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1 **Flupirtine is a safe alternative drug in patients with hypersensitivity to NSAIDs**

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29 Dear Sirs:

30 Adverse drug reactions (ADR) may be dose (type A) or non dose dependent (type B,  
31 hypersensitivity drug reactions/HDR). [1] HDR to nonsteroidal anti-inflammatory drugs  
32 (NSAIDs) are reported to show a prevalence of 0.5-2.5% in the general population. [2]  
33 They most frequently manifest shortly after drug intake in form of immediate type  
34 reactions (i.e. urticaria, angioedema, dyspnea, anaphylaxis); also, non-immediate type  
35 reactions (i.e. maculopapular exanthema) may appear. There is a central role of  
36 arachidonic acid mediators in immediate type hypersensitivity to NSAIDs. In a subset of  
37 patients, the reactions may have an immunologically mediated, allergic background. [2]

38 In patients concerned, there often is a need for safe alternative drugs which leads to  
39 consultation of allergologists. Cross-intolerance may appear even to non-chemically  
40 related preparations. [3] Most patients with history of hypersensitivity to selected NSAIDs,  
41 tolerate COX-2 inhibitors [4], of which the use – as well as the long term use of other  
42 NSAIDs – is limited, because of possible cardio- and cerebrovascular effects. [5]

43 Flupirtine, a non-opiate centrally acting analgesic of the aminopyridine type (dosage orally  
44 3x100-200mg/day; AWD.pharma GmbH&Co.KG, Radebeul, Germany), constitutes a  
45 unique class within the group of NSAIDs and activates Kv7 (KCNQ/M) potassium  
46 channels. [6] Its muscle relaxant properties make it popular for orthopaedic use but it is  
47 also used for other pain conditions or in neurodegenerative syndromes (i.e. multiple  
48 sclerosis). [6] Antiparkinsonian and other motor effects relying on its NMDA-antagonistic  
49 effects were demonstrated. [7] Most frequent ADR in flupirtine treated patients (n=110; 3x  
50 100mg/day) were vertigo (13%) and nausea (9%), but rates of these ADR were  
51 significantly lower than in a control group treated with tramadol (n=110) [8]. There are no  
52 studies on its long term cerebro- or cardiovascular effects. [9]

53 As flupirtine seems to be an interesting alternative drug in patients with history of HDR to  
54 NSAIDs, we wanted to assess its tolerability with regard to hypersensitivity reactions in  
55 this group of patients.

56 A retrospective medical chart review involved all patients who had diagnostic work up  
57 including single blind placebo controlled oral provocation test (SB-OPT) because of  
58 history of HDR to NSAIDs in our University Department for Dermatology and Allergology  
59 in 2006-7. All patients underwent allergological skin tests and evaluation of serum tryptase  
60 to exclude underlying systemic mastocytosis favoring immediate type reactions. SB-OPT  
61 started with 12.5% of one drug dose and was increased every 30-60 minutes (25%, 50%,  
62 100%; i.e. in flupirtine 12.5mg, 25mg, 50mg, 100mg).

63 The drugs tested were chosen according to (i) their analgesic potency, (ii) the choice of  
64 the referring doctor and (iii) the eliciting drug at previous HDR with regard to possible  
65 cross reactions. Flupirtine was the most frequently applied alternative drug at SB-OPT (in  
66 83% of 70 patients; see all drugs applied in table 1). SB-OPT elicited mild nausea in three  
67 patients after intake of tramadol (known pharmacological reaction). ADR classified as  
68 being of hypersensitivity origin were noticed in 6/149 SB-OPT with an alternative and in  
69 1/6 SB-OPT with the suspicious drug.

70 Within 4 to 34 months (median 13) after SB-OPT patients were contacted for a  
71 standardized interview, considering: (1) any use of tested drug since last SB-OPT, (2)  
72 reason for use, if any, (3) tolerance and (4) efficiency.

