

ESTIMATION OF THERAPEUTIC EQUIVALENCE USING BIOEQUIVALENCE STATISTICAL METHODS FOR ALGOPIRIN TABLETS VERSUS EXCEDRIN ANALGESIC FORMULATIONS

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Abstract

A clinical study was performed in order to prove the non-inferiority in relieving headache of a unique dose of treatment using Algopirin[®], a fixed combination with acetylsalicylic acid (ASA, aspirine), acetaminophen, caffeine and clorpheniramine a new analgesic combination *versus* Excedrin[®], which contains the same active substances but in much higher doses. Pain intensity was quantified using a Visual Analog Scale (VAS) score which was established by patients on a 1 – 100 points scale, before and 30 min, 60 min, 120 min, 180 min and 240 min after drug intake.

The clinical trial was a cross-over study with two periods and two sequences, usual in bioequivalence studies, each subject being its own control. Consequently in this study were applied specific statistical methods for bioequivalence studies.

The primary endpoint in the statistical evaluation was the Area Under the Pain Curve (AUC).

For verification of therapeutic equivalence there were applied both parametric (method of confidence intervals) and non-parametric methods (Wilcoxon-Man Whitney two one-sided test for bioequivalence, and confidence interval associated with Wilcoxon signed rank statistic based of Hodges - Lehmann estimator).

If the 90 % confidence interval for ratio of means of areas under curve was included in the interval 80 – 125 % the products were considered as therapeutically equivalent.

The results of all applied tests indicated a therapeutic equivalence of the formulations though amounts of active substances are much lower in Algopirin[®].

Rezumat

S-a efectuat un studiu clinic în scopul demonstrării non-inferiorității unei doze unice de Algopirin[®], o noua combinație conținând acid acetilsalicilic, acetaminofen, cofeina și clorfeniramină, față de Excedrin[®], combinație asemănătoare dar în doze de peste două ori mai mari, în reducerea durerii de cap.

Intensitatea durerii a fost apreciată cu ajutorul unei scări analogice vizuale cu o sută de gradații, imediat înainte de administrare și apoi la 0.5 h, 1 h, 2h, 3h și 4 ore după administrare.

Studiul clinic a fost unul încrucișat, cu două perioade și două secvențe, similar studiilor de bioechivalență, fiecare subiect fiind propriul său martor. Ca urmare, metodele

statistice aplicate, au fost cele din evaluarea studiilor de bioechivalență. Principalul parametru evaluat a fost aria de sub curbă de durere. Au fost aplicate atât metode parametrice (metoda intervalului de încredere) cât și metode nonparametrice (Wilcoxon-Mann Whitney, intervalul de încredere Hodges Lehmann pornind de la testul Wilcoxon de rang cu semn). Formulările au fost considerate terapeutic echivalente dacă intervalul de încredere 90% pentru mediile ariilor a fost inclus în intervalul 80-125%.

Toate testele au indicat că formulările au fost echivalente terapeutic în ciuda faptului că Algopirinul[®] conține cantități mult mai mici de substanțe active.

Keywords: Algopirin[®], Excedrin[®], bioequivalence, statistical methods

Introduction

Migraine with and without aura as well as vascular type headache, as defined by the International Headache Society, are very common diseases all over the world. Migraine is a chronic neurological disorder characterized by episodic attacks of head pain and associated symptoms, including photophobia, phonophobia, nausea, vomiting and aura. Headache Classification Committee of the International Headache Society. Classification of the diagnostic criteria for headache disorders, cranial neuralgias, and facial pain [1].

About 5–9% of males and 12–25% of females suffer from migraine [2, 3, 4, 5, 6].

In 1993, the Non-prescription Drug Advisory Board of the Food and Drug Administration recommended the classification of caffeine when combined with acetylsalicylic acid (ASA) plus acetaminophen as 1st category analgesic adjuvant – ‘recognized as safe and effective’ [7]. Caffeine lead to an increase of analgesic potency of about 40% [8]. American Academy of Neurology considers this association as a first-line migraine treatment [9].

