

Detection of intake of nonsteroidal anti-inflammatory drugs in elderly patients with heart failure. How to ask the patient?

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Summary

Principles: Heart failure hospitalisations may be related to non-steroidal anti-inflammatory drug (NSAID) use. Since NSAIDs are usually prescribed by general practitioners or taken without prescription, their use may be largely underestimated. Therefore, we assessed the impact of a focussed analgesic medication history as compared to a usual medication history on detection of NSAID intake in elderly heart failure patients and the potential effect of medical advice on discontinuation of this therapy in a non-controlled study design.

Methods: A structured and stepwise history of analgesic intake (firstly open questioning about medication intake, secondly with a focus on analgesic intake, finally focussing on behaviour in case of pain) was done in 197 elderly heart failure patients taking part in the TIME-CHF study at baseline and up to 3 follow-up visits. All participants were informed about the potential hazardous effects of NSAIDs and alternative analgesic therapy was proposed in case of NSAID intake. Patients were aged 60 years or older with

clinical signs of heart failure NYHA \geq II, elevated NT-BNP, and had been hospitalised due to heart failure within the last year. Details of this study have been described previously.

Results: At baseline, 43 patients (22%) were taking NSAID. Almost half ($n = 19$) taking NSAID reported the use only after specific questioning. Therefore, a focussed analgesic medication history was superior as compared to a usual medication history to detect patients taking NSAIDs (22% vs 12%; $p < 0.001$). After instruction and proposal of alternative analgesic therapy, NSAID intake dropped from 22% to 7% ($p < 0.001$). No risk factor for continuous use was identified.

Conclusions: NSAID use in heart failure patients is relatively common. Specific questioning may help to increase detection of NSAID intake and information on its hazardous effects to decrease NSAID use.

Key words: heart failure; non-steroidal anti-inflammatory drug; medication history

Introduction

Non-steroidal anti-inflammatory drugs (NSAIDs), non-selective and cyclo-oxygenase-2 (COX-2) selective, have a variety of negative renal and cardiovascular effects by inhibiting prostaglandin production [1, 2]. In the kidneys, prostaglandins are involved in the regulation of salt and water balance. Furthermore, prostaglandins are involved in the regulation of the endothelial and platelet function as well as peripheral vascular tone. Thus, the intake of NSAIDs may worsen renal function, promote water and salt retention, increase cardiac afterload and cardiovascular thrombotic events [2–5]. It has been suggested that NSAIDs may be responsible for up to 20% of hospital admissions due to worsening heart failure [6]. Because of the high prevalence of rheumatic or orthopaedic co-morbidities,

the use of these drugs is frequent in geriatric patients, who are at higher risk for NSAID related side effects [7]. Since NSAIDs are often used intermittently, sometimes taken by patients without prescription, or prescribed by other physicians, their use may be largely underestimated and not recognised.

Therefore, we assessed the impact of a focussed analgesic medication history as compared to a usual medication history on detection of NSAID intake in elderly heart failure patients. Furthermore, we evaluated the potential impact of patient instruction for the discontinuation of this potentially hazardous therapy in a subset of the patients included. This aspect of the study was conducted with a non-controlled design.

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Conflict of interest: none of the authors has a conflict of interest.
Ethics: the study has been approved from the local ethic committee.

Methods

Patients

A structured medication history focussed on analgesic intake was done prospectively in all consecutive patients with symptomatic heart failure taking part in the TIME-CHF study and visited in the University Hospital of Basel between July 2004 and September 2006 ($n = 197$). None of the patients included in the TIME-CHF study during this period refused to also participate in this study, but no visits in addition to those planned for TIME-CHF were scheduled for this study. Since TIME-CHF started earlier, some patients included in this study had already been included in TIME-CHF earlier. Thus, not all patients had a complete follow-up with 3 visits (e.g. patients who were included in this study at the last planned follow-up visit of TIME-CHF had no-follow for this study, patients included at second last TIME-CHF visit had only one follow-up visit, etc.). Patients were aged 60 years or older with clinical signs of heart failure NYHA \geq II, elevated NT-BNP, and had been hospitalised due to heart failure within the last year. Patients with acute coronary syndrome within the past 10 days, serum creatinine >220 mmol/l, a life expectancy of less than 3 year because of co-morbidities other than cardiovascular, and severe dementia, were excluded. Details of the TIME-CHF study have been described previously [8]. All patients gave written informed consent and the study was approved by the local Ethics Committee. The investigation conforms to the principles outlined in the Declaration of Helsinki.

