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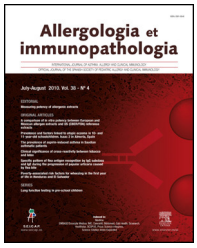

ORIGINAL ARTICLE

The safety of codeine in patients with non-steroidal anti-inflammatory drug hypersensitivity: A preliminary study

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Abstract
Background: Drug provocation testing should be performed before safely prescribing an analgesic for patients that are hypersensitive to non-steroidal anti-inflammatory drugs (NSAIDs). Whether or not the direct histamine releasing effect of codeine renders it useful in NSAID-hypersensitive patients is unknown. This study aimed to determine if codeine could be recommended as a safe treatment option for NSAID-hypersensitive patients without the need for oral drug provocation testing.
Methods: The study included NSAID-hypersensitive patients with and without concurrent asthma, rhinitis, and chronic urticaria that presented to the allergy clinic between 1 January 1991 and 31 December 2010. Patient data were collected from the allergy clinic computer database. Patients challenged with codeine were included in the codeine group. The non-codeine group included those patients that were tested with analgesics other than codeine.
Results: In total, data for 1071 patients, of whom 301 were in the codeine group, were analysed. The reaction rate to codeine was 7.3% and when compared in pairs, the rate was significantly lower than to meloxicam and nimesulide (odds ratios = 0.26–0.31, respectively). The reaction rate to codeine did not differ from that to benzydamine, rofecoxib, and paracetamol. Symptomatic dermographism was associated ($p = 0.009$) with test positivity to any drug.
Conclusions: Although, codeine was among the safest alternative drugs and none of the patients had an anaphylactic reaction to it, thus a challenge with codeine may be considered especially in patients with dermographism. The results of this preliminary study should be confirmed in a prospective study including a control group.

Introduction

Non-steroidal anti-inflammatory drug (NSAID) hypersensitivity can be isolated or associated with chronic urticaria, asthma, or rhinitis.[1] Inhibition of the enzymes of the arachidonic acid cascade, especially cyclooxygenase-1 (COX-1) and to some extent cyclooxygenase-2 (COX-2) is responsible for the reactions attributable to NSAIDs. However, the exact mechanism of NSAID hypersensitivity cannot be reduced to COX-mediated effects alone, and the role of leukotrienes released from mast cells and other leukocytes in response to culprit NSAIDs requires further investigation.[1–3]

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Some patients may have a high degree of hypersensitivity to NSAIDs and 28% of highly NSAID-hypersensitive patients may also be hypersensitive to highly selective COX-2 inhibitors, especially coxibs; however, coxibs are still considered a safe alternative for a considerable number of patients.[2,4,5] The choice of a safe analgesic alternative can be quite restricted in some patients; some patients cannot use any analgesics at all, and adverse reactions can be life-threatening and are feared both by patients and doctors.[6]

Codeine is an opioid analgesic widely prescribed for the relief of pain, cough, and diarrhoea. The mechanism of codeine's analgesic action differs from that of NSAIDs. Whether or not the direct histamine-releasing effect of codeine renders it useful in NSAID-hypersensitive patients is unknown. To the best of our knowledge the literature contains just one letter about codeine as an alternative and safe analgesic in chronic urticaria patients with NSAID hypersensitivity.[7]

Drug provocation testing is a special procedure that can be performed in specialised centres. The present study aimed to determine if codeine could be safely recommended to NSAID-hypersensitive patients without the need for oral drug provocation testing.

Materials and methods

Patients

Data of 1153 patients with suspected NSAID-hypersensitivity with and without concurrent asthma, rhinitis, and chronic urticaria that presented to our clinic between 1 January 1991 and 31 December 2010 were retrospectively reviewed. Patient age, gender, characteristics of NSAID hypersensitivity, underlying diseases (rhinitis, asthma, urticaria, metal allergy, atopic status as defined by skin prick testing), and diagnostic work-up findings were obtained from our allergy clinic computer database. A reliable clinical history of $\geq$ 2 events with the same NSAID or $\geq$ 2 events with unrelated NSAIDs was required for the diagnosis of NSAID hypersensitivity. Suspicious clinical histories were confirmed via oral single-blind aspirin provocation testing.[8] Patients that reported having had severe reactions to aspirin did not undergo oral aspirin challenge. Asthma, rhinitis and chronic urticaria were diagnosed according to international guidelines.[9–11] All patients met the indication criteria for drug provocation testing described by The European Network for Drug Allergy and European Network on Hypersensitivity to Aspirin and Non-Steroidal Anti-Inflammatory Drugs.[8,12]

Patients were tested with codeine, aspirin, paracetamol, nimesulide, meloxicam, Sodium-salicylate (Na-salicylate), rofecoxib, celecoxib, benzydamine, etodolac and nabumetone, and analgesics to be tested in each patient were randomly selected. The study protocol was approved by Hacettepe University Ethical Committee.

