REVIEW ARTICLE

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Heart Failure Induced by Non-Cardiac Drugs

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Abstract

Although heart failure is predominantly caused by cardiovascular conditions such as hypertension, coronary heart disease and valvular heart disease, it can also be an adverse reaction induced by drug therapy. In addition, some drugs have the propensity to adversely affect haemodynamic mechanisms in patients with an already existing heart condition. In this article, non-cardiac drugs known to be associated with the development or worsening of heart failure are reviewed. Moreover, drugs that may adversely affect the heart as a pump without causing symptoms or signs of heart failure are also included.

The drugs discussed include anticancer agents such as anthracyclines, mitoxantrone, cyclophosphamide, fluorouracil, capecitabine and trastuzumab; immu-

nomodulating drugs such as interferon-α-2, interleukin-2, infliximab and etanercept; antidiabetic drugs such as rosiglitazone, pioglitazone and troglitazone; antimigraine drugs such as ergotamine and methysergide; appetite suppressants such as fenfulramine, dexfenfluramine and phentermine; tricyclic antidepressants; antipsychotic drugs such as clozapine; antiparkinsonian drugs such as pergolide and cabergoline; glucocorticoids; and antifungal drugs such as itraconazole and amphotericin B. NSAIDs, including selective cyclo-oxygenase (COX)-2 inhibitors, are included as a result of their ability to cause heart disease, particularly in patients with an already existing cardiorenal dysfunction.

Two drug groups are of particular concern. Anthracyclines and their derivatives may cause cardiomyopathy in a disturbingly high number of exposed individuals, who may develop symptoms of insidious onset several years after drug therapy. The risk seems to encompass all exposed individuals, but data suggest that children are particularly vulnerable. Thus, a high degree of awareness towards this particular problem is warranted in cancer survivors subjected to anthracycline-based chemotherapy. A second group of problematic drugs are the NSAIDs, including the selective COX-2 inhibitors. These drugs may cause renal dysfunction and elevated blood pressure, which in turn may precipitate heart failure in vulnerable individuals. Although NSAID-related cardiotoxicity is relatively rare and most commonly seen in elderly individuals with concomitant disease, the widespread long-term use of these drugs in risk groups is potentially hazardous. Pending comprehensive safety analyses, the use of NSAIDs in high-risk patients should be discouraged. In addition, there is an urgent need to resolve the safety issues related to the use of COX-2 inhibitors.

As numerous drugs from various drug classes may precipitate or worsen heart failure, a detailed history of drug exposure in patients with signs or symptoms of heart failure is mandatory.

Heart failure is a term used to describe the state that develops when the heart cannot maintain an adequate cardiac output. Common symptoms and signs include fatigue, peripheral oedema, dyspnoea and pulmonary crepitations. Moreover, the function of the heart as a pump may be adversely affected although no clinical symptoms or signs of heart failure are present.

Numerous underlying mechanisms for heart failure exist. First, the contractility can be affected *per se*, either by alterations in the normal myocardial processes (e.g. reversible myocardial depression, myocarditis and cardiomyopathy), or by changes in the heart rhythm. Secondly, the afterload can be increased, such as in systemic or pulmonary hypertension or pulmonary or aortic valve stenosis. Thirdly, the preload might be affected. It may be increased in conditions such as mitral or aortic regurgitation or atrial or venticular septal defects or after fluid overload, whereas it may be decreased in conditions such as mitral or tricuspidal stenosis. As will be discussed in this review, drug-induced heart failure may principally be mediated via these mechanisms. Moreover, the drugs included in this review may also cause cardiac dysfunction via these mechanisms without causing overt heart failure.

The aim of this article is to present an overview of non-cardiac drugs that may adversely affect the heart as a pump, including the precipitation or worsening of heart failure. The issue is of interest because numerous drugs from various drug classes have cardiotoxic effects and because some of the drugs implicated are in widespread clinical use. Moreover, in many cases (albeit not in all), the

Table I. Non-cardiac drugs known to induce or worsen heart failure according to the suggested mechanism(s) implicated

Drug class	Drug
Cardiomyopathy	
Cytotoxic drugs	Doxorubicin, epirubicin and other anthracyclines, mitoxantrone, cyclophosphamide, 5-fluorouracil, capecitabine
Immunomodulating drugs/antibodies	Trastuzumab, interferon-α-2, interleukin-2, infliximab, etanercept
Antifungal drugs	Itraconazole, amphotericin B
Antipsychotic drugs	Clozapine
Pulmonary hypertension	
Antimigraine drugs	Methysergide, ergotamine
Appetite suppressants	Fenfluramine, dexfenfluramine, phentermine
Heart-valve abnormalities	
Antimigraine drugs	Methysergide, ergotamine
Appetite suppressants	Fenfluramine, dexfenfluramine, phentermine
Antiparkinsonian drugs	Pergolide
Fluid overload	
NSAIDs, including cyclo-oxygenase-2-inhibitors	All
Antidiabetic drugs	Rosiglitazone, pioglitazone, troglitazone
Glucocorticoids	All
Herbal drugs	Herbal drugs containing liquorice or adulterated with NSAIDs

adverse effect is reversible after discontinuation of the offending drug.

1. Literature Search Methodology

A MEDLINE search was carried out using the search term 'heart failure' with the MeSH subheading 'chemically induced' for the period 1966–2004. In addition, our own files with articles and book chapters previously collected for research purposes were rechecked. The reference lists from relevant articles and book chapters were scrutinised in order to identify further articles.

Numerous case reports or small case series describing possible drug-induced heart failure precludes attempts to include all such drugs within the frames of this article. Moreover, in many cases, causality is not conclusively established. Primarily, we have chosen to focus on drugs that are in regular use worldwide and where a causal relationship is established or at least highly suspected (table I). In addition, for completeness and because it illustrates important mechanistic aspects, some drugs recently withdrawn from the market are also included. All cardiac drugs are excluded because the adverse reactions affecting the heart are generally predictable from the mechanism of action of these drugs. Moreover, the haemodynamic effects of drugs inducing cardiac arrhythmias, cardiac infarction and thromboembolic states will not be discussed in detail because these conditions are generally present with other and more prominent symptoms and signs than those associated with cardiac failure.

