



## NON-INFERIORITY STUDY CONCERNING A NEW ANALGESIC FORMULATION VERSUS AN ACETYLSALICYLIC ACID, ACETAMINOPHEN AND CAFFEINE FIXED COMBINATION IN PATIENTS WITH HEADACHE

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**Abstract.** Headache, one of the most frequent conditions with negative impact on the patient quality of life, represents the reason for over-the-counter self-medication. The **aim** of this study was to determine the non-inferiority of one tablet of Algopirin, a new analgesic combination (patent RO120818/2006), versus one tablet of Excedrin (Novartis), fixed combination with acetylsalicylic acid, acetaminophen and caffeine for relieving headache. **Material and methods.** There were included 46 patients diagnosed with headache, which treated two independent headache episodes with 1 tablet of Algopirin, respectively with 1 tablet of Excedrin, in a randomized order. There were recorded: date and time of headache, the time of drug administration, the pain severity using Visual Analogue Scale, before and 30, 60, 120, 180 and 240 min after drug intake, persistence of pain 2 h and 4 h after drug intake. **Results.** Time to 50% pain relief in mean curves was 60 min for Algopirin and 45 min for Excedrin. Time to 80% pain relief was practically the same for both products (160 min). Comparisons of the two sets of the normalized mean pain intensity curves led to the conclusion that the equivalence hypothesis cannot be rejected. **Conclusions.** The values of the differences and of the ratio between areas under curve of Algopirin and Excedrin suggest that administration of one tablet of Algopirin is equivalent to one tablet of Excedrin for the treatment of headache. It concerns a clinical point of view, the effect was installed somewhat more rapid in case of Excedrin but the extent was approximately similar. Since doses of active components in Algopirin tablets are half of the doses in Excedrin, Algopirin could be considered as an alternative at least in the case of patients with gastric and hepatic sensibility.

**Keywords:** headache, analgesic, over-the-counter, fixed combination, non-inferiority study.

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### Introduction

Headache (migraine, tension-type headache and other types) is one of the most frequent conditions with a major impact on the patient quality of life and represents the reason for self-medication using over-the-counter medications. About 5–9% of males and 12–25% of females suffer from migraine [1].

Drugs of first choice for mild to moderate tension-type headache are over-the-counter analgesics such as acetylsalicylic acid, ibuprofen, acetaminophen, metamizole etc. Over-the-counter analgesics offer several advantages including easy access, lower cost and fewer adverse effects in comparison with prescription drugs. The combinations containing acetylsalicylic acid, acetaminophen and caffeine are among the most widely prescribed drugs for relieving headache [2].

Evidence of efficacy in migraine treatment in at least one placebo-controlled study has been obtained for acetylsalicylic acid (ASA) up to 1000 mg, for ibuprofen 200–800 mg, for diclofenac

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50–100 mg, for metamizole 1000 mg, and for acetaminophen 1000 mg [3], [4], [5], [6]. In addition, the fixed combination of ASA, acetaminophen, and caffeine is effective in acute migraine treatment and is also more effective than the single substances or combinations without caffeine [7]. Clinical evidence supports the safety and efficacy of fixed combined analgesics with doses of 250–265 mg ASA, 200–265 mg acetaminophen, and 50–65 mg caffeine per tablet [8].

This study was performed to determine the non-inferiority of unique dose treatment using a new analgesic association [9] versus Excedrin® fixed combination with acetylsalicylic acid, acetaminophen and caffeine for relieving the headache. The study included patients who are used to treating their headache with over-the-counter analgesics. There were no predefinition of headaches into migraine or tension-type headache.

## Materials and methods

### Patients

The study was conducted in the Ilfov County Hospital between January and September 2010. The protocol and informed consent form were approved by Carol Davila University of Medicine and Pharmacy Ethic Committee and all participants gave written informed consent prior to study participation. The study was conducted according to International Conference on Harmonisation (ICH) Good Clinical Practice, to the Guidelines for Controlled Trials of Drugs in Migraine [10] and to the Note for Guidance on Clinical Investigation of Medicinal Products for the Treatment of Migraine [11].

