Přehledový článek | Review article

Drug-induced pericarditis

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SOUHRN

Léky vyvolané perikarditidy nejsou časté, ale závažné onemocnění, protože případná tamponáda perikardu může ohrozit život pacienta. Vzhledem k tomu, že nabídka nových léků se neustále rozšiřuje, zvyšuje se i podíl léčiv schopných perikarditidu vyvolat. Autoři vyhodnotili práce s touto tematikou uvedené v databázi PubMed a doplnili informacemi z databáze VigiBase. Ve svém článku autoři uvádějí současné poznatky o mechanismech vzniku i stupni rizika vzniku léky vyvolané perikarditidy. Uvádějí relevantní informace o jednotlivých lécích rozdělených do sedmi skupin. U některých léčiv je riziko vzniku perikarditidy vysoké a při léčbě těmito přípravky je nutné toto riziko brát v úvahu.

ABSTRACT

Though not common, drug-induced pericarditis is a serious condition, since pericardial tamponade, should it develop, may be life-threatening. As the number of drugs is constantly expanding, so does the proportion of those capable of causing pericarditis. The authors reviewed the relevant literature in the PubMed database and complemented it with information from the VigiBase database. In their article, the authors present current knowledge about the mechanisms of origin and level of risk of drug-induced pericarditis and discuss relevant information on individual drugs divided into 7 classes. Some medicines are associated with a high risk of developing pericarditis, a fact to be taken into account when treating patients with these agents.

Introduction

Though a relatively frequent condition, epidemiological data on pericarditis are scarce. An Italian observational study, published in 2008, reported an incidence of acute pericarditis of 27.7 cases per 100,000 person-years.[1] The incidence of hospitalization for acute pericarditis was found to be 3.32 per 100,000 person-years. Acute pericarditis was behind 0.2% of all hospitalizations for cardiovascular causes and less than 5% of admissions for chest pain.[2–4]

Table 1 lists the most frequent causes of pericarditis, which may be an isolated condition or a manifestation of another, systemic disease.[5] The cause of pericarditis remains unexplained in up to 80–90% of cases and it is assumed that the majority of them are of viral etiology. This is apparently in contradiction with the low incidence (1–2%) of viral pericarditis given in Table 1. This is because virological tests (viral culture, serum antibody tests, and so on) are not performed on a routine basis as their use would not be clinically informative. An exception of routine serological tests are those for human immunodeficiency virus (HIV) and hepatitis C virus (HCV). Besides, most cases of viral pericarditis resolve spontaneously.

Drug-induced pericarditis is a less common type of pericarditis.[6] Its mechanisms of development can be divided into several types. The first type presents with clinical lupus-like features including pericarditis.[7] The second type is caused by a spectrum of allergic (esosinophilic) reactions.[8] It was recently reported that an important role in the pathogenesis of immune responses leading to the development of pericarditis is played by natural (innate) lymphoid cells.[9] The third type of causative factors includes agents with a potent cardiotoxic action[10,11] resulting in myocardial injury and associated pericarditis. These cases are referred to as myopericarditis or perimyocarditis if pericarditis is the dominant feature. The fourth type comprises agents with which the mechanism of development

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Table 1 – Causes and estimated incidence of acute pericarditis. Adapted from Khandaker.[5]

Cause	Estimated incidence (%)
Idiopathic	85–90
Infective	
Viral	1–2
Bacterial	1–2
Tuberculous	4
Fungal	Rare
Parasitic	Rare
Cancers	7
Systemic autoimmune disease	3–5
After cardiac or thoracic surgery	Rare (< 1)
Aortic dissection	Rare (< 1)
Chest injury/trauma	Rare (< 1)
Chest irradiation	Rare (< 1)
Side effects of drugs	Rare (< 1)
Acute myocardial infarction	5–20[1]
Myocarditis	30[1]
Uremia	
Pre-dialysis	5
Post-dialysis	13

[1] Population-specific data.

of pericarditis is poorly understood. In some cases, the individual mechanisms may combine.

As the range of new drugs is constantly expanding, so does the proportion of drugs capable of inducing pericarditis. Examples include anti-TNF agents and a new class of immunotherapy drugs called checkpoint inhibitors.

The aim of our study was:

- to explore the body of relevant knowledge about drug-induced pericarditis currently available;
- to systematically review the current literature and to provide the most recent concepts and data.