2. Anthracyclines and Derivatives

Anthracycline-induced heart failure was first reported by Tan et al.[1] in 1967, and is a major impediment for the expanded use of these often highly effective drugs.[2] The cardiotoxic effects induced by anthracyclines can be divided into two forms: an acute or subacute form, which can occur during the first few weeks post-therapy; and a chronic progressive cardiotoxicity. During or shortly after administration, anthracyclines may induce arrhythmias with or without heart failure. A subacute, pericarditis-like syndrome may appear up to a couple of weeks after exposure. These effects are not considered to be dose related, and do not impede later use of anthracycline therapy.[3-5]

The chronic progressive cardiotoxicity is the clinically significant form of anthracycline-induced

heart failure. It is often subdivided into an early onset form, which presents within the first year post-therapy, and a late onset form, which may appear years after completion of treatment.[5] However, there are no pathophysiological characteristics that differentiate the early and late forms, and the chronic progressive anthracycline cardiotoxicity appears to occur along a continuum in time.[6] The mechanism that may cause this cardiac injury is not fully understood; however, lipid peroxidation and free-radical generation by anthracycline-iron complexes are considered to be of pivotal importance.[5-8]

2.1 Incidence

In a retrospective study,[9] cardiac function was investigated in 3941 doxorubicin-exposed patients. At doxorubicin doses <400 mg/m^2, the incidence of clinical heart failure was 0.14%, whereas heart failure was observed in 7% of patients administered 550 mg/m^2 and 18% of patients receiving 700 mg/m^2. The overall incidence of heart failure was 2.2%, and the cardiac abnormalities occurred within 231 days post-exposure. It is notable that in this series, none of the five patients who received doxorubicin doses exceeding 1000 mg/m^2 developed heart failure.[9]

A recent retrospective analysis of three clinical trials, which included 630 patients who were administered doxorubicin, found an overall incidence of doxorubicin-related heart failure of 5.1% and concluded that this adverse effect is more common and occurs at lower cumulative doses than hitherto acknowledged.[10]

By monitoring patients treated with doxorubicin for leukaemia up to 15 years post-therapy, an incidence of increased cardiac afterload and/or decreased contractility as high as 65% after total doses of doxorubicin as low as 230 mg/m^2 have been demonstrated.[11] Steinherz and colleagues[12] have shown that both the incidence and severity of cardiac dysfunction increases with the length of follow-up. In a prospective, blinded observational investigation of 120 patients who received epirubicin 850–1000 mg/m^2, Jensen et al.[13] found that 20% of patients deteriorated into heart failure. It seems reasonable to expect that the combination of improved diagnostic methods and attention towards this problem will give more information as to the true incidence of anthracycline-induced cardiac dysfunction in the future.

2.2 Risk Factors

Based on the report by von Hoff et al.[9] and other investigations, it is recognised that cardiotoxicity of anthracyclines and derivatives to some extent can be predicted by the cumulative dose of drug administered. The safe maximum cumulative dose for doxorubicin in clinical practice is generally considered to be 550 mg/m^2. The corresponding doses for other commonly used anthracyclines are 600 mg/m^2 for daunborubicin, 1000 mg/m^2 for epirubicin, 100 mg/m^2 for idarubicin and 160 mg/m^2 for the anthracendione mitoxantrone.[2,14,15] Cardiotoxicity has also been linked to peak plasma drug concentrations. Although the antineoplastic activity of anthracycline drugs has been correlated to the area under the time-concentration curve,[2,6] there is evidence suggesting that high peak drug concentrations are associated with increased toxicity to the heart.[16]

Other risk factors for the development of cardiac toxicity induced by anthracyclines include >70 years of age;[9] combination chemotherapy, in particular with cyclophosphamide,[13] taxanes[17,18] or the monoclonal antibody trastuzumab[19] (see section 5); previous or concomitant mediastinal radiotherapy; previous cardiac disease; hypertension; liver disease and whole-body hyperthermia.[8]

Sex has not been found to predict cardiotoxicity in adults;[9] however, in paediatric patients, girls are more susceptible to develop heart failure after anthracycline treatment than boys.[20] In general, children appear to be particularly susceptible to the cardiotoxic effects of anthracyclines: this is reflected in findings of increased probability of late elevated cardiac afterload with low age at diagnosis as well as the observation that children may develop cardiac failure at lower cumulative anthracycline doses than adults.[18] Black ethnicity, trisomy 21 and previous amsacrine therapy are risk factors specific for early onset cardiotoxicity in children.[18]

The recent observation that expression of cyclooxygenase (COX)-2 limits doxorubicin-induced injury in rat cardiomyocytes may suggest that concomitant use of NSAIDs could constitute a risk for the development of cardiac injury during anthracycline therapy.[21]

2.3 Risk Minimisation

Measures to minimise cardiotoxicity in patients given anthracyclines include the following: adherence to maximally recommended cumulative doses of the drug used; diagnostic procedures to allow the early identification of patients developing heart injury to terminate or postpone therapy; the modification of dose intensity in relation to putative risk factors, such as previous use of other cytotoxic drugs or chest radiation therapy; alteration in administration schedules; the use of analogues with a possibly more favourable toxicity profile; and the use of pharmacological agents that may protect the myocardium against injury.

Diagnostic procedures should ideally be both specific and highly sensitive to be able to identify patients developing anthracycline-induced cardiotoxicity before widespread and irreversible damage has occurred. Clinical examination, electrocardiographic procedures, chest radiograms and measurements of enzymes, such as the levels of cardiac isoform of creatine kinase (CK-MB), have generally been found to be of little use to identify patients at risk.[22]

In recent years, the possibility of using other moieties such as troponins, natriuretic peptides and endothelin-1 as markers of anthracyclin-induced cardiac injury has been evaluated.[23]

Lipshultz et al.[24] have shown that elevations in serum or plasma cardiac troponin T levels predicted cardiac complications in a small number of children treated with anthracyclines. Investigating 78 patients treated with anthracyclines, Auner et al.[25] reported that serial measurements of troponin T could identify patients at risk for development of myocardial dysfunction. However, a study of troponin T levels measured a median of 12 months after high cumulative doses of doxorubicin in 24 children did not find a correlation between troponin T levels, doxorubicin doses and cardiac function.[26]

On the other hand, in a study of 211 patients, Cardinale et al.[27] reported that elevated plasma levels of cardiac troponin I soon after high-dose chemotherapy was a sensitive and reliable marker for the prediction of future impaired left ventricular ejection fraction. Of the patients, 64% were being treated with anthracyclines, whereas the remaining had received anthracyclines in the past. In a study of 703 recipients of several different high-dose cancer chemotherapy regimes, the same investigators have recently shown that the release pattern of troponin I in multiple samples may be of use to identify patients at high risk for the development of cardiac complications, but they found no particularly increased risk after anthracycline therapy in this selected population.[28]

Although the results are not uniform,[23] recent studies also seem to suggest a role for atrial natriuretic peptide, its N-terminal propeptide and/or the mainly ventricular-derived B-type natriuretic peptide as markers of chronic cardiac injury in both adults[29] and children[30] exposed to anthracyclines.

