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Pharmacokinetics of Indomethacin in Chronic Migraine Patients after Withdrawal from the Overused Combination of Indomethacin, Prochlorperazine and Caffeine

Anna Ferrari[1,*], Diego Pinetti[1], Daniela Gallesi[1], Alfio Bertolini[1], Grazia Sances[2], Emilio Sternieri[1]

[1]Division of Toxicology and Clinical Pharmacology, Headache and Drug Abuse Inter-Department Research Centre, University of Modena and Reggio Emilia, Modena, Italy
[2]Headache Unit, IRCCS C. Mondino, University of Pavia, Pavia, Italy
*Corresponding author: anna.ferrari@unimore.it

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Abstract Indomethacin, in combination with prochlorperazine and caffeine (IPC), is often overused by migraine patients who develop medication-overuse headache. Indomethacin clearance is slower in chronic migraine patients overusing IPC combination than in migraine patients only occasionally taking it. The objective of this study was to verify if indomethacin reduced clearance reverted to normal values after withdrawal of the overused IPC combination. Therefore, we repeated the study of indomethacin pharmacokinetics in 9 female chronic migraine patients after 3 months from inpatient withdrawal treatment from IPC combination overuse. The IPC combination (indomethacin 50 mg, prochlorperazine 8 mg, caffeine 150 mg) habitually taken was administered by rectal route to each patient. Blood samples were drawn before dosing and at the following post-dose times: 0.5, 1, 2, 3, 4, and 6 h. Indomethacin concentrations were measured by HPLC method. We found that 4 of 9 patients (group A) who were still overusing the combination and suffering from daily headache had still high indomethacin concentrations after 6 hours, therefore showing a slow elimination of the drug. Instead, in the 5 patients (group B) who had discontinued overuse of IPC combination after withdrawal treatment, indomethacin concentrations after 6 hours were significantly lower than those measured before withdrawal ($P < 0.05$, Student's *t*-test for paired data), and also than those observed in group A ($P < 0.05$, ANOVA and Newman-Keuls'test). Hence, by suspending IPC abuse indomethacin clearance reverts to normal values and this is associated with an improvement of migraine. Instead, the higher plasma levels of indomethacin in patients who continue IPC abuse do not solve migraine and might support medication-overuse headache.

Keywords: *indomethacin, pharmacokinetics, chronic migraine, medication-overuse headache, drug combinations*

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1. Introduction

Indomethacin, an indole acetic acid derivative [1-(P-chlorbenzoyl)-5-methoxy-2 methylindole-3-acetic acid], structurally related to serotonin, is a potent non-selective inhibitor of cyclooxygenases, with central analgesic properties [1]. In Italy, it is one of the most used drugs for acute headache treatment, in a fixed combination with prochlorperazine and caffeine, which is available on the market in oral (tablets: indomethacin 25 mg, prochlorperazine 2 mg, caffeine 75 mg) and rectal (suppositories: indomethacin 50 mg, prochlorperazine 8 mg, caffeine 150 mg; mild suppositories: indomethacin 25 mg, prochlorperazine 4 mg, caffeine 75 mg) formulations. This combination (IPC) is indicated for acute headache treatment, according to the guidelines by the Italian Society for the Study of Headaches [2], at the third level of recommendation, when triptans, which are first recommended, result ineffective against nausea and vomiting. It is instead not recommended if migraine attacks have a medium/high frequency, because of the potential risk of overuse [2]. In spite of this, a large number of chronic daily headache patients who overuse IPC combination are referred to the Headache Centre of the University of Modena, Italy [3]. These patients reported that this medication was initially an extraordinarily effective antimigraine drug, but then, year by year, they had to increase daily dosages and intake frequency gradually, sometimes up to true abuse, because of a gradual reduction in its effectiveness (both in the intensity and duration of the effect). At the same time,

their headache turned into chronic daily headache. We supposed that this gradual reduction in the effectiveness of IPC combination was related to an accelerated elimination of its components and, consequently, to plasma levels insufficient for therapeutic effects. We therefore studied the pharmacokinetics of each component of this medication in migraine patients occasionally taking it and in chronic migraine patients overusing it [4]. Contrary to our hypothesis, the elimination of the components of IPC combination is not accelerated in overusing subjects: indomethacin clearance is instead reduced and its half-life longer in chronic migraine patients overusing this combination than in episodic migraine patients only occasionally taking it. On the other hand, there are no significant differences in the kinetics of caffeine and prochlorperazine between subjects occasionally taking IPC combination and patients overusing it [4]. These results suggest that in chronic migraine patients overusing IPC combination, just indomethacin high concentrations could have sustained and perpetuated medication-overuse headache, causing rebound headache.