Methods

Relevant articles (exclusively English-language ones) for our review were searched for in the PubMed database using the keyword "drug-induced pericarditis". There were no limits in terms of age or sex of study participants. Additional information about individual drugs was obtained from VigiBase, the global WHO database of suspected adverse reactions (Uppsala Monitoring Centre, Sweden).

Results

Upon entering the above keyword, the search in the PubMed database produced a total of 496 papers (of which number 357 were full-text articles) published between January 1, 1961 and January 7, 2022. The overwhelming majority (270) were case reports describing one or several patients. The number included 88 reviews, 5 systematic reviews (focused on individual agents such as clozapine and colchicine, use of non-steroidal anti-inflammatory drugs in myocarditis, cardiovascular manifestations in inflammatory bowel disease and cardiovascular adverse effects [AEs] of herbal remedies). The search identified 8 clinical trials (with half of them conducted before 2000), of which number 3 were Phase 1 trials. The largest number of studies[5] were related to oncology, 2 concerned a topic in cardiology while 1 dealt with treatment of patients with HIV. The Phase I studies involved trials with lexatumumab (n=24), quizartinib (n=19) and SCH 532706 (a chemokine receptor-5 [CCR5] antagonist) (n=12); all 3 trials reported pericarditis in one case each. The topic of pericarditis was not addressed in any of the 3 meta-analyses found.

The numbers of reported cases of pericarditis as an AE with individual drugs are given in Table 2.

Relevant information about individual pericarditis-inducing agents is provided separately for the 7 groups.

Discussion

There is only scant literature, mostly case reports, addressing the topic of drug-induced pericarditis, which makes it difficult, if not impossible, to determine the frequency of this AE attributable to individual drugs, hence being mostly rough estimates. Even data from AE registries are not more specific. The numbers of AEs reported from developing countries are very low, e.g., less than 1%. However, even in industrialized nations, the numbers of reported AEs are about 5%, or 10% at most, with the implication that at least 90% of AEs go unreported.

Clinical trials are very few and none designed specifically to explore this issue. Our search identified only 4 trials in the PubMed database published after the year 2000, of which number 3 were Phase I trials enrolling only a small number of participants. The newer agents associated with a more frequent incidence of pericarditis (immune checkpoint inhibitors) should presumably undergo clinical trials focused on this particular topic. The text below presents the current knowledge about individual pericarditis-inducing drugs.

Anti-infective agents

Among antibiotics, pericarditis was reported after the use of penicillin[12] and tetracycline derivatives, in particular after minocycline.[13,14] Piette et al.[15] described AEs of minocycline in 4 patients. While, in one patient, the AE manifested itself as lupus-like syndrome, the other three experienced hypersensitivity reactions with eosinophilia and dominant involvement of other organs.

Among anti-tuberculosis drugs, pericarditis occurred most often after isoniazid[16] whereas the condition was most frequently associated with the chemotherapeutic agent co-trimoxazole.[17] Pericarditis (and pleuritis) can also develop after treatment with the antifungal agent

Table 2. Drugs of various classes most often inducing pericarditis

Class of drugs	Medication	Incidence of pericarditis (%)	VigiBase* (pericarditis + pleural effusion)
I Anti-infective agents	Minocycline	0.01–1,0	27 + 10
	Co-trimoxazole	0.01–0.1	20 + 25
	Interferon	0.01–1,0	2 + 1
II Anti-inflammatory drugs	Sulfasalazine	0.01–0.1	63 + 19
	Adalimumab	0.01–0.1	263 + 374
III Antihypertensive drugs	Hydralazine	5	28 + 61
	Minoxidil	3	61 + 199
	Methyldopa	NA	7 + 3
	Enalapril	Rare	4 + 7
	Lisinopril	Rare	11 + 38
IV Anticoagulants	Apixaban	Rare	16 + 132/142/85**
	Dagibatran	Rare	34 + 288/293/286
	Rivaroxaban	0.02	32 + 250/435/173
	Streptokinase	1	4 + 11/22/7
V Anti-cancer drugs	5-fluorouracil	1.4	50 + 43
	Clofarabine	8–39	10 + 29
	Carfilzomib	Up to 1	19 + 27
	Bortezomib	1	25 + 67
	Dasatinib	29	41 + 507
	Pentostatin	1–10	2 + 5
	Ceritinib	4–6	21 + 25
VI Neuroleptic (anti-psychotic) agents	Clozapine	NA	466 + 570
VII Others	Bromocriptine	Rare	10 + 8
	Dantrolene	Rare	4+ 7
Vaccines	Comirnaty (COV-19) +		
	Spikevax	NA	9,215/1,840***