Previous studies [10, 11] were performed to prove the non-inferiority of a unique dose of Algopirin[®], a new analgesic combination [12] *versus* Excedrin[®], fixed combinations with acetylsalicylic acid, acetaminophen and caffeine for relieving the headache. It was found that Algopirin[®] has a lower effect than Excedrin[®] but the difference was not statistically nor clinically significant. Concerning the clinical evaluation, the effect was installed somewhat more rapid in the case of Excedrin[®] but the extent was approximately similar. Taking into consideration that the concentrations of active components in Algopirin[®] tablets are less than half of the ones in Excedrin[®] (table I), from a global, efficacy and safety point of view, Algopirin[®] was considered as an alternative treatment at least in the case of patients with gastric and hepatic sensibility.

Table I
Concentrations of active ingredients

Drugs	Dose and active ingredients
Algopirin [®]	Algopirin [®] (LaborMed Pharma) tablets (125 mg aspirine + 75 mg acetaminophen + 15 mg caffeine + 2 mg clorpheniramine)
Excedrin [®]	Excedrin [®] (Novartis) tablets (250 mg aspirine + 250 mg acetaminophen + 65 mg caffeine)

Since the first part of the clinical trial, the comparison of the analgesic effect of 1 tablet of Algopirin[®] and 1 of tablet Excedrin[®] was a cross-over study, in the present paper there are applied specific statistical methods for bioequivalence studies. These methods are most appropriate in studies where each subject is its own control. In these conditions the intravariability is cancelled and, for obtaining a given statistical power of the tests, it is sufficient a significant lower number of subjects than in the case of parallel studies.

Materials and Methods

Patients. The study was conducted in the Ilfov County Hospital, Romania. The study was approved by “Carol Davila” University of Medicine and Pharmacy Ethic Committee and was conducted according to International Conference on Harmonization (ICH) Good Clinical Practices, to the Guidelines for Controlled Trials of Drugs in Migraine [13] and to the Note for Guidance on Clinical Investigation of Medicinal Products for the Treatment of Migraine [14]. All participants gave their written informed consent prior to the study participation and were instructed how to record the characteristics of their headache.

There were selected 46 patients, male and female which met the International Headache Society criteria for migraine with or without aura or for tension-type headache, usually treated with over-the-counter analgesics [15,16].

Endpoints. The first difficulty in studies concerning analgesic effect is to choose the markers of clinical effects as well as their quantification. In the particular case of migraine, the first marker is pain, its characteristics and its duration.

The simplest method is to evaluate only the existence and disappearance of pain but, since pain is not limited to a single time point, but to time intervals, and since it is not constant, it is more useful to evaluate a series of time points which lead to “pain curves”.

Pain intensity was quantified using a Visual Analog Scale (VAS) score which is selected by the patient on a 1 – 100 points scale, before and 30 min, 60 min, 120 min, 180 min and 240 min after drug intake.

The primary endpoint in the statistical evaluation in this paper was the Area Under the Pain Curve (AUC).

Usual in pain assessment is the area under the Pain Intensity Difference (PID) curve, when it is obtained a parameter somewhat similar with the Area Under the Curve which is called [17] Sum of PID differences (SPID). In fact SPID is the sum of PID scores multiplied by the interval between ratings:

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

For slow decreasing curves the areas are approximately equal, but for time intervals with rapid change of pain, the differences can not be neglected anymore.

Statistical analysis

In order to evaluate the bioequivalence of drugs containing the same active substances statistical methods were applied.