The objective of our study was therefore to verify if the reduced systemic indomethacin clearance found in patients overusing IPC combination disappeared once overuse was discontinued. Hence, we studied again the kinetics of indomethacin in the same patients who had been previously studied, 3 months after withdrawal treatment from overuse, and we analysed if there were differences in the kinetics of indomethacin, following IPC combination administration, between patients who had steadily discontinued overuse, with a clear improvement in their headache, and those who had instead relapsed into overuse and whose headache was still chronic.

2. Patients and Methods

2.1. Subjects

We studied again the kinetics of indomethacin after giving IPC combination to 9 female subjects (all Caucasian) suffering from chronic migraine and medication-overuse headache according to ICDH-II classification criteria [5], 3 months after withdrawal treatment from overuse (7-10 days of hospitalization with standardized treatment; at discharge, a prophylactic treatment with amitriptyline in the oral dosage of 30-60 mg/day was prescribed to every patient). Before withdrawal treatment, all these patients had only been overusing IPC combination for at least one year, taking daily one or more suppositories of this medication, containing indomethacin 50 mg, prochlorperazine 8 mg, and caffeine 150 mg. In these patients, the diagnosis of headache at the onset was migraine without aura. In time, their migraine became chronic. In each patient, the kinetics of indomethacin had already been studied before withdrawal treatment [4]. At the follow-up, 3 months later, 4 of these patients (group A) had relapsed into daily use of one or more suppositories of IPC combination and still suffered from daily headache, while 5 patients (group B) had a reduced headache frequency and were taking IPC combination only occasionally and with full effectiveness (Table 1). The frequency of drug intake was recorded in the diaries that patients kept until the follow-up. Informed consent was obtained from each subject, following the description of the study's procedures and objectives. The study was approved by the ethical committees of Modena and Pavia and it was conducted in compliance with the declaration of Helsinki, latest version.

Table 1. Patients' characteristics (mean+S.D.; range in brackets)

	Group A (n=4)		Group B (n=5)	
Characteristic	Before withdrawal from the overused IPC combination	Three months after withdrawal	Before withdrawal from the overused IPC combination	Three months after withdrawal
Age, years	45.3 ± 12.5 (31 - 52)		51.1 + 7.3 (41 - 53)	
Weight, kg	61.0 ± 4.1 (53 - 64)	59.5 ± 3.5 (50 - 63)	66.4 ± 6.8 (59 - 83)	64.4 ± 6.2 (57 - 74)
Years of use	6.7 ± 5.7 (1 - 20)		6.5 ± 6.7 (1 - 19)	
N° of doses/month	161.75 ± 46.09 a (120 - 224)	108.75 ± 17.91 b (84 - 125)§	76.40 ± 25.86 c (56 - 112)	7.4 (5 - 9)
Headache frequency, days/month	daily	daily	daily	6 + 1.58 (5 - 9)

[a] $P < 0.05$ vs. after withdrawal, group B before and after withdrawal (ANOVA and Newman-Keuls'test)
[b] $P < 0.05$ vs. group B after withdrawal (ANOVA and Newman-Keuls'test)
[c] $P < 0.05$ vs. group B after withdrawal (ANOVA and Newman-Keuls'test)

No patient was a smoker, had kidney or liver dysfunction or was taking drugs able of causing drug-drug interactions with the components of IPC combination. In particular, no patient was taking other drugs known as inducers or inhibitors of cytochrome P450 2C9 (CYP2C9) [6]. All patients complained of gastrointestinal troubles, two patients of group A were taking lansoprazole 30 mg/day, and three (one in group A and two in group B) were taking antihypertensive agents (lisinopril, candesartan, amiloride/hydrochlorothiazide). At the time of the experimental session, patients did not present acute diseases, according to histories and physical and laboratory evaluations (blood chemistry, blood count, urine).