Notes: * Numbers of reported cases of pericarditis and pericardial effusion as adverse effects of drugs in the WHO VigiBase system in Uppsala, Sweden since the time of introduction of each of the above drugs. ** In the class of anticoagulants (VI), the third and fourth numbers give the numbers of cases of hemorrhagic pericardium and pericardial tamponade, respectively. *** Data applicable to both vaccines. NA, not available.

itraconazole; however, the dominant clinical features include congestive heart failure, fluid retention and arterial hypertension.[18]

Regarding antiviral drugs, pericarditis has been reported after treatment with interferon.[19] The authors observe that pericarditis can develop through two mechanisms, either an autoimmune or a cardiotoxic effect. Pericarditis can also be induced by ribavirin and this AE is included in its *Summary of Product Characteristics (*SmPC hereinafter) as a rare one. When treating patients with hepatitis C, ribavirin is co-administered with interferon making it difficult to determine, which of the two agents, and to what extent, contributes to the development of pericarditis. There was also a report linking other antiviral drugs (ledipasvir/sofosbuvir combination) to myopericarditis.[20]

Anti-inflammatory drugs

The mainstay of treatment of inflammatory bowel disease had long been sulfasalazine (5-aminosalicylate [5-ASA] + sulfapyridine). Given its AEs (myocarditis, pericarditis, myopericarditis),[21] sulfasalazine was replaced by 5-aminosalicylic acid alone also known as mesalazine or mesalamine. However, it later turned out that mesalazine can also cause pericarditis and myocarditis.[22,23] Olsalazine, a prodrug of mesalazine, is a substance cleaved in the colon into 2 active molecules of 5-ASA; hence, it can also induce pericarditis. This usually occurs within 2–4 weeks of therapy initiation, or even later when co-administered with glucocorticoids. The mechanisms of its AEs include, in particular, IgE-mediated hypersensitive reaction, a direct cardiotoxic effect, cell-mediated hypersensitivity and hormonal antibody activity. Pericarditis will gradually re-

solve upon therapy discontinuation. A detailed review of this issue was recently published by Patel et al.[24]

Regarding the newer anti-inflammatory drugs, pericarditis has been linked to the use of anti-TNF drugs, in particular adalimumab, infliximab, and etanercept, with the most recent additions being certolizumab and golimumab.[25,26] Pericarditis can develop as early as one to several months of therapy. In addition to immune factors, pericarditis can also be caused by infection (increased infection rates were observed during treatment with anti-TNF agents). The infectious cause of pericarditis as a complication of therapy has been most often linked to treatment with adalimumab.

Antihypertensive drugs

Pericarditis associated with the use of antihypertensive agents has been reported after older agents such as minoxidil, methyldopa, and hydralazine. Pericardial effusion, with an incidence of about 3%, has been shown to resolve after therapy discontinuation.[27] Methyldopa-induced pericarditis is most often considered a component of lupus-like syndrome[28] and is also listed as an AE in the SmPCs. A similar mechanism has been incriminated in the development of pericarditis during therapy with hydralazine.[29] Risk factors include higher-dose hydralazine and therapy duration of more than 3 months. There have been rare reports of pericarditis developing in patients receiving ACE inhibitors.[30,31]

Anticoagulants

Pericardial bleeding is a rare AE of anticoagulant drugs and thrombolytic agents.[32,33] While the problem is hemopericardium in most cases, in terms of hemodynamics it behaves like effusion in the other types of pericarditis including cardiac tamponade; hence, this topic is often addressed in the context of pericarditis.[6]

A meta-analysis of 6 randomized clinical trials (45,995 patients treated with apixaban, dabigatran, edoxaban or rivaroxaban and 32,905 patients treated with vitamin K antagonists) showed that the incidence of pericardial bleeding was very low being 0.02% in either group.[34] Similarly, thrombolytic therapy of acute myocardial infarction was linked to pericardial bleeding in 1% of thrombolysis-treated patients.[35] By contrast, Table 2 shows unusually high rates of pericardial tamponade compared with the total of reported cases of pericarditis and pericardial effusion in this patient subpopulation.