As “metrics” i.e. measures of rate and absorption, the official guidance’s (EMA, FDA) consider the following: $C_{\max}$ and AUC and drugs are bioequivalent if

$$P\left(0.8 < \frac{\mu_{AUC}^T}{\mu_{AUC}^R} < 1.25\right) \geq 0.9$$

From this point the problem of establishing bioequivalence becomes a matter of building a confidence interval (CI) for the ratio of means of main pharmacokinetic parameters. Statistical model for the random variable $AUC_{0-\infty}$ is:

$$Y_{ijk} = \mu + S_{ik} + P_j + F_{(j,k)} + C_{(j-1,k)} + e_{ijk}$$

where: μ = general mean, S_{ik} = the effect of the i-th subject within the k-th sequence, which, for the sake of testing hypotheses, we must assume to be a normally distributed random variable with mean 0 and variance σ_s^2 ;

P_j = the effect of the j-th period ; $F_{(j,k)}$ = the direct effect of the drug ;

$C_{(j-1,k)}$ = the residual effect of the drug; e_{ijk} = the random fluctuation which is normally distributed with mean 0 and variance σ_e^2 , and is independent of the S_{ik} .

Comparative analysis of "pain curves"

Normalized individual data were used to calculate the pain relief (data were normalized to an initial value of 100).

It was tested the following statistical hypothesis:

H_0 : effect of Algopirin[®] = effect of Excedrin[®] versus

H_A : effect of Algopirin[®] < effect of Excedrin[®], considering risk $\alpha = 0.10$.

For estimating the formulation effects it was used the difference between areas under curves of the two treatments at the same subject:

$$d_{ik} = \frac{1}{2} \cdot (y_{i2k} - y_{i1k})$$

These random variables are estimations of the formulation effects in the absence of carry-over effects.

For testing therapeutic equivalence there were applied both parametric (method of confidence intervals) and non-parametric methods.

90 % Confidence Interval (CI^{90}) for the ratio of the mean areas of the two pain curves was built starting from the random variable:

$$T_{n_1+n_2-2} = \frac{(\bar{Y}_T - \bar{Y}_R) - (\mu_T - \mu_R)}{\hat{\sigma}_d \sqrt{\frac{1}{n_1} + \frac{1}{n_2}}}$$

Results and Discussion

Some patients proved no relief of pain in the 4 hours interval. These pain curves of non responding patients were dropped out.

Individual pain curves were normalized, scores being calculated as percent of the score before treatment. Mean normalized curves are presented in figure 1.

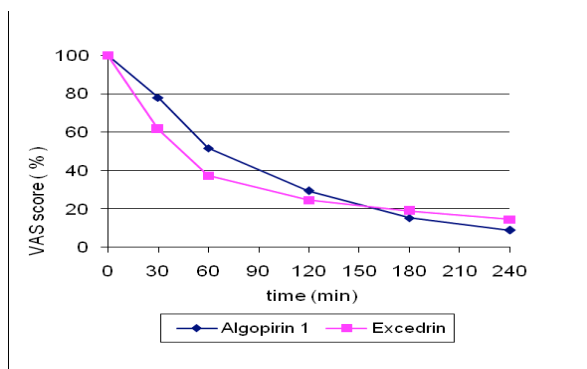


Figure 1

Normalized Visual Analogue Scale (VAS) pain scores mean curves for Algopirin[®] and Excedrin[®]

Regarding the contrasts $d_{ik} = \frac{1}{2} \cdot (y_{i2k} - y_{i1k})$ the results of the calculus are presented in Table II.

It can be seen easily that $\overline{Y_T} - \overline{Y_R} = \overline{d_{\bullet 1}} - \overline{d_{\bullet 2}}$

In these conditions confidence intervals for differences of drug effects were found to be :

$$IC_S^{90} = \overline{Y_T} - \overline{Y_R} - t_{n_1+n_2-2;0.90} \cdot S_d \cdot \sqrt{\frac{1}{n_1} + \frac{1}{n_2}} = 10.89 ;$$

$$IC_D^{90} = \overline{Y_T} - \overline{Y_R} + t_{n_1+n_2-2;0.90} \cdot S_d \cdot \sqrt{\frac{1}{n_1} + \frac{1}{n_2}} = 60.76 ;$$

where S_d is the pooled variation in the conditions of H_0 hypothesis.

