Journal of Applied Biomedicine
1: 127–139, 2003
ISSN 1214-0287

Amiodarone – excellent antiarrhythmic drug?
(Happy end after 40 years of problems)

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Summary
Amiodarone, discovered forty years ago and in general use as an anti-anginal drug, has become a wide-spectrum anti-arrhythmic, used as the drug of preference in cardiac failure and after myocardial infarction, where it is the only drug (besides some betablockers) which does not increase overall mortality. It is successfully used in therapy and prophylaxis for life threatening arrhythmias, even when electro physiological testing has failed to disclose the detailed mechanism of arrhythmia. In cases of myocardial infarction it should be regarded as the anti-arrhythmic drug of first choice. Amiodarone is a drug which is capable with high probability of anticipating arrhythmias, combining, in an exclusive exceptional entity, beneficial effects on cardiac electrophysiology, neurochemical parameters, coronary flow and haemodynamics with a unique local antithyroid effect. A detailed survey of the current experimental and clinical basis for practical use is given, based on 93 cited sources from the last 30 years.

Keywords: anti-arrhythmic drug – electrophysiology – indications – interactions – adverse effects

INTRODUCTION

Amiodarone was discovered in 1962 (the same year as verapamil), to an important extent because of systematic research on benzophurane derivatives (Amiodarone and a butoprozine synthesis programme, Labaz, Belgium) (Fejfar et al. 1980, Tardos et al. 1979).

Used as an anti-anginal drug from 1967 (Tardos et al. 1979), it became an anti-arrhythmic in 1969, (Fejfar et al. 1980, Medicamenta Nova 1983, Mutschler 1991, Schlant et al. 1992) and reported in the prevention of supraventricular tachycardias from 1970 (Fejfar et al. 1980, Medicamenta Nova 1983). Its short life as an anti-anginal drug should by no means be underestimated.

The experimental proof of its beneficial influence on ischemic myocardium remains until now a suggestive and perhaps even promising feature of its pharmacological profile. The myocardium-protective effect was described in 1979 by Takáts and co-workers (Tardos et al. 1979) and quantified by means of indexing of changes in metabolic indicators as developed and described by Fedelesova M. et al. in 1976. (Tardos et al. 1979)

At first amiodarone was used mainly in France, South America, and the Scandinavian countries (Fejfar et al. 1980) in the treatment and prevention of supraventricular and ventricular dysrhythmias. (Fejfar et al. 1980, Medicamenta Nova 1983) In spite of its "bizarre" pharmacokinetics and ample portfolio of adverse events, amiodarone has been hailed and welcomed as an "ideal anti-arrhythmic".

As to dosage, two early schools can be distinguished, one of "rapid impregnation" (the so

called American school, starting with up to 1200 mg/1st day) and the other of "slow impregnation" (the British school with up to 800 mg/1st day). The term "impregnation" reflects the well known fact that the tissue concentrations of amiodarone in myocardial muscle exceed by approximately 44–50 times plasma levels (not to mention fat tissue, with figures up to 500 times higher concentrations as compared with plasma levels).

Intravenous administration in Europe became more common at the beginning of the eighties, and in the mid-eighties was not unusual even in regional hospitals in socialist countries (Petr 1986).

Because of frequent and partially dangerous adverse effects, amiodarone has been increasingly removed from its prime position as an ideal anti-arrhythmic. In the mid-nineties it was classified as a "reserve anti-arrhythmic" which could be used in case of lasting resistance to other anti-arrhythmic treatment (Mutschler 1991). Classified as a Class III drug in the Vaughan-Williams scheme and more meticulously characterised in the Sicilian Gambit approach (Marek 1998) it practically never ceased to provoke investigators also by its other than electrophysiological properties, and has been tested for its influence on haemodynamics, mainly on LVDF (Left Ventricular Diastolic Filling) (Schlant et al. 1992, Kaye et al. 1999).

At the end of the nineties, but mainly in the new millennium, amiodarone has acquired an extremely high profile and has won back the promising position which characterised its appearance forty years ago (Bytešník 2000, Kaye et al. 1999, Špinar et al. 2001, What is What 1997, Caron et al. 2001, Dorian et al. 2002, Pleskot et al. 2000).

In Central Europe, the 20 years between Zlín in Moravia, (in what is now the Czech Republic) in 1980 when the position of amiodarone was discussed (Fejfar et al. 1980), and Zlín in 1999 – when the current position of this "enfant terrible" of drugs was well defined by Widimsky from the point of view of safety, (Widimský 1999, Widimsky 2000) and by Bytešník, from the point of view of indications and efficacy (Bytešník 1999, Bytešník 2000), could be regarded as a strategic gain and success for the drug, and it is today, for example in the Czech Republic, marketed by five producers under six registered names.