Drug provocation tests

Single-blind oral drug provocation tests (DPTs) were performed as single, double, or triple test. Triple testing for analgesics was performed, as previously described.[13–15] Double and triple tests were performed by randomly selecting two or three analgesics the patient was not intolerant to based on history. All the selected drugs were tested during the same day.

Written informed consent was obtained from each patient before each provocation. DPTs were performed at our outpatient clinic under the guidance and direct supervision of an allergy specialist. Emergency equipment was kept ready throughout the observation period. Patients were allowed to have a light breakfast on the test day. Physical examination, peak expiratory flow (PEF) rate, blood pressure, and heart rate were recorded in the beginning and prior to the administration of each drug dose. Tests were performed between 09:00 and 12:00, and observation was completed at 17:00 in patients without a reaction, while patients with a positive challenge were observed until resolution of the reaction. Time interval between doses was 30 min and codeine was administered in 20 mg and 30 mg doses (total: 50 mg). The challenge was terminated when a reaction was detected, and the patient was appropriately treated. A reaction was considered objective, if any one of the following was observed: $\geq$15% drop in the PEF rate, urticaria, angio-oedema, naso-ocular reactions, and anaphylaxis.

Patients challenged with codeine were included in the codeine group. The non-codeine group included those patients that were tested with analgesics other than codeine. As skin prick testing has no utility in the evaluation of opioid hypersensitivity, we used single-blind oral codeine challenge.[16]

Statistical analysis

Statistical analysis was performed using SPSS v.15. Categorical variables are expressed as frequencies, versus mean and standard deviation for continuous variables. The codeine group was compared to the non-codeine group. Patients with positive test results were compared to those with negative test results. Comparisons between groups were made using the chi-square test for categorical variables and Student's *t*-test for continuous variables. Significant factors according to univariate analysis were analysed using logistic regression with adjustment for age and sex to determine independent associations.

Codeine test results were compared with other analgesic test results in pairs; pairs were defined as two drugs with similar results, i.e. both with positive or negative results, and as two drugs with different results, i.e. codeine positive and other analgesic negative, or codeine negative and other analgesic positive (discordant pairs). Patients with a positive history to the tested drug were excluded from the analysis. Matched pairs odds ratios were calculated to compare the rate of codeine test positivity with that of other analgesics, as follows:

matched odds ratio (OR) = the number of pairs with (codeine-positive and other analgesic-negative results)/ number of pairs with (codeine-negative and other analgesic-positive results). Variance estimation and the 95% CI were calculated according to the formula for matched odds ratios. Two-sided p value < 0.05 were considered statistically significant.

Results

The COX-1 mediated mechanism of NSAID hypersensitivity seemed uncertain in 166 (14.4%) of the patients, all of whom underwent oral aspirin challenge. Among these 166 patients, 82 (49.4%) had a negative aspirin challenge and were excluded from further analysis. The study included 1071 patients; 301 in the codeine group, and 770 in the non-codeine. Patient demographics and basic clinical data are shown in Table 1. Nearly half of the patients (42%) had aspirin-exacerbated respiratory disease (AERD) in the codeine group (see also Table 1).

Table 1 Patient characteristics.

Characteristics	Codeine group *n* (%) 301 (100)	Non-codeine group *n* (%) 770 (100)
Females	224 (74.4)	550 (71.4)
Age (years), mean (SD)	39.82 (12.1)	39.83 (12.5)
Concomitant rhinitis	26 (8.7)	114 (14.8)
Concomitant AERD	129 (42.8)	285 (37)
NSAID hypersensitivity only	146 (48.5)	371 (48.2)
+History to Aspirin	164 (54.5)	399 (51.8)
+History to Paracetamol	86 (28.6)	173 (22.5)
Chronic urticaria	66 (21.9)	167 (21.7)
Metal allergy	44 (14.6)	113 (14.7)

Table 2 Patients with a positive reaction to codeine.