Finally it was obtained:

$$\mu_T - \mu_R \in (10.89 ; 60.76) ; \frac{\mu_T}{\mu_R} \in (1.05 ; 1.25) \in (0.8 ; 1.25)$$

Table II
The calculus of differences of effects and ranks of differences

	P ₁	P ₂	d_{ik}	$\overline{d_{\bullet k}}$	$d_{ik} - \overline{d_{\bullet k}}$	$(d_{ik} - \overline{d_{\bullet k}})^2$	$b_{ikL} = d_{ik} - \theta_L$	$R(b_{ikL})$	$b_{ikU} = d_{ik} - \theta_U$	$R(b_{ikU})$
sequence 1 RT	338	293	-22	12	-34	1178	38	22	-83	6
	341	350	5		-7	53	65	26	-56	10
	214	283	35		23	508	95	35	-26	26.5
	213	250	19		7	46	79	29	-42	15
	155	175	10		-2	4	70	27	-50	12.5
	275	275	0		-12	144	60	24	-60	8
	54	41	-6		-18	341	54	23	-67	7
	342	107	-117		-129	16707	-57	3	-178	1
	296	365	35		23	510	95	26	-26	26.5
	230	154	-38		-50	2491	22	18	-98	3
	106	341	117		105	11066	178	29	57	39
	338	341	2		-10	109	62	25	-59	9
	231	25	-103		-115	13252	-43	6	-164	2
	138	163	13		1	0	73	28	-48	14
	288	338	25		13	169	85	30.5	-35	17.5
	180	329	74		62	3880	135	37	14	33
	186	367	90		78	6159	151	38	30	37
	271	335	32		20	404	92	34	-28	25
	279	338	29		17	295	90	32.5	-31	22.5
	279	338	29		17	295	90	32.5	-31	22.5
	288	338	25		13	169	85	30.5	-35	17.5
						57780		556		354.5

	P ₁	P ₂	d_{ik}	$\overline{d_{\bullet k}}$	$d_{ik} - \overline{d_{\bullet k}}$	$(d_{ik} - \overline{d_{\bullet k}})^2$	$b_{ikL} = d_{ik} - \theta_L$	$R(b_{ikL})$	$b_{ikU} = d_{ik} - \theta_U$	$R(b_{ikU})$
sequence 2 TR	230	279	25	-24	48	2343	25	19.5	25	35.5
	367	341	-13		11	117	-13	16	-13	32
	368	268	-50		-26	685	-50	5	-50	12.5
	331	221	-55		-31	985	-55	4	-55	11
	131	163	16		39	1556	16	17	16	34
	338	268	-35		-11	125	-35	7.5	-35	17.5
	338	271	-33		-10	90	-33	10	-33	21
	341	280	-30		-6	40	-30	11	-30	24
	306	263	-22		2	5	-22	12	-22	28
	171	138	-17		7	47	-17	13	-17	29
	50	21	-14		10	91	-14	14.5	-14	30.5
	305	375	35		59	3461	35	21	35	38
	367	183	-92		-68	4602	-92	1	-92	4
	338	268	-35		-11	125	-35	7.5	-35	17.5
	343	275	-34		-10	102	-34	9	-34	20
	344	175	-85		-61	3708	-85	2	-85	5
	194	244	25		49	2384	25	19.5	25	35.5
	375	346	-14		10	91	-14	14.5	-14	30.5
						20558				

Since IC^{90} for $\frac{\mu_T}{\mu_R}$ is included in the confidence interval required for bioequivalence (0.8;1.25) it results that the tested formulations are therapeutically equivalent.

Nonparametric methods

Since we have no certitude that the areas under the pain curves are normally distributed and the amount of data is not sufficient to obtain a reliable testing concerning normality, it was considered useful to apply also non-parametric methods in testing the bioequivalence.

