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Effect of overuse of the antimigraine combination of indomethacin, prochlorperazine and caffeine (IPC) on the disposition of its components in chronic headache patients

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Abstract

Background: The combination of indomethacin, prochlorperazine and caffeine (IPC) is one of the most utilized formulations for the treatment of migraine attacks in Italy. Several patients suffering from chronic headache overuse this symptomatic medication in the attempt to control their headache.

Objective: To verify whether overuse of IPC combination by chronic headache patients is associated with modified disposition of its components.

Methods: We studied indomethacin, prochlorperazine, and caffeine disposition in 34 female subjects suffering from primary headaches, subdivided into four groups: eight migraine patients occasionally using IPC combination suppositories—group 1; nine patients with chronic headache and probable medication-overuse headache, daily taking one or more suppositories of the IPC combination—group 2; 11 migraine patients occasionally using "mild" suppositories of the IPC combination—group 3; six migraine patients occasionally taking tablets of the IPC combination—group 4.

The IPC combination habitually used was administered to each patient. Blood samples were taken at baseline and at fixed intervals up to 6 h after administration. Plasma levels of indomethacin and prochlorperazine were assayed by high-pressure liquid chromatographic (HPLC) method; caffeine levels were assayed by enzyme multiplied immunoassay test (EMIT). Pharmacokinetic parameters were calculated by means of a computer software (P K Solutions 2.0. Summit Research Services, Montrose, CO, USA).

Results: Half-life of indomethacin was longer, and clearance lower, in group 2 than in the other groups; AUC of indomethacin in group 2 was twice that in group 1 ($P < 0.05$, Newman–Keuls' test). Peak concentrations and $AUC_{0\rightarrow\infty}$ of caffeine were significantly higher in group 2 than in the other groups ($P < 0.05$, Newman–Keuls' test). We could not define prochlorperazine disposition because it was not detectable in the majority of blood samples.

Conclusion: Overuse of IPC combination in chronic headache patients is associated with increased plasma levels of indomethacin and caffeine, and with delayed elimination of indomethacin; the high and sustained concentrations of these drugs may cause rebound headache, organ damages, and perpetuate medication-overuse headache.

Keywords: Indomethacin; Prochlorperazine; Caffeine; Pharmacokinetics; Medication-overuse headache

1. Introduction

The antimigraine combination of indomethacin, prochlorperazine, and caffeine (IPC) is included in the guidelines of the Italian Society for the Study of Headache at the third level of recommendation [1]. This medication should act upon the most

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significant symptoms of migraine attack: indomethacin against head pain, prochlorperazine against nausea and vomiting, and "caffeine should contrast the depression typical of headache attack [2]".

Indomethacin, a potent, non-selective inhibitor of cyclooxygenase enzymes, is widely used in the treatment of various rheumatic diseases, in daily doses of 50–150 mg [3]. The efficacy of indomethacin in the treatment of migraine, and of other rare primary headaches identified as "indomethacin-responsive headache syndromes" [4] might be due (i) to its central activity on nociception [5], (ii) to its vasoconstrictive effect on cerebral vessels [6], (iii) to its ability to inhibit neurogenic inflammation [7].

Prochlorperazine is a phenothiazine, competitive antagonist at dopamine D2 receptors, which is used mainly as antiemetic. The recommended oral dose is 5 mg, three or four times a day; the rectal dose is 25 mg twice daily. The antiemetic activity increases with the increase of the dose, but adverse effects such as hypotension, sedation, extrapyramidal symptoms limit its use [8].

Caffeine is used worldwide as a stimulant of the central nervous system (CNS) and is present, as an adjuvant, in various analgesic combinations together with aspirin or acethaminophen. Its positive effects in the symptomatic treatment of headaches are attributed to (i) increased analgesic action of other drugs [9], (ii) central cholinergic analgesia [10], and (iii) vasoconstrictive activity [11].

