

Amiodarone-induced vasculitis and polyserositis

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Summary: A dose-dependent cutaneous leukocytoclastic vasculitis developed in a 34 year old man who was given amiodarone for supraventricular tachycardias resistant to other drugs. This adverse reaction disappeared within 2 weeks after discontinuation of amiodarone despite its very long half-life of 52 days in this patient. During previous treatment periods with amiodarone, the patient had experienced photosensitivity and dose-dependent polyserositis. Since high doses of amiodarone have been recently proposed for the treatment of resistant cardiac arrhythmias, dose-dependent adverse effects as described here may be encountered with increasing frequency.

Introduction

With increasing use of the highly effective antiarrhythmic drug amiodarone, a growing number of adverse effects and unfavourable interactions have been reported (Heger *et al.*, 1981; Jonckheer *et al.*, 1973; Stäubli *et al.*, 1983; Tartini *et al.*, 1982), the most serious being ventricular tachycardia (Tartini *et al.*, 1982), peripheral neuropathy (Heger *et al.*, 1981; Meier *et al.*, 1979), thyrotoxicosis (Jonckheer *et al.*, 1973; Wimpfheimer *et al.*, 1982), and pulmonary infiltration (Heger *et al.*, 1981; Rotmensch *et al.*, 1980). The present report deals with two hitherto unrecognized and potentially dangerous complications, polyserositis and cutaneous vasculitis, which deserve due attention.

Case report

A 34 year old man weighing 70 kg with recurrent sustained and incapacitating supraventricular tachycardias was unsuccessfully treated from 1973 to 1979 with digoxin, practolol, propranolol, quinidine and oral verapamil. In 1979, when amiodarone was started (400 mg per day), tachycardias became rare and were of short duration. After nine months, amiodarone was withdrawn because of a suspected photosensitivity reaction to the drug. Tachycardias gradually returned when his amiodarone plasma concentration had declined from a steady state concentration of 2.5 mg/l to 1.0 mg/l. A further treatment period with 600 mg per day of amiodarone again resulted in satisfactory control of arrhythmia.

However, at steady state serum amiodarone levels of 3.7 mg/l, the patient developed myalgia, muscular weakness, bilateral pleural and knee joint effusions, arthralgias in both shoulders and hips, photosensitivity and elevation of alanine aminotransferase. Laboratory investigations for antinuclear and antimitochondrial antibodies, circulating immunocomplexes, rheumatoid factor and antistreptolysin-O titre revealed normal results. Sedimentation rate was 10 mm/h. The effusions and arthralgias disappeared within 2 weeks after withdrawal of amiodarone, when serum levels were below 2.6 mg/l. Myalgia and muscular weakness improved slowly within 3 months after discontinuation of amiodarone treatment.

Tachycardias recurred at serum levels below 1.0 mg/l. Consequently, the patient was instructed to inject 5 to 10 mg verapamil intravenously for each attack of tachycardia, a procedure found to be effective in most instances. However, as the incidence of tachycardias and as the heart rate during attacks progressively increased, finally leading to daily verapamil injections, it was decided to give amiodarone again.

In view of the previous pharmacokinetic experience with amiodarone in this patient (mean serum half-life: 52 days; mean apparent volume of distribution: 175 l/kg; linear relationship between daily dose and steady state level (Stäubli *et al.*, 1983); residual amount of 5 g of total body amiodarone resulting from the second course), a loading dose of 11 g and a maintenance dose of 200 mg per day were calculated to achieve steady state plasma concentrations of 1.3 mg/l. At this plasma concentration tachycardias had been sufficiently well tolerated previously and the apparently dose dependent side effects during the second treatment period had disappeared. The loading dose of 1.6 g divided in 2 equal daily doses for 7 days initiating the

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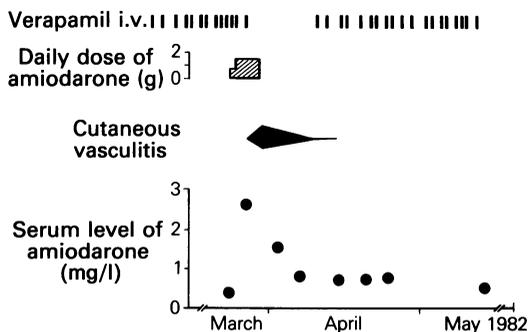


Figure 1 Temporal relationship between drug treatment, serum levels of amiodarone and cutaneous vasculitis during treatment period III. (1 mg amiodarone = 1.55 μ mol).

third treatment period was started on March 23, 1982 (Figure 1). On March 28 the patient noted red spots on the distal half of his lower legs and on the dorsal surfaces of his feet. Otherwise he felt well. He stopped amiodarone intake on March 30, because the red spots increased in number and size (up to 1 cm in diameter). As tachycardias had ceased since March 28, verapamil was stopped after a final injection on March 27 (Figure 1). On April 2 he presented with plain red spots (2 to 4 mm in diameter) on the dorsal surfaces of both

feet, on both insteps and on the distal thirds of the lower legs.

Physical findings were otherwise normal except for photosensitivity which had reappeared. A careful history gave no indication for intake of other drugs. Laboratory investigations including sedimentation rate, urine analysis, determination of serum C_3 and C_4 , circulating immune complexes, IgG, IgA, IgM, IgE and alanine aminotransferase, gave normal results. Leucocytes were $8.2 \times 10^9/l$, with normal differential count. Platelets were $210 \times 10^9/l$.

