Side effects of aluminium –or iron– chelators used in dialysis patients

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The aim of this article is to review the most important side effects of chelators of aluminium or iron, as far as they are pertinent to their use in dialysis patients. The only chelator clinically available nowadays is desferrioxamine (DFO). This review will therefore mainly concentrate on DFO. At the end of this article, data concerning investigational chelators will be shortly mentioned.

Most important side effects of DFO can be classified as: A) non-infectious, and B) infectious.

Non-infectious side effects of DFO

Ocular toxicity

Visual toxicity is well known from the use of chronic subcutaneous DFO in non-uraemic patients with chronic iron overloed (e.g. thalassaemia). Visual toxicity may be subclinical or may be symptomatic, with bilateral visual loss, impaired colour vision or defective adaptation to the dark. In this patient population, gross iron overload seems to protect against this toxicity. A similar ocular toxicity has been reported in haemodialysis patients on DFO. More importantly, an acute visual reduction occurred in some patients shortly after a single intravenous DFO dose of 40 mg/kg, used for the so-called DFO-test. This acute visual disorder was reversible in most but not all patients, as a progressive damage of the pigmented epithelium occurred in some patients[1]. In a prospective evaluation, Cases et al. observed visual toxicity in 7/41 (17 %) of their haemodialysis patients treated with DFO at 10 to 40 mg/kg 3 times weekly. This toxicity was symptomatic in 3 patients (on DFO at 40 mg/kg), manifesting itself by abnormal colour vision, night blindness or decreased visual acuity. Simptoms subsided in all 3 patients[2].

The ophtalmological findings in most studies point to a DFO-induced retinopathy. In man as well as in experimental animals, microscopical changes are mainly found in the retinal pigment epithelium. The precise mechanism of the retinal toxicity of DFO remains unclear. It has been suggested that the toxicity results either from a direct effect of DFO upon the retina or indirectly by chelating a trace metal.

Although cataracts have been reported in patients on DFO, the causal attribution of such lens opacities to DFO seems doubtful.

Auditory toxicity

Symptomatic or asymptomatic sensorineural hearing loss is encountered in haematological patients on chronic DFO therapy. The risk of ototoxicity increases with the use of higher DFO doses and with lower serum ferritin values. This side effect has been reported in only a few haemodialysis patients treated with DFO. However, Cases et al. identified, in their prospective evaluation of haemodialysis patients treated with DFO at 10 to 40 mg/kg 3 times weekly, auditory toxicity in 6/41 cases (15 %): 3 patients complained of hearing loss, while the audiogram disclosed subclinical toxicity in 3 others. After stopping DFO, hearing recovered in the patients with clinical toxicity and also improved in those with subclinical toxicity[2]. Audiograms and auditory-evoked potentials suggest that the toxicity is of cochlear origin and does not involve the auditory nerve. The mechanism of this cochlear toxicity remains poorly defined.

Encephalopathy

Several dialysis patients with aluminium encephatolopathy developed worsening of their neurological symptoms soon after DFO therapy has been initiated, with marked deterioration in mental status, obtundation and seizures. Less frequently, new encephalopathy symptoms appeared in patients with aluminium osteomalacia, who had started on DFO[3]. This neurotoxicity could be related to the DFO-aluminium chelate, allowing increaed aluminium to reach the central nervous system. Another possibility, however, is that DFO itself penetrates the cerebrospinal fluid and directly produces neurotoxicity.

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Miscellaneous

Hypotension during DFO infusion is not uncommon and ussually responds to a reduction in the rate of DFO infusion. Allergy and anaphylaxis to DFO are rare and succesful desensitization has been reported. Leucopenia or thrombocytopenia has rarely been ascribed to DFO.

Infectious side effects of DFO

Pathophysiology

Iron is of paramount importance in the survival and growth of all microorganisms, the only exception being lactobacilli. The iron concentration is between 0.3 and 4 μM[4]. It is not astonishing therefore that the host has developed several defensive strategies to withhold growth-essential iron from potential microbial invaders. Microorganisms have developed their own means of obtaining access to at least some of the iron in the host organisms. One of the most common mechanism used by microorganisms, when grown under iron-limiting conditions, is the synthesis and secretion of low-molecular-weight, high-affinity iron chelators, known as siderophores[4,5]. These compounds solubilize ferric iron in the medium and transport it to the microbial cell via a receptor-mediated mechanism, where upon the iron is released and the siderophore is either recycled or destroyed. The two most prevalent types of siderophores are catechols and hydroxamates[6]. DFO is one of such hydroxamates, being the main siderophore produced by the procaryotic *Streptomyces, Nocardia* and *Actinomycete spp.* As expected, the producer species are able to take up radioiron from ^{55}FO (ferrioxamine). Moreover, some bacterial and even fungal species are also able to utilize this «exogenous» siderophore, although they lack the capacity to synthesize DFO. For such microorganisms, able to utilize iron taken up from FO, the presence of DFO should act as a growth factor, enhance *in vitro* growth and aggravate experimental infection. On the contrary, for microorganisms which are unable to take up iron from FO, the presente of DFO causes iron-deprivation, resulting in suppression of *in vitro* microbial growth as well as protection against *in vitro* experimental infection. Microorganisms can be classified into two categories: the one stimulated and the other ones suppressed by DFO[7] (Table I). Nevertheless, clinical reports of infections developing in patients treated with DFO have, with very rare exceptions, been limited to *Yersinia spp.* and to *Zygomycetes* causing mucormycosis. Further discussion will be restricted to data reported on dialysis patients.

