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Non-Steroidal Anti-Inflammatory Drugs, Acetaminophen and Hypertension

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Summary

Selective- and non-selective non-steroidal anti-inflammatory drugs (NSAIDs) as well as acetaminophen belong to the most widely prescribed therapeutic agents worldwide. Their efficacy in pain relief notwithstanding, the use of NSAIDs is associated with an increased cardiovascular risk, which can be partly attributed to their blood pressure rising potential. Adequately powered placebo-controlled trials specifically evaluating cardiovascular safety of NSAIDs vs. selective COX inhibitors are currently underway. This review summarizes the current knowledge on cardiovascular effects of NSAIDs and acetaminophen and its potential clinical consequences.

Introduction

Non-selective nonsteroidal anti-inflammatory drugs (NSAIDs) are among the most used drugs worldwide. The therapeutic efficacy of these painkillers, however, comes at the cost of certain side effects, gastrointestinal and cardiovascular, in particular.

Because the prolonged use of NSAIDs, and selective cyclooxygenase-2 (COX-2)-inhibitors was shown to be associated with a rise in blood pressure and an increased risk of coronary artery disease and myocardial infarction,[1-3] current guidelines recommend avoiding NSAIDs and COX2-inhibitors in patients with high cardiovascular risk or established coronary artery disease (CAD), if feasible.[4]

Arterial hypertension is a major risk factor for stroke, ischemic heart disease and heart failure,[5] and non-pharmacological and pharmacological antihypertensive therapies[6] [7] have been well documented to reduce morbidity and mortality in hypertension. Since NSAIDs and selective COX inhibitors may worsen blood pressure control,[8, 9] there is ongoing concern of their use in patients with arterial hypertension, particularly in resistant hypertension, where the concurrent use of painkillers including selective and nonselective NSAIDs, as well as acetaminophen should be excluded. This review aims to summarize the current knowledge about the effect of these drugs on blood pressure and cardiovascular outcome.

NSAIDs

Nonselective NSAIDs and COX-2 selective inhibitors increase blood pressure, in both normotensive subjects as well as in patients with hypertension, an effect independent of the presence of antihypertensive treatment.

Two large metaanalysis[8, 9] evaluated the effect of nonselective NSAIDs in persons with normal blood pressure, demonstrating a small increase in mean

arterial pressure with regular use of NSAIDs. The mechanism for the increase in BP is most likely due to their impact on vasoactive endothelium-derived factors, particularly via the inhibition of prostaglandin synthesis, important for the regulation of vascular tone and sodium excretion. Other possible mechanisms underlying the hypertensive effects of NSAIDs are summarized in **Table 1**

The blood pressure raising effect likely translates to higher cardiovascular risk, but this varies according to different types of NSAIDs as demonstrated in several meta-analyses of observational studies[10, 11] demonstrating an higher cardiovascular risk associated with the use of diclofenac, indomethacin and ibuprofen as compared to naproxen.[12, 13] Interestingly, a large cohort study evaluated safety of NSAIDs in 50,000 patients recently hospitalized because of serious coronary heart disease, suggested a superior cardiovascular safety of naproxen compared with diclofenac, ibuprofen, rofecoxib, and celecoxib.[14]

Selective COX2-Inhibitors

Selective COX-2 inhibitors (etodolac, meloxicam, celecoxib, rofecoxib, etoricoxib, valdecoxib and lumiracoxib) were developed to reduce the risk of gastrointestinal side effects (such as symptomatic gastrointestinal ulcers and complications such as bleeding, perforation or gastric outlet obstruction) and to avoid the antiplatelet effect of traditional NSAIDs.

Unfortunately, the gastrointestinal safety benefit of selective COX-2 inhibitors may come at the cost of an increased cardiovascular risk. The first concerns regarding the cardiovascular safety of COX2-inhibitors were related to the VIGOR study.[15] This study, planned to evaluate the upper gastrointestinal side effects of rofecoxib and naproxen in patients with rheumatoid arthritis, showed a significantly higher

incidence of cardiovascular thrombotic events in the group of patients receiving rofecoxib.[16] Remarkably, patients receiving rofecoxib 50 mg showed a five-fold increased risk of myocardial infarction (MI) as compared to the patients receiving naproxen 1000 mg. These observations were confirmed in the APPROVE study[17] designed to evaluate the incidence of adenomatous polyps in patients treated with rofecoxib 25 mg compared to placebo. The results of this study demonstrated a two-fold increase in myocardial infarction risk in patients treated with rofecoxib versus placebo and resulted in the removal of the drug from the market. Similarly, in the Adenoma Prevention with Celecoxib trial[18] an increased cardiovascular risk was found in the patients receiving celecoxib when compared to placebo. It is of note that these trials in colon polyp patients did not include traditional NSAIDs leaving the question unanswered whether these unselective COX-inhibitors would have increased cardiovascular risk as well.