No.	Age	Sex	Comorbidity	Reaction to codeine	Can receive (history)	Cannot receive (history)	Can receive (DPT−)	Cannot receive (DPT+)
1	46	F	U	U	None	Asp, Met, Par	Na- salicylate	–
2	43	M	–	U	None	Par, Met, Asp	Mel, Benz	–
3	33	F	AERD	B	None	Met	Mel, Nim	Par, Rof, Na-salicylate (B)
4	48	F	U + AERD	R	Nap	Met, Asp	Par, Benz	Mel (U)
5	42	F	–	A	None	Nap	Par, Nim	–
6	74	F	AERD	B	None	Not known	Nim	–
7	32	F	AERD	U	None	Par, Nap, Met, Asp	Na-salicylate, Mel, Rof	Nim (U)
8	31	F	–	U	Nap, Par	Met, Asp	–	–
9	29	F	AERD	B	None	Nap, Met	Par, Mel	–
10	40	F	AERD + U	B	None	Nap, Met	Par	Na-salicylate (B)
11	61	F	–	U	Par, Met	Asp	Par, Nim	Na-salicylate (U)
12	48	F	–	U	None	Par	Na-salicylate	Mel (U)
13	20	F	U	U	None	Nap, Asp	Par, Rof	Nim, Mel (A)
14	40	F	U + R	U	None	Asp	Par	–
15	30	F	AERD	U	None	Met	Par	Na-salicylate (U)
16	55	F	AERD	B	Par	Asp	Par	–
17	34	F	AERD	U	None	Par, Met	Par	Na-salicylate (U)
18	44	F	R	R	None	Met, Asp	–	–
19	33	F	AERD	A	Par	Nap, Met, Asp	–	Nim (A)
20	27	F	–	U	None	Par	Eto, Cel, Rof	Par (A)
21	25	F	AERD	U	Par	Nap, Asp	Par	Na- salicylate (U)
22	21	F	–	B	None	Par, Met	Nap, Mel, Nim	–

U: urticaria; AERD: aspirin-exacerbated respiratory disease; R: rhinitis; B: bronchospasm; A: angio-oedema; Nap: naproxen; Par: paracetamol; Met: metamizol; Asp: aspirin; Mel: meloxicam; Nim: nimesulide; Benz: benzydamine; Rof: rofecoxib; Cel: celecoxib; Eto: etodolac.

Table 3 Alternative drugs that were tested in the codeine group and patient reaction rates.

Drugs	Codeine group ($n = 301$)	
	Total, *n* (%)	DPT +, *n* (%)
Paracetamol	139 (46.2)	18 (12.3)
Nimesulide	88 (29.2)	19 (21.6)
Meloxicam	146 (48.5)	22 (15.0)
Rofecoxib	61 (20.3)	3 (4.9)
Benzydamine	75 (24.9)	3 (4.0)
Na-salicylate	23 (7.6)	6 (26)
Celecoxib	33 (11)	4 (12)
Etodolac	7 (2.32)	4 (57)
Nabumetone	6 (1.2)	2 (33.3)

Codeine oral provocation test results were positive in 22 (7.3%) patients (21 female and 1 male), of whom 12 (54.4%) had urticaria as a reaction. Additionally, 11 (50%) of these 22 patients had concomitant AERD. None of the reactions observed in these patients was life-threatening. Clinical characteristics of the patients with positive codeine oral provocation test results are shown in Table 2.

In the codeine group 139 (46.2%) patients were also tested with paracetamol and the reaction rate was 12.3% ($n = 18$). The rate of positive reactions to the other NSAIDs tested in the codeine group is shown in Table 3.

Patients in the codeine group with negative DPT results to all the drugs tested were compared to the patients that reacted to codeine and to those with $\geq$1 positive DPT result (Table 4). Symptomatic dermographism and chronic urticaria were strongly associated with a reaction to at least one of the drugs tested ($p = 0.009$ and $p = 0.03$, respectively). However, among the patients that had chronic urticaria were those with symptomatic dermographism, and when the patients with chronic urticaria were analysed separately the significance of chronic urticaria disappeared. Logistic regression analysis with adjustment for age and sex showed that the odds ratio and 95% CI for symptomatic dermographism and chronic urticaria were 2.59 (1.25–5.38) and 1.84 (1.04–3.26), respectively.