Bacterial infections

Does DFO therapy in dialysis patients increase the risk of bacterial infection? Three retrospective studies addressed this question and conclude that DFO does not influence the overall incidence of bacterial infection in this patient population[8-10]. Bacteraemias caused by *Yersinia*, however, are one possible exception to these reassuring data. Seventeen episodes of *Yersinia* bacteraemia have been reported to develop in 16 dialysis patients (Table II). No patient died. In 15 cases, sufficient details on the iron status and on possible DFO therapy were provided. Whereas 14/15 patients were iron-overloaded and the only not iron-overloaded patient was on iron therapy, only 6 of them (40 %) were treated with DFO at the time of occurrence of the *Yersinia* bacteraemia. The conclusion, therefore, is that iron overload is able to promote generalization of yersiniosis by itself and that DFO possibly played a role in some patients, who were also iron-overloaded.

Table I. Classification of microorganisms according to the effect of desferrioxamine

	Stimulated by DFO	Suppressed by DFO
Bacteria	*Klebsiella spp.* *Pseudomonas aeruginosa* *Salmonella typhimurium* *Vibrio vulnificus* *Yersinia enterocolitica*	*Campylobacter jejuni* *Escherichia coli* *Haemophilus influenzae* *Legionella pneumophila* *Neisseria gonorrhoeae* *Neisseria meningitidis* *Pasteurella multocida*
Fungi/Yeast	*Aspergillus fumigatus* *Cryptococcus neoformans* *Rhizopus spp.*	
Protozoa		*Plasmodium spp.* *Typanasoma cruzi*
Uncertain classification **Pneumocystis carinii**		

Table II. *Yersinia enterocolitica* bacteraemia in haemodialysis patients

References	Number of episodes
Beucler (1983)	1
Boelaert (1987)	10
Boyce (1985)	1
Eijgenraam (1988)	1
Fakir (1992)	1
Hoen (1988)	1
Mollaret (1971)	1
Robins-Browne (1983)	1
	17
Fe overload 14/15	
therapy 1/15	
15/15 (100 %)	
DFO therapy 6/15 (40 %)	

Fungal infections

Since 1986, several reports have drawn the attention of nephrologist to an unusual fungal infection, associated with DFO therapy in dialysis patients: mucormycosis. An international registry on this fungal infection in dialysis patients has been reported[11]. Forty-six of the 59 patients (78 %) were treated with DFO when this infection appeared. Indication for DFO therapy was aluminium-overload in 84 % of cases. Mucormycosis was disseminated in 44 % of cases. The fatality rate was 86 %. The causative fungus was always *Rhizopus*. Since the end of the registry, 3 more DFO-related cases have been reported. The incidence of mucormycosis in dialysis patients was higher in the dialysis units using more DFO and during the years of more intense DFO prescription. DFO as well as its iron chelate FO significantly aggravate mucormycosis, when experimentally induced in guinea-pigs[12] or in mice. Iron salts[12] but not aluminium salts also aggravate experimental mucormycosis. Even at nM concentration, FO leads to iron accumulation by *Rhizopus;* this is accompanied by growth stimulation[13, 14]. These effects on *Rhizopus* are specific to DFO and are not found with iron chelators of other chemical classes, such as L_1[15]. After administration of DFO, FO accumulates in the plasma of dialysis patients, when compared to non-uraemic persons[16]. Such a retention of FO could render dialysis patients particularly susceptible to mucormycosis during DFO therapy. Since mucormycosis may also, although uncommonly, manifest in dialysis patients not treated with DFO, it appears that other factors (iron overload, diabetes mellitus,...) may have played a role in some patients[11].

Comment

At present, DFO is the only aluminium –or iron– chelator clinically available world wide and it remains an important drug for dialysis patients. Therefore, the potential side effects of this drug should be known in detail to the prescribing nephrologist. There are strong indications that most of the side effects (ocular, auditory and cerebral toxicity, as well as mucormycosis) are related to the high DFO dose used. Decisions on the DFO dosage have to take therapeutic benefits and risks into account. New guidelines on the dosage of DFO to be used for diagnostic means (DFO-test) as well as for therapy have been proposed during a consensus conference (Paris, June 1992) on the diagnosis and treatment of aluminium overload in dialysis patients[17].

Other chelators

Several compounds, unrelated to DFO, are being developed as iron-chelating agents. One of them is 1.2-dimethyl-3-hydroxypyridin-4-one (CP 20 or L_1). It is to be used orally and has already been given to at least 200 patients[18]. Preliminary results show that L_1 and DFO have a comparable effect on aluminium removal in the aluminium overloaded rat[19]. Toxicity in humans included transient episodes of agranulocytosis, musculoskeletal and joint pains, as well as a lupus-like syndrome in one case[18]. It is reassuring that L_1 does not stimulate the growth of *Rhizopus* and does not aggravate experimental mucormycosis[20]. It should be stressed, however, that more extensive toxicological data are needed before the long-term use of this or related compounds can be advocated in patients and more particularly in dialysis patients.

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