

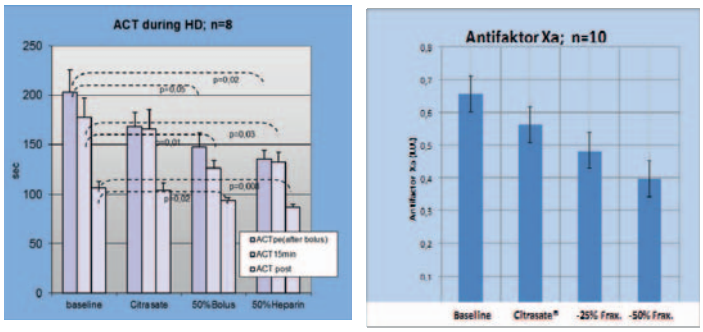
	units	Citrasate®	standard-dialysate
Sodium	mmol/L	139.75	138.0
Calcium	mmol/L	1.25 or 1.5	1.25
Magnesium	mmol/L	0.5	0.5
Potassium	mmol/L	2.0	2.0
Chloride	mmol/L	106.0	106.3
Acetate	**mmol/L**	**0.3**	**3.0**
Citrate	**mmol/L**	**0.8**	**-**
Glucose	g/L	1.0	1.0
Bicarbonate	mmol/L	37.4	34.2

* The table shows one example, however numerous different compositions are possible

CITRASATE® - The innovative dialysis concentr

50% Reduction of heparin

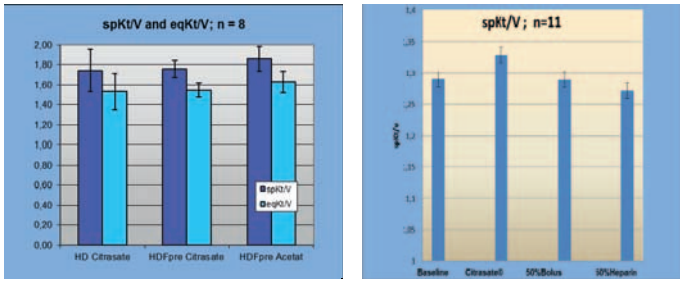
In comparison to standard dialysate (baseline) the dosage of unfractionated or fractionated heparin (fraxiparine®) can be reduced by 50% without clotting events inside of the dialyser capillaries or extracorporal circuit by means of Citrasate®. The reduction of heparin dosage was shown to be possible for Low- and High-Flux-Dialysis as well as Online-Hemodiafiltration (HDF) in post- or prediltion mode (1, 2, 6-8, 11).



Postdialytic changes of ACT respectively Antifactor Xa after change-over from standard dialysate to Citrasate® and subsequent reduction of heparin resp. fraxiparine® dosage during High-Flux-Dialysis[6,8] resp. Low-Flux-Dialysis[7]

Maintenance of dialysis dose

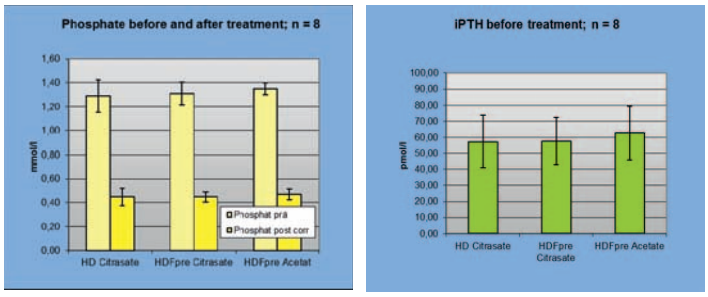
After changeover from standard dialysate to Citrasate® and a reduction of heparin dose by 50% there was no significant difference of dialysis dose (spKt/V resp. eqKt/V) (6-8) as described in former investigations (2, 9).



The comparison of dialysis dose (spKt/V) between standard dialysate (baseline) and Citrasate® shows no significant differences during High-Flux-Dialysis[6,8] (left figure) or Low-Flux-Dialysis[7] (right figure) after reduction of heparin dosage

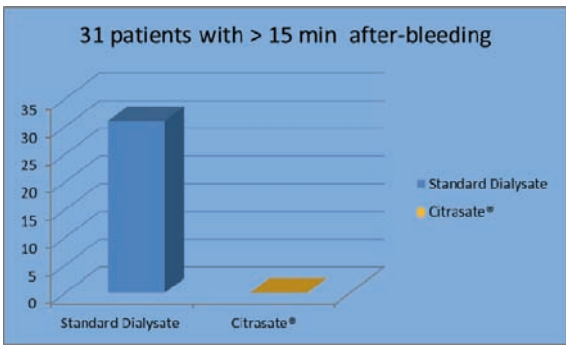
No influence on phosphate and parathyroid hormone level

The calcium-phosphate balance is determined largely by the level of intact parathyroid hormone. Disruptions of this balance do not appear because no significant differences were found between standard dialysate and Citrasate® using different treatment modes (High-Flux-Dialysis or Online-HDF postdilution (6)).