Serial echocardiographic investigations allow the monitoring of the cardiac ejection fraction in a non-invasive manner and are routinely employed in the care of patients receiving anthracycline therapy. Radionuclide angiocardiography, usually with labelled technetium bound to albumin or red blood cells, is also widely employed and such measurements have been the basis of algorithms proposed to be helpful for the management of patients who experience the onset of reductions in left ventricular ejection fraction.[6] Indeed, Schwartz and co-workers[31] have shown that adherence to guidelines based upon such measurements for a mean follow-up period of 1 year could reduce the incidence of heart failure in these patients by a factor of four.

In a recent prospective, blinded, observational study, 120 patients who had received epirubicin therapy were monitored by serial radionuclide angiocardiography for a median of 3 years.[13] The authors concluded that monitoring in close connection with anthracycline administration is ineffective,

and advocated monitoring strategies for substantial periods of time post-drug exposure to improve the detection of late cardiac dysfunction. Endomyocardial biopsy is an additional helpful procedure in the detection of anthracycline-induced damage, but there is understandably considerable reluctance to expose patients to this invasive procedure.[6,14]

Instigated at least in part by the observation that high peak drug concentrations may induce cardiotoxicity,[16] administration of anthracyclines as continuous infusions rather that bolus delivery has been investigated. There is a considerable body of evidence to support the theories that continuous infusions of doxorubicin are less cardiotoxic than bolus infusions, that long term infusions do not compromise the anticancer effects of the drug, and that continuous infusion regimes may allow the cumulative doxorubicin dose to be increased by a factor of two or more without increasing the risk of cardiotoxicity.[16,32-35]

In the first of these studies,[16] morphological changes indicating cardiac injury were apparent in heart muscle biopsy specimens in 14 of 30 (47%) patients given intravenous bolus injections of doxorubicin compared with 2 of 21 (10%) patients given the drug by intravenous infusions over 48–96 hours. Moreover, in non-randomised settings, injections of lower doses of doxorubicin at weekly intervals have been claimed to offer similar efficacy but less cardiotoxicity than correspondingly higher doses every 3 weeks.[32,33]

In a study of 274 consecutive patients with metastatic breast cancer, >75% reduction in the frequency of heart failure at cumulative doxorubicin doses exceeding 450 mg/m^2, but comparable response and survival rates, was seen when the drug was given as an infusion over 48–96 hours as opposed to bolus administration.[34]

In a prospective, randomised study that compared rapid bolus administration of doxorubicin with infusions over 6 hours in patients with breast cancer or cancer of the ovary, 4 of 31 (13%) patients in the former and none in the latter group developed heart failure.[35] However, it should be noted that these investigations have been carried out in adults, and that a recent study of children who received doxorubicin either as bolus infusions or 48-hour continuous infusions found that continuous infusions offered no cardioprotective advantage over bolus infusions.[36] A comparison of the incidence of cardiotoxicity in children who were treated with daunorubicin as bolus injections or as 6-hour infusions also failed to show a cardioprotective effect of the infusion regime.[37]

Considerable effort has been invested in the development of anthracycline analogues with an improved therapeutic index. Preclinical and clinical studies with idarubicin, epirubicin, zorubicin, alcarubicin, esorubicin and mitoxantrone have failed to demostrate clinically significant advantages over first-generation anthracyclines such as doxorubicin with regard to cardiotoxicity at doses with comparable tumoricidal efficacy.[14]

Another approach has been the application of liposomal formulations of anthracyclines. Liposomal formulations alter the pharmacokinetic properties of the drug, evident as a decreased drug accumulation in cardiac tissue and higher drug concentrations in parenchyma and tumour tissue.[38] Despite a lack of information regarding long-term safety, liposomal anthracyclines are considered to offer some clinical benefit for patients at risk for developing anthracycline-induced cardiotoxicity.[39-41]

A wide variety of putative pharmacological cardioprotectants have been employed to reduce the spectrum of anthracycline-induced cardiotoxicity, including dexrazoxane, amifostine, probucol, tocopherol (vitamin E), acetylcysteine, prednisone, ubidecarenone (coenzyme Q10), digitalis glycosides, calcium channel antagonists, β-adrenoceptor antagonists (β-blockers), antihistamines, carnitine and ascorbic acid.[8,14]

The free-radical scavenger dexrazoxane has been shown to reduce anthracycline-induced cardiotoxicity in patients with many types of cancer, and although further research is needed, a recent review by an international expert panel of cardiologists and oncologists concluded that the clinical use of dexrazoxane should be expanded.[42] In a recent study comparing the incidence of myocardial injury

as assessed by troponin T level elevations in a total of 158 children treated with doxorubicin alone or dexrazoxane followed by doxorubicin, pretreatment with dexrazoxane reduced the likelihood of elevated (21% vs 50%) or extremely elevated (10% vs 32%) troponin T levels. However, the rate of event-free survival did not differ significantly between the groups at 2.5 years.[43]

The thiophosphate compound amifostine and the lipid-lowering antioxidant probucol are still under evaluation for a possible role in alleviating anthracycline-induced cardiotoxicity. There is little evidence to support the clinical use of the other putative modulators.[14] The observation that COX-2 inhibition may aggravate the cardiac injury from anthracycline exposure raises the possibility of the use of prostaglandins to prevent cardiotoxicity.[21] However, the putative modulatory effects of NSAIDs on anthracycline-induced cardiotoxicity remain speculative.[44]