REMARKS ON ELECTROPHYSIOLOGY

From the point of view of its electrophysiological effects, as demonstrated on Môn cellular models and sub cellular structural models, amiodarone shows a blocking effect on K, Na and Ca channels, and further, depresses the sinoatrial node's activity, diminishes the conduction velocity in atrioventricular node and broadens the refractory phase (Mutschler 1991). As to the degree of this influence, the effects on Na channels and Ca channels are characterised as "medium strong", the effect on K channels as "strong" (Marek 1998).

The alpha-sympatolythic and beta-sympatolythic effects are described as "medium strong" (Marek 1998). The knowledge and the awareness of these properties should help physicians to make "evidence based" decisions in the choice of an appropriate anti-arrhythmic in the sense of the Sicilian Gambit approach (Marek 1998).

The electrophysiological properties have other stimulating effects on theoretical considerations and practical attitudes, mainly from the point of view of predicted responders' , prediction of adverse effects, search for possible amiodarone successors.

Malik et al. reported in 2000 (Malik et al. 2003, Špinar et al. 2001, What is What 1997) on the possibility of identifying post infarction patients, who might benefit from prophylactic treatment with amiodarone. This sub study of EMIAT (Špinar et al. 2001, What is What 1997) shows that a depressed heart rate variability perhaps identifies a subgroup with a lesser mortality rate when on amiodarone.

Brembilla-Perrot and co-workers demonstrated recently that patients who are non-responders to amiodarone as an anti-arrhythmic can be identified by an absence of change in the signal-averaged electrocardiogram (Brembilla-Perrot et al. 2002).

An attempt to predict the patients who may suffer adverse effects has been made by Matsuyama et al. (2001) by demonstrating that T-wave alternant (microvolt T wave alternant TWA) was observed as a predictor of exacerbation of ventricular tachycardia and an increased defibrillation threshold. They conclude that TWA might be useful in predicting the pro-arrhythmic effects of amiodarone.

The search for possible successors to amiodarone is based on, for example, the findings of reverse rate dependence of the potential widening of the drug induced cardiac action (Weirich and Wenzel 2000). The drug induced prolongation of cardiac action potential is minimized with high rates. On the other hand, during bradycardia the pronounced action potential prolongation may cause early after depolarisations and triggered activity, leading to torsades de pointes arrhythmias (acquired QT syndrome). That is why class III substances – inhibiting the slowly activating K channel component – are currently under investigation and are expected to show direct rate dependence, or at least, to be rate independent.

Opincariu et al. demonstrated (2002) that GYKI 16638 (an experimental code for pre-clinical drug testing substance) in human ventricular heart muscle

shows electrophysiological manifestation seen after chronic amiodarone treatment, demonstrating in this paper the lasting interest – from 1979 – of the research group headed by G. Papp, in this topic (Opincariu et al. 2002, Tardos et al. 1979).

An extremely interesting feature of amiodarone, i.e. its ability to prolong cardiac repolarisation, and at the same time to inhibit thyroid hormone action in the heart, gave rise to the revival of interest in the benzophurane derivatives, which was the original intellectual condition that gave rise to the synthesis of amiodarone (Fejfar et al. 1980, Tardos et al. 1979). Carlson et al., reported in 2002 on a new series of carboxymethoxybenzoyl and benzyl derivatives of benzophurane, revealing the most promising in vitro data. The research should aim at a substance less toxic than amiodarone, but preserving its electrophysiological properties and local antithyroid effect.

REMARKS ON PHARMACOKINETIC AND PHARMACODYNAMIC

Amiodarone, the iodized benzophurane, is poorly soluble in water. The iodine content is very high; in a 200 mg tablet 75 mg of iodium are present (Marek 1998). After oral administration, the c-max could be expected at t-max = 7 hours, the therapeutic concentration is 0.5–1.5 mg/ml (Lüllmann et al. 2002).

The apparent distribution volumes are dV = 66 l/ per kg, the plasmatic $t_{½}$ is 30–50 days for benzophurane structure (Lüllmann et al. 2002), and 18–22 days for iodium as an atom (Mutschler 1991). This unique pharmacokinetic profile is perhaps responsible for particularly stable plasmatic levels, and a balanced and stable influence on myocardium (Bytešník 2000).

