REVIEW ARTICLE

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Risks versus Benefits of NSAIDs Including Aspirin in Myocarditis

A Review of the Evidence from Animal Studies

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Contents

Abstract

NSAIDs, including aspirin (acetylsalicylic acid), are frequently used and effective in a broad variety of inflammatory diseases, i.e. rheumatic carditis and pericarditis. Myocarditis may constitute another suitable indication for NSAIDs in order to relieve the symptoms of the presumed viral infection or because pericardial effusion is often associated with this condition. However, concerns have been raised about their indiscriminate use in myocarditis. To clarify this issue, we conducted a systematic review of the literature concerning myocarditis, aspirin and NSAIDs.

We examined five animal studies of NSAIDs (indomethacin and ibuprofen) and aspirin in coxsackievirus B3- and B4-induced myocarditis. These studies indicated a deleterious effect of NSAIDs and aspirin in this setting, demonstrating a 2- to 3-fold increase in inflammation, myocytes necrosis and even mortality when compared with placebo. This possible deleterious effect was more predominant when NSAIDs or aspirin were administered during the acute and subacute phases of myocarditis; however, it was still noted when NSAIDs were administered during the late phase of the disease (the effect of aspirin was not evaluated in late phase studies). According to these animal studies, such effect might be attributed to decreased viral clearance (possibly via interferon inhibition) and/or exaggerated cytotoxic response (via interleukin-2 or inhibition of suppressor cells factors) and/or coronary artery spasm.

We found one animal study looking at autoimmune myocarditis and it did not demonstrate any beneficial or detrimental effect of aspirin.

Moreover, recent data suggest that aspirin and NSAIDs may counteract part of the efficacy of ACE inhibitors and be deleterious in chronic heart failure.

Taken together, these studies point to a possible deleterious effect of aspirin and NSAIDs in human myocarditis. In view of these animal studies and in the absence of controlled studies of aspirin or NSAIDs in human myocarditis, we do not recommend indiscriminate treatment with NSAIDs or high-dose aspirin in patients with myocarditis where there is no or minimal associated pericarditis.

Myocarditis is a poorly understood disease and its prevalence is probably largely underestimated.[1] It is defined as an inflammatory infiltrate of the myocardium with necrosis and/or degenerative changes with no typical sign of infarction.[2] Viral infection is assumed to be the most common cause of myocarditis.[3] Myocarditis may have diverse clinical features, and pericarditis commonly coexists with myocarditis.[4]

NSAIDs and aspirin (acetylsalicylic acid) are frequently used in patients with acute myocarditis, particularly in those with associated pericarditis,[5,6] or to relieve symptoms of viral infection such as myalgias and arthralgias. However, concerns have been raised about their indiscriminate use when myocarditis is present. In fact, some authors report a possible exacerbation of myocarditis by aspirin and hypothesised several mechanisms for such exacerbation, such as enhancement of vasoconstrictor tone, decrease of viral clearance and exaggerated cytotoxic immune response. To clarify this issue, we conducted a systematic review of published data on the effect of aspirin and NSAIDs in myocarditis.

1. Method for Data Selection

We conducted a Medline search (Pub Med database up to November 2002) of published studies on the impact of aspirin, colchicine and NSAIDs in myocarditis using the terms "myocarditis" and "viral myocarditis" alone or in combination with "aspirin" and "NSAID". Bibliographies of selected articles were used to extend the search. Articles were screened and selected on the basis of title and abstract. All articles referring to aspirin and NSAID use in myocarditis, including case reports, were selected and are commented on in this review and principal experimental results are shown in table I. To expand the search, controlled studies of aspirin and NSAIDs in other inflammatory heart disease were also included.