Structure of the medication history

Firstly, the patients were asked about medication intake other than those listed on their medication card (usual medication history). Secondly, if no use of analgesics was reported with this first open question or was already listed on the medication card, the patients were specifically asked if they are using analgesics. Finally, in the absence of a positive response, they were asked what they are doing in case of pain.

Contents of the medical advice about analgesic therapy

If NSAID intake was reported, discontinuation of this therapy was recommended and an alternative strategy for pain control was proposed. Independently of NSAIDs intake, all patients were informed about the potential hazardous effects of the NSAIDs in case of heart failure. Paracetamol was recommended as first line medication for pain control (up to 4 g/day). In case of insufficient pain control, a combination with low dose opioids was proposed. A new reassessment of analgesic intake and, if necessary, a medical advice for analgesic therapy was done at each visit during follow-up.

Data collection

Baseline characteristics of the patients were assessed at study entry. The medical history, structured in 3 distinct steps, was done at baseline in all 197 patients. The prevalence of NSAIDs intake and the effect of the specific medical advice for adjustment of analgesic therapy were prospectively assessed over the follow-up period. In 142 patients (72%), structured follow-up was available after one to six months during follow-up visits; two follow-up visits were available in 106 patients (54%) and three in 92 patients (47%).

Statistics

Numerical variables are depicted as means \pm standard deviation (SD). Nominal variables are depicted as frequencies and percentages. Comparison between the groups was done using the student's t-test for numerical variables since all were normally distributed. The Fisher exact test was used for the comparison of nominal variables between groups. Comparison between the usual medication history and the focussed analgesic medication history was tested by Chi-Square test. The McNemar test was used to test changes in analgesic intake over time. Analyses were performed using the commercially available statistical package SPSS version 15.0. All reported p-values were two-sided. A p-value of ≥ 0.05 was considered statistically significant.

Results

Study population

Baseline characteristics are summarised in table 1. The mean age of the 197 patients was almost 80 years; approximately half of the patients were male. Coronary artery disease was the main cause of heart failure, followed by hypertensive heart disease. The majority of patients had a history of hypertension and more than half were affected by chronic renal failure. The global burden of co-morbid conditions was high as only 3% of the patients had no additional co-morbidity and more than half had 3 or more additional co-morbidities.

Analgesic use

At baseline, 43 patients (22%) reported to take either non-selective NSAIDs ($n = 36$), COXibs ($n = 5$), or both ($n = 2$). Thirty-one patients (16%) were taking paracetamol and 2 patients

opioids (1%). Any analgesic was taken by 67 patients (34%) (fig. 1). In NSAID users, a daily intake was reported by almost half of the patients, a regular intake, i.e. 2–3 \times /week, in a minority, and in the other half, intake once a week or a month was reported (fig. 2). NSAIDs were taken without medical prescription in 4 patients; prescribed by general practitioners in 34 patients and by hospital surgeons in 5 patients. Over the entire follow-up, 53 patients (27%) were taking either non-selective NSAIDs ($n = 46$, 23%), COXibs ($n = 5$, 3%), or both ($n = 2$, 1%).