2.2. Procedures

Experimental sessions were conducted at the in-patient ward of the Headache Centres of Modena and Pavia University Hospitals. Under medical surveillance, the IPC combination habitually taken (indomethacin 50 mg, prochlorperazine 8 mg, and caffeine 150 mg) was rectally administered to each patient, at 7 AM, after overnight fasting. Patients were maintained in supine position for the subsequent 30 minutes. Venous blood samples were drawn from an indwelling cannula into heparinized tubes, before dosing and at the following post-dose times: 0.5, 1.0, 1.5, 2.0, 3.0, 4.0, and 6.0 hours. Samples were immediately centrifuged, and kept at –20° C until the time

of assay. Indomethacin concentrations were measured on deproteinized serum, by means of a slightly modified reversed-phase high-pressure liquid chromatographic (HPLC) method [7]. A detailed description of the method has been previously published [4].

2.3. Analysis of the Data and Statistical Evaluation

Pharmacokinetic parameters were calculated by means of the P K Solutions 2.0 program (Non compartmental pharmacokinetics data analysis, Summit Research Services, Montrose, CO, USA). The following parameters were determined for indomethacin: $C_{max,}$ peak plasma concentration (maximum observed plasma concentration) (μg/ml); T_{max}, time to peak plasma concentration (hr); $t_{1/2,}$ half-life clearance**,** time for concentration to diminish by one-half (hr); MRT, mean residence time, time for 63.2% of administered dose to be eliminated (hr); $AUC_{0\rightarrow t}$, cumulative area under the plasma concentration time curve, only using observed data points (μg-hr/ml); $AUC_{0\rightarrow\infty}$, total AUC, computed using data points extrapolated to infinity (μg-hr/ml); Vd, apparent volume of distribution, based on AUC_{∞} and clearance rate normalized by weight (ml/Kg); Cl, systemic clearance, based on AUC_{∞} normalized by weight (ml/hr/Kg).

All data were expressed as mean ± S.D. When appropriate, Student's *t*-test for paired and unpaired data, and ANOVA, followed by Newman-Keuls post hoc testing, were performed to assess statistical difference between the groups. A level of $P < 0.05$ was considered significant [8].

3. Results

The plasma time course of indomethacin levels, following administration of one IPC suppository (Figure 1), had a similar pattern in the same group of patients, even when repeated after 3 months, in spite of the wide inter-individuals variations observed above all in group A, and in the first 2 hours. After withdrawal treatment from overuse of IPC combination, plasma indomethacin levels had decreased at all times of the curve, both in group A and B, but only patients in group B, who had steadily discontinued overuse and whose headache had consequently improved, did not have measurable concentrations at baseline. Patients in group A, who were still overusing the combination (even if less than before) and suffering from daily headache, had still high indomethacin concentrations (even if much lower than before) after 6 hours, therefore showing a slow elimination of the drug. In patients of group B, who had discontinued overuse of IPC combination after withdrawal treatment, indomethacin concentrations after 6 hours were significantly lower than those measured before withdrawal ($P < 0.05$, Student's *t*-test for paired data) and also than those observed in group A ($P < 0.05$, ANOVA and Newman-Keuls'test).

Before withdrawal treatment from overuse of IPC combination, pharmacokinetic parameters of indomethacin (Table 2) did not show statistically significant differences between groups A and B (Student's *t*-test for unpaired data). After withdrawal from overuse, the kinetics of indomethacin was still unchanged in patients of group A, who at the 3-months follow-up resulted to have relapsed into overuse of IPC combination (Student's *t*-test for paired data). Instead, patients of group B, whose headache had improved after discontinuing overuse, had faster indomethacin elimination than before ($P < 0.05$, Student's *t*-test for paired data) and also faster clearance than patients of group A, who were still overusing the combination ($P < 0.05$, ANOVA and Newman-Keuls'test), as it was shown by the statistically significant increase of clearance and by the reduction, even if not statistically significant, in $t_{1/2}$, $AUC_{0\text{-}t}$, and $AUC_{0\text{-}\infty}$, in the absence of T_{max} and Vd.

