A practical guide to detecting amiodarone neurotoxicity

Amiodarone and the “dizzy” patient
Daniel Eschle
Kantonsspital Uri, Switzerland

Introduction
Cardiologists regularly receive referrals to investigate “dizzy” patients, which in many instances means ruling out or treating arrhythmia (depending on the case at hand). And this is where amiodarone might come into play — and in the end maybe also a neurologist. The initial cardiovascular “dizziness” can end up as a neurological problem because of possible amiodarone-induced neurotoxicity. Whereas most physicians will be familiar with the risk of thyroid dysfunction during anti-arrhythmic therapy with amiodarone, potential neurotoxicity is less well known among its numerous other side effects [1]. What should the cardiologist look for, when trying to fathom amiodarone neurotoxicity, and in particular “dizziness”? This review will discuss a few easy-to-use clinical tests to detect potential neurotoxicity in the “dizzy” patient, without delving too much into the intricacies of the neurological examination or the complexities of amiodarone pharmacology and toxicology.

Clinical presentation and epidemiology
Two important publications from 1974 illustrate many of the typical aspects of amiodarone neurotoxicity. Lustman and Monseu described a 65-year-old patient who was given amiodarone 400 mg/day [2]. Within 1 month he presented with paraesthesiae in both legs, tremor of his hands and ataxia. The symptoms and signs increased, so after about 10 months amiodarone was replaced with propranolol and within 1 month the paraesthesiae and ataxia disappeared.

Kaeser published the case of a 67-year-old patient who was treated with an amiodarone maintenance dose of 1800 mg/day [3]. After 2 years he complained of weakness in his legs and loss of dexterity in his hands. At the time of his neurological consultation (about 6 months later), he could hardly walk or get up from a chair unaided. A decrease in all sensory modalities was noted in his feet, as well as profound muscle weakness and a decrease in motor conduction velocities. Because of bluish skin pigmentation, known to occur as an amiodarone side effect, the neurological signs and symptoms were also attributed to the drug. Amiodarone was stopped and at the next follow-up visit 3 months later, weakness and sensory deficits were improved.

The frequency of neurotoxicity is reported to be in the range of 35% to over 50% in older publications and ≤5% in more recent ones [4–6]. In comparison, thyroid dysfunction is seen in about 14–18% of patients [7]. Older studies included many patients treated with a maintenance dose of ≥600 mg/day, whereas nowadays it is more likely that doses in the range of 200 mg/day will be prescribed.

According to a study of patients from Olmsted County, it would seem that neurotoxicity is determined by the cumulative amiodarone dose: “those with neurotoxic effects took amiodarone for significantly longer” than those without (mean 31.6 vs 17.2 months) [8]. Although this point is intuitively plausible, there are other — at present unknown — factors at play, which influence the emergence of neurotoxicity on an individual basis, as exemplified by the case reports presented above. The first patient reported symptoms after 1 month of treatment with amiodarone 400 mg/day,
and the second patient only noticed symptoms after 2 years on 1800 mg/day (the cumulative dose differed by a factor of 100).

The relevant literature describes the following neurological symptoms and signs in conjunction with amiodarone [9]:

1. Tremor, for example when trying to hold a full spoon of soup without spilling it [10].
2. Numb or tingling hands and feet (paraesthesiae) due to distal-symmetric polyneuropathy with reduced perception of various sensory modalities, in particular diminished pallaesthesia. This is not always painful and can only be diagnosed if you look for it. Polyneuropathy causes a deficit of sensory input and thus leads to a “dizzy” feeling.
3. Muscle weakness (which can be caused directly by myopathy and/or indirectly via polyneuropathy). A number of case reports have described patients who were progressively confined to a wheelchair and then recovered after discontinuing amiodarone. When taking a history, even patients with frank weakness might use the word “dizziness” to describe their symptoms!
4. Optic neuropathy due to amiodarone will convey a “dizzy” feeling or a sense of unsteadiness. Of course these patients will attribute their “dizziness” to deteriorating vision and so the diagnosis can be elicited without much effort. Readers are referred to Wang and Chen for further information [11]. Surprisingly, corneal deposits (affecting nearly all patients during amiodarone treatment) do not impair vision to the same degree [1].
5. Bilateral vestibulopathy has been implicated as an amiodarone side effect by specialised “dizziness” clinics [12].
6. We cannot rule out toxic effects on the cerebellum [13], see also next section.
7. Rarely, extra-pyramidal symptomatology (akin to parkinsonism) has been reported [14].

The sequela of neurotoxicity lead to reports of “dizziness” or, to be more exact, the feeling of an unsteady gait – in neurological jargon the term “ataxia” is quite often used in this context. It is not clear from the literature if cases of “ataxia” actually represent cases of “demyelinating” pattern with reduced nerve conduction velocities. The sequelae of neurotoxicity lead to reports of “dizziness” or, to be more exact, the feeling of an unsteady gait. Typically, amiodarone-induced neurotoxicity has an insidious onset. Any neurological symptoms and signs with an abrupt presentation bring other differential diagnoses to mind and referral to a neurologist should be considered.

