**Chloramine, a sneaky contaminant of dialysate**

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**What are chloramines?**

Chloramines, derived from chlorine and ammonium, are added to water as disinfectants and may contaminate dialysis fluid and enter the blood of dialysis patients causing haemolytic anaemia.

Depending on the number of chlorine atoms that bind to nitrogen in exchange for hydrogen, monochloramines, dichloramines or trichloramines are formed [1]. The type of chloramine formed depends on the molar proportion of chlorine and nitrogen and the pH of the solution. If the pH is greater than 6 and if the molar proportion of chlorine is less than 5, monochloramines preferentially are formed. Since these conditions are present in the majority of city water supplies, monochloramines are most frequently encountered, and these have the least oxidative potential.
For what purpose are chloramines used?

Amongst the methods to render city water suitable for drinking, chlorination is the most important one. One of the methods of chlorination entails the formation of chloramines when ammonium and chlorine are added to the water. These substances are added to water as disinfectants in many cities throughout the world, above all in the USA [2]. This manipulation is the main reason for the presence of chloramines in municipal water supplies, although there is always in water some natural ammonium and chlorine which are able to form chloramines. The advantages of chloramines compared to other water disinfectants are: (i) hydrolysis yields the disinfectant hypochloric acid; (ii) they have intrinsic oxidizing and bactericidal properties (on a molar basis one fourth of the potency of hypochloric acid); (iii) their half-life in water is greater than that of chlorine, since free chlorine is highly diffusible; and (iv) finally, this form of chlorination reduces the formation of organic chlorinated compounds, such as trihalomethanes which are carcinogenic and probably teratogenic.

Chloramines should be added in the minimum concentration necessary to achieve adequate disinfection of water. In Madrid they are added to the water at a concentration of between 0.8 and 2 mg/l (p.p.m.). Public water typically contains chloramines in the range of 1–2.5 mg/l. Only when bacterial contamination of the water increases is it necessary to increase the concentration of chloramines. For all these reasons chloramines are not found in all city water supplies. Not all city water samples have the same concentrations, and finally, the concentration of chloramines may vary in the course of the year [3–6].

How can chloramines be eliminated from water?

Chloramines have a low molecular weight, are neutral, and can pass through semipermeable membranes including those of reverse osmosis. They are not trapped by decalcifying or deionizing columns. Consequently, special treatment is necessary for their elimination or neutralization [7,8]. There are three approaches to eliminate chloramines and to prepare water for haemodialysis: (i) activated charcoal; (ii) sodium bisulfite; and (iii) ascorbic acid. The main and most effective method for elimination of chloramines is activated carbon filter. This eliminates chlorine and soluble organic compounds, and is the best method for preventing chloramines reaching the patient. Activated charcoal has two types of action on chlorine: a physical one, i.e. adsorption of chlorine; and a chemical one, i.e. catalysis of the reactions listed in Table 1. These reactions proceed with variable velocity depending on the type of charcoal and other circumstances. If the concentration of chloramines is high, the time of contact between water and activated charcoal becomes critical. The following conditions determine these reactions: (i) relation of the quantity of charcoal and of water to be treated; (ii) the concentration of the chloramines in the water to be treated; (iii) the type of activated charcoal, e.g. the best is bituminous charcoal because of its great catalytic capacity; (iv) activated charcoal particle size, i.e. the smaller the better; (v) distribution of charcoal in the filter to maximize contact time of charcoal with chloramines which should exceed 45 s; and (vi) water temperature is directly related to the elimination capacity for chloramines and for the time charcoal remains active [9]. It is useful to periodically wash the activated charcoal filters by perfusion in the reverse direction. This allows the elimination of particles and the removal of some charcoal to expose new layers to the circuit. However, this is not a manoeuvre which reactivates charcoal, so periodically the activated charcoal has to be replaced. A practical system to arrange activated charcoal which guarantees an optimally low final concentration of chloramines, is to place two filters in series. The chloramine concentrations should be taken between the two filters and when they exceed the safety level, the first filter should be taken out, the second put into the place of the first and the second filter should be replaced. With this system one is certain to have reliably low water chloramine concentrations. This system of arranging activated charcoal is obligatory in dialysis centres in California [10]. Nevertheless, the disadvantage is that contact time between water and charcoal is less than if the water was divided between two parallel filters.

There have been measurements of the quantity of active charcoal necessary to eliminate a certain quantity of chloramines [11]. The intention was to calculate the time after which the charcoal has to be exchanged as a function of the water volume treated and the concentration of chloramines. Nevertheless because the saturation of charcoal depends on the many variables mentioned above, it is more useful to control the chlorine concentrations in the treated water for haemodialysis. One would need a minimum of 200 kg of activated charcoal to produce 1000 l/h of water. The optimum would be to arrange two filters of 100 kg each in series. Sodium bisulfite and ascorbic acid are the other two methods used to eliminate or to neutralize the effects of chloramine. The first is more effective to treat the chlorine and would be useful for certain types of water. The reactions that bisulfite undergo with the chloramines are explained in Table 1.