In contrast to APPROVE[17], APC[18] and PreSAP[19] in colon polyp patients, the analysis of the Alzheimer's Disease Anti-inflammatory Prevention Trial (ADAPT)[20] offered the opportunity to assess the effect of a COX-2 inhibitor (celecoxib) versus a traditional NSAID (naproxen) and placebo. While the results of the ADAPT trial was stopped prematurely because of concerns in the aftermath of the publication of the APC trial, ADAPT provides first prospective outcome trial evidence comparing a conventional NSAIDs versus a COX-2 selective agent. Importantly, naproxen did not appear to be safer than celecoxib, but rather showed a worrisome trend towards increased incidence of cardiovascular events.[20]

In the MEDAL trial[21] in more than 30,000 patients with osteoarthritis and rheumatoid arthritis comparing the COX-2 inhibitor etoricoxib to diclofenac, the rate of thrombotic cardiovascular events with etoricoxib was similar to those in patients on diclofenac (even a small trend towards less fatal MI in the etoricoxib group: 6 vs

17; with no difference seen in the incidence of non-fatal MI).

While two head-to-head clinical trials of coxibs versus traditional NSAIDs (PRECISION and SCOT) are currently underway[22, 23] observational studies showed the risk of myocardial infarction associated with the use of rofecoxib (OR 1.32) to be similar to the one of non selective NSAIDs as diclofenac (1.55) and ibuprofen (1.24), once again emphasizing that conventional NSAIDs might be deleterious in this respect as well.[14]

It was suggested that this excess of cerebrovascular events seen with COX-2 inhibitors, especially rofecoxib, could be related to the effects on blood pressure.[16, 24, 25] However, in the MEDAL study[21, 26] the use of etoricoxib was associated with a substantially greater blood pressure increase than diclofenac, but this increase in blood pressure was not related to the increased cardiovascular events in patients with osteoarthritis and rheumatoid arthritis treated with etoricoxib and diclofenac, indicating that other mechanisms than blood pressure alone contribute to the cardiovascular side effects of coxibs and NSAIDs. The so-called “COX-2 hypothesis”, had suggested an increased cardiovascular toxicity of COX-2 inhibitors because of their higher COX-2 selectivity, which results in greater prostacyclin/thromboxane imbalance. Vascular health, however, is not determined by prostanoids alone, but by a variety of other endothelial factors, such as nitric oxide. Interestingly, differences with regard to endothelial function have been proposed to account for potential differences of different COX inhibitors. While rofecoxib does not improve endothelial function[27, 28], celecoxib improves nitric oxide bioavailability and endothelium-dependent vasodilatation and reduces vascular inflammation and oxidative stress in patients with ischemic heart disease, hypertension and rheumatoid arthritis.[29-31]

In a prospective study by Sowers and coworkers[27] the effect of rofecoxib,

celecoxib and naproxen on ambulatory blood pressure in 400 patients with arterial hypertension, diabetes mellitus and osteoarthritis was evaluated. Patients received stable antihypertensive and antidiabetic drugs during the whole study. Rofecoxib, but not celecoxib and naproxen, significantly increased 24-hour systolic blood pressure after 6 weeks of therapy. Other COX-2 inhibitors, like etoricoxib, did also elevate blood pressure,[25] while in the TARGET study ibuprofen (800 mg tid) and naproxen (500 mg bid) were associated with significantly greater changes in systolic blood pressure as compared to lumiracoxib (400 mg once daily).[32]

Available information suggests that very few of any drug classes truly act as a class for structure, pharmacology, mode of action, efficacy and safety. Each individual agent should be therefore evaluated on its merits. Prospective randomized trials with adequate powered and independently run are needed to clarify the association between pain relief drugs and cardiovascular outcomes. The PRECISION – Prospective Randomised Evaluation of Celecoxib Integrated Safety vs. Ibuprofen and Naproxen - trial in more than 20,000 patients with osteoarthritis is currently under way. Until this trial and the ongoing SCOT trial by MacDonald and colleagues are completed, careful risk benefit analysis needs to be undertaken for all these agents with regard to their potential gastrointestinal benefit versus cardiovascular risk.