Figure 2 shows a typical lesion in a skin biopsy obtained from the dorsal surface of the right foot, chiefly characterized by a leucocytoclastic vasculitis involving small blood vessels of the corium cutis. Using immunohistology, no deposits of C_3 , C_4 , IgG, IgA or IgM could be demonstrated.

The cutaneous lesions had completely disappeared by April 14, 1982, but intravenous verapamil had to be restarted on April 9th. At amiodarone levels between 0.8 and 0.7 mg/l (Figure 1) attacks of tachycardia had recurred.

Discussion

Leucocytoclastic vasculitis due to amiodarone has not been described to our knowledge. It could be argued that verapamil might have played an aetiological role.

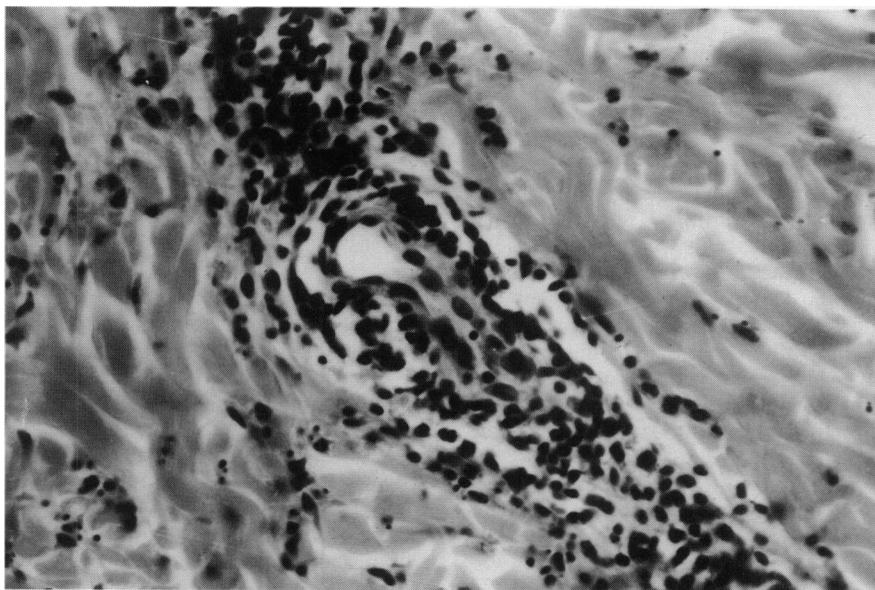


Figure 2 Perivascular infiltrate around a small arteriole of the corium cutis consisting of small lymphoid cells and neutrophils which can also be seen in the surrounding connective tissue. Numerous black points corresponding to nuclear debris can be observed. (Stain: H & E \times 560.)

However, vasculitis only appeared after termination of verapamil injections, it improved when amiodarone was stopped, and did not reappear on restarting verapamil later. Residual amounts of amiodarone were still present in the serum during verapamil treatment. Therefore it is unlikely that vasculitis was a consequence of the combination of the two drugs. Mainly because of the close temporal relationship between amiodarone challenge and dechallenge and, as a careful history revealed, that the patient did not take any other drugs, we conclude that amiodarone was responsible for the occurrence of vasculitis (Kramer *et al.*, 1979).

Necrotizing (leucocytoclastic) vasculitis of the type observed in the present case is currently thought to be mainly due to immune reactions, immune complex-induced wall damage playing a crucial role (Braverman & Jen, 1975; Sams *et al.*, 1976). In our case, amiodarone could theoretically have led to vasculitis based on such a mechanism. We could, however, demonstrate neither circulating immune complexes nor local deposits of immunoglobulin or complement in the vessel walls. The failure to detect immune complexes and immunoglobulin/complement components may have been due to the time-lag between the onset of clinical signs of regression and the corresponding laboratory investigations (Braverman & Jen, 1975; Sams *et al.*, 1976). On the other hand, the possibility that vasculitis in this case was not mediated by immunological mechanisms alone must be considered. It appears that onset and expression of vasculitis in this patient were dose dependent: when amiodarone treatment was reinstated for the third

time, the residual serum level was still 0.4 mg/l. The vasculitis appeared at amiodarone serum levels above 2.6 mg/l and the cutaneous lesions had already disappeared three weeks after onset when amiodarone serum levels were still above 0.65 mg/l. A similar dose dependence of the adverse reactions had also been observed during the second period of treatment.

As the planned steady state level of amiodarone of 1.3 mg/l was far below those levels at which polyserositis, myalgia, muscular weakness and alanine aminotransferase elevation were observed previously, readministration of amiodarone appeared to be justified once more.

It remains unknown why the patient reacted with photosensitivity alone the first time he received amiodarone, with photosensitivity and a rheumatic syndrome the second time and with vasculitis the third time. Perhaps, the peculiar syndrome during the second treatment period which disappeared gradually after amiodarone withdrawal, might, in retrospect, also be interpreted as vasculitis as well as pleural effusions observed recently in other patients under amiodarone treatment (Heger *et al.*, 1981). More frequent biopsy investigations in such cases appear warranted.

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