Anti-cancer, immunosuppressive, and immunomodulatory agents

Among the older agents, pericarditis can be induced by cyclophosphamide and busulfan, alkylating agents whose cardiotoxic action was documented a long time ago. Cyclophosphamide-induced pericarditis was described as early as 1976 as a component of severe toxic injury to the myocardium,[36] often associated with high mortality rates. Busulfan has been incriminated in cardiac tamponade in children diagnosed with thalassemia. In an Italian study with 400 participants, eight children (2%) undergoing bone marrow transplantation and chemotherapy developed cardiac tamponade resulting in 6 deaths.[37] Late pericarditis developing after stem cell transplantation is believed to be due to graft-versus-host disease (GVHD).

5-fluorouracil is just another substance shown to exert a cardiotoxic effect and, in addition to myocardial injury, it can induce pericarditis.[38] In an analysis of 377 fluorouracil-treated patients, pericarditis was diagnosed in only 1.4% of patients.[39] Capecitabine is an oral fluorouracil precursor with AEs similar to those occurring with fluorouracil.[40]

In the class of antimetabolites, pericarditis (mostly together with left ventricular dysfunction) was diagnosed after clofarabine (a purine analog),[41] cytarabine,[42] and azacitidine (pyrimidine analogs).[43] Pericarditis tends to occur on multiple doses of these agents.

Among the other antimetabolites (pyrimidine analogs), a cardiotoxic effect including pericarditis has been shown for gemcitabine.[44] Cardiotoxicity including pericarditis has also been documented with taxans (docetaxel)[45] and anthracyclines (daunorubicin, idarubicin). In a group of 171 children treated with anthracyclines for lymphoblastic leukemia, pericarditis was diagnosed in 14 (8.19%).[46] Pentostatin is a purine analog reducing $CD4^+$ T cells used in the treatment of hairy cell leukemia. Its AEs include pericarditis listed also in its SmPC.

Similarly, pericarditis can be induced by the proteasome 26S inhibitors and immunomodulators carfilzomib and bortezomib used in the treatment of myeloma;[47,48] however, its incidence is generally below 1%.

Another class of anti-cancer agents inducing pericarditis and pericardial effusion are BCR-ABL tyrosine kinase inhibitors, in particular imatinib, nilotinib, dasatinib, and bosutinib. Pericardial effusion can also develop as a feature accompanying pleuropericarditis. With dasatinib, pleuritis was reported in 10–35% of patients and co-existing pericarditis in up to 29% of patients.[49] However, these often quoted data in the literature were obtained in a relatively small group of patients (n = 138). The mechanism of effusion formation is drug-induced serositis.[50] Symptoms of serositis may not present until within 3 weeks to 2 years of therapy initiation.

Among the class of ALK tyrosine kinase inhibitors, pericarditis has been linked to treatment with ceritinib. In a group of 925 ceritinib-treated patients included in 7 clinical trials, pericarditis was reported in 5.8% making it a frequent AE.[51] In another clinical trial enrolling 189 patients, pericarditis was diagnosed in 4.2% of participants.[52]

Pericarditis has also been reported in patients receiving immune checkpoint inhibitors used in the treatment of a variety of cancers.[53] Although myocardial injury is more severe with this therapeutic option (high mortality, 25–50%), pericarditis combined with tamponade can also be a life-threatening condition. In a retrospective study, patients treated with checkpoint inhibitors were at a fourfold higher risk of developing pericarditis compared with a control group of cancer patients not receiving this treatment.[54] The incidence of pericarditis is not high and the condition is diagnosed in some 1.5% of patients. Pericarditis has been reported in those treated with ipilimumab[55] and nivolumab[56] as well as other agents of this class of drugs, often used in combination.

In the class of immunosuppressive agents, pericarditis was reported in patients treated with leflunomide;[57] however, its occurrence is rare, developing and presenting more often after methotrexate. In cancer patients receiving methotrexate, serositis symptoms are present in up to 5–12% of patients[58] with the risk rising on multiple dosing. The prevailing condition is pleuritis combined, less often, with pericarditis, and even less frequently with peritonitis. In a group of 168 methotrexate-treated female patients, serositis was reported in 42 (25%) subjects, with pericarditis recorded in only one.[59]

Out of immunomodulators employed in the treatment of multiple sclerosis, pericarditis, and pleuritis were diagnosed in 2% and 0.8%, respectively, of linomide-treated patients. By contrast, pericarditis was diagnosed in only 2 patients enrolled in a clinical trial of laquinimod. While, in one case, the diagnosis of pericarditis was questionable, in the second case, a causal relation with laquinimod is doubtful.[60]