In experimental animal models, in vivo, IPC combination had an analgesic activity significantly superior to that of its components [12]. In a randomized, open, crossover clinical study, a fixed combination of indomethacin 25 mg, prochlorperazine 4 mg, and caffeine 75 mg (suppositories) was significantly more effective than sumatriptan 25 mg (suppositories) in the acute treatment of migraine attacks [13]. This antimigraine combination, 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, is widely used in Italy, and it ranks among the five medications most used by the 1632 patients who were examined at the Headache Centre of the University of Modena and Reggio Emilia in 2002 [14]. A considerable number of these patients were suffering from chronic headache and frequently utilized the IPC combination as a symptomatic treatment. They told that, over the years, they had to progressively increase the doses of IPC combination, sometimes reaching a level of actual abuse, in order to manage their headache, which had become more and more frequent despite the intake of this medication. While, in fact, the high number of daily doses taken by these patients should have ensured plasma concentrations widely sufficient for the analgesic effect, especially in view of the fact that efficacy and tolerability of indomethacin seem to be related more to the steadiness of plasma levels during chronic treatment rather than to peak concentrations [15].

Chronic daily headaches, defined as headaches occurring more than 15 days a month (or 180 days a year), lasting more than 4 h, associated with medication overuse (>15 times/month) are an increasing problem worldwide. It is estimated that from 0.5 to 5% of the general population, and up to 80% of patients seen in specialized clinics [16] is affected by this condition. Two concurrent processes equalize these headaches: the increase in the use of analgesics keeps up with an increase in the frequency of headache. Any acute medication, if taken frequently for a sufficient period of time, causes rebound-drug-induced headache which can transform self-limited headaches, and particularly migraine, into chronic daily headache. Only the discontinuation of the offending medications makes it possible to obtain an improvement of the headache [17]. The revised 2004 International Headache Society Classification introduces formalized criteria for diagnosing these conditions as "medication-overuse headaches (MOH)" [18]. The pathogenesis of MOH is still unclear. There are several different theories, particularly of dynamic type, including: central sensitisation from repetitive activation of nociceptive pathways [19] or a direct effect of the medication on the capacity of the brain to modulate pain sensitivity [20]. However, the possible role of kinetic factors in the mechanism of medication overuse-headache has been scarcely explored.

Our aim was to verify whether overuse of IPC combination by chronic headache patients was associated with modified disposition of its components. Hence, we compared IPC disposition between migraine patients occasionally using it by rectal route, and chronic headache patients overusing the same drug by the same route. Finally, we analyzed whether the pharmacokinetic parameters differ among the various formulations of IPC.

2. Materials and methods

2.1. Subjects

We enrolled 34 females, all Caucasians, suffering from primary headaches (migraine without aura: 25 patients; probable MOH: 9 patients, according to ICHD-II classification criteria [18]) which were consecutively referred to the Headache Centres of the University Hospitals of Modena or Pavia by their general practitioners. The population (Table 1) was subdivided into four groups: eight migraine patients occasionally using suppositories of the IPC combination—group 1; nine patients with probable MOH, daily taking one or more suppositories of the IPC combination—group 2; 11 migraine patients occasionally using "mild" suppositories of the IPC combination—group 3; six migraine patients using occasionally tablets of the IPC combination—group 4. The nine patients of group 2 sequentially underwent inpatient withdrawal of the offending medication. In these patients the diagnosis of headache at the onset was "migraine without aura". In time their migraine transformed into chronic daily headache. These patients for at least 1 year overused only IPC combination.