2. Data on NSAID or Aspirin Use in Experimental Myocarditis

After the Medline search, only six animal studies on the effect of aspirin or NSAIDs in myocarditis were detected, five in viral myocarditis[7-11] and one in autoimmune myocarditis. These studies pointed out a possible deleterious effect of NSAIDs in viral myocarditis.[12]

Costanzo-Nordin et al.[9] demonstrated that ibuprofen exacerbates myocardial inflammation and necrosis, when given during the acute or subacute phase of murine coxsackievirus B3 myocarditis. The effect of immediate and deferred administration of ibuprofen in infected mice was compared with infected and nontreated mice and to control mice treated with ibuprofen. None of control mice had inflammation or necrosis, and infected treated mice had significantly more inflammation and necrosis than infected nontreated mice. Based on the findings of negative myocardium viral culture, the authors assumed that this deleterious effect was independent of viral clearance. Furthermore, they hypothesised that both coronary artery vasospasm, and inhibition of an immunoregulatory suppressor cell population[13] could be responsible for such increase in myonecrosis. Two other studies confirmed the deleterious effect of NSAIDs in the acute phase of murine myocarditis and tried to investigate its mechanism. In a study reported by Rezkalla et al.,[10] mice were infected with coxsackievirus B3 and randomly assigned to aspirin, indomethacin or placebo. Khatib

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Table I. Animal studies assessing the effect of NSAIDs (including aspirin [acetylsalicylic acid]) in viral myocarditis

	Khatib et al.[7]	Khatib et al.[8]	Costanzo-Nordin et al.[9]	Rezkalla et al.[10]	Rezkalla et al.[11]
Animal model	2-day-old mice	2-day-old mice	3-week-old mice	3-week-old mice	3 week-old mice
Virus	CB4	CB4	CB3	CB3	CB3
Study design	Randomised at 1 hour; indomethacin vs placebo for 7 days	Randomised on day –10; indomethacin vs placebo for 10 days	Ibuprofen from day 1 to day 14 vs ibuprofen from day 7 until day 14 vs placebo	Randomised at 1 hour; indomethacin vs aspirin vs placebo for 10 days	Randomised on day 10; indomethacin vs placebo for 10 days
Mortality	45.7% vs 17.7%*	46.7% vs 16.7% (NS)	Not reported	26.7% vs 6.1 vs 0%	3 vs 0 mice
Virus replication[a]	5.3 ± 0.7 vs 3.9 ± 1.1*	Not reported	Not reported	Not reported	Not reported
Virus titres in the heart[a]	1.2 ± 0.5 vs 0.4 ± 0.4*	Not reported	Negative in all	4.9 ± 1.1* vs 5.3 ± 0.1* vs 4.2 ± 0.9	Not reported
Antibodies	NS	Not reported	Not reported	NS	Not reported
Interferon level (IU)	160 ± 54.8 vs 440 ± 261*	Not reported	Not reported	267 ± 231 vs 300 ± 283 vs 980 ± 402 (p = 0.06, 0.07)	Not reported
Involved myocardium	6.4 ± 4.9 vs 1.2 ± 1.5*	149.8 ± 202.0 vs 35.3 ± 45.4*	Not reported	Severe changes: 46.7%* vs 23.3%* vs 3.2%	Not reported
Inflammation (histological score)	Not reported	NS	3.1 ± 0.7* vs 2.9 ± 1.0* vs 2.1 ± 0.6	Not reported	1.7 ± 1.5 vs 1.4 ± 1.2
Necrosis (histological score)	Not reported	NS	3.0 ± 0.9* vs 2.7 ± 1.1* vs 1.5 ± 0.8	Not reported	1.0 ± 0.7 vs 1.7 ± 0.8
Comments	Increased virus virulence	Independent of viral clearance	Independent of viral clearance	Suspected immunological mechanism	

a Logarithmic representation (to the base 10) of mean ± 2 SD.

CB3 = coxsackievirus 3; **CB4** = coxsackievirus 4; **NS** = nonstatistical significant variation. * $p < 0.05$ versus placebo.

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et al.[7] compared the effect of indomethacin versus saline solution in coxsackievirus B4 neonatal myocarditis. Both studies showed more severe histological changes after NSAID therapy with similar neutralising antibodies, lower interferon levels, and higher virus titres in the heart. However, interferon classes were not given. Furthermore, Khatib et al. demonstrated that indomethacin resulted in increased mortality when compared with placebo.

