Problems of Calcification of Dialysis Fluid with Acidification of 3 mmol/l Acetate

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How did we deal with lemons ➔ when we use acetate for acidification?
why acidification?

• Mammals and Man produce a great deal of CO$_2$-Gas $\Rightarrow$ transported in Blood as HCO$_3^-$ and eliminated via the lungs by diffusion

• This is driven by metabolism ($37^\circ$C, motion, function of the body)

• CO$_2$ 40 Torr = 1.2 mmol/l acidification
what is the Problem of Bicarbonate Dialysis?

with Acetate Dialysis (1965-1978) you *never* have a Problem with Calcification - there is only the exceeding of the metabolic capacity of the Liver

in Bicarbonate Dialysis you have the alternative between Calcification or CO$_2$ Overload

Problem: short time of HD Treatment (> 12 – 24 h per one week with 168 h of living) ➔ Buffer Concentration was set to 32 mmol/l
Acidification in Bicarbonate Dialysis - but how?
Acidification and its relation to pH?

\[ \text{pH} \downarrow \sim \frac{\text{HCO}_3^-}{\text{pCO}_2} \]

Addition of acid

Partial transformation from \( \text{HCO}_3^- \) to \( \text{CO}_2 \)

That is how the solubility of calcium, magnesium & bicarbonate can be achieved
how the acidification bicarbonate-dialysis was achieved?

- W. Kolff (1943): acid Na\(^+\)-phosphate
- N. Alwall (1945): carbogen-gas
- since 1978 3 mmol/l acetate
- in France 4 or 5 mmol/l acetate

→ Perhaps French doctors are better!

No, they aren‘t (!): COLD & weaning from Respirator
A-Component 3 mmol/l Acetate

BiCart

High-Flux

Permeation

De-Air

Dialysis-Fluid

pH 7.2
pCO₂ 85

Treatment and Calcification
Dialyzer as Oxygenator (for Exchange of CO$_2$)

- $pCO_2$ 85 mm Hg
- 3 mmol/l acid

Calcification

- $pCO_2$ 100 – 130 mm Hg
- 4 to 5 mmol/l acid

Problems for COLD-Patients, as well as for ICU-Patients being on a respirator
Limits of HCO₃⁻ / CO₂ buffer system

Henderson-Hasselbalch's Equation

Dr. Th. Ryzlewicz / Dr. F.F. Becker
Stand: 06-2006
Limits of HCO₃⁻/CO₂ buffer system

Henderson-Hasselbalch’s Equation

Dr. Th. Ryzlewicz / Dr. F. F. Becker
Stand: 06/2006
. . . and after the treatment . . .

the patient . . .

*however,*

*cannot be de-scaled*

. . . the monitor
must be de-scaled
immediately . . .
the coefficients of solubility . . .

- are known and defined at 20°C and 25°C
- for 37°C they are NOT KNOWN(!)
- Sodium-bicarbonate is soluble (8.4 % or ~ 9 % as BiCart)
- the solubility of Na-bic is dependent on the temperature
the coefficients of solubility . . .

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as a drug this prescription of the dialysis fluid of today never would be allowed
Meal with high amounts of Phosphate

1.25-Vit.-D

decomp. HPT

Cinacalcet

Sevelamer

Ca^{++} containing PO_4 binders

bicarbonate-HD (acidification with citric acid)

FGF 23

bicarbonate-HD (acidification with acetate)
Clearance 15 ml/min: when does the calcification begin?