All patients were no-smokers and all usually consumed between 1 and 4 cups of coffee every day. The frequencies of drug assumptions was recorded in the diaries that the patients kept for 3 months before visiting the centre. No patient had kidney or liver dysfunction or was taking drugs able to cause drug–drug interactions with the components of IPC combina-

Table 1
Patients' characteristics

Characteristic	Group 1 ($n=8$)	Group 2 ($n=9$)	Group 3 ($n=11$)	Group 4 ($n=6$)
Diagnosis	Migraine without aura	Probable medication-overuse headache	Migraine without aura	Migraine without aura
Mean age ± S.D. (years)	55.0 ± 6.7[a]	46.4 ± 8.7	51.1 ± 7.3	38.7 ± 12.9[b]
Range	46–61	31–53	37–61	29–57
Mean weight ± S.D. (kg)	70.7 ± 9.2[c]	64.6 ± 5.5	63.0 ± 7.6	56.2 ± 5.8
Range	58–77	53–83	55–79	49–63
Composition of medication used				
Indomethacin	50 mg	50 mg	25 mg	25 mg
Prochlorperazine	8 mg	8 mg	4 mg	2 mg
Caffeine	150 mg	150 mg	75 mg	75 mg
Route of administration	Rectal	Rectal	Rectal	Oral
Years of use (mean ± S.D.)	5.7 ± 3.2	6.7 ± 5.7	3.9 ± 2.5	3.6 ± 1.5
Range	1–10	1–20	1–8	1–5
No of doses/month (mean ± S.D.)	6 ± 1.3	114 ± 56.1[d]	4.5 ± 1.1	5 ± 2.1
Range	4–8	56–224	3–6	2–7

[a] $P<0.05$ vs. group 2 (ANOVA and Newman–Keuls' test).
[b] $P<0.05$ vs. groups 1–3 (ANOVA and Newman–Keuls' test).
[c] $P<0.05$ vs. group 4 (ANOVA and Newman–Keuls' test).
[d] $P<0.05$ vs. groups 1, 3 and 4 (ANOVA and Newman–Keuls' test).

tion. All patients of group 2 complained of gastrointestinal troubles, two had gastric ulcers, and three had hypertension. No patient was taking drugs for the prophylactic treatment of headache. Informed consent was obtained from each subject, following an exhaustive description of the study procedures and objectives. The study was approved by the Ethical Committees of Modena and Pavia and it was conducted in strict compliance with the Declaration of Helsinki.

Before starting the study, all subjects underwent medical examination, and standard biochemical and haematological screenings were performed. At the time of the experimental session, patients did not present acute diseases as determined by histories, 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 was administered to each patient, in the morning at 7 a.m., after overnight fasting. Patients were maintained in the supine position for the subsequent 30 min. Coffee intake was not allowed during the experimental session. Venous blood samples were drawn from an indwelling cannula into heparinized tubes (for assay of indomethacin and prochlorperazine) and in non-heparinized tubes (for assay of caffeine), before dosing and at the following post-dose times: 0.5, 1.0, 1.5, 2.0, 3.0, 4.0 and 6.0 h. Samples were immediately centrifuged, and kept at −20 °C until the time of assay.

2.3. Assay of indomethacin

Indomethacin concentrations were measured on deproteinized serum, by means of a slightly modified reversed-phase high-pressure liquid chromatographic (HPLC) method [21]. Analysis was performed on a Beckman System Gold HPLC instrument equipped with an UV detector set at 258 nm. The analytical column was a Phenomenex Hypersil 5ODS (250 mm × 4.6 mm i.d., 5 μm ps) preceded by a guard column of the same kind. The mobile phase consisted of acetonitrile:acetate buffer (100 mM, pH 6.9) (34:66, v/v) and the flow rate was 1.3 ml/min. A 0.5 ml aliquot of serum was added of 0.1 ml of a 10 mcg/ml phenacetin methanolic solution (internal standard), then 1.4 ml of methanol was added. The sample was vortex-mixed, centrifuged at 2100 × g and a 20 μl aliquot was injected. The linear calibration range ($R^2 = 0.997 \pm 0.002$) was 0.2–8.0 μg/ml and the limit of detection was 0.1 μg/ml. Intra-day precision, measured as a percent coefficient of variation (CV%) for indomethacin concentrations of 0.2, 1.0 and 6.0 μg/ml, was 12.3%, 11.5% and 9.8%, respectively, while inter-day precision was 13.1%, 12.2% and 9.6%. The extraction efficiency, measured as absolute recovery of indomethacin, was 75.8%. The possible interference of prochlorperazine and caffeine on indomethacin quantization was ruled out.