Minimised after-bleeding

After changeover from 31 patients with longer bleeding times (›15 min) from standard dialysate to Citrasate® and a reduction of heparin dose by 55% the bleeding from needle sites was totally minimised (1).

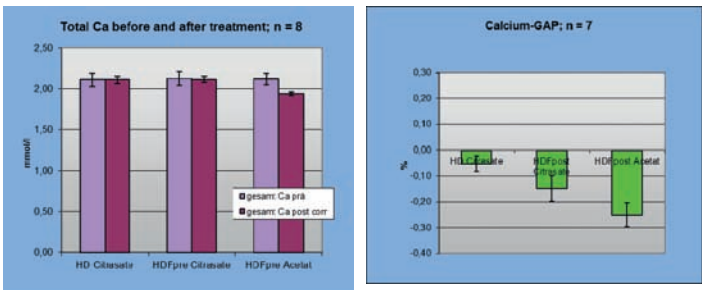


ate improves the treatment quality of patients

Optimal metabolisation of Citrasate®

The extent of intracorporal metabolisation of citrate ions can be estimated by the measurement of the so called "Calcium-GAP". Values lower than 0.2 indicate a sufficiently quick metabolisation, which also improves also the base excess within the blood. The Ca-GAP can be calculated as follows (5):

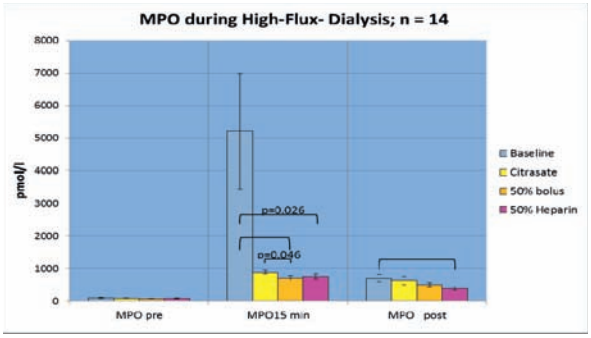
$$Ca\text{-}GAP = (Total\ Ca_{post} - Total\ Ca_{pre}) - (Ca^{2+}{}_{post} - Ca^{2+}{}_{pre})$$



Comparison of mean values of total Calcium respectively Calcium-Gap (Ca-GAP) during High-Flux-Dialysis (HD) and Online-HDF postdilution using standard dialysate (acetate) or Citrasate®. In all cases the value of Calcium-GAP was lower than 0.2, which indicates a sufficient quick total metabolisation of citrate ions[6,8]

Improved treatment quality by reduced oxidative stress

Myeloperoxidase (MPO) is considered as a marker for oxidative stress and inflammation in patients suffering from kidney disease (4). By changeover from standard dialysate to Citrasate® a significant reduction of MPO-concentration was achieved within the blood. In this way the treatment quality of chronic dialysis patients can be improved considerably (6,8).

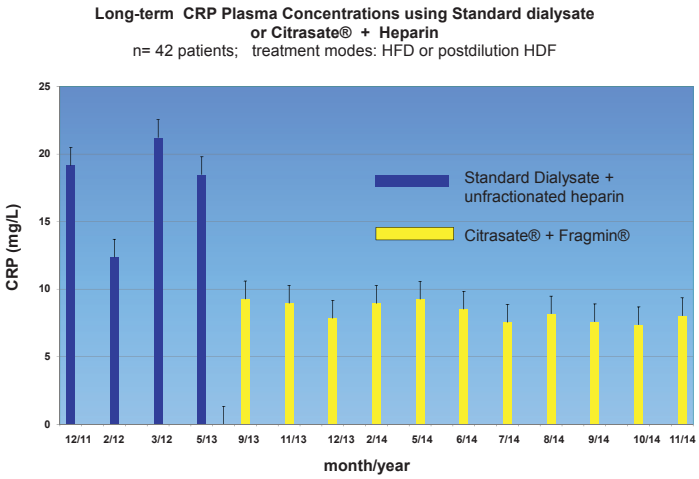


Inside the extracoporal cicuit the oxidative stress increases tremendously 15 min after beginning of High-Flux-Dialysis. By means of Citrasate® this rise will be reduced considerably, whereas the following reduction of heparin dose has only a very small influence[8]thi