Table 2. Pharmacokinetic parameters (estimated by non-compartmental method) of indomethacin following rectal administration of IPC combination (indomethacin 50 mg, prochlorperazine 8 mg, caffeine 150 mg) in 9 chronic migraine patients before and after 3 months from in-patient withdrawal from the overused IPC combination (Group A: patients who relapsed into overuse; Group B: patients who steadily discontinued overuse)

	Group A (n=4)		Group B (n=5)	
Parameter (mean+S.D.)	Before withdrawal from the overused IPC combination	Three months after withdrawal	Before withdrawal from the overused IPC combination	Three months after withdrawal
Dosage μg/Kg	839.7 ± 57.25	842.5 ± 49.7	759.15 ± 74.87	782.0 ± 72.70
Ct zero, μg	1.79 ± 1.62	0.51 ± 0.15	0.51 ± 0.29	0.00 a b
Tmax hr	2.17 ± 1.18	1.75 ± 0.50	1.80 ± 0.45	1.40 ± 0.55
Cmax μg/ml	3.78 ± 1.70	4.53 ± 2.84	2.42 ± 0.85	1.56 ± 0.65
t1/2 hr	3.43 ± 2.44	2.35 ± 0.41	2.74 ± 0.98	1.45 ± 0.34
MRT hr	5.48 ± 2.52	3.98 ± 0.39	5.58 ± 1.91	3.04 ± 0.29 a
AUC0-t μg-hr/ml	17.10 ± 11.21	14.18 ± 6.75	10.52 ± 6.52	4.96 ± 2.19
AUC0-∞ μg-hr/ml	20.75 ± 12.83	17.13 ± 7.95	13.02 ± 6.62	5.36 ± 2.36
Vd ml/Kg	201.8 ± 73.26	222.75 ± 121.06	247.96 ± 86.65	240.12 ± 75.11
Cl ml/hr/Kg	51.72 ± 25.41	70.76 ± 39.92	64.05 ± 30.16	123.98 ± 39.91 a c

[a] $P < 0.05$ vs before (Student's *t*-test for paired data)
[b] $P < 0.05$ vs group A before (ANOVA and Newman-Keuls'test)
[c] $P < 0.05$ vs group B before, group A before and after (ANOVA and Newman-Keuls' test)