Male and female patients (18–65 years) who met International Headache Society criteria [12] for migraine or for tension-type headache and who had headaches which they treated with over-the-counter analgesics were enrolled by general and internal medicine specialists. Diagnosis of headache was based on a structured questionnaire. Patients' medical data (history, physical and neurologic evalu-

a minimum of two headaches within the previous 3 months. At least moderate headache severity most of the times and periods between attacks free from headache were also required.

Patients were excluded if they used prescription analgesics or migraine drugs, if they need higher doses of non-prescription analgesics than indicated in patient information leaflet, if they had headache episodes more than 10 per month or that lasted untreated less than 4 hours, if menstrual migraine. There were excluded patients currently taking analgesics, antirheumatic, anti-inflammatory drugs, antidepressants or antipsychotic drugs, patients taking drugs for migraine prophylaxis or ergot derivatives during the month of screening, patients taking drugs for treating headache more than 10 days per months. Other exclusion criteria were alcohol abuse, serious illness (including psychiatric diseases), pregnancy and lactation, hypersensitivity to ASA, acetaminophen or caffeine, participation to other clinical study within 4 weeks of entering this study.

### Study medication

Study medication for reference treatment (R) was Excedrin delivered by Novartis and for tested treatment (T) was Algopirin, Romania. Medication was recommended as a single dose as soon as possible when the headache of moderate severity occurred. Patients were required to not take any other drug during the first 4 h after study medication. If the headache persisted, rescue medication was allowed only 4 h after the administration of the study medication (except drugs containing ergot, serotonin agonists, NSAID).

### Study design and treatments

This study was designed as a two-sequences, two periods cross-over randomized, double-blind, uni-center study. Two independent headache episodes were treated for every patient. Patients were randomly allocated to one of the two sequences of treatment: TR or RT (table I).

Treatment	Medication, dose and active ingredients
tested treatment (T)	Algopirin® 1 tablet (125 mg ASA + 75 mg acetaminophen + 15 mg caffeine + 2 mg chlorpheniramine)
reference treatment (R)	Excedrin® (Novartis) 1 tablet (250 mg ASA + 250 mg acetaminophen + 65 mg caffeine)

Table I. Study treatments

ation) were recorded by a study physician. Included subjects were trained to fill in the study diary.

Patients were eligible for inclusion if they had experienced headaches for at least 12 months, with

Patients treated each headache episode with one of the investigational study medications (T or R), in a randomized order. Access to randomization code was strictly controlled and the treatment assignment

remained unknown to all patients and physician until the end of the study. Two hours before and during the headache, after administration of study medication, patients were not permitted to take coffee or beverages containing caffeine.

### Efficacy measurement

All patients were asked to record in their diary cards headache pain: date and time of headache, the time of drug administration, the pain severity measured with a 100 mm visual analogue scale (VAS) immediately before administration of treatment and 30 min, 60 min, 120 min, 180 min and 240 min after drug intake, if the pain remained 4 h after the administration of the study medication, if rescue medication was used (the drug and dose). The headache pain intensity of the episode should be greater than 30 mm to be considered of moderate severity.

The current IHS guidelines for migraine clinical trials recommend assessment of pain relief at 2 hours as a primary endpoint [13] but the expectation of complete headache release within 2 hours might be unrealistic. If we define 0 as pain free marker we lose almost all patients and automatically a great part of information and statistical significance.

In comparisons of treatments we need endpoints more sensitive for detecting differences in pain response. Or in our paper we were mainly interested in evaluation of differences between treatments and less for absolute value of effects.

The primary endpoint in this paper was the time calculated to 50% pain relief based on the pain intensity curve recorded on a 100 mm VAS. The time to 50% pain relief was calculated by linear interpolation between adjacent observation time points.