Until now, all anti-inflammatory drugs, non-selective NSAIDs as well as selective COX-2 inhibitors should be individually evaluated regarding their risk benefit profile.

Aspirin

Aspirin may be considered a special nonselective NSAID, especially as it inhibits prostaglandin synthesis, and thus may therefore affect blood pressure as well.

Two meta-analyses evaluate the effect of aspirin on blood pressure in patients with arterial hypertension. Pope et al[9] included four trials studying the effect of aspirin in 39 hypertensive patients who took at least 1.5 g of aspirin daily (a dose notably much higher than suggested for prevention of CV disease). The authors showed that the use of aspirin was associated with an increase in mean blood pressure ($+0.61 \pm 1.82$ mmHg), an effect, however, not seen anymore after statistical adjustment for salt intake (mean blood pressure -1.76 ± 2.04 mmHg).

These results were similar to those of another meta-analysis[8] of 8 trials evaluating the effect of aspirin on supine blood pressure in 105 patients, where the administration of aspirin (1.5-2 gr/day) did not change blood pressure significantly.

Of note, aspirin at higher doses may reduce the antihypertensive efficacy of angiotensin-converting enzyme (ACE) inhibition by interfering with prostaglandin synthesis. Therefore patients taking higher doses of aspirin may not profit as much from ACE inhibition as other patients.[33]

In the Hypertension Optimal Treatment (HOT) Study[34-36] 18,790 patients with hypertension (mean age 61.5 ± 7.5 years; blood pressure $169 \pm 14 / 105 \pm 3.4$ mmHg) were randomized to receive either aspirin 75 mg or placebo daily in addition to their antihypertensive treatment for a follow-up period of 3.8 years. In this study[36] there were no differences in mean blood pressure achieved between patients randomized to low-dose aspirin or placebo (from 6 months to end of treatment, SBP 141.9 ± 11.7 and 141.3 ± 11.6 mmHg; DBP 83.3 ± 5.3 and 83.0 ± 5.3 mmHg, respectively). Moreover, low-dose ASA did not interfere with the BP-lowering effect of antihypertensive agents, including combinations with ACE inhibitors.

In conclusion the available data suggest that low-dose aspirin, as recommended for middle or high risk patients for prevention of cardiovascular events does not affect blood pressure in patients with arterial hypertension. These conclusions may not

hold true for larger doses of aspirin used for pain relief, or for patients with congestive heart failure.[35]

Acetaminophen and blood pressure

Because of concerns for negative cardiovascular effects of selective and non-selective NSAIDs, acetaminophen has been suggested as a safer alternative for pain reducing and anti-inflammatory therapy in patients with osteoarthritis and comorbid cardiovascular disorders.^[4]

Prospective controlled studies with acetaminophen, however, are scarce, and the results inconsistent.[37] While one study showed a 4-mm Hg increase, two further studies showed no change in blood pressure associated with the use of acetaminophen in patients with hypertension.[38-40] It is of note that these studies were performed in patients with hypertension, not in the high-risk group of patients with established coronary heart disease in whom the use of acetaminophen is recommended by current guidelines.[4]

In 2005 the risk of incident hypertension for women using aspirin, other NSAIDs, and acetaminophen was evaluated in the population included in the Nurses' Health Study I and II.[41] The multivariable adjusted relative risk of incident hypertension for women who took acetaminophen >500 mg per day was increased almost twofold compared with women who did not use acetaminophen.

Two years later, the association between analgesic use and risk of incident hypertension was analyzed in the Health Professionals Follow-up Study's population[42]. Information about the use of acetaminophen, NSAIDs, and aspirin were collected at baseline and after 2 years follow-up in 16,031 male health professionals without a history of hypertension at baseline. This study showed that men who used acetaminophen 6 to 7 days per week compared with nonusers had

an increased relative risk for incident hypertension compared to non-steroidal anti-inflammatory drugs.[42]

In line with these epidemiological data, the results of our recently published prospective placebo-controlled study question the presumed acetaminophen's cardiovascular safety. This study was planned to evaluate the effect of acetaminophen (1g tid for 2 weeks) as compared to placebo on 24-hours blood pressure and endothelial function. In this study we provide evidence that acetaminophen increases ambulatory blood pressure in patients with stable coronary artery disease under stable cardiovascular therapy (Figure 1).[37] Importantly, the observed increase in blood pressure associated with the use of acetaminophen was within the range of the hypertensive effects of traditional NSAIDs, particularly diclofenac and ibuprofen.[43]