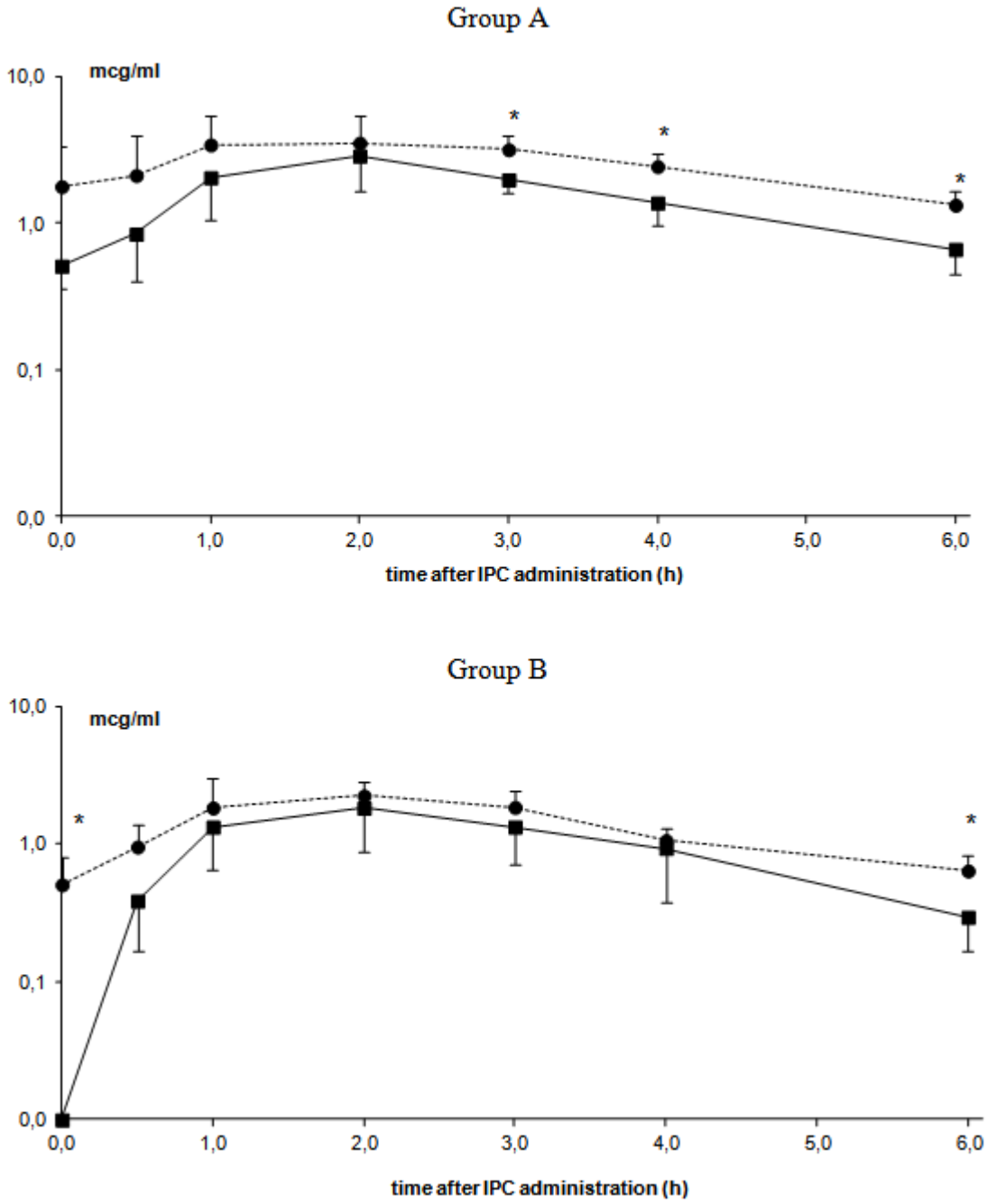

Figure 1. Plasma levels (mean ± S. D.) of indomethacin in patients of group A (upper panel) and of group B (bottom panel) before (●) and after (■) withdrawal from the overused IPC combination (statistical differences between mean levels: * $P < 0.05$, Student's *t*-test for paired data)

4. Discussion

Delayed indomethacin elimination, that we observed in patients with chronic migraine overusing IPC combination (containing indomethacin 50 mg, prochlorperazine 8 mg, and caffeine 150 mg), was reversible once overuse was discontinued. Indomethacin clearance (Table 2) increased significantly in these patients (group B), passing from 64.05 ± 30.16 ml/hr/Kg during overuse to 123.98 ± 39.91 ml/hr/Kg after steadily discontinuing overuse of IPC combination. All pharmacokinetic parameters of indomethacin, calculated in subjects in group B after withdrawal from overuse of IPC combination, were consistent with published data obtained following administration of therapeutic dosages of indomethacin to healthy volunteers and rheumatic patients (T_{max} 1 to 4 hours, $t_{1/2}$ 2-11 hours, Cl 0.44 to 109 ml/min/kg, Vd 411-450 ml/kg) [9-13] and comparable to those calculated in migraine patients only occasionally taking IPC combination (T_{max} 1.62 ± 0.7 hours, $t_{1/2}$ 1.27 ± 0.4 hours, Cl 130.90 ± 30.2 ml/min/kg, Vd 235.31 ± 69.3 ml/Kg) [4]. Notably, the normalization of the kinetics of indomethacin in patients of group B, who had definitively suspended overuse (Table 1), was also associated with an improvement in migraine, which turned from daily into occasional, reducing its mean frequency to 6 ± 1.58 days per month. The high and sustained levels of indomethacin (Figure 1), observed in patients of group A, both at baseline (as likely residual of previous assumptions) and 6 hours after IPC administration, were instead associated with overuse and chronic migraine. This pattern of plasma indomethacin concentrations was certainly the consequence of several and repeated daily intakes of IPC

combination, since repeated doses of indomethacin tend to accumulate [14]. Moreover, indomethacin undergoes enterohepatic circulation [15]. In patients overusing IPC combination, a higher and continual enterohepatic circulation could have caused reduced indomethacin clearance. This modified disposition of indomethacin did not depend on metabolic characteristics of the patients studied. No patient, neither in group A nor B, suffered from hepatic or kidney failure, or was taking medications capable of inducing or inhibiting CYP2C9-mediated metabolism of indomethacin [16].