The reaction rate in the codeine group to codeine was compared to that of paracetamol, meloxicam, nimesulide, rofecoxib, and benzydamine (comparison to other alternative drugs that were tested is not mentioned because of the limited number of such tests). The reaction rate to codeine was significantly lower than that to meloxicam and nimesulide, whereas it did not differ from that to benzydamine, rofecoxib, and paracetamol (Table 5). The reaction rate to meloxicam did not differ from that to nimesulide (OR: 0.77; 95% CI: 0.41–1.45), although it was higher than that to paracetamol (OR: 2.6; 95% CI: 1.25–5.39) and rofecoxib (OR: 8.33; 95% CI: 2.51–27.6).

Discussion

The literature includes many studies on the safety of various analgesics in NSAID-hypersensitive patients, namely nimesulide, meloxicam, and coxibs.[2–4,17] To the best of our knowledge, the relative safety of various analgesics and codeine in NSAID-hypersensitive patients has not been previously studied. As such, the present study is the first to evaluate the safety of codeine and to compare its safety to that of other relatively safe analgesics in NSAID-hypersensitive patients.

Opiates and their synthetic counterparts provide pain relief and effectively manage disease. The opiate codeine has been used as a positive control for skin prick testing for many years, and is widely prescribed for the relief of pain, cough and diarrhoea; however, hypersensitivity reactions may be a concern when prescribing these drugs. The exact mechanism of such reactions remains unclear, but non-IgE-mediated release of mediators from mast cells and basophils can lead to pseudo-allergic reactions to opioids.[18] Although there are case reports that describe

Table 4 Comparison of patients in the codeine group in which all test results were negative, and those in which any test result was positive or those with a positive codeine test result.[a]

	n (%)	All test results −($n = 209$)	Any test result +($n = 92$)	Codeine test result +($n = 22$)	*p* value[b]	*p* value[c]
Age, mean (SD)	39.8 (12.0)	39.5 (12.2)	40.3 (11.8)	39.8 (13.1)	0.62	0.80
Female sex	224 (74.4)	159 (76.1)	65 (70.7)	21 (95.4)	0.32	0.05
Smoking	87 (28.9)	57 (27.3)	30 (32.6)	4 (18.2)	0.34	0.45
Skin prick test*+	63 (30.0)	45 (30.0)	18 (30.0)	5 (31.3)	1.00	0.91
Rhinosinusitis	116 (38.5)	73 (34.9)	43 (46.7)	12 (54.5)	0.05	0.07
Asthma	129 (42.8)	82 (39.23)	47 (51.08)	11 (50.0)	0.05	0.28
Atopic dermatitis	5 (1.7)	3 (1.4)	2 (2.2)	1 (4.5)	0.64	0.33
Antibiotic allergy	75 (24.9)	57 (27.3)	18 (16.9)	4 (18.2)	0.15	0.35
Metal allergy	44 (14.6)	27 (12.9)	17 (18.5)	4 (18.2)	0.20	0.51
Dermographism	34 (11.3)	17 (8.1)	17 (18.5)	4 (18.2)	0.009	0.12
Chronic urticaria	66 (21.9)	39 (18.7)	27 (29.3)	5 (22.7)	0.03	0.58

[a] Patients in whom any test result was positive included those with a positive codeine result. In all, 10 patients had a positive codeine result only, 12 had a positive codeine and other drug result, and 70 patients had a positive result to any drug, except codeine.
[b] Patients in whom any test result was positive versus those in whom all test results were negative.
[c] Patients with a positive codeine result versus those in whom all test results were negative.
* Skin prick testing was performed in 210 of the patients in the codeine group. Percentages are given based on these 210 cases.

Table 5 Comparison of the codeine reaction rate and that of other test drugs in pairs.

Compared drug	n[a]	Compared Drug DPT + n (%)	Codeine DPT + n (%)	Both Drugs DPT + n (%)	OR[b]	95% CI
Paracetamol	113	11 (9.7)	10 (8.8)	1 (0.9)	0.9	0.36–2.21
Rofecoxib	61	3 (4.9)	4 (6.6)	1 (1.6)	1.5	0.25–8.97
Benzydamine	75	3 (4.0)	2 (2.7)	0 (0)	0.66	0.11–3.98
Nimesulide	88	19 (21.6)	8 (9.1)	3 (3.4)	0.31	0.11–0.85
Meloxicam	146	22 (15.1)	8 (5.5)	3 (2.1)	0.26	0.09–0.7

[a] The number of patients in whom the compared drug and codeine were tested; patients with a positive history for the tested drug were not included in the analysis.
[b] Odds ratio: the positive codeine reaction rate versus that of the test drug, based on matched pairs analysis.

hypersensitivity to codeine, the precise incidence in the general population and in patients with NSAID hypersensitivity is not known.[19,20] Whether or not patients with NSAID hypersensitivity are susceptible to the histamine-releasing properties of codeine is also unknown.