Neuroleptic (antipsychotic) agents

Clozapine is an agent used frequently in the treatment of resistant forms of schizophrenia. A literature report suggested that clozapine-induced pericarditis can develop within a long range of 9 days to 7 years of therapy initiation, but most often between 3 and 5 weeks from the start of therapy.[61] Pericarditis is a relatively rare condition. While its incidence is unclear, there are relatively many case reports on this topic (see a summary in reference 61). A Danish retrospective study did not find a single case of pericarditis within an interval of 2 months of therapy initiation.[62] A condition far more serious is myocarditis (0.7–3%), which can develop within 2 months of therapy initiation. A grim prognosis is associated with cardiomyopathy (chronic contractile impairment) not developing until several months of therapy and reported to have high mortality rates of 12.5% to 24%.[63]

Agents with a chemical structure similar to that of clozapine include quetiapine and olanzapine, with both implicated in the development of pericarditis, or even constrictive pericarditis in the case of quetiapine.[64,65] The effusion is presumably due to the immune response to the agents administered; the patients often present with eosinophilia and elevated levels of inflammatory markers; the condition resolves upon therapy discontinuation.

Other classes of drugs

Ergot derivatives

Bromocriptine is used especially in the treatment of acromegaly and hyperprolactinemia-related conditions. Its AEs include profibrotic activity affecting various parts of the body (heart valves, retroperitoneum, lungs, and pleura, pericardium). Pericardial fibrosis can progress to constrictive pericarditis,[66] which occurs rarely and is listed, e.g., in its SmPC. Pericarditis can also be induced by other substances of this class of drugs such as lisuride, cabergoline, pergolide, and the antimigraine agent methylsergide.[67] Constrictive pericarditis has also been associated with methamphetamine.[68]

Muscle relaxant

Dantrolene is a muscle relaxant potentially inducing eosinophilic pleural and pericardial effusion.[69]

Ephedra

Ephedra (*Ephedra L.*) is an herb containing substances with a potent pharmacological and/or psychoactive action. Its main alkaloids are ephedrine and pseudoephedrine with a strong sympathomimetic effect. The herb is used as a dietary supplement (tea) to lose body weight, to improve physical appearance or airway patency. Adverse effects include myocarditis and cardiomyopathy and, less often, myopericarditis.[70–72]

Vaccines

Pericarditis may pose a complication post-vaccination (especially when using live virus vaccines), most often after vaccination against hepatitis B, varicella and DiTePe (diphtheria, tetanus, and pertussis). Development of myopericarditis has been reported rarely, but literature data are often discrepant. In a study by Eckart et al.,[73] the incidence of myopericarditis was 12/100,000 of those vaccinated against varicella. By contrast, in a study by Kuntz et al.,[74] the estimated incidence was as low as 0.24/100 000 vaccinees. This was explained by the more modern type of vaccines and smaller number of AEs. Engler et al. reported an incidence of myopericarditis of 463/100,000 those vaccinated against varicella.[75] The authors of the latter study employed more sensitive techniques of examination including cardioselective enzymes and showed that, in a considerable proportion of patients, myopericarditis can follow a subclinical course suggesting a longer-term study with these patients is warranted. Likewise, myopericarditis and pericarditis can be induced by COVID-19 vaccines, although this is a rare scenario.[76] In a cohort of 2.000,287 vaccinees, pericarditis was diagnosed in a total of 37 individuals (15 and 22 after the first and second dose, respectively); overall, these numbers translate into an incidence of 1.8 cases of pericarditis per 100,000 vaccinees.[77,78] This complication is experienced mainly by younger individuals and follows a benign course in most cases. The question also necessarily arises how often the course is asymptomatic. Likewise, it is unclear whether the myopericarditis is induced by the virus per se or is due to the immune response to the vaccine; however, the condition is diagnosed more often after mRNA vaccines.

Conclusion

While generally not frequent, drug-induced pericarditis requires the attention of any prescribing or attending physician. Literature data are scarce and are based mostly on case reports, with the incidence of complications associated with individual drugs being only rough estimates. As the spectrum of novel drugs increases, so does the risk of development of pericarditis. When prescribing some newer drugs (anti-TNF agents, immune checkpoint inhibitors, and others), the potential of development of pericarditis during therapy should be taken into account and the physician should be aware of this complication and risk of tamponade. Drugs associated with a higher incidence of pericarditis should undergo specific clinical trials to explore the issue of adverse effects in as great detail as possible.

Conflict of interest
The authors certify that there is no conflict of interest.

Authors' contributions
Both authors have read and approved the final version of the manuscript.

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