3. Alkylating Drugs

The anticancer mustard gas derivative cyclophosphamide may induce acute cardiotoxic effects, which may range from subtle electrocardiographic changes to a potentially fatal cardiomyopathy. This toxicity is dose dependent and is most commonly seen at doses exceeding 200 mg/kg bodyweight as a part of bone marrow transplantation regimes but appears not to be a function of the cumulative dose of cyclophosphamide.[5] Fatal cardiotoxicity after high-dose cyclophosphamide has been reported as frequently as in 11% of cases.[5] Myocarditis, and more rarely heart failure, may appear during the first couple of weeks post-therapy. The risk is increased by previous therapy with other cardiotoxic agents such as anthracyclines and in individuals >50 years of age.[5,45] The underlying mechanism has not been identified. Several other alkylating agents, most notably ifosfamide, have also been reported to induce cardiotoxicity.[5,45,46]

4. Pyrmidine Derivatives

After infusions of fluorouracil, patients may experience angina-like chest pain. Some patients may develop cardiac toxicity, usually in the forms of arrhythmias, ischaemia, heart failure and, occasionally, sudden death. The incidence of fluorouracil-induced cardiotoxicity has been estimated at 1–18%, is most often encountered during or shortly after infusions, is typically seen when the drug is administered as continuous infusions and may necessitate the discontinuation of therapy.[5,46] Heart failure after fluorouracil therapy is rare. The cardiotoxic effects do not appear to be dose dependent, and the underlying mechanism is not fully understood. Not surprisingly, the orally administered fluorouracil prodrug capecitabine has also been reported to cause acute cardiotoxic effects.[5,46,47]

5. Trastuzumab

The human epidermal growth factor receptor (HER)-2 is a transmembrane tyrosine kinase receptor involved in growth regulation. HER-2 is overexpressed in approximately 20% of breast cancers and is associated with a poor prognosis. Trastuzumab is a monoclonal antibody against the HER-2 receptor protein used for the treatment of HER-2 positive breast cancer in combination with paclitaxel or as a single agent in patients previously treated with taxanes or anthracyclines.

The protocols for the initial trials with trastuzumab as first-,[48] second- or third-line[49] monotherapy or in combination with paclitaxel or anthracycline chemotherapy[50] did not foresee any significant cardiotoxicity, but emerging safety data led to the establishment of a Cardiac Review Evaluation Committee for trastuzumab.[51]

The data have recently been analysed in depth and demonstrate an incidence of heart failure of 2.6% when trastuzumab is used as first-line monotherapy, rising to 8.5% in second- or third-line monotherapy, which included previous treatment with anthracyclines in a majority of patients.[52] In the protocol where patients were randomised to receive either trastuzumab or placebo in combination with paclitaxel or an anthracycline, the incidence of heart failure was 4.2% (paclitaxel alone), 8.8% (paclitaxel and trastuzumab), 9.6% (anthracycline alone) and 28.0% (anthracycline and trastuzumab),

respectively.[52] Of the patients who experienced symptomatic cardiac dysfunction after trastuzumab in the trials, 78% improved, whereas 12% experienced a progression of the cardiac failure.

Risk factors for the development of cardiac dysfunction include previous or concomitant anthracycline exposure, >50 years of age and New York Heart Association (NYHA) functional status class II or more prior to enrolment.[52] The mechanism underlying trastuzumab-induced cardiotoxicity is unknown, but has been suggested to represent an exacerbation of anthracycline-induced cardiac effects.[52] Another recent analysis of pooled data from six clinical trials showed that decreases in left ventricular ejection fraction of ≥15% occurred in 22.2% of patients who had previously received anthracyclines, whereas such decreases were seen in only 1.7% of anthracycline-naive patients.[53]

Despite cardiotoxic effects, the beneficial therapeutic ratio for trastuzumab in HER-2 positive breast cancer is considered to provide a strong rationale for the continued exploitation of HER-2 antibodies with other treatment modalities in breast cancer.[54]

6. Interferons

Numerous cases of dilated cardiomyopathy have been reported after treatment with interferon-α.[55-58] In these reports, interferon-α was used for various malignant conditions, such as Kaposi's sarcoma, hairy cell leukaemia, renal cell carcinoma and multiple myeloma. In addition to heart failure, other manifestations of cardiac toxicity such as arrhythmias and ischemic heart disease have been reported.[59]

In a literature review of a total of 44 reported cases of cardiotoxicity, five patients presented with cardiomyopathy.[59] All patients were treated with interferon-α, and when the specific subtype was stated, with interferon-α-2. Possible risk factors included high dosage, advanced age, previous cardiac failure and exposure to other cardiotoxic drugs.[59]

Since no systematic studies have been conducted, the true frequency of heart failure during treatment with interferon-α is unknown. Notably, no published reports on heart failure exist for interferon-β.

7. Interleukin-2

Several case reports and case series have described an association between interleukin-2 therapy and the development of myocarditis and cardiomyopathy in patients with renal cell carcinoma and malignant melanoma.[60-63] In these reports as well as in other studies,[64,65] the diagnosis of myocarditis has been confirmed by endomyocardial biopsies or by necropsy. The frequency of cardiac toxicity was evaluated in a study of 199 patients treated with interleukin-2.[66] Hypotension and atrial fibrillation/supraventricular tachycardia were the most common symptoms, observed in 53% and 5.2% of the patients, respectively. Myocarditis or cardiomyopathy were not diagnosed in any of the patients, but it should be noted that 1.6% of the patients had increased plasma levels of CK-MB, indicating myocardial toxicity.