2.4. Assay of prochlorperazine

Serum concentrations of prochlorperazine were measured using high-pressure liquid chromatography (HPLC) with electrochemical detection [22], after an extraction procedure [23]. The analytical column was a Supelco Supelcosil LC-CN (150 mm × 4.6 mm i.d., 5 μm ps) and the mobile phase, flowing at 1.5 ml/min, consisted of acetonitrile:ammonium phosphate (100 mM, pH 6.5) (45:55, v/v) and EDTA 50 g/l. Analytical cells 1 and 2 were respectively set at 400 and 550 mV. Prochlorperazine linear calibration curves covered the range 0.5–6.0 ng/ml with an average coefficient of correlation $R^2 = 0.982 \pm 0.007$. The limit of detection was 0.05 ng/ml. Intra-day and inter-day precision, measured as CV% for prochlorperazine concentrations of 1, 2, and 4 ng/ml, were respectively 3.7%, 11.2%, and 2.3% and 8.5%, 12.8%, and 13.1%. The recovery of analyte

after the extraction procedure was 66.4% at 1 ng/ml while it was 54.9% for the internal standard, chlorpromazine.

2.5. Assay of caffeine

Caffeine concentrations in the serum were measured by an enzyme multiplied immunoassay technique (EMIT caffeine assay, Syva Company, Dade Behring diagnostic products, Rhodes, IL, USA) which measures the total (protein-bound plus protein unbound) drug concentration in the range 1–30 mcg/ml. The three metabolites of caffeine, paraxanthine, theobromine, and theophylline, do not interfere with EMIT caffeine assay. Within-run precision, measured as CV% at 7 ng/ml, was 4.0%, while between-run precision, measured at 11 ng/ml, was 3.9%.

2.6. 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). This program employs two non-compartmental techniques. The trapezoidal rule is used to computer the area under the curve (AUC). The method of residual (also called curve stripping), which resolves the curve into a series of exponential terms, is used to computer the elimination phases that occur during the time course of the drug in blood.

The following parameters were determined for indomethacin, prochlorperazine, and caffeine from individual subjects data: C_{max}, peak concentration (maximum observed plasma concentration) (μg/ml); T_{max}, time to peak plasma concentration (h); $t_{1/2}$, elimination half-life, time for concentration to diminish by one-half (h); MRT, mean residence time, time for 63.2% of administered dose to be eliminated (h); $AUC_{0\rightarrow t}$, cumulative area under the plasma concentration time curve using observed data points only (μg h/ml); $AUC_{0\rightarrow\infty}$, total AUC computed using data points extrapolated to infinity (μg h/ml); V_d, apparent volume of distribution based on AUC_∞ and elimination rate normalized by weight (ml/kg); Cl, systemic clearance based on AUC_∞ normalized by weight (ml/h/kg).

All data, except indomethacin plasma levels, are expressed as the mean ± S.D. The one-way analysis of variance (ANOVA) was used, followed by Newman–Keuls post hoc testing, to determine whether there was a significant difference between the mean values of the four groups. Student's *t*-test for independent samples was performed to assess statistical difference between pharmacokinetic parameters of prochlorperazine of group 3 and group 4, and between indomethacin plasma levels of group 1 and group 2. A level of $P < 0.05$ was considered significant [24].

3. Results

3.1. Indomethacin pharmacokinetics

Following administration of the IPC suppositories (Fig. 1), the plasma time course of indomethacin levels showed significant differences between group 1, composed of migraine patients who only occasionally took this medication, and group 2, composed of chronic headache patients overusing it. Despite wide inter-individual variations, at every time of the curve, group 2 had mean levels higher than group 1; in particular, indomethacin concentrations were already detectable at baseline, and mean levels were significantly higher in group 2 than in group 1 after 2, 3, 4, and even 6 h after administration.