Verner M. demonstrated repeatedly the fact, that almost two thirds (e.g. 63%, in 2002? 165 out of 261 measurements) of registered plasma-levels figures in routine therapeutic drug monitoring (TDM) at his department are in the range of 0.5–1.5 mg/ml , i.e. inside the optimal therapeutic range. When calculated in the range of accuracy and precision estimated at 17%, (Jun et al. 2001) the total number of acceptable results is 76%. (e.g. in 2002: 199 out of 261 measurements). (Personal communication, M. Verner). The tissue concentration in heart muscle is approximately 50 times higher than that in plasma, and in fat tissue even 500 times higher (Lüllmann et al. 2002).

Amiodarone is nowadays estimated by high-performance liquid chromatography assay. Jun A.S., et al. demonstrated in 2001 (Jun et al. 2001), that a quantization limit of at least 0,035 mg/ml can be expected. The accuracy and precision were found to be less than 17%, for the concentration range of 0.0035 up to 5 mg/ml. For a clinician cooperating with a clinical pharmacologist this means that a plasma level of 1.5 mg/ml has an interval from 1.245 to 1.755 mg/ml and could, in reality with the same probability, be any figure lying inside of this interval.

The bioavailability of amiodarone is strikingly affected by concomitant food intake. Meng et al. have proved (2001) that for amiodarone being administered after a standard high fat breakfast, the c-max and AUC (area under the curve) are 3.8, respectively 2.4 times the respective values under fasting conditions (Ha et al. 2001). The t-max to c-max diminishes from 7.1 hours in fasting condition to 4.5 hours after the standard high fat breakfast. Thus, food significantly enhances both the rate and extent of absorption of amiodarone, which is attributed partially to the effect of food on drug release from its formulation. Therefore, it is recommended that amiodarone tablets be taken consistently with meals.

Amiodarone is biotransformed in vivo and in vitro to desethylamiodarone (mono-N-desethylamiodarone-MDEA). Recently, it has been observed, that MDEA is further hydroxylated to n-3-hydroxybutyl-MDEA. This substance can now be also quantified by HPLC, as described by Ha H.R., et al. in 2001 .This finding could be of the utmost importance for usage of the data from animal experiment to human physiology, because the differences of hydroxylase activity in mammalians may be the origin of the species dependency observed in the amiodarone biotransformation.

The pharmacodynamic effects of amiodarone on sympathetic nervous activity, mainly in patients with congestive heart failure, are the topic of interest of Kaye D.M., et al. (Kaye et al. 1999). They evaluate the influence of amiodarone on neurochemical parameters of sympathetic nervous activity and suggest that amiodarone really exerts a sympatholytic effect.

They conclude, that amiodarone may exert beneficial effects on failing human heart through a sympatholytic process, and that this action appears to be relatively cardio selective.

REMARKS ON ATRIAL FIBRILLATION

From the very beginning, amiodarone has been regarded as a drug appropriate for the termination and prevention of atrial fibrillation and other supraventricular tachyarrhythmia (Fejfar et al. 1980, Medicamenta Nova 1983).

Intravenous administration of 150–300 mg i.v., directly or in short-term intravenous drip-infusion was recommended to terminate the atrial fibrillation, and a tiny dose of 200 mg p.o. once daily to prevent the recurrence of paroxysms of atrial fibrillation (Marek 1998).

Quite recently, S. Levy, summarises the therapeutic attitudes to atrial fibrillation (Levy 2001). The role of amiodarone both in the termination and prevention of atrial fibrillation is highly estimated, and also as an appropriate pharmacotherapeutic regimen in the prevention of recurrent atrial fibrillation for patients who are successfully cardioverted.

Amiodarone can be administered per orally as well as parenterally, in doses of 600 mg/d for the restoration of sinus rhythm, and of course, afterwards for the maintenance of sinus rhythm, in doses of 200 mg/d, as reported by Galperin et al, and confirmed by a prospective, randomised, double blind trial (Galperin et al. 2001). Similar results were produced by Brilakis and co-workers (Brilakis et al. 2001).

A noteworthy shift from class I to class III anti-arrhythmic agents for suppression of atrial fibrillation has occurred recently, and of all the agents tested (sotalol, amiodarone and dofetilide) amiodarone appears to be the most efficacious (Tsikouris et al. 2001).

In spite of the fact that oral administration of amiodarone is also effective in termination of atrial fibrillation, (Brilakis et al. 2001, Galperin et al. 2001) the parenteral, (i.e. intravenous administration) is still the leading method of terminating a recent onset (i.e. existing shorter than 7 days) of atrial fibrillation. The meta analysis of randomised, controlled clinical trials performed by Hillemann D.E., et al. has shown that amiodarone is effective and safe in this regard (Hilleman et al. 2002). Those findings and results are confirmed by Kontoyannis D.A. et al. (Kontoyannis et al. 2001).