Role of the specific medical history for detection of NSAID intake

Among the 43 NSAID users at baseline, the intake was recognised without specific questions in approximately half of the patients. The other patients had to be specifically asked about anal-

Table 1

Baseline characteristics	Overall (n = 197)	NSAID-users (n = 43)	Non-users (n = 154)	p-value*
Male gender (%)	104 (53)	18 (42)	86 (56)	0.15
Age (mean ± SD)	79±7	78±7	79±7	0.33
LVEF (mean ± SD)	38±13	40±15	37±12	0.31
LVEF >45% (%)	47 (24)	16 (37)	31 (20)	0.03
Cause of heart failure				0.11
CAD (%)	115 (58)	19 (44)	96 (62)	
Dilatative cardiomyopathy (%)	27 (14)	10 (23)	17 (11)	
Hypertensive heart disease (%)	46 (23)	12 (28)	34 (22)	
Other cause (%)	9 (5)	2 (5)	7 (5)	
Risk factors				
Hypertension (%)	146 (74)	37 (86)	109 (70)	0.05
Diabetes mellitus (%)	64 (33)	15 (35)	49 (32)	0.71
Cigarette smoking (%)	96 (49)	22 (51)	74 (48)	0.43
Hypercholesterolaemia (%)	78 (40)	19 (44)	59 (39)	0.44
Family history of CAD (%)	50 (25)	13 (30)	37 (24)	0.43
Co-morbidities				
Prior TIA/stroke (%)	25 (13)	7 (16)	18 (12)	0.44
Peripheral vascular disease (%)	46 (23)	13 (30)	33 (21)	0.23
Chronic pulmonary disease (%)	32 (16)	10 (23)	22 (14)	0.16
Chronic renal failure (%)	110 (56)	26 (60)	84 (55)	0.60
History of cancer (%)	28 (14)	2 (5)	26 (17)	0.05
Arthritis (%)	56 (28)	18 (41)	38 (25)	0.03
Gout (%)	29 (15)	7 (16)	22 (14)	0.42
≥3 co-morbidities (%)	116 (59)	28 (65)	88 (57)	0.49

Abbreviations: LVEF: left ventricular ejection fraction (%); LV: left ventricle; CAD: coronary artery disease; HF: heart failure
 * differences in baseline characteristics has been tested with student's t-test for numerical variables and Fisher exact test for nominal variables

Figure 1

Intake of different kinds of analgesics at baseline and during follow-up.
 ■ Non-selective NSAIDs and COXibs
 ▨ Paracetamol
 □ Opioids

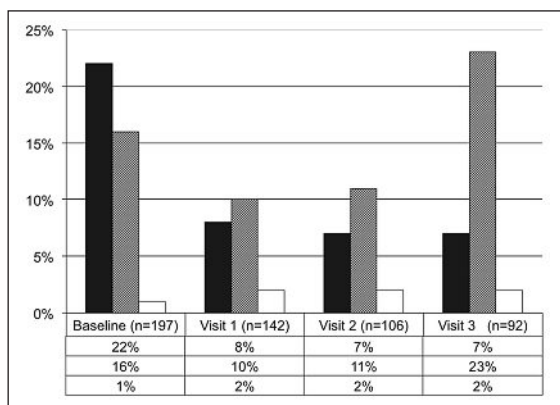
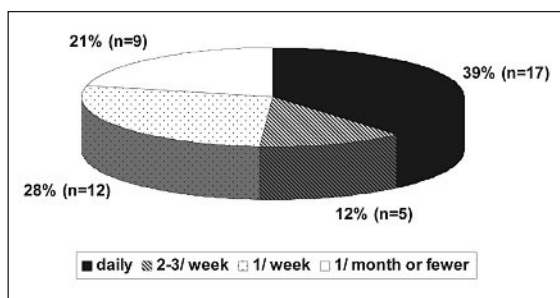


Figure 2

Frequency of NSAID intake.



gesic intake or about their response to pain (fig. 3). Therefore, a focussed analgesic medication history was superior as compared to a usual medication history to detect patients taking NSAIDs (22% vs 12%; p <0.001). We did not find any pre-

dictor for more frank reporting of NSAID intake (data not shown).