Since a relationship between indomethacin plasma levels and degree of pharmacological effect has been reported [17], chronic migraine patients overusing IPC combinations should steadily be free from headache. Instead, these patients said to have had to take more and more IPC combinations over time, because this medication had become less and less effective against their migraine. Some patients of group A took up to 8 doses a day of IPC combination, that is, 400 mg/day of indomethacin, the double of the maximal therapeutic daily dosage of 200 mg. This apparently paradoxical effect of the overuse of IPC combination in migraine treatment (higher concentrations of indomethacin associated with reduced effectiveness) can be explained considering the unique features of indomethacin, different from those of the other NSAIDs. Indomethacin causes cerebral vasoconstriction, which is rapid in onset and resolution, closely related to plasma concentrations [18,19,20]. The mechanism of vasoconstriction induced by indomethacin is not fully understood. The other NSAIDs have been shown to have no effects on cerebral blood flow [21]. Moreover, the most common dose-dependent CNS adverse reaction to indomethacin is headache. It has been attributed to compensatory vasodilatation that follows vasoconstriction [22]. In some cases, especially in the morning, headache may be so severe to require discontinuation of the drug [23]. These peculiar pharmacological properties are similar to those of ergotamine [24] and could support the ability of indomethacin to induce rebound headache, headache as a toxic reaction, and, as a consequence, medication-overuse headache. In addition, caffeine contained in the IPC combination can increase the antimigraine effect of indomethacin, potentiating vasoconstriction but, at the same time, it may contribute to the risk of inducing headache as a symptom of toxicity and withdrawal [25].

Ergotamine, triptans, and also indomethacin share some characteristics, such as structural similarity to serotonin, the capacity of blocking neurogenic inflammation in meningeal tissue, and vasoconstrictive properties, even if with a different degree of selectivity for blood vessels [26,27,28]. Furthermore, indomethacin is the only NSAID reported to be effective in the treatment of cluster headache attacks [29,30,31,32], like ergotamine and sumatriptan. We think that migraine patients overusing IPC combination can develop a state of physical dependency on this medication. The condition looks like ergotamine dependency, which is characterized by an irresistible and predictable daily use of ergotamine as the only mean of alleviating rebound headache [24].

Our results have the limitation of having been obtained in a small number of patients, which, however, represent a homogeneous group for demographic characteristics, kind of headache, and overused medication. We did not study the kinetics of all three components of IPC combination, because the disposition of caffeine and prochlorperazine is unchanged in migraine patients overusing IPC combination [4].

The present is one of the few studies on the kinetics of an acute migraine medication during overuse, apart from those on ergotamine [33,34]. In the same way as unrestricted use of ergotamine is often associated with ergotamine medication-overuse headache [5], frequent use of IPC combination can lead to reduced effect and dosage escalation in trying to control headache. Hence, plasma indomethacin levels which stayed higher than those in the therapeutic range for a long time [proposed therapeutic concentration is 1 μg/ml [14] did not resolve the headache but, on the contrary, might have sustained medication-overuse headache. On the other hand, in patients who only occasionally took IPC combination after withdrawal treatment, headache improved, the effectiveness of this medication was restored, indomethacin levels were lower and its clearance reverted to normal.

IPC combination is a widely used drug for acute treatment of migraine attacks [35]. In our opinion, it is important to warn patients using this medication, and physicians prescribing it, that, even if IPC combination is composed of low dosages of three active principles, overuse of this medication might induce rebound headache and sustain medication-overuse headache.

Declaration of Interest

The authors have no competing interests

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