Two studies evaluated the effect of NSAIDs administration during the late phase of viral myocarditis in mice and also pointed out a possible deleterious effect. Rezkalla et al.[11] showed no adverse effect of indomethacin in the chronic stage of the disease, after virus clearance; however, only heart weight, inflammation and necrosis pathological scores were evaluated. In a neonatal murine model of coxsackievirus B4 myocarditis, Khatib et al.[8] found that indomethacin did not affect either inflammation or necrosis score but resulted in greater extent of damage and focal thinning compared with placebo.

Only one study evaluated the effect of aspirin, prednisolone and cyclosporin in auto-immune myocarditis.[12] Lewis rats were immunised with cardiac myosin, resulting in severe myocarditis with congestive heart failure and multinucleated giant cells, a close model to fulminant human myocarditis, especially giant cell myocarditis.[14] In this study, aspirin did not demonstrate any favourable or deleterious effect compared with saline solution, whereas cyclosporin was effective. Indeed, rats treated with aspirin or placebo became immobile, hearts were markedly enlarged, had pericardial effusion and their histological scores were significantly higher than those treated with cyclosporin.[12]

3. Data of NSAID or Aspirin Use in Human Myocarditis and Current Recommendations

To date, no controlled studies have been conducted in human myocarditis with NSAIDs or aspirin. Some controlled studies have evaluated the effect of immunosuppressive therapies, not including aspirin or NSAIDs, in human myocarditis and show apparent discordant results. Immunosuppressive therapy (prednisone alone or in combination with azathioprine) demonstrated a positive effect on left ventricular function[15,16] but not on clinical endpoints. Furthermore, Mason et al. failed to demonstrate any benefit on left ventricular function in a study with important limitations such as a high percentage of patients lost to follow-up.[17]

The only available data concerning aspirin or NSAIDs in human myocarditis were found in a case report on NSAID-induced myocarditis and therefore is not relevant.[18] In the absence of any prospective controlled studies, no guidelines are available. Nevertheless, on the basis of experimental studies, some authors recommend avoiding aspirin or other NSAIDs during myocarditis.[19,20]

4. Effect of NSAIDs, Aspirin and Colchicine in Other Inflammatory Heart Diseases

Apart from myocarditis, aspirin, NSAIDs and colchicine have been extensively evaluated in other inflammatory heart diseases.

Rheumatic carditis may represent one of the most frequent inflammatory heart diseases, especially in developing nations. It may be complicated by severe valvular heart disease resulting in high levels of mortality and morbidity. Its treatment is based on antibiotics to eradicate streptococci and both aspirin and corticosteroids have demonstrated their efficacy in lowering valvular injury, with no clear difference between these regiments in a recent meta-analysis.[21,22]

Pericarditis is a worldwide disease characterised by an acute inflammation with infiltration of the pericardium. It may have various causes, including viral infection, and often coexists with myocarditis.[4] Moreover, recurrence of pericarditis occurs in 15–30% of cases. In acute pericarditis, NSAIDs, including aspirin, are usually considered as first choice agents as they result in rapid resolution of symptoms,[23] suppression of pericardial friction rub and pericardial effusion and normalisation of inflammatory tests.[6]

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In case of recurrent or refractory pericarditis, colchicine has been shown to be of particular interest.[24,25]

5. Discussion and Practical Issues

The animal studies reviewed show that aspirin and NSAIDs may have various deleterious effects in experimental myocarditis. NSAIDs could increase viral virulence, resulting in more severe lesions, as shown in one experimental study on coxsackievirus B4 myocarditis.[7] This conclusion is based on the knowledge that cytopathogenicity is the accepted mechanism for coxsackievirus B4 myocardial damage,[7,26,27] and on the demonstration of higher viral titres in the heart of these coxsackievirus B4-infected mice treated with NSAIDs.[7] This observed enhancement of viral titres in the heart may be related to interferon inhibition after NSAIDs compared with placebo, thus reducing virus clearance.[7] Nevertheless, the authors could not rule out a supplementary direct stimulation of viral replication as previously observed *in vitro* with aspirin.[28]