The mechanism of cardiac toxicity induced by interleukin-2 is unknown, but two hypotheses have been proposed based upon the findings from a study in rats:[67] ischemic necrosis secondary to microcirculatory disturbances, and cytotoxic or cytolytic necrosis due to the contact between interleukin-2-activated lymphocytes and cardiac myocytes. In addition, apoptopic myocardial cell death may occur.[63]

8. NSAIDs

NSAIDs exert their action through inhibition of COX enzymes, which are responsible for the conversion of arachidonic acid to prostaglandin G_2. Prostaglandin G_2 is further metabolised to other prostaglandin species, prostacyclins and thromboxanes. Several types of COX enzymes have been identified; COX-1 is a consitutively expressed protein that exerts a number of important regulatory functions in the body, whereas the COX-2 isoform is inducible and commonly overexpressed in inflammation.[68] Although classical NSAIDs inhibit both COX-1 and COX-2, the selective COX-2 inhibitors exert most of their inhibitory action on the COX-2 isoenzyme.[68,69]

In addition to their gastrointestinal and reproductive effects, NSAIDs may cause renal and cardiovascular perturbations, which may induce or worsen hypertension or heart failure. Prostaglandins act locally in renal tissue by regulating sodium and water resorption. Some prostaglandin species, such as prostacyclin I_2, are vasodilators in their own right. Renal prostaglandin synthesis increases the renal perfusion rate, and in situations where the renin-angiotensin axis and the adrenergic system are activated, renal function is maintained through prostaglandin-induced compensatory vasodilation. Thus, NSAID-induced reductions in renal function are most commonly encountered in patients with activated renin-angiotensin and adrenergic systems as seen in various forms of cardiorenal disease and dehydration. In susceptible individuals, NSAID-induced inhibition of the renal prostaglandin synthesis may lead to sodium retention and oedema with occasional hyperkalaemia. Acute renal failure, nephrotic syndrome and/or papillary necrosis have also been observed.[70] Prostaglandins may also affect haemodynamics through effects on the renin or angiotensin systems, by inhibiting the release of the vasopressor endothelin-1, and by interactions with vasopressin (antidiuretic hormone).[71-74]

Two epidemiological investigations published more than a decade ago have addressed the impact of classical NSAIDs on blood pressure in the elderly. Johnson et al.[75] found that NSAID use predicted the presence of hypertension (odds ratio [OR] 1.4, 95% CI 1.1, 1.7) and that 29% of instances of hypertension were attributable to NSAID use. Gurwirtz et al.[76] found that recent NSAID users had a 1.7-fold increased risk of receiving antihypertensive therapy compared with non-users, and that the use of antihypertensive drugs could be attributed to NSAID use in nearly 10% of all cases. Meta-analyses of clinical data have confirmed that classical NSAIDs may increase blood pressure in both normotensive and hypertensive individuals,[77,78] and have shown that NSAIDs may antagonise the effect of antihypertensive drugs such as diuretics, β-blockers and vasodilators.[78] The incidence and levels of hypertension associated with selective COX-2 inhibitors are of the same magnitude[73] or higher[79] than are observed with classical NSAIDs.[73] Regular monitoring of blood pressure should be mandatory in patients given long-term NSAID therapy.

There is considerable concern regarding the cardiovascular safety of selective COX-2 inhibitors. This was instigated by the VIGOR (Vioxx Gastrointestinal Outcomes Research) trial, which reported that patients taking rofecoxib 50mg once daily were five times more likely to have a myocardial infarction than those taking the comparator naproxen 500mg twice daily.[80,81] No such association was reported in the CLASS (Celecoxib Long-term Arthritis Study) trial.[80,82] This was initially considered to imply that naproxen confers cardioprotective effects or that rofecoxib may cause myocardial damage, or both. Subsequent studies have shown conflicting results; investigators have reported no cardioprotective effects of classical NSAIDs including naproxen,[83,84] cardioprotective effects of naproxen,[85-87] an increased incidence of serious coronary heart disease in patients taking rofecoxib[88,89] or no effect of NSAIDs (celecoxib, rofecoxib, naproxen or other nonselective NSAIDs) on the incidence of myocardial infarction.[90] The most recent data suggest that all NSAIDs, including COX-2-inhibitors, may confer an increased risk of cardiovascular disease.[91,92]

This controversy is highlighted by the worldwide withdrawal of rofecoxib subsequent to the APPROVe (Adenomatous Polyp Prevension on Vioxx) trial, which demonstrated that rofecoxib in a dose of 25mg daily was associated with a 3.5% risk of myocardial infarction or stroke compared with the 1.9% risk in patients receiving placebo.[93] A similar placebo-controlled study of celecoxib has found a dose-dependent increase in risk for cardiovascular disease with a factor of 2.3 (95% CI 0.9, 5.5) and 3.4 (95% CI 1.4, 7.8) at daily doses of 400mg and 800mg, respectively.[94] So far, evidence suggest that this increased risk of cardiovascular disease is a group effect conferred by all selective COX-2 inhibitors. This evidence calls for caution

and additional in-depth investigations of the overall safety of these drugs.

Several observational studies suggest an association between the use of NSAIDs and development of heart failure. In a cohort of elderly patients taking a diuretic, Heerdink et al.[95] observed that concomitant use of NSAIDs increased the relative risk for hospitalisation from heart failure by a factor of 1.8 (95% CI 1.4, 2.4). In a case-control study, it was found that use of an NSAID in the preceding week was associated with a 2.1-fold (95% CI 1.2, 3.3) increased risk for hospitalisation from heart failure.[96] A Swedish nationwide ecological study also demonstrated an increased risk for hospitalisation after NSAID use.[97] A large population-based Dutch investigation in a cohort of elderly NSAID users found that drug intake was not associated with an increased risk for onset of heart failure, but that it was associated with a 9.9-fold (95% CI 1.7, 57) increased risk of relapse in patients with previous hospitalisation for heart failure.[98] In a case-control study nested in a population-based cohort of individuals aged 40–84 years in the UK, a relative risk of first-diagnosed episode of heart failure associated with NSAID prescription was 1.6 (95% CI 1.2, 2.1). Interestingly, the relative risk was 1.9 (95% CI 1.3, 2.8) in patients with hypertension, diabetes mellitus or renal failure, and 1.3 (95% CI 0.9, 1.9) in subjects without these ailments.[99]

In a study of a Canadian cohort, Mamdani et al.[100] reported that the use of nonselective NSAIDs and rofecoxib, but not celecoxib, was associated with an increased risk for hospital admission with heart failure. The increase in relative risk was 1.8 (95% CI 1.5, 2.2) for rofecoxib and 1.4 (95% CI 1.0, 1.9) for non-selective NSAIDs. This study confirmed earlier findings by Feenstra et al.[98] that the use of non-selective NSAIDs was associated with a worsening of heart failure, but not with the onset of disease. Another recent Canadian study has also reported an association between the use of nonselective NSAIDs and rofecoxib, but not celecoxib, and the risk of death and recurrent heart failure in elderly patients.[101]

Although a majority of studies as well as mechanistic considerations indicate that the association between NSAID use and heart failure is a group effect, the results of the latter two studies suggest that induction of heart failure may not be a group effect, but that some NSAIDs have a more unfavourable toxicity profile with regard to heart failure than others. However, this issue must be further investigated before firm conclusions can be drawn. In general, heart failure constitutes a contraindication for the use of NSAIDs.