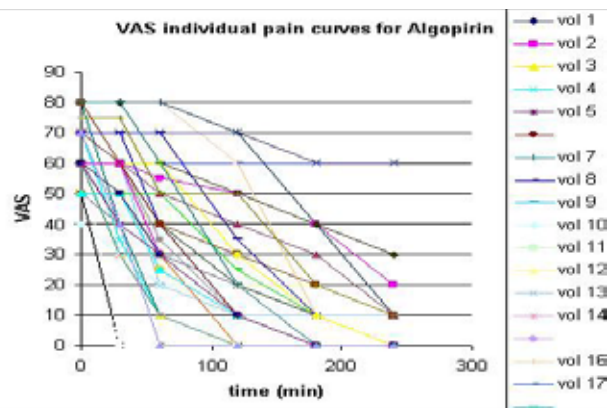


Figure 1a.

In order to obtain a more adequate comparison of pain curves, independent of initial pain, data were normalized to this initial value which was set as 100.

### Statistical analysis

A first statistical analysis was applied to measured main pain intensities at different time points. Data set of mean curves (before administration of treatment and 30 min, 60 min, 120 min, 180 min and 240 min after drug intake) were considered as independent and normally distributed.

A second set of tests were applied to populations of parameters associated to individual pain curves. In all cases, tested and alternative hypothesis were:

- $H_0$ : effect of 1 tablet of Algopirin = effect of 1 tablet of Excedrin versus
- $H_A$ : 1 tablet of Algopirin < 1 tablet of Excedrin, considering the risk  $\alpha = 0.10$ .

### Results and discussions

#### Individual pain curves

There were included 46 patients diagnosed with headache, which treated two independent headache episodes with Algopirin, respectively with Excedrin, in a randomized order. Individual pain curves are presented for tested treatment Algopirin in fig. 1a and for reference treatment Excedrin in fig. 1b.

As it can be seen in fig. 1, some patients proved no relief of pain in the 4 hours interval. These pain curves of non responding patients were dropped out. It is important to note that, as a rule, non-responders appeared in the first period. Since they were no more non responders in the second period, it was rather a problem of not well understanding of instructions.

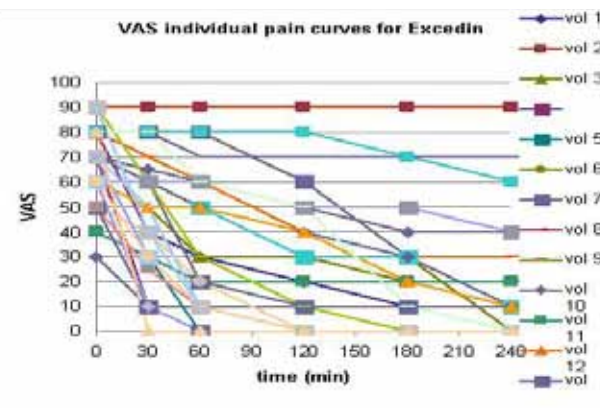


Figure 1b.

Figure 1. VAS individual pain curves for Algopirin (1a) and for Excedrin (1b)

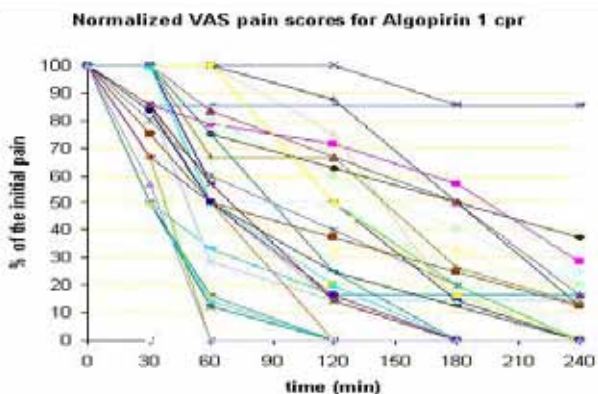


Figure 2a.