Lack of in vitro studies and the scarcity of centres that perform drug provocation tests often lead to physicians withholding NSAID treatment from patients with urticaria, angio-oedema, and AERD.[21] Although paracetamol in doses not exceeding 1000 mg, coxibs, and codeine are recommended as optimal choices for patients with acute pain and AERD, current guidelines recommend performing a previous challenge.[22,23] The literature contains just one relevant publication; Giavina-Bianchi et al. published a letter describing 25 chronic urticaria patients who reported exacerbation with multiple NSAIDs that underwent oral challenge with 30 mg of codeine without any observed adverse effects.[7] In contrast, Asero reported 28 chronic urticaria patients with NSAID hypersensitivity, of which 18% did not tolerate tramadol.[24] In the present study the reaction rate to codeine was 7.3% and 50% of those that had a reaction had accompanying AERD. The reaction to codeine challenge was urticaria in four (36.4%) of the AERD patients, but had been expected to be rhinitis and/or bronchospasm. The majority of reactions to codeine were urticaria and/or angio-oedema (total, $n = 14$, 63.6%). The reaction rate to codeine among the patients with chronic urticaria was 7.6%. Anaphylactic reaction was not observed in the codeine group, and none of the reactions that were observed required adrenaline injection or hospitalisation. As such, we think that oral codeine challenge can safely be performed on an outpatient basis with close observation.

Symptomatic dermographism was strongly associated with a positive reaction. We previously reported that 16% of patients with NSAID hypersensitivity and bronchial asthma had accompanying dermographism, and that 25% of patients with chronic urticaria had NSAID hypersensitivity.[25,26] Based on those findings, we think that symptomatic dermographism is a risk factor for a positive test result to an alternative analgesic in patients with a history of NSAID hypersensitivity.

Chronic use of opioids is associated with abuse and addiction, tolerance, and hyperalgesia, and although opioid use for acute pain, post surgical pain, and palliative care is accepted in many countries, their use for chronic non-cancer-related pain is still not clear.[27] Prescription of codeine in Turkey is controlled by The Ministry of Health. Among our patients who tolerate codeine as an alternative analgesic, only one is addicted to it.

The present study has some limitations. Aspirin was not tested in all patients to confirm the COX enzyme-mediated mechanism of NSAID hypersensitivity; however, the diagnosis of aspirin hypersensitivity is primarily based on the self-report of a history of adverse reactions to aspirin and/or other NSAIDs.[8] Suspicious clinical histories were always confirmed via aspirin provocation. The rate of hypersensitivity to codeine in the general population is not known and we did not include a control group to examine this issue, but we expect that the rate would be much lower than 7.3%.

In conclusion, the safety of codeine in NSAID-hypersensitive patients is not well known. The present study, in addition to DPT-proven reaction rates to alternative drugs, provides data on their relative reaction rates, as compared to codeine. The results of this study show that the codeine tolerability rate was higher than that to nimesulide and meloxicam, whereas codeine was not safer than benzydamine, rofecoxib, and paracetamol. Although, codeine appeared to be among the safest analgesic alternatives and anaphylaxis as a reaction to codeine was not observed in the present study, challenge with codeine may be considered, especially in patients with dermographism. The results of this preliminary study should be confirmed in a prospective study including a control group.

Ethical disclosures

Patients' data protection. Confidentiality of data. The authors declare that they have followed the protocols of their work centre on the publication of patient data and that all the patients included in the study have received sufficient information and have given their informed consent in writing to participate in that study.

Right to privacy and informed consent. Right to privacy and informed consent. The authors have obtained the informed consent of the patients and/or subjects mentioned in the article. The author for correspondence is in possession of this document.

Protection of human subjects and animals in research. Protection of human and animal subjects. The authors

declare that no experiments were performed on humans or animals for this investigation.

Conflict of interest

The authors declare no conflicts of interest relevant to this study. No financial support for the research was received.

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