<table>
<thead>
<tr>
<th>Table 1. Chloramine reactions</th>
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<tr>
<td>Chloramine generation</td>
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<tr>
<td>Cl₂ + H₂O → ClH + HClO</td>
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<tr>
<td>NH₂ + HClO → NH₂Cl₂ + H₂O</td>
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<tr>
<td>Reactions for removing chloramines</td>
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<tr>
<td>Activated carbon</td>
</tr>
<tr>
<td>C₂+ 2 HClO → CO₂ + 2 ClH</td>
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<tr>
<td>C₂+ 2 NH₂Cl₂ + 2 H₂O → CO₂ + 2NH₄ + 2 Cl⁻</td>
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<tr>
<td>Bisulfite reaction</td>
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<tr>
<td>Cl₂ + H₂O + Na₂SO₄ → Na₂SO₄ + 2 ClH</td>
</tr>
<tr>
<td>Cl₂ + H₂O + NaSO₃H → NaSO₃H + 2 ClH</td>
</tr>
<tr>
<td>NH₂Cl₂ + SO₃H₂ + H₂O → NH₂SO₄H + ClH</td>
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</tbody>
</table>
Ascobic acid allows neutralization of chloramines [12–14]. The half time of reaction between ascobic acid and chloramine is about 4 min. It was used principally for dialysis batch systems, but can be also used for machines with a proportioning delivery system [14], although at the price of poorer results [15]. It is necessary to add ascobic acid in a quantity sufficiently to achieve at least a concentration of 1.7 mg/dl in the dialysate fluid. The infusion of 500 mg of ascobic acid per week to haemodialysis patients has also been shown to be useful to diminish the anaemia of chloramines [6]. Administration of ascobic acid is more expensive and more complex than dialysate treatment with activated charcoal filters. In certain circumstances it could be used as a complementary measure.

**Acceptable concentrations of chloramines**

Which concentrations of chloramines can be tolerated in the water used for haemodialysis? The direct determination of chloramines is not easy. As a substitute one determines total and free chlorine: bound chlorine (p.p.m.) = total chlorine − free (available) chlorine. The difference, i.e. the bound chlorine, corresponds almost completely to chloramines in this type of chlorinated water [16,17]. Commercial kits are available for the determination of total and free chlorine. They are based on the reaction between chlorine and DPD (N,N-diethyl-p-phenylene diamine) in two steps. The detection limit of the colourimetric method is 0.1 mg/l and the minimum difference that can be detected is 0.1–0.2 mg/l. The maximum permissible chloramine concentration in dialysis water, according to the AAMI and the majority of other countries, is 0.1 mg/l (0.1 p.p.m.) and 0.5 mg/l for total chlorine [18,19]. These limits have been questioned and it has been suggested that for total chlorine it should be 0.3 mg/l in drinking water [20,21] and 0.05 mg/l of chloramines for dialysis water. Taking into consideration the difficulties of determination, it is presumably more practical to put two filters of activated charcoal in series as mentioned above.

**What are the toxic effects of chloramine and the clinical presentation?**

Chlorine is toxic for humans [20]. The chloramines react with the body fluids and liberate hypochloric acid, hypochlorite, and free oxygen radicals [22]. They are all capable of modifying cellular proteins and lipids and of causing protein denaturation and haemolysis. The most obvious clinical manifestation in dialysed patients is haemolytic anaemia [6,23,24]. Oxidation of bivalent iron in haemoglobin to trivalent iron leads to the formation of methaemoglobin which is unable to transport either O2 or CO2. Methaemoglobin leads to the appearance of Heinz bodies, which are seen when chloramine concentrations exceed 0.5 mg/l. They increase in number and in proportion to the chloramine concentrations [6,24]. This, and in addition oxidation of erythrocyte membrane phospholipids, leads to erythrocyte membrane fragility and reduced half-life of erythrocytes.

It is difficult to state at which chloramine concentration in the dialysis fluid clinical signs are seen in patients. Presumably the effect is gradual and increases with the concentration. At low concentrations, the effects are countered by the action of natural antioxidants which are generally diminished in uraemic patients [25]. This interaction is suggested by the fact that plasma vitamin E concentrations are diminished in haemodialysed patients with exposure to chloramines compared to patients with no exposure [26]. When the dialysate water is contaminated with chloramine at a concentration of 0.1–0.2 mg/l, erythrocyte half-life of dialysed patients is diminished and this translates clinically into a greater requirement of rhEpo. We have noted that when the charcoal filter was exchanged, a significant decrease of the required dose of rhEpo occurred when chloramine concentrations were around 0.1 mg/l. The chloramine concentration in the dialysis fluid at which clinical manifestations appear are approximately 0.2–0.25 mg/l [3,6,27]. In the paper by Tippel et al. [3], when city water chloramine concentrations were between 1 and 2.8 mg/l and when an insufficient quantity of charcoal relative to demand of water was used, chloramine concentrations in the treated water were between 0.2 and 0.5 mg/l. This significantly increased transfusion requirements, and total mortality was greater, although a cause and effect relationship remains uncertain [28]. Chloramine-induced haemolysis presenting as Epo resistance has recently been also reported from the UK (29; Richardson et al., pp. 2626–2627, this issue). Exposure of dialysis patients to chloramines may have effects mediated via oxidation, which have not yet been validated.

**Conclusions**

The addition of chloramines is one of the most commonly utilized procedures used to disinfect city water. Not all water supplies used for haemodialysis contain significant chloramine concentrations. When chloramine is present in water, however, the best method to eliminate it is to use activated charcoal filters, preferably in series, and to monitor chloramine concentrations between the filters, where they should be less than 0.1 mg/l. Chloramine concentrations above 0.2–0.25 mg/l in the dialysis water may cause real ‘epidemics’ of anaemia in dialysis units. In the era of Epo, a tendency to develop anaemia is more difficult to detect because it may be masked by a requirement for increased doses of Epo. Chloramine concentrations between 0.1 and 0.2 mg/l probably cause Epo resistance in some patients.

**Acknowledgements.** We thank Professor Ritz for translating the text from Spanish to English.
References

13. Wiseman KC. Use of ascorbic acid to remove chloramine from dialysate water. *ANNA J* 1997; 24: 67–68

Editor’s note

Please see also *Dialysis and Transplantation News* by Richardson *et al*. (pp. 2625–2627 in this issue).