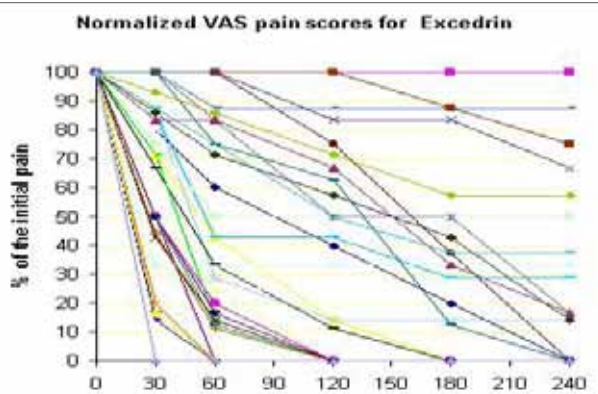


Figure 2b.

Figure 2. Normalized VAS pain scores for Algopirin (2a) and for Excedrin (2b)

**Individual normalized curves**

For a comparison of curves, since basic pain was in general different not only from patient to patient but also for the same subject, the values were normalized to the pain value just before the treatment. Normalized curves for each treatment are presented in fig. 2.

**Mean curves**

An easy global analysis of differences between treatments can be undertaken starting from mean pain curves. Since, as it can be seen in fig. 3 and 4, starting pain intensities and even entire curves were not shared in different clusters and were practically homogenously distributed in space, mean curves were considered as meaningful global information.

Since for many readers it is somewhat difficult to understand that upper curve means lower effect, the complement of pain intensity (100 – value) was calculated and represented in the figure as effect of formulations. Operation is usual in pain analysis,

the obtained values being called Pain Intensity Differences (PID(t)). Sometimes, in order to underline that pain intensities represent VAS scores, PID are changed in PAID [14].

**Estimation and comparison of parameters associated with mean curves**

Time to 50% pain relief ( $T_{50}$ ) can be estimated as time corresponding to intersection of 50% gridline with pain intensity curves.

As can be seen from fig 3 and 4,  $T_{50}$  is 60 min for Algopirin and 45 min for Excedrin. The 15 minutes difference can be considered somewhere at the frontier between significant and non-significant difference.

Time to 90% pain relief ( $T_{10}$ ) can be calculated by linear interpolation or extrapolation and it has very close values for the two treatments, respectively 230 min for Algopirin and 240 min for Excedrin.

More significant from a clinical point of view could be the time to 80% pain relief ( $T_{20}$ ) since, as

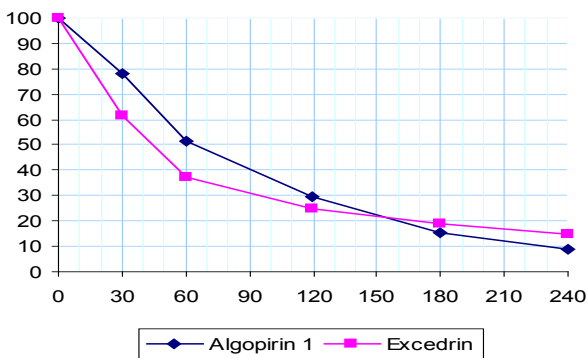


Figure 3. Normalized pain intensity (mean values calculated on normalized individual data) for Algopirin and Excedrin

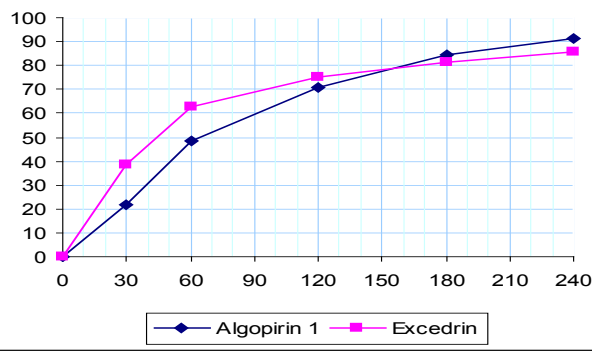


Figure 4. Mean pain relief effects (mean Pain Intensity Differences)

a general rule, a significant clinical difference could be considered at least 20% differences in effect. In case of  $T_{20}$  we have almost the same values for each product (approximately 160 min).