As the use of acetaminophen is so prevalent, a hypertensive effect of this drug could be of public health concern. Indeed, in view of the established continuous incremental risk of cardio- and cerebrovascular disease in relation to blood pressure, an increase in blood pressure associated with the use of acetaminophen as observed could further substantially increase the risk of myocardial infarction and stroke, in patients at high cardiovascular risk or established cardio- or cerebrovascular disease in particular.[37, 43]

Concerning the underlying mechanisms, acetaminophen however, is generally considered to be a relatively weak inhibitor of the prostaglandin synthesis[44, 45] compared to traditional NSAIDs. Moreover, the hypertensive effect of acetaminophen could be mediated by such central COX-3 activity or COX-2 inhibition by acetaminophen[46] or by an indirect activation of cannabinoid CB(1) receptors.[47]

Intriguingly, in our study[37] the blood pressure increase induced by acetaminophen was paralleled by an increase, rather than the expected decrease in heart rate indicating a potential central effect of acetaminophen.

Conclusions

The use of selective and unselective NSAIDs as well as acetaminophen, particularly at high doses, is associated with an increase in blood pressure and an excess of cardiovascular risk.

Because of the excess cardiovascular risk associated with pain-relieving drugs, many patients are now being withheld effective pain treatment. This is unethical and from a cardiovascular point of view counterproductive, as pain is increasingly considered as an important cardiovascular risk factor. Indeed, untreated pain increases heart rate, blood pressure and neurohumoral activation that combined with the forced immobilization further aggravates cardiovascular risk, thus potentially outweighing any putative risk of pain-relieving drugs. As such, patients in need of treatment for pain must not be withheld effective (pharmacological or non-pharmacological) pain relieving therapy, but a close follow-up with regard to potential cardiovascular and gastrointestinal side effects is recommended.

Hence, until evidence from the PRECISION and SCOT trial become available, careful risk benefit analysis needs to be undertaken for all pain-relieving agents with regard to their potential gastrointestinal benefit versus their potential cardiovascular risk hazard.

Conventional NSAIDs, including acetaminophen and high-dose aspirin, should be scrutinized as rigorously as COX2 selective inhibitors.

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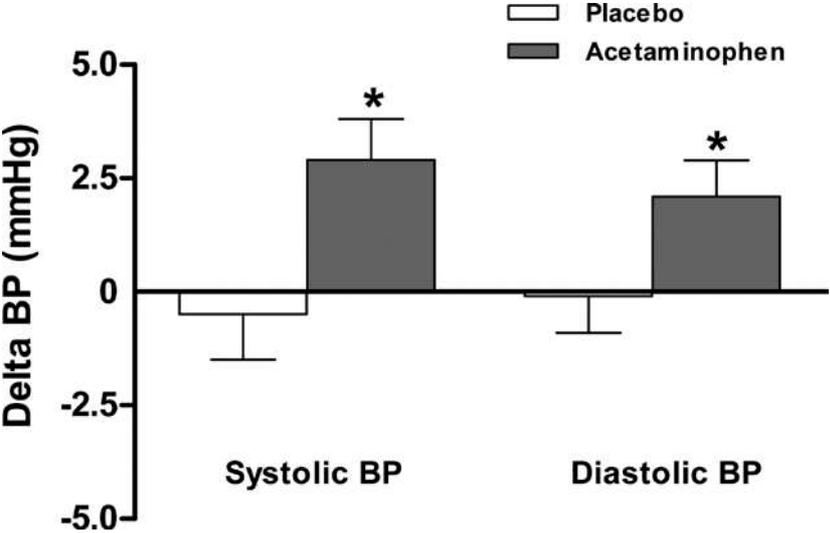
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Table 1 Potential mechanism underlying the blood pressure raising effects of non-steroidal anti-inflammatory drugs

Inhibition of PGE ₂ and PGI ₂ production via the COX enzymes
Greater vasoconstrictive effects from endothelin and increased release of norepinephrine due to reduced PGs production
Decreased natriuresis
Increased production of vasoconstrictive arachidonic acid derived substances
Inhibition of aldosterone glucuronidation

PG: prostaglandin, COX: cyclooxygenase,

Figure 1



Difference in mean 24-hour ambulatory blood pressure (Delta BP, mmHg) between baseline and treatment with acetaminophen and placebo. *: $p < 0.05$ acetaminophen versus placebo. From Sudano I et al.[37]

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