9. Thiazolidinediones (Glitazones)

In experimental studies, antidiabetic drugs belonging to the thiazolidinedione (glitazone) group, such as rosiglitazone, pioglitazone and troglitazone, have been found to exert potential positive as well as negative effects on cardiac function.[102] Nevertheless, in clinical studies, symptoms implicating a tendency towards heart failure are predominantly described. In general, the glitazones increase the plasma volume by 6–7%, and peripheral oedema has been reported in 3–8% of the patients.[103]

A recent retrospective cohort study[104] using data from a health insurance database found that in patients with type 2 diabetes, the adjusted incidence of heart failure at 40 months of follow-up was 8.8% in the glitazone group and 5.5% in the control group, a hazard ratio of 1.8 (95% CI 1.4, 2.2). In a clinical study of 111 consecutive patients with type 2 diabetes and heart failure who were treated with glitazones, fluid retention developed in 19 (17%) patients. The symptoms were reversible after drug withdrawal, and no association between the risk of fluid retention and the baseline degree of severity of heart failure was observed.[105] Unpublished data from the manufacturers indicate that the risk of heart failure is also increased during concomitant treatment with insulin.[106,107]

In conclusion, it is recommended to follow patients receiving glitazones closely with respect to manifestations of heart failure and to change to alternative therapies for patients who develop symptoms of heart failure.[106-108] Some authors recommend that glitazones should not be prescribed to

patients with NYHA class III or IV functional status,[108] whereas the manufacturers discourage the use of these drugs in all patients with heart failure irrespective of the NYHA class.[106,107]

10. Tumour Necrosis Factor Antagonists

The tumour necrosis factor (TNF) antagonists infliximab and etanercept are used as immunosuppressive agents in disorders such as rheumatoid arthritis and Crohn's disease. Early clinical studies indicated that inhibition of TNFα could favourably modify the course of heart failure.[109,110] Based upon this finding, a study, in which infliximab 5 mg/kg/day, infliximab 10 mg/kg/day and placebo were compared, was initiated.[111] A total of 150 patients with NYHA class III or IV heart failure and with a left ventricular ejection fraction of ≤35% were included and followed for 28 weeks. However, excess mortality and hospitalisation for heart failure were observed among patients who received infliximab; 4 of 101 (4%) patients died versus 0 of 49 patients in the placebo group and 14 of 101 (14%) patients versus 5 of 49 (10%) patients were hospitalised for heart failure, respectively. The combined risk of death from any cause or hospitalisation for heart failure was particularly increased in the patients receiving infliximab 10 mg/kg (hazard ratio 2.8; 95 % CI 1.0, 8.0).

The manufacturer of etanercept refers to two unpublished studies that were terminated before completion, and where at least one indicated a possible worsening of heart failure.[112]

In a recent publication based on data from the US FDA MedWatch Programme, 47 patients who had developed new (n = 38) or worsened (n = 9) heart failure during treatment with TNFα inhibitors are presented.[113] A total of 29 patients received etanercept and 18 received infliximab. Although only 19 of the 38 patients with new-onset heart failure had any risk factors for heart failure identified, it should be noted that 5 of the 47 patients in the total group used NSAIDs concomitantly (see section 8).

These data imply that caution should be exercised when treating a patient with heart failure with TNFα inhibitors. In fact, the manufacturer of infliximab discourages its use in patients with NYHA class III and IV heart failure, and states that patients with NYHA class I and II heart failure should be closely monitored and the drug stopped if the symptoms of heart failure worsen.[114] In contrast, the manufacturer of etanercept does not contraindicate its use in patients with heart failure, but recommends close monitoring.[112]

11. Appetite Suppressants

The appetite suppressants fenfluramine, dexfenfluramine and phentermine may cause heart failure by inducing pulmonary hypertension and/or cardiac valve disease.

In a case-control study on pulmonary hypertension in 35 centres in Europe, 95 cases and 355 controls were scrutinised. The risk of pulmonary hypertension when using an appetite suppressant (mainly fenfluramine or dexfenfluramine) was found to be increased 6.3-fold (95% CI 3.0, 13).[115] If the cumulative exposure was >3 months, the risk was increased 23-fold (95% CI 6.9, 77). In a prospective surveillance study from North America, 205 patients with primary pulmonary hypertension and 374 patients with pulmonary hypertension from other causes were recruited. The OR for primary pulmonary hypertension when taking fenfluramine was 7.5 (95% CI 1.7, 32). However, also in the group with pulmonary hypertension from other causes, 11.4% of the patients had used anorexiogens, raising the possibility that these drugs could precipitate pulmonary hypertension also in patients exposed to other known risk factors.[116]

An increased risk of heart-valve disease has been observed in several studies, but the observed frequencies have varied considerably from 0.1% to 38%.[117] The most important reasons for the wide difference in incidence rates between studies are variable doses, differences in drug combinations and treatment durations, and differences in sensitivity for detecting minor changes in heart-valve anatomy due to the methodology used.

There is strong evidence that the prevalence of heart-valve malformations also increases with the

duration of therapy. For example, in a study of 1835 patients treated with fenfluramine plus phentermine, the prevalence of aortic regurgitation was 3.6% in the control group, which was not significantly different from the prevalence in the group that had been treated with the drugs for <6 months.[118] However, when the duration of drug use was 6–12 months, the prevalence was 7% (adjusted OR 2.4 compared with controls), when the duration was 12–24 months, the prevalence was 14% (adjusted OR 4.6), and when the duration was >24 months, the prevalence was 17% (adjusted OR 6.2).

In a prospective, double-blind, placebo-controlled study of dexfenfluramine in monotherapy,[119] 1072 patients underwent echocardiography after an average of 2–3 months of treatment. The frequency of mitralic valve regurgitation was 61% in the dexfenfluramine group, but also as high as 54% in the placebo group (p = 0.01). The frequency of aortic valve regurgitation was 17% among patients receiving dexfenfluramine and 12% in the placebo group (p = 0.03). In most cases, the regurgitation was classified as having little, if any, clinical significance. There were no significant differences with respect to severe regurgitations. It should, however, be noted that the duration of treatment in this study was relatively short because the study had to be terminated when fenfluramine was withdrawn from the US market.