Another approach associated with mean curves is comparisons of the two sets of five points (Table II), which define normalized pain intensity using t-Student pair test

$$T_{n-1} = \frac{\bar{d}}{S_d / \sqrt{n}} = 1.17$$

Time (min)	Algoipirin	Excedrin	$d_i$
0	100	100	0
30	78	61	17
60	52	37	14
120	29	25	5
180	15	19	-4
240	9	15	-6

Table II. Mean values of VAS

For our number of data and assuming a 10% risk, theoretical t is  $t_{n-1;1-\alpha} = t_{4;0.9} = 1.53$  (fig. 5). Consequently hypothesis of the equality of effects cannot be rejected.

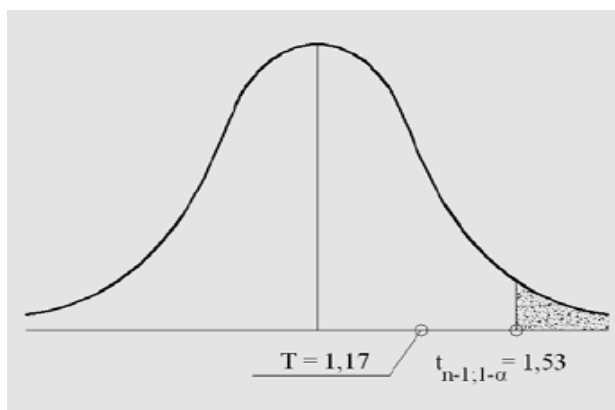


Figure 5. T-Student test

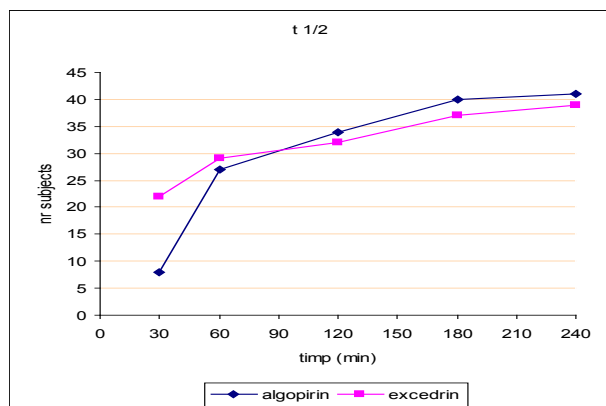


Figure 6. Percent of patients with 50% pain relief

A disadvantage of comparisons based on mean curves is the fact that we have no idea about the variability of the parameters and we cannot calculate confidence intervals for it. Also we cannot check if the obtained difference is statistically significant or not. For obtaining these intervals we have to calculate the parameters for each individual pain curve.

Percent of patients with 50% pain relief as function of time after the two treatments is presented in fig. 6. The curve of Excedrin is above the curve of Algoipirin.

If this difference is statistically significant or not is another problem since we do not know what law of distribution follow the points on this curves. Naked eye global examination suggests that differences are rather random effects.

### Area Under Pain Curves (AUC)

Area under curves is proposed as a global parameter useful first of all in comparison of curves. Area under plasma levels curves of active substances is the most significant parameter in defining bio-availability of a drug. Statistical methods applied in comparison of populations of areas under curves achieved by two drugs evaluate the bioequivalence of drugs containing the same active substances. A natural method for calculation of this area is the trapezoid rule:

If we calculate the area under Pain Intensity

$$\sum_{i=1}^n \frac{f(t_{i-1}) + f(t_i)}{2} * (t_i - t_{i-1})$$

Difference (PID) curve, we obtain a parameter somewhat similar with the Sum of PID differences (SPID). In fact SPID is the sum of PID scores multiplied by the interval between ratings:

$$SPID = \sum_{i=1}^n PID(t_i) * (t_i - t_{i-1})$$

The formula which calculates AUC plus triangles is represented in fig. 7.