Wilcoxon-Man Whitney two one-sided test for bioequivalence [18]

For the standard 2x2 crossover design consisting of a pair of dual sequences (i.e. RT and TR), the distribution – free Wilcoxon rank sum test can be applied directly to the two one-sided tests concerning bioequivalence [19, 20, 21]. Using the above standard notations we obtained:

$$\theta = \mu_T - \mu_R$$

The usual set of unilateral hypotheses concerning bioequivalence are:

$$H_{01} : \theta_L^* \leq 0 \quad \text{vs} \quad H_{A1} : \theta_L^* > 0 \quad \text{where} \quad \theta_L^* = \theta - \theta_L \quad \text{and}$$

$$H_{02} : \theta_U^* \geq 0 \quad \text{vs} \quad H_{A2} : \theta_U^* < 0 \quad \text{where} \quad \theta_U^* = \theta - \theta_U$$

The estimates of θ_L^* and θ_U^* can be obtained from the linear combination (contrast) of period differences d_{ik} , $i=1,\dots,n$; $k=1,2$. It resulted the following:

$$b_{hik} = \begin{cases} d_{ik} - \theta_h; & h=L, U \text{ for subjects in sequence 1} \\ d_{ik}; & \text{for subjects in sequence 2} \end{cases},$$

where: $i = \overline{1, n_k}$, $k=1,2$, $d_{ik} = (Y_{i2k} - Y_{i1k})/2$, and $h=L$ or U index for Lower respectively upper limits of confidence interval.

When there are no carryover effects, the expected value and variance of b_{hik} , are given by:

$$E(b_{hik}) = \begin{cases} \frac{1}{2}[(P_2 - P_1) + (\theta - 2\theta_h)] & \text{for } k=1 \\ \frac{1}{2}[(P_2 - P_1) + \theta] & \text{for } k=2 \end{cases}$$

The difference between the means of b_{hik} in the two sequences equals the formulation effect $E(b_{hi1}) - E(b_{hi2}) = (\theta - \theta_h) = \theta_h^*$

Let R_L be the sum of the ranks of the responses for subjects in sequence 1:

$$R_L = \sum_{i=1}^{n_1} R(b_{Li1}) \text{ and } W_L = R_L - \frac{n_1(n_1+1)}{2}.$$

For testing the second hypothesis we considered similarly $R_U = \sum_{i=1}^{n_1} R(b_{Ui1})$

and

$$W_U = R_U - \frac{n_1(n_1+1)}{2}$$

We reject H_{01} if $W_L > w_{1-\alpha}$, where $w_{1-\alpha}$ is the $(1-\alpha)$ th quantile of the distribution of W_L which can be found in tables for Mann – Whitney test, and H_{02} if $W_U < w_\alpha$; ($w_{1-\alpha} = n_1 n_2 - w_\alpha$)

Hence, bioequivalence is concluded if both H_{01} and H_{02} are rejected; that is, $W_L > w_{1-\alpha}$ and $W_U < w(\alpha)$

Analysis AUC data for the two formulations

We estimated the $-\theta_L$ and θ_U as 25% of the mean AUC for R (estimation of μ_R)

$$\overline{AUC_R} = \frac{\sum AUC_R}{n_1 + n_2} = 242 \quad ; \quad -\theta_L = \theta_U = 0.25 \cdot \overline{AUC_R} = 60$$

It was obtained $b_{L11} = d_{11} - \theta_L = -22 + 60 = 38$, etc.

The complete set of obtained values is given in table II. We ordered the values of b_{Lik} (b_{Uik})

$$R_L = \sum_{i=1}^{n_1} R(b_{Li1}) = 556; \quad W_L = R_L - \frac{n_1(n_1+1)}{2} = 352$$

$$R_U = \sum_{i=1}^{n_1} R(b_{Ui1}) = 354.5; \quad W_U = R_U - \frac{n_1(n_1+1)}{2} = 123.5$$

In tables it was found $w_\alpha = W_{21;18;0.05} = 508$ and $w_{1-\alpha} = n_1 n_2 - w_\alpha = 251$.

Since $123.5 < 508 \Rightarrow W_U < w_\alpha$ and $352 > 251 \Rightarrow W_L > w_{1-\alpha}$, it was obtained that the products are bioequivalent.