A special effort has been used to elucidate the role of amiodarone in persistent atrial fibrillation (Noble et al. 1999), and low-dose amiodarone has been found to produce a beneficial response in the prevention of paroxysmal atrial fibrillation (Kerin et al. 2000).

As a special question and task the role of amiodarone in the prevention of early reinitiating atrial fibrillation (ERAF) following an external or internal electrical cardio version has been studied by Reithmann C., et al. in 2001 (Reithmann et al. 2001), and by Veloso H.H. et al. in the same year (Veloso 2001) with the conclusion, that ERAF in patients on amiodarone could be treated with atropine, and that the PP interval preceding the beat reinitiating atrial fibrillation is longer in patients on amiodarone.

Another role of amiodarone, which is today studied and assessed thoroughly, is the prevention of atrial fibrillation after heart surgery.

Routine prophylaxis with amiodarone is found to be cost-effective (Reddy et al. 2002), intravenous administration of amiodarone in this situation has been found to be more effective than digoxin plus metoprolol, with 8.3% versus 16.8% of fibrillation occurrence (Tokmakoglu et al. 2002), and has been meticulously compared with therapeutic regimens using diltiazem and betablockers (Kim et al. 2002).

In an extensive meta analysis Haan C., et al. has proved that the evidence strongly suggests that perioperative treatment of cardiac patients with amiodarone may reduce the incidence of atrial fibrillation with minimal adverse effects (Haan et al. 2002).

The meta-analysis of clinical trials comparing sotalol and amiodarone as prophylaxis against atrial fibrillation/ flutter would suggest that both regimens are equipotent (Wurderman et al. 2002). So called hybrid therapy, i.e. concomitant use of radiofrequency catheterisation ablation (RFA) and anti-arrhythmic therapy with amiodarone is widely discussed by Neužil P., et al. (Neužil et al. 2000.)

REMARKS ON VENTRICULAR ARRHYTHMIAS

The role of amiodarone in the management of ventricular arrhythmias has been long recognised and respected (Fejfar et al. 1980, Marek 1998, Medicamenta Nova 1983). In prevention of the recurrence of ventricular arrhythmias in the broader sense, doses of 400 mg/d once daily (Bytešník 1999) or 200–400 mg once daily or divided in two doses, have been recommended (Marek 1998).

The CAMIAT and EMIAT studies in 1997 produced ample information on the importance of amiodarone in the lowering of the incidence of dangerous ventricular arrhythmias (Špinar et al. 2001, What is What 1997). Amiodarone lowers the incidence of ventricular fibrillation, and arrhythmic mortality, in ischemic heart disease as well as in non-ischemic cardiomyopathy (Špinar et al. 2001). Singh et al. documented, in 1995 and 1996, the concomitant lowering of ventricular arrhythmias and improvement of ejection fraction in patients with non-ischemic cardiomyopathy, when on amiodarone, in a therapeutic per oral regimen starting with 800 mg/d, ant lasting for 50 weeks with doses of 400 mg/d (Špinar et al. 2001).

In October 2001 the position of amiodarone in the new AHA guidelines for ventricular tachyarrhythmia was discussed and assessed by Caron M.F., et al. (Caron et al. 2001) concluding

that Amiodarone should be classified as a IIb therapeutic intervention, which makes it an acceptable, safe and useful agent with fair to good evidence to support its use. This is particularly true in ventricular fibrillation and pulse-less ventricular tachycardia (Stewart 2001).

Amiodarone has been in this regard critically tested and compared with lidocaine (Dorian et al. 2002) for terminating shock-resistant ventricular fibrillation, and with sotalol (Kovoor et al. 1999) with the aim of assessing its efficacy in preventing spontaneous sustained ventricular tachyarrhythmia. In the case of lidocaine, amiodarone proved to be more effective. Sotalol seemed to be more effective then amiodarone.

A special focus of research work, as well as of daily routine in specialised cardio centres has occurred recently, rising from the concomitant use of anti-arrhythmics, and implantable cardioverters/ defibrillators (ICD).

Pleskot M., et al. reported in 2002 (Pleskot et al. 2000, Pleskot et al. 1999) in two comprehensive papers based on their own experimental data discussing also the role of programmed ventricular cardio – stimulation (PVCS). They report (Pleskot et al. 2000) that Amiodarone results in substantial reduction (–29%) of sudden cardiac death mortality, and total mortality (–13%). In their series, they continued amiodarone even when PVS did not confirm its experimental efficacy.

In their second paper, focussed primarily on the role of revascularisation of myocardium on its electrical stability (Pleskot et al. 1999), they have found amiodarone effective in 17.7% when tested by PVCS. The current practices of concurrent/concomitant use of ICD and amiodarone are discussed in several papers (Dubin et al. 2001, Manolis et al. 2002, Schlapfer et al. 2002).