Role of medical advice and patients' instruction on discontinuation of NSAID intake

After the instruction about the potential hazardous effect of NSAID intake and proposal of an alternative analgesic regime including paracetamol (up to 4 grams/day) or opioids if necessary, the intake of NSAID therapy was reduced whereas the use of paracetamol increased during long-term follow-up (fig. 1). Among the 142 patients with at least 1 follow-up visit, 31 (22%) were NSAID users. Of these, 26 patients (84%) discontinued NSAIDs at first follow-up, whereas they were newly commenced in another 5 patients. Thus, the intake of NSAIDs decreased significantly from 22% to 7% (p <0.001) in patients with follow-up. We were not able to find any difference in regards of demographic characteristics, cardiovascular diseases or co-morbidities between patients who discontinued or kept taking the NSAID therapy. During long-term follow-up, the intake of NSAIDs remained low, whereas the use of paracetamol (16% vs 23%) and opioids (1% vs. 2%) increased slightly but not significantly compared to baseline (fig. 1). Of note, whilst the number of patients using NSAIDs decreased rapidly after baseline, the use of paracetamol and opioids increased only slowly, suggesting that repeated patients information may be necessary for an effective modification of the analgesic therapy.

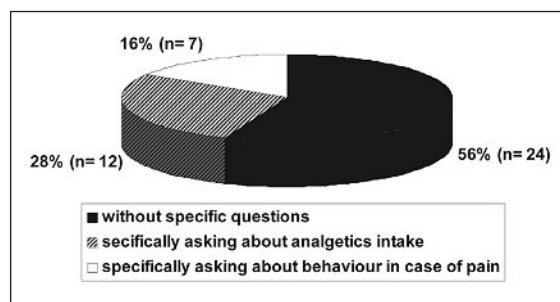
The influence of co-morbidities on the prevalence of NSAID intake

NSAID users were more likely to have arthritis, arterial hypertension, and left ventricular diastolic dysfunction and less likely to have a history of cancer (table 1). Neither were potentially painful co-morbidities apart from arthritis, such as gout, diabetes, peripheral occluding artery disease (POAD), nor were advanced age or gender associated with NSAID intake.

Patients at higher risk for potential cardiovascular or renal NSAID-related side effects, such as patients with documented and symptomatic atherosclerotic disease (coronary artery disease, POA, stroke), marked cardiovascular risk profile or renal dysfunction, were equally exposed to NSAIDs (table 1).

Figure 3

Impact of a specific medication history on NSAID intake detection.



Interpretation

Although generally accepted as contraindicated, NSAIDs are frequently used by heart failure patients. In our collective of elderly patients, more than ¼ were NSAID users and almost half of them would not have been recognised without specific questioning. Notably, the NSAID intake prevalence was equally high in patients with a high risk of NSAID related cardiovascular side effects (e.g. patients with concomitant renal failure). Importantly, most NSAIDs were prescribed by medical doctors, suggesting that not all are aware of the potentially hazardous effects of these drugs in heart failure. Although the use of NSAIDs was more frequent in rheumatic diseases, particularly arthritis, and patients with preserved left-ventricular ejection fraction, other patients often also took these drugs. Thus, independently of co-morbidities, heart failure patients should be asked specifically for NSAID intake.

Importantly, adequate patient instruction was effective for the discontinuation of NSAID intake, although it is impossible to exclude that some patients might not have reported continuation of intake as they knew they should not be taking these drugs. After explanation of the potential hazardous NSAID related cardiovascular effects and proposal of alternative strategies for pain control, based on paracetamol and low-dose opioids, the majority of the patients stopped NSAID intake. On the other hand, some patients never stopped taking NSAIDs despite adequate instruction and others newly start with this therapy during follow-up. In contrast to the use of NSAIDs at baseline, we were not able to identify predictors of continuous intake during follow-up.