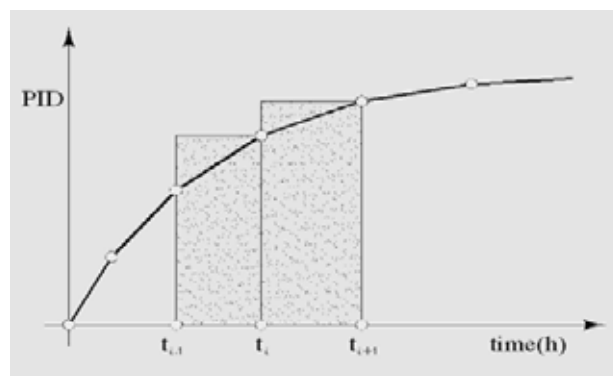


Figure 7. Calculation of area under Pain Intensity Difference (PID) curve

For slow decreasing curves the areas are approximately equal but for time intervals with rapid change of pain, the differences can no more be neglected.

**Comparison of areas under mean curves**

The areas under mean curves at 2 h and 4 h are represented in fig. 8. It can be seen that the areas for Excedrin are somewhat greater than the areas for Algopirin but differences seem not to be significant. In fact the difference is 11% at 2h and 4% at 4h.

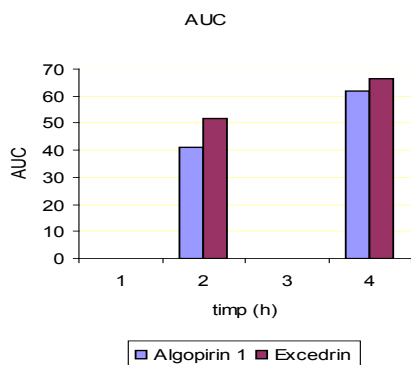


Figure 8. Comparisons of area under mean curves

**Comparison of population of half-times of pain starting from individual curves associated with treatments.**

The methods based on parameters of mean curves present the disadvantage that information about variability of parameters is neglected. Consequently we obtain only pointwise estimations, not confidence intervals for true means. For this reason we calculated the above used parameters for each individual curve and then we compared using statistical methods the populations of parameters for the two tested drugs. Apparently this approach is more appropriate but the estimation of parameters of individual curves is not possible in all cases.

Time to 50% pain relief for each patient was calculated by linear interpolation between adjacent observation time points. The calculation of this parameter is useful for statistical analysis, but there are difficulties in its application in practice, even in case of some subjects which cannot be considered outliers. In some cases, as for example depicted in fig. 9 and 10, the curve did not intersect the 50 score line, but it extrapolated the curve associated with the majority of points. The last point recorded for Excedrin in volunteer 19 (fig. 9) is outlier compared to the other points. It seems that the pain will not be reduced to half, so we decided to use the linear extrapolation from the points from 0 to 180 min and considered 210 min as time to 50% pain relief. For patient 29 (fig. 10), it seems that the time to 50% pain relief for Excedrin is around 5-6

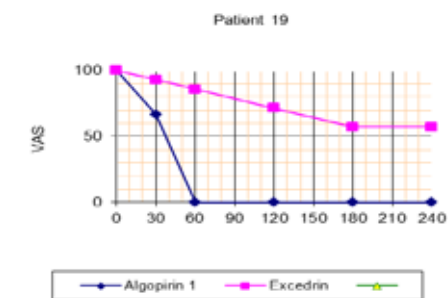


Figure 9. Individual VAS for patient 19

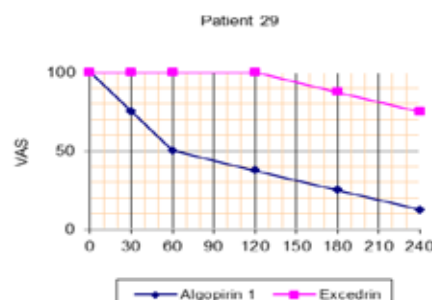


Figure 10. Individual VAS for patient 29

hours, which is out of recording time. In this case we considered 240 min as time to 50% pain relief.