REMARKS ON PRE-EXCITATION SYNDROME AND RE-ENTRANT TACHYCARDIAS

The beneficial, propitious effect of amiodarone on electrophysiology in patients with accessory pathways, pre-excitation, and recurrent tachycardias was quickly recognised. (Fejfar et al. 1980, Medicamenta Nova 1983). Amiodarone has been and still is recommended as “a drug of first choice” in WPW and LGL syndromes, and as the main if not the only efficacious drug in atrioventricular nodal re-entrant tachycardias and atrioventricular re-entrant tachycardias in general (Fejfar et al. 1980, Lüllmann et al. 2002, Marek 1998, Medicamenta Nova 1983, Mutschler 1991).

In the early nineties, in the period of the diminishing use of amiodarone in wide therapeutic practice, those situations were regarded as the one and only realm of amiodarone (Mutschler 1991).

Nowadays, the role of amiodarone and radiofrequency ablation of the slow atrioventricular pathway is discussed, studied and critically evaluated (Levy et al. 1997, Starmer 1997).

REMARKS ON CARDIAC FAILURE

References more theoretical and experimental than clinically-based, to amiodarone use in cardiac failure (Tardos et al. 1979), and to the improvement of metabolic (Tardos et al. 1979) and haemodynamic (Schlant et al. 1992) parameters when on amiodarone, have been confirmed to a wide extent and high probability quite recently.

From GESICA trial results, published by Doval H.C. et al. (Špinar et al. 2001, What is What 1997) in 1994 in The Lancet over EMIAT and CAMIAT results (Špinar et al. 2001, What is What 1997) and sub-study CHF-STAT (Špinar et al. 2001, What is What 1997) the evidence is accumulated that amiodarone in patients with heart failure diminishes arrhythmic mortality and overall morbidity and that its pro-arrhythmic effect is low.

Kaye D.M. et al. (Kaye et al. 1999) studied the neurochemical and haemodynamic parameters in human heart failure, and found that in neurochemical parameters, the patients treated with amiodarone present substantially better results than those not treated with amiodarone; the improvement was 42% for norepinephrine, 74% for dopamine, 44% for dihydroxyphenylglycol (an intraneuronal metabolite of norepinephrine) and 51% for 3H-dihydroxyphenylglycol, (i.e. the intraneuronal metabolite of 3H-norepinephrine).

In haemodynamic parameters, the patients on amiodarone revealed higher cardiac output and slightly lower pulmonary wedged pressure than untreated patients.

Similarly, the original observations as published in (Tardos et al. 1979) and (Schlant et al. 1992) have been confirmed after twenty and ten years, respectively.

REMARKS ON INDICATIONS

Because the situations in which anti-arrhythmics in general, and amiodarone in particular are administered are extremely varied, ranging from an intravenous bolus given in the case of a pulseless ventricular tachycardia managed in the street, to

prophylactic use starting during a chat of two distinguished gentlemen sitting in comfortable arm-chairs, the general recommendations could be regarded as a sacrilegium immediatum. Nevertheless, nowadays we have in hand a set of general recommendations about, and knowledge of the characteristics of amiodarone, as well as more special recommendations touching the most exclusive or specialised agendas.

In the standard Remedial-Compendium in the Czech Republic, which could be regarded as physician's companion homologous to the famous British "Yellow book", amiodarone is, from the point of view of indications, characterised in these words (Suchopár et al. 1997): "A broad spectrum anti- arrhythmic, with an exclusive position It is successfully used in therapy and prophylaxis of life-threatening arrhythmias. In prophylaxis of the recidives of tachyarrhythmia it is used even when the electrophysiological testing has failed to assess the type of the arrhythmias in a more detailed form".

This obviously optimistic statement reflects the tendency to find and use an anti-arrhythmic which could act "upstream" to the arrhythmias, i.e. to influence the most profound metabolic, electro physiologic and haemodynamic bases of their initial expression. (Bytešník 2000, Caron et al. 2001, Dorian et al. 2002, Japanese circulation journal 1998, Kaye et al. 1999, Pleskot et al. 2000, Schlant et al. 1992, Špinar et al. 2001, Tardos et al. 1979, What is What 1997) This recommendation, which it should be noted, is given in a publication serving those who are confronted daily with an extremely wide spectrum of medical problems, reflects also the fact that the usefulness of even the best and most sophisticated classification of anti-arrhythmics is of a limited nature and degree. For instance, the Sicilian Gambit, as characterised by Lau W. et al., requires in-depth knowledge of the cellular and molecular targets of anti-arrhythmic agents which may make it intimidating or simply impractical for clinical use (Lau et al. 2000). That is why attempts to formulate recommendations to guide the practical use of amiodarone are concomitant with a tremendous effort to predict the positive responders, mainly after myocardial infarction (Wichterle 2000).