73 70 patients (58 female, 12 male; age at OPT 52 years, range 17-80) had reported on  
74 history of 131 HDR (n=104 immediate type, n=25 non-immediate type, n=2 unclear;  
75 median age of at HDR 49 years, range 12-80). The median interval between HDR and  
76 SB-OPT was 12 months (range 1 – 120). The drugs suspicious for eliciting HDRs (more  
77 than one drug in 37/70; 53%) were: acetylic salicylic acid/ASA (n=29; 22.1%), ibuprofen  
78 (n=25;19.1%), acetaminophen (n=16; 4.6%), diclophenac (n=16; 4.6%), metamizol (n=15;  
79 4.3%), others (n=30; 22.9%). Skin testing and serum tryptase levels (ruling out underlying  
80 mastocytosis in immediate type reactions) were of no avail.

81 38/70 patients (63.3%) responded to the interview, of whom (1) 25/38 (65.8%) reported  
82 new drug intake of any of the tested drugs tolerated at SB-OPT because of the following  
83 31 events (2): bone/muscle pain (15/31, 48.3%), tooth pain (6/31;19.4%), headache

84 (5/31;16%), flu/others (5/31, 16%). In those patients, flupirtine (9/31, 29%), was taken  
85 exclusively because of musculoskeletal pain. The following other drugs were taken:  
86 acetaminophen (9/31, 29%), COX-2 inhibitors (5/31, 16%) and other NSAIDs (5/31; 16%),  
87 opioid analoga (3/31;10%). No new hypersensitivity reaction (3) was noticed in any of the  
88 patients to any of the drugs. Analgesic efficacy (4) was judged as being sufficient in 23/31  
89 (74%) events, and in all patients having received flupirtine.

90 In summary, SB-OPT led to identification of safe alternative drugs in patients with history  
91 of hypersensitivity to NSAIDs. The good tolerability of flupirtine in this group of patients  
92 may as well be explained by its lacking effect on COX-inhibition as by a presumed less  
93 immunogenic effect. According to our data, flupirtine should be taken into consideration as  
94 an alternative drug in patients with hypersensitivitiy to NSAIDs suffering from moderate to  
95 severe pain, especially of the musculoskeletal system. Further investigations are required  
96 to confirm our data and should also focus on the question if flupirtine has a superior drug  
97 profile to other NSAIDs regarding cerebro-/cardiovascular and renal effects.

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132 Legend to the table:

133 Results of single blind oral provocation tests in 70 patients with history of

134 hypersensitivity reactions to NSAIDs

135 Table 1

	SB-OPT (n)	SB-OPT with suspected drug (n)	Hypersensitivity reaction at SB-OPT (n)
Total number of patients (n)	70	6	6 of which only in one the suspicious drug was tested
Total number of procedures (n)	155	6	6
Acetaminophen	18 (12% <sup>2</sup> , 26% <sup>3</sup> )	4	paresthesia of tongue n=1 (suspicious drug)
<b>Flupirtine</b>	<b>58 (37%<sup>2</sup>, 83%<sup>3</sup>)</b>	-	<b>none</b>
COX-2 Inhibitor	26 (17% <sup>2</sup> , 37% <sup>3</sup> )	-	Celecoxib leading to erythema n=2, urticaria n=1
Other NSAIDs <sup>1</sup>	18 (12% <sup>2</sup> , 26% <sup>3</sup> )	2	ASA leading to dyspnea n= 1
Opioid analoga	35 (23% <sup>2</sup> , 50% <sup>3</sup> )	-	Tramadol leading to erythema n= 1

136 SB-OPT-Single blind oral provocation test; <sup>1</sup> other NSAIDs: Diclofenac, Metamizol, Ibuprofen, Acetylic salicylic acid/ASA, <sup>2</sup>percentages are  
137 calculated in relation to total number of events, <sup>3</sup> percentages are calculated in relation to total number of patients, each drug was tested only once  
138 in one patient)

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