Values obtained for  $T_{50}$  for each individual curve are presented in fig. 11a for Algopirin and fig. 11b for Excedrin. It can be observed that data are more or less normally distributed since a tail appears in the upper part of the values domain.

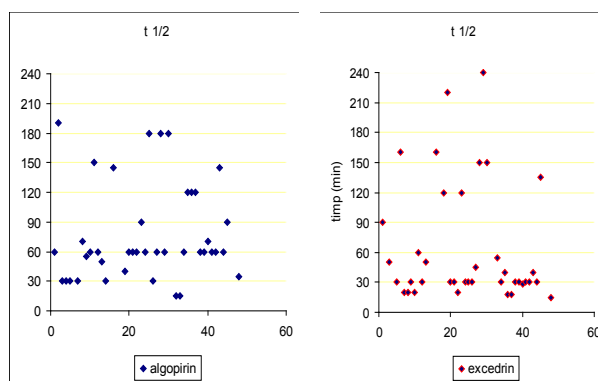


Figure 11. Distribution of T50% for each individual curve for Algopirin (11a - left) and for Excedrin (11b - right)

The results of calculation of means and standard deviations led to the results presented in table III.

Here is to remark the huge variability of data (Coefficient of Variation – CV, 64% for Algopirin and 94% for Excedrin).

Application of test t, in hypothesis of normal distribution led again to the conclusion on the lack of significance for difference between two treatments. The result is not doubtful since data were not symmetrically distributed and non-normality was put in evidence previously by other authors [15].

The population approach suggests also lack of significant difference between the effects of formulations. It is to note that the difference of means is higher (24 minutes) than in the case of parameters of mean curves.

In this case we could calculate also confidence intervals (CI) for difference between means:

$$CI_{90} = (-6.77; 33.10)$$

Length of the interval is huge since variability of data and consequently errors were huge. For a more reliable estimation a more would be possible to obtain only in case of studies on more large populations.

## Conclusions

The study tested the null hypothesis of equivalence between Algoripin one tablet versus Excedrin one tablet, administered to persons with migraine versus the alternative hypothesis of inferiority of Algoripin.

Time to 50% pain relief ( $T_{50}$ ) in mean curves was 60 min for Algoripin and 45 min for Excedrin. The 15 minutes difference can be considered somewhere at the frontier between significant and non-significant difference.

Time to 80% pain relief ( $T_{80}$ ) was found practically the same for both products - 160 minutes.

Comparisons of the two sets of five points of the normalized mean pain intensity curves using Student test led to the conclusion that the equivalence hypothesis cannot be rejected.

In agreement with statistics based on mean curves, the population approach suggested a difference not significant enough between the effects of formulations to reject the equivalence hypothesis.

A global and more significant analysis compared the values of AUC of the two treatments. The values of the differences and of the ratio between AUC of Algoripin and AUC of Excedrin suggest that administration of one tablet of Algoripin is equivalent to one tablet of Excedrin for the treatment of headache.

As a final conclusion all tests put in evidence as a rule a greater effect of Excedrin 1 tablet versus Algoripin 1 tablet but all applied statistical test to parameters suggested that this difference is not statistically different. It concerns a clinical point of view, the effect was installed somewhat more rapid in the case of Excedrin but the extent was approximately similar. Keeping in mind that doses of active components in Algoripin tablets are half of the doses in Excedrin, from a global, efficacy plus safety, point of view Algoripin could be considered as an alternative at least in the case of patients with gastric and hepatic sensibility.

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