In the studies cited previously, no baseline echocardiographic examinations were available. In one study with baseline echocardiography data included,[120] 479 patients receiving dexfenfluramine, 455 patients receiving fenfluramine/phentermine and 539 untreated matched controls were included. In this study, the risk of developing aortic valve regurgitation was significantly higher in the treatment groups than in the control group (relative risks 2.18 [95% CI 1.32, 3.59] and 3.34 [95% CI 2.09, 5.35], respectively). In contrast, the risk of developing mitral valve regurgitation or cardiac valve thickening was not significantly different between groups. This lack of difference could, however, be attributed to the relatively short treatment periods of 6 and 11.9 months, respectively, in the two drug groups.

The changes in heart-valve function are generally irreversible but are not expected to worsen after discontinuation of the offending drug. In a study of patients followed for 1–2 years after withdrawal of dexfenfluramine (n = 371) or a combination of fenfluramine and phentermine (n = 340), >90% of the lesions remained stable, 5–6% improved whereas <4% deteriorated further.[121] Nevertheless, in some cases, the regression of the lesions has been marked over a longer period of time.[122]

Fenfluramine and dexfenfluramine produce their anorexiogenic actions through the activation of serotonergic pathways in the brain. The alterations in the heart-valve anatomy, with its lengthened, thickened, white and shiny appearance, closely resemble those associated with serotonin-producing carcinoid tumours. A common pathogenetic factor could thus be increased levels of serotonin in the systemic circulation. Although fenfluramine and dexfenfluramine have been withdrawn from most markets, their history illustrates the important principle that drugs that are powerful enhancers of peripheral serotonin might induce cardiovascular lesions similar to those found in patients with serotonin-producing carcinoid tumours.

In contrast to fenfluramine and dexfenfluramine, the recently introduced appetite suppressant sibutramine has been found not to have a significant affect on pulmonary artery pressure or heart-valve anatomy.[123,124]

12. Antimigraine Drugs

Methysergide and ergotamine are ergot derivatives used in the treatment of migraine. Both drugs are associated with mitral-, aortic- and tricuspidal-valve lesions. Most data exist for methysergide, for which the reactions were recognised >30 years ago.[125] For ergotamine, a few cases have been described more recently.[126] However, as no systematic studies have been conducted, the risk cannot be further quantified. Both methysergide and ergotamine are partial serotonin agonists, which may explain the fact that the valvular affection found close-

ly resembles those seen in the carcinoid syndrome and those associated with the appetite suppressants fenfluramine and dexfenfluramine.

13. Antiparkinsonian Drugs

The dopamin receptor agonists pergolide and cabergoline are ergot derivatives used in the treatment of Parkinson's disease. As foreseen from their chemical origin, these drugs have been associated with heart-valve lesions and heart failure.

In two recent reports, a total of six patients with heart failure due to severe tricuspidal regurgitation after treatment with pergolide were described.[127,128] Echocardiographic and histological investigations revealed lesions closely resembling those seen in patients with carcinoid tumour, but this diagnosis was subsequently excluded. In another report,[129] two additional patients with symptomatic heart failure and eight patients with echocardiographic changes of valvular disease without any signs of heart failure were presented. All patients had been treated with pergolide.

A few case reports exist for cabergoline.[128,130,131] In the first report,[128] a 58-year old woman who had been treated with cabergoline for a total of 20 months developed symptoms and signs of heart failure. An echocardiograpic examination demonstrated mitral, aortic, tricuspidal and pulmonary valve regurgitation as well as thickening of the valves. After stopping the drug, the lesions showed definite, but not complete, regression. The two other patients[130,131] developed symptoms and signs of heart failure during cabergoline treatment and where subsequently diagnosed as having a constrictive pericarditis. Although constrictive pericarditis is different from the cardiac affections seen after treatment with other ergot derivatives, a connection with the drug cannot be excluded.

14. Antidepressants

The cardiovascular effects of tricyclic antidepressants have been a source of concern, particularly in patients with coexisting cardiovascular morbidity. Besides the well known effects on heart rate, blood pressure and cardiac rhythm, a direct effect on cardiac contractility has been suspected, predominantly based upon experimental studies in animals.[132] Moreover, a study using antimyosin antibodies as a marker for possible myocardial cell damage found that patients treated with amitriptyline had a higher uptake than the groups treated with clomipramine or imipramine, which did not differ from the control group.[133]

A few clinical reports of heart failure attributed to tricyclic antidepressants exist,[134,135] and some systematic studies have indicated that cardiac function might be impaired.[136] However, in these studies, older, indirect methods for the assessment of cardiac function were used. In contrast, other studies employing modern technology have failed to demonstrate left ventricular impairment;[137,138] however, these studies had a limited follow-up time and included relatively few subjects.

Overall, the evidence that tricyclic antidepressants might cause heart failure is not very convincing and most likely the effect on left ventricular function, if any, is without major clinical significance. Accordingly, specific risk estimates cannot be given. It might, however, be prudent to observe patients with existing heart failure when treatment with a tricyclic antidepressant is instituted.

Current available data on the selective serotonin reuptake inhibitors indicate that they do not seem to have any influence on myocardial function and are not associated with the cardiac effects documented for the tricyclic antidepressants.[139,140]

15. Antipsychotics

Several antipsychotic drugs have been associated with myocarditis and cardiomyopathy. Most evidence for a link exists for clozapine, for which several studies have been published.[141-143]

Two studies have specifically summarised reported cases on clozapine and myocarditis or cardiomyopathy. In the first study,[141] 15 cases from Australia were described. In the second study,[142] eight cases from Sweden were presented and 18 cases previously published as single case reports in the literature were reviewed. About 60–80% of the

cases were diagnosed during the first month of treatment. However, this proportion could be too high because it is based upon spontaneous reporting and the association would be less likely to be discovered with increasing time intervals from onset of therapy to diagnosis of the reaction. A total of 42% of the cases were found to be fatal in one of the reviews.[142] Based upon sales data, the risk of myocarditis induced by clozapine has been estimated to be at least 1 per 2000 to 1 per 500 treated patients.[141,142]

In a study using the WHO international database for adverse drug reactions, there were statistically significant associations between use of several antipsychotic drugs and myocarditis/cardiomyopathy when a data-mining approach was applied.[143] The association was most pronounced for clozapine, but was also evident for chlorpromazine, fluphenazine, haloperidol and risperidone. However, because spontaneous reporting of adverse drug reactions is subject to bias, the database is heterogeneous, and no causality assessments have been made in the majority of the cases, these findings only represent a statistical association and need to be investigated further with other methodologies to establish whether a causal relationship exists.