Group 2 had delayed elimination of indomethacin (Table 2), as reflected by significantly longer half-life ($t_{1/2}$) values (150% of increment) and a lower systemic clearance (Cl) (52% of decrement) than group 1, while time to peak concentration (T_{max}) and apparent volume of distribution (V_d) were similar in the two groups. Although the administered IPC dose was the same, the patients of group 2 had been exposed to an amount of indomethacin significantly greater than the patients of group 1, as indicated by increased C_{max} (69% of increment), and $AUC_{0\rightarrow t}$ (121% of increment). All pharmacokinetic parameters of indomethacin 25 mg, either taken as IPC combination by rectal (group 3) or oral (group 4) route, were comparable.

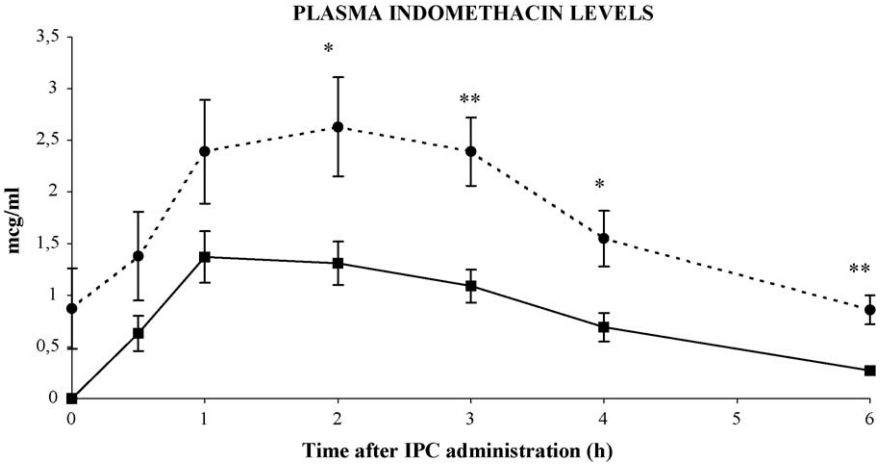

Fig. 1. Plasma levels (mean ± S.E.M.) of indomethacin in patients of group 2 (●) and of group 1 (■) following rectal administration of IPC combination (indomethacin 50 mg, prochlorperazine 8 mg, caffeine 150 mg) (statistical differences between the mean levels: $^{*}P < 0.05$, $^{**}P < 0.005$, Student's *t*-test).

Table 2
Pharmacokinetic parameters (estimates by non-compartmental method) of indomethacin following rectal (groups 1–3) and oral (group 4) administration of IPC (indomethacin, prochlorperazine, caffeine) combination