Screening and differential diagnosis

Obviously it is useful to have a baseline neurological history and examination before starting the patient on amiodarone, and to plan regular follow-up visits so as not to miss emerging neurotoxicity. First of all, ask the patient about mobility issues, if there have been any falls, what (s)he actually means by “dizziness” and if his/her feet are numb. When taking the history, the patient may report difficulties with climbing stairs, but this could be a symptom of congestive heart failure and not necessarily due to neurotoxicity. But if the patient needs a cane or a walker for ambulation, then suspect neurotoxicity.

Before making a diagnosis of amiodarone neurotoxicity, rule out relevant hyponatraemia (≤130 mmol/l), which can mimic various neurological symptoms.

Further points to look for are dosing errors and amiodarone-induced thyrotoxicosis. To reach therapeutic amiodarone levels, so-called “loading” doses of amiodarone are prescribed. This is obviously a scenario where mistakes are bound to happen and patients may continue with higher loading instead of lower maintenance doses. And, needless to say, tremor due to hyperthyroidism may mimic neurotoxicity in sensu strictu.

If the patient complains of generalised weakness (without additional paraesthesiae), look for elevated creatine kinase levels and consider statin myopathy as a differential diagnosis for amiodarone-induced myopathy.

Numb feet as an isolated symptom (without additional weakness) are a hallmark of distal-symmetric polyneuropathy, which can have other causes than amiodarone.

Consider (pre)diabetes, vitamin B12 deficiency, paraproteinaemia or previous chemotherapy as additional polyneuropathy risk factors [16]. Because amiodarone-induced polyneuropathy has a characteristic “demyelinating” pattern with reduced nerve conduction velocities, a neurology consultation might be able to pinpoint the most likely aetiology [9].

Watching how the patient walks and stands are essential when looking for neurotoxicity. A broad-based and quite often irregular gait with short steps (like walking on ice) or increased body sway in the Romberg test are typical for the “dizzy” patient. The “Romberg” is a generic test for “dizziness” or “ataxia” at various levels of
the nervous system. The patient is asked to stand with feet together and then to close his/her eyes. Obviously it is more difficult to keep steady with eyes closed. But this extra effort is hardly perceptible when observing a healthy person. The test is positive (i.e., pathological) if there is excessive body sway or the patient falls (so be ready nearby). If the test is already positive with eyes open, then the patient will probably refuse testing with eyes closed and you might dispense with this step altogether. What constitutes “excessive body sway” is a matter of clinical judgement and not always easy to determine – when in doubt refer the patient to a neurologist.

Continue by measuring vibration perception (pallaesthesia) on the great toe with a Rydel-Seiffer tuning fork (fig. 1) [17]. The Rydel-Seiffer tuning fork is a cheap and fast way to look for polyneuropathy and should always be used in patients with (pre)diabetes or other known risk factors for polyneuropathy (such as amiodarone). Values for pallaesthesia below the physiological age-dependant decline are suggestive of polyneuropathy, correlate with nerve conduction studies [18], and are associated with increased body sway [19], which will be reported as “dizziness” by the patient. And in the long run, polyneuropathy increases the risk of amputations. Readers who want to go into more detail about clinical polyneuropathy assessment can consult current diabetes guidelines [20].

What to do next?

Once neurotoxicity occurs, it is reversible, or at least can change for the better, in most cases if you stop the drug. You will feel more comfortable with stopping amiodarone if you find additional toxic effects in other organ systems, but this is not without its perils (and has to be discussed with the patient), given the indication for amiodarone to prevent sudden cardiac death. Due to the long half-life of amiodarone (between 20 and 100 days), reversal of symptoms is a waiting game for most patients.

Key messages

- There is a degree of idiosyncrasy regarding amiodarone-induced neurotoxicity, so one should always be on the look-out for pertinent signs and symptoms.
- Patients will typically complain of tremor but also “dizziness” – as an umbrella term for an unsteady gait.
- Amiodarone can cause “dizziness” at various levels of the nervous system: (1) optic neuropathy, (2) distal-symmetric polyneuropathy, (3) cerebellar toxicity, (4) peripheral vestibulopathy, and (5) myopathy.
- A broad-based gait (like walking on ice) or increased body sway in the Romberg test are typical for the “dizzy” patient.

Figure 1: The Rydel-Seiffer tuning fork.
Place the base of the vibrating Rydel-Seiffer tuning fork on the great toe. As vibration diminishes, you will see the (black) triangle come into focus and “climb” upward. Ask the patient to tell you at which point the vibration stops and compare the tip of the triangle to the markers. That value (on a scale from 0 to 8) is compared to age-standardized norms for pallaesthesia (vibration perception) [17]. A healthy person up to the age of 40 years should be able to feel ≥4.5/8th, and at least 3/8th above the age of 85.

Source: photographs and illustration by the author.
– Measure vibration perception (pallaesthesia) on the great toe with the Rydel-Seiffer tuning fork, which is a cheap and fast way to look for polyneuropathy.

– Once neurotoxicity occurs, it is reversible in most cases if you stop the drug.

– This is not without its perils (and has to be discussed with the patient), given the indication for amiodarone to prevent sudden cardiac death.

Acknowledgements
I would like to offer my special thanks to Dr Yvonne Brun-Odermatt, consultant cardiologist at the Kantonsspital Uri, for her review of the manuscript.

Conflicts of interest and ethics
The author declares that there are no conflicts of interest, in particular none with a manufacturer of pharmaceutical products or a competitor. This manuscript is not under review by another journal. This paper is based on previously published work, so no new studies in humans or animals were necessary.

References