Bytešník J. summarises and concludes the contemporary "state of the art" in this way (Bytešník 2000): Broad spectrum ant-arrhythmic, with acceptable level of pro-arrhythmic risk, pharmacokinetic enabling highly balanced and stable influence on the myocardium, in spite of bioavailability. Pharmacodynamic (the presynaptic sympatholytic effect) still deserves elucidation. Cardiac adverse effects are not (in general) serious. Non cardiac adverse effects are frequent, but not unexpected.

Amiodarone is (besides some betablockers) the one and only anti-arrhythmic, which does not bring about an increment in total mortality in cardiac failure. In atrial fibrillation, amiodarone could be recommended in patients with an enhanced risk of recurrent ventricular tachyarrhythmia (i.e. those after myocardial infarction, or with cardiac failure). Amiodarone should be preferably used in patients with serious ventricular tachyarrhythmia and in cases of myocardial infarction, should be regarded as the drug of first choice.

Intravenous administration of amiodarone is appropriate in frequent paroxysms of sustained haemodynamicaly serious ventricular tachycardia, in "electric storms in patients with an implantable cardio verter/ defibrillator and ventricular tachyarrhythmia resistant to electric conversion.

The special role of amiodarone use in perioperative tachyarrhythmia is treated with high expertise and in a concise, comprehensive manner by David I., recently in 2002 (David 2002). The role of ICD is treated recently by Herold M., (Herold 2002) and there is a reappraisal of intravenous administration by James and co-workers (James et al. 2001).

REMARKS ON INTERACTIONS

Knowledge of amiodarone´s potential for drug-drug interactions is well established particularly for its interaction with warfarin, resulting in enhancement of warfarin´s effect (Marek 1998, Suchopár et al. 1997). The nature and basis of this interaction has been elucidated by Micuda S. et al., in 2001, by their suggestion that the possible mechanism is the proven inhibitory activity of amiodarone on the activity of CYP3A (Micuda et al. 2001).

Further, the interaction with digoxin, resulting in the enhancement of dioxin plasma levels (Marek 1998, Suchopár et al. 1997) and dioxin bioavailability (Marek 1998) is also well known and discussed. Concomitant administration of amiodarone with class Ia and Ic anti-arrhythmics as well as with phenothiazines, tricycle antidepressants and saluretics could result in the enhancement of amiodarone´s pro-arrhythmic effect (Suchopár et al. 1997).

The interaction with betablockers and Ca channel blockers, resulting in possible bradycardia, hypotension and even cardiac arrest (Suchopár et al. 1997) must be further discussed. By no means should this fact be interpreted in favour of betablocker withdrawal. Quite in the opposite, for, as documented by Routitie (Routitie et al. 1999), risks for all – cause mortality, cardiac death, arrhythmic death or resuscitated cardiac arrest are

lower for patients receiving betablockers and amiodarone than for those without betablockers, receiving amiodarone or not.

More evidence for the fact, that amiodarone-warfarin drug-drug pair interaction is a cytochrome P 450 mediated process, and more detailed insight into the effect of biotransformation of amiodarone on this interaction has been presented by Naganuma and co-workers (Naganuma et al. 2001). They conclude that desethylamiodarone, the active metabolite of amiodarone, is responsible for cytochrome P 450, mainly CYP2C9, activity inhibition.

The magnitude of the amiodarone/warfarin interaction is highly dependent on the maintenance dose of amiodarone, as reported by Sanoski C.A. et al., in 2002 (Sanoski et al. 2002). The data from their cohort of 43 patients on amiodarone, with INR (international normalised ration) of 2 to 3, receiving concomitantly amiodarone were analysed. The interaction of amiodarone and warfarine peaked at seven weeks, which resulted in a 44% mean maximum reduction in the warfarin dose.

Clinicians must be aware of this interaction, and adjust the dose of warfarin in patients receiving long-term amiodarone treatment.

REMARKS ON ADVERSE EFFECTS

Amiodarone was from the very beginning identified as a drug with considerable potential to bring about adverse effects (Marek 1998, Mutschler 1991). This unpleasant feature is moderated by the fact, that these effects are not unexpected, and mainly non-cardiac (Bytešník 1999, Bytešník 2000).

Widimsky J. summarised the risks of amiodarone in a comprehensive survey (Widimský 1999) and published an ample article recently, in 2000 (Widimsky 2000). This should be regarded as a "state of the art" survey of adverse effects and is highly recommended for all those aiming at amiodarone therapy and informed use of this drug.