16. Glucocorticoids

The propensity of glucocorticoids to produce hypertension, fluid retention, central obesity, hyperglycaemia and dyslipidaemia has long produced concern regarding possible cardiac adverse effects.[144,145] Recently, one case-control study[146] and one cohort study[147] both reported a significantly increased risk of cardiovascular disease associated with oral glucocorticoid use.

It has also been suggested that glucocorticoids may precipitate or worsen heart failure, most likely by stimulation of mineralocorticoid receptors. Mechanistic studies indicate that mineralocorticoid receptor activation would exacerbate heart failure, not only by increasing sodium and fluid retention, but also by promoting fibrotic remodelling in the heart.[148] The two epidemiological studies cited previously[146,147] have also addressed the risk of heart failure. In the first study,[146] current glucocorticoid use was associated with an increased risk of heart failure (OR 2.7; 95% CI 2.5, 2.9). The second study[147] found that glucocorticoid exposure was associated with a dose-dependent increased risk for heart failure. For prednisolone equivalent dosages of <7.5 mg/day, the relative risk was 1.5 (95% CI 1.3, 1.8), whereas the relative risk was 3.7 (95% CI 2.7, 5.1) when the daily dose in prednisolone equivalents was ≥7.5mg.

Although these studies were observational and confounding cannot be excluded, they both indicate an increased risk of heart failure during glucocorticoid use. No clinical studies on the association between glucocorticoid use and heart failure exist, and such studies are clearly needed to address this issue further.

17. Antifungal Drugs

The systemic antifungal agent itraconazole has been associated with heart failure. In a study using the US FDA Adverse Event Reporting System database, 58 potential cases of heart failure were summarised.[149] Although a causal relationship was difficult to prove because most patients also had cardiovascular diseases and were taking other drugs concomitantly, animal studies and early clinical studies indicate that itraconazole may exert negative inotropic effects.[127] The underlying mechanism of this effect is not known.[149]

Since no systematic studies have been conducted, no risk estimate for the induction of heart failure can be given. On the basis of the preliminary findings, it has, as a precaution, been recommended that patients should be monitored for symptoms and signs of heart failure during itraconazole therapy and that the use of itraconazole should be discouraged in patients with evidence of ventricular dysfunction.[149]

Before conclusive recommendations can be given, additional studies with other methodologies should be conducted to confirm or refute the suspected association between itraconazole and heart failure. In addition, no published data on a possible

association with heart failure exist for the related drugs ketoconazole and fluconazole.

Treatment with amphotericin B has been associated with dilated cardiomoypathy. In an early report, three cases of reversible cardiomegaly and heart failure were described.[150] These patients were, however, also treated with hydrocortisone, and the authors postulated that the mechanism was a hypocalemic cardiopathy following salt and water retention secondary to the mineralocorticoid effects of hydrocortisone (see section 16), together with a nephrotoxic effect of amphotericin B. The symptoms resolved within 2 weeks after discontinuation of hydrocortisone.

More recently, two cases of cardiomyopathy and heart failure after treatment with amphotericin B in monotherapy have been presented.[151,152] In both patients, the symptoms of heart failure resolved and the cardiac size normalised after cessation of amphotericin B, within 6 months in the first case[151] and within 10 days in the second case.[152]

18. Herbal Drugs

Many herbal drugs, particularly of Chinese origin, contain liquorice (*Glycyrrhizia glabra*), which is also an ingredient in some types of candy. The pharmacologically active substance in liquorice, glycyrrhizin, inhibits the enzyme 11β-hydroxy-steroid dehydrogenase.[153] This inhibition causes excessively high levels of cortisol at the mineralocorticoid receptors, thereby stimulating these receptors.[153,154] The effect of liquorice to increase blood pressure is well documented, and occurs particularly after prolonged use of high doses. A case report of a 42-year-old woman prescribed a Chinese herbal tea consisting of liquorice and multiple unknown ingredients has been published.[155] The patient developed symptoms of heart failure, which resolved after stopping the tea. However, since liquorice was only one of several ingredients in the tea and this particular case of heart failure was secondary to cardiomyopathy, other substances are more likely to be causative. Although no obvious cases of heart failure due to liquorice has been reported in the literature, the mechanism of action with increased blood pressure and sodium and water retention indicates that it at least might worsen the symptoms in patients with an already existing heart failure.

Blue cohosh (*Caulophyllum thalictroides*) has been associated with heart failure in a single case report.[156] An infant whose mother took a herbal drug containing blue cohosh in the month before delivery developed heart failure shortly after delivery. No other causes were identified, and the effect is consistent with the fact that blue cohosh contains glycosides and alkaloids that have been shown to produce toxic myocardial effects in animal studies.[156] However, owing to the lack of data, it remains speculative whether there was a causal association in this particular case or not.

Finally, it should be noted that herbal medicines have also been reported to be adulterated by drugs that can induce heart failure, such as NSAIDs.[157-161]

19. Conclusion

Heart failure is predominantly caused by cardiovascular diseases such as hypertension, coronary heart disease and valvular heart disease. In some patients, the occurrence of heart failure can be attributed to the use of a particular drug. Moreover, some drugs also have the propensity to adversely affect haemodynamic mechanisms in patients with an already existing heart failure. The drugs reviewed may also adversely affect the function of the heart as a pump without causing overt heart failure.

Notably, the symptoms and signs of heart failure caused by some drugs, particularly the anthracyclines, may first appear several years after the drug has been discontinued. Because of the widespread use, the extent of heart failure induced by NSAIDs (including selective COX-2 inhibitors) may pose another problem of considerable proportions. Although the documentation is sparse, it is important to be aware that herbal drugs and health remedies might also have the potential to cause heart failure.

In patients with a new-onset or a worsened heart failure, detailed documentation of current and previous drug use is mandatory.

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