Reduced inflammation by means of long-term use

The long-term use of Citrasate® over more than 15 months decreases significantly the plasma level of C-reactive protein CRP) in chronic dialysis patients (10), not depending on the type of anticoagulant used before (11).

Therefore Citrasate® is suited to reduce the impact of dialysate as proinflammatory factor in chronic dialysis patients (11).



Guidelines for use of CITRASATE®

Treatment modes, used so far

- Low-Flux-Dialysis [7]
- High-Flux-Dialysis [1-6, 8, 9]
- Online-Hemodiafiltration in pre or post-dilution mode [6, 9, 11]

Dialysis machines, used so far[9]

- Dialog (B.Braun)
- 4008/5008 (Fresenius)
- AK 100/200/200S (Gambro)
- DBB05/07 (Nikkiso)

Recommendation during changeover to Citrasate®

Treatment mode	Ca^{2+} - concentration of dialysate
Low-Flux-Dialysis*	equal to standard dialysate
High-Flux-Dialysis**	0.25 mmol/l above standard dialysate
Online-HDF pre or post-dilution**	0.25 mmol/l above standard dialysate

* based on results of Low-Flux studies (7, 8) or **High-Flux and Online-HDF studies (1-6, 8, 9, 11)

Time schedule* for heparin reduction by Citrasate®

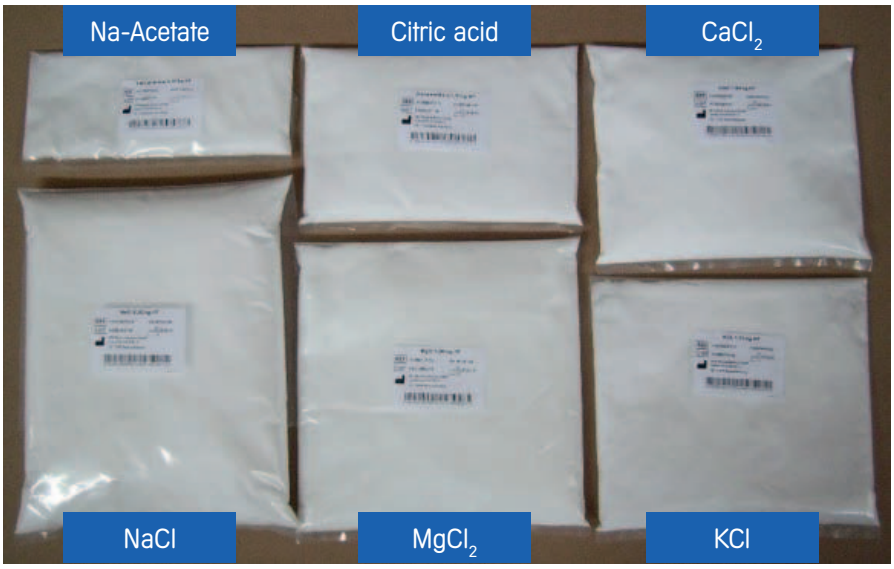
Anticoagulant	week 0	after week 2	after week 4
unfractionated heparin	as before	50% in the bolus	50% in the bolus + 50% in the continuous dose
fractionated heparin	as before	25% in the bolus	50% in the bolus

* The stepwise reduction of heparin is choosen in line with former studies to avoid clotting complications in patients, which could not be suited for anticoagulant reduction by unknown reasons (1-3, 6-8)

Delivery

Citrasate® can be delivered in canisters of 5, 6, 8 or 10 l, bags of 3.8 l, 4.5 l and 5.5 l or containers of 300, 500 and 800 l as well as 500 l Bag in Box from MTN Neubrandenburg GmbH*.
The components of Citrasate® can be also delivered as powder set for preparation of 100, 500 and 1000 l in self mixing units.

10 l canister



powder set for self mixing units

* MTN Neubrandenburg GmbH Germany is the licensed manufacturer for Citrasate® for Germany and many other European countries.

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