Parameter	Group 1 ($n = 8$) IPC combination suppository indomethacin content: 50 mg, (Mean ± S.D. (range))	Group 2 ($n = 9$) IPC combination suppository indomethacin content: 50 mg, (Mean ± S.D. (range))	Group 3 ($n = 11$) IPC combination mild suppository indomethacin content: 25 mg, (Mean ± S.D. (range))	Group 4 ($n = 6$) IPC combination tablet indomethacin content: 25 mg, (Mean ± S.D. (range))
Dosage (μg/kg)	724.32 ± 102.68[a] (602.4–943.3)	782.90 ± 51.04[a] (649.4–862.5)	401.62 ± 44.49 (316.5–454.5)	442.25 ± 48.08 (396.8–510.2)
T_{max}, h (observed)	1.62 ± 0.74 (1.0–3.0)	1.83 ± 0.86 (0.5–3.0)	1.63 ± 0.96 (1.0–4.0)	2.75 ± 0.95 (2.0–4.0)
C_{max}, μg/ml (observed)	1.83 ± 0.28 (1.4–2.3)	3.11 ± 1.33[b] (1.6–5.6)	1.19 ± 0.25 (0.8–1.5)	1.40 ± 0.29 (1.0–1.7)
$t_{1/2}$ (h)	1.27 ± 0.41 (0.8–2.3)	3.20 ± 1.27[b] (1.6–7.3)	1.75 ± 0.68 (0.9–2.8)	1.18 ± 0.43 (0.6–1.5)
MRT (h)	3.03 ± 0.55 (2.4–3.9)	5.07 ± 1.66[b] (3.7–9.2)	3.41 ± 0.75 (2.4–4.9)	3.37 ± 0.55 (2.6–3.9)
$AUC_{0\rightarrow t}$ (μg h/ml)	5.16 ± 1.42 (3.7–8.2)	11.41 ± 5.40[b] (6.7–21.8)	3.87 ± 0.52 (3.4–4.8)	3.91 ± 0.91 (3.1–5.0)
$AUC_{0\rightarrow\infty}$ (μg h/ml)	5.57 ± 1.55 (4.0–9.0)	15.68 ± 9.39[b] (8.4–37.6)	4.41 ± 0.82 (3.7–6.3)	4.07 ± 0.87 (3.3–5.1)
V_d (ml/kg)	235.31 ± 69.37 (150.6–336.8)	256.85 ± 73.99 (118.9–372.3)	229.98 ± 82.23 (116.9–396.1)	198.22 ± 87.86 (99.4–276.5)
Cl (ml/h/kg)	130.90 ± 30.20 (99.34–189.9)	62.62 ± 26.60[b] (22.9-112.6)	115.81 ± 18.43 (81.3–121.5)	103.34 ± 12.28 (99.5–126.6)

[a] $P < 0.05$ vs. groups 3 and 4 (ANOVA and Newman–Keuls' test).
[b] $P < 0.05$ vs. groups 1, 3 and 4 (ANOVA and Newman–Keuls' test).

Table 3
Pharmacokinetic parameters (estimates by non-compartmental method) of caffeine following rectal (groups 1–3) and oral (group 4) administration of IPC (indomethacin, prochlorperazine, caffeine) combination

Parameter	Group 1 ($n = 8$) IPC combination suppository caffeine content: 150 mg, (Mean ± S.D. (range))	Group 2 ($n = 9$) IPC combination suppository caffeine content: 150 mg, (Mean ± S.D. (range))	Group 3 ($n = 11$) IPC combination mild suppository caffeine content: 75 mg, (Mean ± S.D. (range))	Group 4 ($n = 6$) IPC combination tablet indomethacin content: 75 mg, (Mean ± S.D. (range))
Dosage (μg/kg)	2156.06 ± 317.81[a] (1807.2–2830.1)	2333.67 ± 185.62[a] (1948.20–2586.20)	1197.56 ± 139.44 (949.36–1271.18)	1333.30 ± 127.83 (1190.47–1530.61)
T_{max}, h (observed)	1.87 ± 1.24 (1–4)	2.62 ± 0.91 (1–4)	1.90 ± 0.73 (1–3)	1.33 ± 0.52[b] (1–2)
C_{max}, μg/ml (observed)	6.37 ± 4.10 (1.2–14.5)	11.16 ± 4.41[c] (7.2-18.9)	5.20 ± 2.99 (2.3–11.1)	5.46 ± 1.71 (4.1–7.8)
$t_{1/2}$ (h)	4.63 ± 1.99 (2.6–7.6)	5.07 ± 1.04 (2.9–6.16)	4.85 ± 1.81 (2.4–7.2)	4.66 ± 0.46 (4.1–5.2)
MRT (h)	7.98 ± 2.41 (5.3–11.5)	8.53 ± 1.71 (5.2–10.4)	8.12 ± 2.33 (5.2–11–4)	6.10 ± 0.62 (5.1–6.8)
$AUC_{0\rightarrow t}$ (μg h/ml)	38.67 ± 23.72 (21.0–90.2)	59.15 ± 29.85 (33.2–111.40)	27.62 ± 15.86[d] (11.2–61.4)	31.70 ± 6.18 (24.1–37.8)
$AUC_{0\rightarrow\infty}$ (μg h/ml)	68.75 ± 34.26 (32.9–114.0)	116.23 ± 54.82[c] (54.3–202.9)	52.16 ± 35.12 (16.4–136.5)	43.80 ± 8.21 (33.2–53.2)
V_d (ml/kg)	210.20 ± 69.30 (214.5–321.6)	171.32 ± 56.89 (92.2–252.5)	177.04 ± 94.16 (25.8–354.5)	169.08 ± 46.75 (105.4–242.6)
Cl (ml/h/kg)	47.69 ± 18.66 (30.5–74.1)	34.11 ± 9.94 (23.3–50.3)	36.35 ± 18.70 (20.8–66.1)	38.12 ± 3.13 (32.8–42.5)