CKD-4: phosphate-elimination will be improved by FGF 23

⇒ „no phosphate binders“ and „no calcification“

CKD-5: same as CKD4
Now bicarbonate dialysis is started (acetate-acidification)

⇒ calcification:
⇒ now the patient needs „phosphate binders“
the challenge of acidification with acetate: „calcification or too high pCO₂“

the Solution: acidification with citric acid

Why? with the same power of acid & CO₂ production nothing will calcify because Ca²⁺ is disguised in the chelate lattice
Transparency of a Solution

Acetate Acidification

Laymen & Patients see the difference

Citrate Acidification

Nephrologists didn't see this

NaCl 0,9 %

BfArM ignores this
Acidification with Citric Acid
Acidification with Citric Acid

Select Bag Citrate
1.0 mmol/l Citric Acid

Citrasate
0.8 mmol/l Citric Acid & 0.3 mmol/l Acetate
<table>
<thead>
<tr>
<th>Problem</th>
<th>3.0 mmol/l Acetate</th>
<th>4/5 mmol/l Acetate</th>
<th>0.8 mmol/l Citric Acid 0.3 mmol/l Acetate (MTN)</th>
<th>1.0 mmol/l Citric Acid Gambro</th>
</tr>
</thead>
<tbody>
<tr>
<td>Calcification</td>
<td>high pCO$_2$</td>
<td>./.</td>
<td>./.</td>
<td>./.</td>
</tr>
</tbody>
</table>

Survey of the different possibilities for acidification
what should be taken into account when acidifying with citric acid?

• NOTHING will calcify (neither the patient nor the monitor)
• Ca\(^{++}\) in the dialysis fluid must be raised a little (Citric Acid – after having passed the dialysis membrane – will bind a smaller part of Ca\(^{++}\))
• so measurement of Ca\(^{++}\) after switching the dialysis fluid is reasonable for the first time
• the dosage of heparin can be reduced to 50 %
Is there a problem of communication when acidifying with citric acid?

Indeed, this exists:
the acidification with citric acid is *not well understood by many doctors*.

nevertheless, a discussion concerning the concentration of Ca$^{++}$ *in the dialysis fluid* is continued . . .
why is the acidification with 1.0 mmol/l citric acid a good concept?

*Do it right the first time!* (RH Herbst)

• no further elevation of pCO$_2$
• no calcification at all
• good anti-thrombogenic effect (< Heparin)
equal acidification with 3.0 meq/l

**Acetate**

- here only one principle is working:
  - a (smaller) part of bicarbonate will be transformed into CO$_2$

**Citric Acid**

- at first the same effect as with acetate
- second effect by disguising Ca$^{++}$ and Mg$^{++}$ by the chelate lattice of citric acid ➔ product for solubility of Ca$^{++}$ x citrate and Mg$^{++}$ x citrate will **not** be reached
Strategy

Discussions with the Industry?

Lecture / Congress?

➡️ without obligation!
Acidification with Citric Acid

3 possibilities

• Study
• Prohibition of the 3 mmol/l acetate-acidification (> BfArM)
• one concerned Patient (> chemist)
• Information of the doctor doesn‘t work here ➔ the theme is too complicated!
why a Chemical Evaluation is necessary?

• the Problem of Calcification with 3 mmol/l Acetate Acidification is a Problem of **Solubility**
• this never can be judged in a qualified way by Physicians
• there does exist the Prescription with 1 mmol/l Citric Acid without any Calcification
• the Medical Authority BfArM Institute ignored the Chemical Evaluation without a serious reason
Steps to reach a Chemical Evaluation:

- Oct. 2012 Letter to BfArM Institute Germany
  Result: Reference Number, Proposal to discuss this at DGN
- Dec. 2013 Letter of a Medical Lawyer
  ➔ no Result(!)
- May 2014 Letter to the German Minister of Health (> Supervision of the BfArM)
- May 2014 Report to FDA (> VMDR & 3500A)
Backfiltration 8 ltr. or online-HDF up to 30 ltr.

Calcifying Fluid

2 well known Chemists . . .

. . . did not mention the Calcification with Acetat-Acidification . . .

BfArM Institute Medical Product . . . refuses a Chemical Evaluation

. . . related with Dialysis Industry

Everything is allowed with a Medical Product

FDA is involved (> VMDR & 3500 A for Chemical Evaluation)
We have to say what we think
We have to do what we say
What we do should reflect this

Alfred Herrhausen
1930 - 1989