THYROID DYSFUNCTION

Perhaps the most complicated and the clinically most confusing effects of amiodarone are those on the thyroid gland, and thyroidal status of the patients (Marek 1998). Amiodarone brings with any single 200 mg tablet, 75 mg of iodine, which exceeds daily need by 500 times (Marek 1998). The most severe cases of factitious hyperthyroidisms are those provoked and brought about by amiodarone administration (Marek 1998). On the other hand, not only cases of amiodarone induced thyreotoxicosis are reported but also cases of amiodarone induced hypothyroidisms. (Pitsiavas et al. 1999) The inhibitory effects of amiodarone are observed in lower concentrations of iodide than those seen in NaI (natrium iodide) induced inhibition.

Pitsiavas concludes that this fact is due to the TSH mechanism involvement (Pitsiavas et al. 1999). The cases of amiodarone-induced destructive thyreotoxicosis (type II amiodarone induced thyrotoxicosis- II AIT) could be treated with prednisolone, or other glucocorticoids, as experimentally confirmed by Nakajima K. et al., in their in vitro studies on amiodarone cytotoxic effects on thyroid follicles (Nakajima et al. 2001). Type I amiodarone induced thyrotoxicosis, (IAIT) being the result of excess iodine-induced thyroid hormone synthesis, is more apt to give a positive therapeutic answer to thionamides and potassium perchlorate, which are regarded as the treatment of choice. Unfortunately, mixed forms occur, which are best treated with a combination of thionamides, potassium perchlorate and glucocorticoids (Nakajima et al. 2001).

Amiodarone induced hypothyroidism (AIH) should be treated by levothyroxine replacement therapy while continuing amiodarone therapy. Alternatively, amiodarone could be discontinued, if possible, and the natural course toward euthyroidism can be accelerated by a short trial of potassium perchlorate (Bogazzi et al. 2001). Vanbesien described two cases of fetal hypothyroidism induced by amiodarone administration (Vanbesien et al. 2001). Those occurred not after an administration to pregnant mothers, but after direct fetal administration for drug resistant fetal tachycardia. An interesting therapeutic attitude to type II amiodarone induced thyrotoxicosis was described by Chopra I.J. et al. using an oral cholecystographic agent sodium iopodate – Orografin, or sodium iopanoate – Telepaque and a thionamide or methimazole. They found this combined treatment to be safe and effective (Chopra et al. 2001). The case of amiodarone-induced thyroiditis was described by Ybarra J. et al., in 2002 (Ybarra et al. 2002).

In an attempt to assess the usefulness of interleukin 6 (IL-6) measurements and colour-flow Doppler sonography (CFDS) as the practical tool to classify the AIT and to distinguish between I AIT and II AIT, Eaton S.E.M. et al. (Eaton et al. 2002) conclude that CFDS could characterise two distinct subtypes in patients with AIT. Conversely, IL-6 seemed to be an unhelpful test in this context. The importance of AIT, well known for many years (Marek 1998) is further discussed by Bartalena (Bartalena et al. 2002) and Leung (Leung et al. 2002). A rather rare case of surgical management of

amiodarone-associated thyrotoxicosis is reported by Gough (Gough et al. 2002).

Osman F. et al. conclude (Osman et al. 2002) that continuing amiodarone has no adverse influence on response to treatment of amiodarone induced thyrotoxicosis.

OCULAR ADVERSE EFFECTS

These are well known since the appearance of amiodarone, and even now provoke the interest of researchers all over the world. Corneal deposits are perhaps the most common and they are found in 100 % of exposed persons. Lens opacities and dry eyes are also very common.

The important feature of the current situation is the fact that vast numbers of drugs are introduced and are widely used in the broad population. Moorthy R.S. et al. (Moorthy et al. 1999) summarised the data on ocular toxicity associated with systemic drug therapy. They found nine drugs, all of them widely used, which are almost consistently connected with ocular toxicity: amiodarone, cidofovir, sildenafil, tamoxifen, hydrochloroquin, chloroquin, vigabatrin, lovastatin and simvastatin. Polak and co-workers (Polak et al. 2001) reported on ocular toxicity of amiodarone, ethambutol and isoniazide. Except for lovastatin/simvastatin and vigabatrin, the probability of causality, as assessed using toxicological criteria, is high.

Not so well known, but very important is the amiodarone-induced optic neuropathy, with unique clinical features, as reported by Macaluso (Macaluso et al. 1999) This neuropathy has slow progress, with bilateral visual loss, protracted disc swelling, and tends to stabilize within several months of discontinuing the medication.