[a] $P < 0.05$ vs. groups 3 and 4 (ANOVA and Newman–Keuls' test).
[b] $P < 0.05$ vs. group 2 (ANOVA and Newman–Keuls' test).
[c] $P < 0.05$ vs. groups 1, 3 and 4 (ANOVA and Newman–Keuls' test).
[d] $P < 0.05$ vs. group 2 (ANOVA and Newman–Keuls' test).

3.2. Prochlorperazine pharmacokinetics

Prochlorperazine was not detectable in samples from patients taking IPC formulations containing 4 mg (group 3, rectal route) or 2 mg (group 4, oral route) of this drug. We could only detect prochlorperazine in few samples from patients of group 1 and of group 2, taking IPC combination suppositories containing 8 mg of prochlorperazine. Considering this limit, it was possible to reliably determine only T_{max} and C_{max}. These parameters were not different between the groups (group 1: T_{max} 1.66 ± 0.5 h, C_{max} 1.43 ± 0.77 μg/ml; group 2: T_{max} 1.75 ± 1.5 h, C_{max} 2.42 ± 0.98 μg/ml).

3.3. Caffeine pharmacokinetics

Comparing caffeine pharmacokinetics after the same IPC suppository (Table 3), C_{max} and $AUC_{0\rightarrow\infty}$ appeared higher in group 2 than in group 1; there were no other significant differences between the two groups. Caffeine disposition did not change following administration of IPC combination with the same 75 mg dose either by rectal (group 3) or oral (group 4) route.

4. Discussion

The results of this study indicate that overuse of IPC combination modifies indomethacin disposition. Following the administration of the IPC combination habitually taken, patients overusing this medication (group 2) presented (Fig. 1) mean plasma levels of indomethacin higher than the proposed therapeutic concentration of 1 μg/ml [25] after just half an hour; this group still had levels close to those in the therapeutic range after 6 h, and even at baseline, as likely residual of previous assumptions. Indeed, it has been reported that repeated doses tend to cause accumulation and result in sustained serum levels of indomethacin during the 24 h [26,27]. In group 2 (Table 2) mean elimination half-life was significantly increased and systemic clearance decreased with respect to the other groups. Despite the wide inter-individual variations in plasma levels (a typical feature for drugs which undergo desmethylation [28] and enterohepatic recycling [29–31]) the pharmacokinetics of indomethacin in patients with occasional use was consistent with published data (T_{max} 1–4 h, $t_{1/2}$ 2–11 h, Cl 0.44–109 ml/min/kg, V_d 411–450 ml/kg) [15,32–35].