There are several reasons, why NSAID use should not be used in heart failure patients. Firstly, the use of NSAIDs is associated with an increased risk of cardiac decompensation [6, 9–11], as it may increase both cardiac pre- and after-load. Additionally, the NSAID-related inhibition of prostaglandin synthesis may promote hydro-saline retention and the rise of the systemic vascular resistance [1, 4, 5, 12]. The risk of cardiac decompensation is especially high within the first days of starting NSAID intake and in case of use of NSAIDs with long half-time pharmacokinetics [6, 11]. Due to rapid vascular and renal responses to the NSAID intake, even the sporadic or intermittent use as in approximately one half of our collective, may be of clinical relevance [12]. Furthermore, the COX-2 enzyme is involved in the regulation of the endothelial and platelet function. Therefore, NSAIDs may increase the cardiovascular risk by activation of the coagulation cascade and promotion of ischaemic events [2]. Finally, NSAIDs have a variety of pharmacological interactions with other cardiovascular therapeutic agents, particularly ACE-inhibitors and coumarins [13–17]. Of note, recent studies have

suggested an inhibitory effect on COX-2 by paracetamol as well, which may explain its negative effects on blood pressure and cardiovascular events [18–20]. Even though, until now, there is no evidence for decompensation of heart failure associated with paracetamol intake and this drug is not mentioned among those to be used with caution in the guidelines for the diagnosis and treatment of chronic heart failure [21]. For this reason, we advised paracetamol as first line analgesic. However, paracetamol should also only be used with caution. Importantly, every analgesic regimen has significant side effects, requiring close control of patients and individual assessment of potential risks and benefit. Additionally, prospective studies investigating the risk of decompensation and other significant adverse effects with different analgesic regimens are required.

The fact that NSAIDs are frequently used only intermittently, in part without medical prescription or prescribed by other physicians, may contribute to the underestimation of the number of patients taking these drugs. Furthermore, it is well known that the assessment of a correct medical history ranks as a major problem in clinical management, particularly in elderly patients [22]. The higher prevalence of cognitive dysfunction and a complex “polypharmacy” may be responsible for the low reliability of drug histories in elderly subjects. Therefore, a specific drug history may be helpful. There are only few studies, which analysed this topic. Lesser *et al.* demonstrated that in adult patients admitted to the emergency department (n = 200), only 48% were able to recall or produce a list of their medications. Only 39% knew the correct intake time of each drug and 24% the exact dosage [23]. Another study showed that a structured and detailed drug history taken before anaesthesia yielded additional information in 59% of the questioned patients compared to the usual medication history [24]. This is surprisingly close to the results of this study, where in approximately one half of the cases, NSAID intake was detected only with specific and focussed questioning. This supports the use of a specific medical history to enhance the identification of NSAID intake in heart failure patients, particularly if they are elderly.

The high prevalence of NSAID users in this high risk population may be an expression of a poor knowledge among physicians and patients about the potential cardiovascular side effects of these drugs. Therefore, exploration for NSAID intake should be done regularly and repetitively in all heart failure patients and special efforts should be taken on patient and physician instruction to increase the awareness of this topic and to reduce the NSAID consumption in heart failure patients.

Study limitations

The absence of a follow-up in all patients and the absence of a direct and objective method to control the actual drug intake are major limitations of this study. The missing complete follow-up for almost half of the patients may have influenced the study results. Therefore, the follow-up data are descriptive only. Furthermore, general practitioners or other doctors, who prescribed the NSAIDs, were not questioned for the precise indication of this treatment and the patient adherence to the proposed analgesic therapy and suggested controls. Still, our data indicate that alter-

native strategies for pain control are successful in a large proportion since after adequate instruction the use of NSAIDs dropped to less than one third. However considering the non-controlled study design, the causal interaction between the patient instruction and the decreased prevalence of NSAIDs intake cannot be proved. For the same reason, we could not investigate the impact of the proposed medication history and patient instruction on outcome. Finally, the number of patients included and the design of the study did not allow investigating the impact of reduced NSAID use on outcome.

Conclusion

Heart failure patients taking NSAID are difficult to identify despite some risk factors for their use. In spite of the potential risk, their use is frequent and largely independent of co-morbidities. Thus, the use of these drugs should be considered in all heart failure patients. Specific analgesic medication history and medical advice were effec-

tive in identifying NSAID intake and reducing their use in heart failure patients. Considering that up to 20% heart failure hospitalisations may be related to NSAID intake, the implementation of the proposed strategy, which is simple to apply in daily practice, may have a substantial impact on patient outcome.

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