Ikaheimo and co-workers (2002) makes a newer contribution to amiodarone ocular toxicity and refer to a slight blue colour vision defect in patients on amiodarone, with otherwise healthy eyes.

This finding could represent an early sign of optic nerve impairment. Corneal deposits were found in 100%, lens deposits in 22.2%, and dry eyes in 9.1% of exposed patients. These findings are confirmed also by Grupcheva and co-workers (2002).

PULMONARY ADVERSE EFFECTS

Amiodarone, a kationtic-amphiphilic substance, is vividly accumulated in lysosomes, (with their inner pH 4–5), and in lymphocytes and macrophages the lamellar deposits are soon found. In pulmonary tissue, the alveoli are filled with microphage, the production of fibrous tissue is stimulated and pulmonary fibrosis occurs (Lüllmann et al. 2002). In X-ray assay this can mimic findings which are found in cardiac failure (Sangha et al. 2002), malignant lymphangiopathy, pulmonary tumours and other pulmonary-mass syndromes (Chouri et al. 2002).

The authors can give a personal testimony of a funny event which happened in 1996. While driving his car, and giving a lift through North Carolina countryside to the authors, an outstanding and famous professor of Family Medicine complained that this could be his very last meeting with us, because of his malignant pulmonary condition of uncertain nature and origin. The case was discussed immediately, on the spot, inside the car; the driver was required neither to stop driving, nor do anything else – just to give us his pharmacotherapeutic anamnesis/ case report. When we realised he was on amiodarone we made a provisional diagnosis of amiodarone pulmopathy, which turned out to be true. After three months of cessation of amiodarone administration the X-ray findings disappeared completely.

Poll et al. (2001) reported on a similar case, also when also the cessation of amiodarone treatment resulted in the complete disappearance after three months of pleural-parenchyma consolidations. Pulmonary toxicity of amiodarone can occur even after a short course therapy, as described by Kaushik et al. (2001) and very soon after the initiation of amiodarone, as described by Kharabesh et al. (2002).

Experimental proof of amiodarone-induced pulmonary toxicity in animal experiment was given by Chung et al. (2001).

DERMATOLOGIC ADVERSE EFFECTS

Photosensitivity is by far the most common and best known dermatologic adverse event of amiodarone. Photo toxicity and photo allergy are widely discussed from the point of view of a dermatologist by Jirásková (2001). Another frequent dermatologic finding in amiodarone treatment is skin pigmentations (High et al. 2001). Unfortunately, the skin damage can reach even the level of toxic epidermal necrolysis (Yung et al 2002) and cutaneous vasculitis, in some cases even together with pulmonary mass (Scharf et al. 2001) or lupus erythematosus syndrome (Sheikzadeh et al. 2002).

Contrary to the overall feeling that a pre-existing skin disease could enhance the probability of amiodarone dermatologic toxicity, Mendez document that amiodarone is a pharmacologically safe drug in porphyries (Mendez et al. 1999).

MISCELLANEOUS ADVERSE EVENTS

Peripheral neuropathy is regarded as an almost "standard" type of amiodarone toxicity (Lüllmann et al. 2002). As an uncommon and interesting adverse event, coital headaches induced by amiodarone are reported from Israel (Biran et al. 2002).

CLOSING REMARKS

Amiodarone, discovered forty years ago and used genuinely as an anti-anginal drug, has become an anti-arrhythmic of broad spectrum, with an exclusive position. It is successfully used in therapy and prophylaxis of life threatening arrhythmias. Its range covers the acute intravenous administration in pulseless ventricular tachyarrhythmia, through perioperative arrhythmias, to prophylactic use in recurrent paroxysmal atrial fibrillation.

In prophylaxis of the recidives of tachyarrhythmia it is successfully used even when the electro physiologic testing has failed do disclose the presence of the detailed mechanism of arrhythmia. Amiodarone is the one and only anti-arrhythmic, (besides some betablockers) which does not bring about an increment in total mortality in cardiac failure.

It is with high probability a drug which is actively "upstream" to arrhythmias, combining in an excellent manner the propitious effects on cardiac electro physiology, neurochemical parameters, and haemodynamic parameters with the unique property and ability of local antithyroid effect in human myocardium. Amiodarone should be regarded as the anti-arrhythmic drug of first choice in cases of myocardial infarction.

Its pharmacokinetics enables a stable and well balanced influence on the myocardium. It is a drug with frequent but not unexpected side effects, with an acceptable level of potential risks. Being hailed in the beginning as an ideal anti-arrhythmic, it is gaining more and more respect and a greater share of use as an anti-arrhythmic.

It is forty years old, at its best age, and still marching on.

Received 15th April 2003.
Published online 9th July 2003.

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