Chronic headache patients overusing IPC combination (group 2) had no kidney or liver dysfunction such to affect indomethacin disposition. Following administration of IPC combination, caffeine pharmacokinetics (Table 3), considered as an index/probe of hepatic drug-metabolizing capacity [36], did not show significant differences, except mean peak concentrations and $AUC_{0\rightarrow\infty}$ higher in group 2 compared to group 1. The other pharmacokinetic parameters of caffeine after IPC combination administration, were comparable with those found following administration of caffeine alone: T_{max} 30–60 min, half-life approximately 3–9 h, V_d 0.53 l/kg, clearance 71–133 ml/h/kg [37–39].

We have no clues to help us explain the reduced clearance of indomethacin in chronic headache patients overusing IPC combination. We exclude that it could be due to interactions among/with its components. In fact, they are metabolized by different isoenzymes: caffeine by CYP 1A2 [40], indomethacin by CYP 2C9 [41], and prochlorperazine by CYP 2D6 [42]. Moreover, no patient was taking other drugs known to be inhibitors of these isoenzymes. In addition, it is quite unlikely that only the patients of group 2 had a form of CYP 2C9 less catalytically efficient (e.g., CYP2C9 *3), so to explain a reduction in indomethacin clearance [41]. However, drug disposition in chronic and high/toxic dosing regimen could be different from that observed after therapeutic and single doses. Patients of group 2 had been taking daily, for at least 1 year, high doses (up to 8 a day, i.e. indomethacin 400 mg/day) of IPC combination. Indomethacin undergoes also phase 2 metabolism and enterohepatic circulation. Since the extent of resorption is highly erratic and has been estimated to range from 27% to 115% [31] it is possible to speculate that a higher degree of enterohepatic circulation have caused indomethacin longer plasma half-life and reduced systemic clearance in patients overusing IPC combination. Unfortunately, no data exist about indomethacin pharmacokinetics in doses chronically higher than the therapeutic ones.

From a clinical point of view, the reduced clearance of indomethacin in chronic headache patients overusing IPC combination could have caused, or contributed to, gastrointestinal disorders and hypertension they suffered from. Actually, common adverse reactions of indomethacin are gastrointestinal and cardiovascular side effects. Such effects are dose-related and appear to increase with increased duration of treatment [43,44].

Indomethacin's features are unique and different from those of the other NSAIDs. It is highly lipophilic, and cerebrospinal fluid and serum concentrations are similar 30 min after intravenous administration [45]. Indomethacin causes cerebral vasoconstriction, which is rapid in onset and in resolution, closely related to plasma concentrations [46]. Furthermore, the most common adverse reactions of indomethacin are dose-dependent CNS effects. They have been attributed to direct effects of indomethacin on cranial blood vessels and have been related to the plasma concentration of the drug [47]. Headache is the most frequently reported among CNS side effects of indomethacin therapy. In some cases, headache may be severe enough to require discontinuation of the drug. Headache has been attributed to compensatory vasodilatation that follows vasoconstriction [48]. Overall, these peculiar properties and the reduced clearance of indomethacin that we observed in chronic headache patients overusing IPC combination, could support its ability to induce rebound headache and, as a consequence, medication-overuse headache.

Our study has some limits: the population was heterogeneous as far as patients' characteristics, doses, and patterns of medication taken are concerned. Our findings cannot be generalized to other patients and context. However, this sample reflects the population of patients who seek medical advice, which is formed by those who suffer from disabling headaches, and are the target of prescription medication [49], as it is, in fact, IPC combination.

The role of prochlorperazine in IPC combination is still to be defined. This drug has low oral bioavailability, only 12.5%, since it undergoes first pass effect which affects systemic concentrations [50]. Following administration of IPC combinations containing 2 and 4 mg of prochlorperazine we were not able to detect the drug in the blood. We think that it is unlikely that such low dosages can act as antiemetics.

In conclusion, the effect of the overuse of the antimigraine IPC combination in our chronic headache patients was a delayed indomethacin elimination. The presence of indomethacin plasma levels higher than those in the therapeutic range for a long time did not alleviate the headache; quite the contrary, it might have sustained medication-overuse headache and caused organic damages.

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