Apart from this enhancement of virus virulence, other mechanisms for deleterious effect of NSAIDs could involve alterations in immune response after viral invasion. This hypothesis is supported by two animal studies that demonstrated a deleterious effect of ibuprofen[9] aspirin and indomethacin[10] in coxsackievirus B3 myocarditis. In fact, in this model, alterations are attributed to an immunological phenomenon because maximal pathological changes occur far after peak viral titres[27] and antithymocyte may be effective.[10] Although not investigated in these studies, an exaggerated cytotoxic immune response may be suspected, possibly via prostaglandins synthesis inhibition.[9,10] In fact, previous experimental studies demonstrated that prostaglandins decrease the release of interleukin 2,[29] potentiate suppressor factors released by macrophages[30] and suppressor T cells.[31] Another possible deleterious effect involves coronary vasospasm. NSAIDs may promote coronary microvascular spasm and therefore increase the risk of evolution of viral myocarditis to dilated cardiomyopathy.[32,33]

Based on the results of these animal studies, we believe that high doses of aspirin and NSAIDs should be avoided in patients with demonstrated enterovirus myocarditis. However, these recommendations may apply only to a minority of patients. In fact, myocarditis is often suggested from a clinical standpoint in a patient presenting with thoracic chest pain, abnormal ECG, elevated cardiac enzymes, localised or diffuse hypokinesia by echocardiography and normal coronary arteries. However, confirmed diagnosis is rare as endomyocardial biopsies are not routinely performed and histological criteria are seldom met. Moreover, the specific viruses associated with adult myocarditis remain unclear, and the majority of cases are probably not related to enterovirus infection.[34,35] Nevertheless, a possible deleterious effect of aspirin and NSAIDs has been demonstrated in the animal studies reviewed here after coxsackievirus infection and although not demonstrated, similar effects on other viruses are conceivable.

Finally, aspirin and NSAIDs inhibit vasodilator prostaglandin synthesis, and therefore may lead to direct arterial vasoconstriction,[36] or interaction with ACE inhibitors,[37-39] and therefore worsen heart failure.

On the other hand, the effects of these drugs in other inflammatory heart disease should be considered. Indeed, in rheumatic carditis, aspirin has demonstrated its efficacy in lowering valvular injury. However, these results are difficult to extrapolate to viral myocarditis. Moreover, several studies have shown that valvular regurgitation, and not myocarditis, was the cause of congestive heart failure in active rheumatic carditis.[40]

Analysing the effects of anti-inflammatory agents in acute and recurrent pericarditis may be more relevant as pericarditis commonly coexists with myocarditis. There is clear evidence that NSAIDs, including aspirin, are effective in acute pericarditis. However, this may be not sufficient to draw a formal conclusion about the management of patients with active myocarditis, and therapeutic recommendations for pericarditis are difficult do extrapolate to myocarditis.

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Collectively, these data do not support indiscriminate use of NSAIDs and aspirin in the treatment of viral myocarditis and point out a possible deleterious effect.

When patients present with acute pericarditis and only limited myocarditis with preserved left ventricular function, aspirin and NSAIDs may be adequate therapeutic options; however, they should be used with caution during the acute and subacute phases. In contrast, when viral myocarditis is associated with no or limited pericardial effusion, we may recommend avoidance of aspirin and other NSAIDs or great caution and paracetamol (acetaminophen)for analgesia should be preferred.

6. Conclusion

NSAIDs, including aspirin, are often used in the treatment of myocarditis, especially when pericarditis is present. Nevertheless, several experimental studies demonstrate that NSAIDs exacerbate both myocardial inflammation and necrosis and may result in unfavourable outcome when administrated in myocarditis. These effects may be due to decreased viral clearance, exaggerated cytotoxic immune response or coronary microvascular spasm. Furthermore, aspirin and other NSAIDs may be deleterious in chronic heart failure. On the other hand, aspirin and NSAIDs are effective in other inflammatory heart disease, such as rheumatic carditis and acute pericarditis.

Nevertheless, in view of these unfavourable experimental data, and in the absence of controlled trials, we do not recommend indiscriminate treatment with high-dose NSAIDs or aspirin in patients myocarditis where no or minimal pericarditis is present.

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