An estimator and the confidence interval associated with Wilcoxon signed rank statistic based of Hodges - Lehmann estimator

Let us consider the Wilcoxon signed rank test [22]. We can compare n pairs of values (X_i, Y_i) , $i=1, \dots, N$ and $Z_i = (X_i - Y_i)$. To compute the statistics T^+ it is necessary to compute the absolute values $|Z_1|, \dots, |Z_n|$ and sort them ascending from the least to the greatest. Let r_i denote the rank of $|Z_i|$ and d the random variable $d_i = 1$ if $Z_i > 0$ and $d_i = 0$ if $Z_i < 0$

Let T^+ be the sum of positive ranks. Then $T^+ = \sum d_i r_i$.

The mean of T^+ is $E(T^+) = E\left(\sum_{i=1}^N d_i r_i\right) = \sum_{i=1}^N r_i E(d_i)$.

But $E(d_i) = 1 \cdot \frac{1}{2} + 0 \cdot \frac{1}{2} = \frac{1}{2}$ and consequently $E(T^+) = \sum_{i=1}^N r_i \frac{1}{2} = \frac{N(N+1)}{4}$.

We can consider the two sided test for the effect of treatment θ :

$H_0: \theta = 0$ $H_a: \theta \neq 0$ at the α level of significance, by comparison of T^+ with w_α and $w_{1-\alpha}$, quantiles of Wilcoxon repartition function.

An estimator of the treatment effect θ and confidence interval for differences of means was given by Hollander and Wolfe [23, 24] based on the Hodges-Lehmann [25] estimator $\hat{\theta}$, defined by the equation:

$$\hat{\theta} = \text{median} \left(\frac{Z_i + Z_j}{2}, i \leq j = 1, \dots, n \right)$$

The $n(n+1)/2$ averages $(Z_i + Z_j)/2$, $i \leq j = 1, \dots, n$, are called Walsh [26] averages. If we define W^+ the number of positive Walsh averages, then (when there are no ties among the $[Z]$'s and none of the Z 's is zero) W^+ is identical with T^+ . This result complies with Tukey [27].

The estimator $\hat{\theta}$ is relatively insensitive to outliers. This procedure was applied by Steinijens and Diletti [28] to differences of pharmacokinetic data. In fact their statistical model is very simple, neglecting both sequence and period effects.

They considered $D_{ij} = d_{i2} - d_{j2}$ or, in another form $D_{ij} = o_{i2} + o_{j2}$

$$E(o_{i1}) = E(d_{i1}) = \frac{1}{2}(P_2 - P_1) + \frac{1}{2}(F_T - F_R) = \frac{1}{2}(F_T - F_R)$$

$$E(o_{i2}) = E(-d_{i2}) = -\frac{1}{2}(P_2 - P_1) - \frac{1}{2}(F_R - F_T) = \frac{1}{2}(F_T - F_R)$$

$$E(D_{ij}) = E(o_{i1} + o_{j2}) = (F_T - F_R)$$

Then we can compute the differences inside sequences also as follows:

$$D_{ij} = d_{i1} - d_{j1} \text{ or } D_{ij} = d_{i2} - d_{j2}$$

Denote the ordered set of $n_1 n_2$ differences $D_{i,i'}$ by $D(1) \langle D(2) \langle \dots \langle D(n_1 n_2) \rangle \dots \rangle \rangle$.

The median of $\{D(i), i = 1, 2, \dots, n_1 n_2\}$ is the a distribution – free point estimator of $\theta = \mu_T - \mu_R$, which is also known as the Hodges – Lehmann estimator, that is:

$$\tilde{\theta} = \begin{cases} \frac{1}{2} \left[D\left(\frac{n_1 n_2}{2}\right) + D\left(\frac{n_1 n_2}{2} + 1\right) \right], & \text{if } n_1 n_2 \text{ is even} \\ D\left(\frac{n_1 n_2 - 1}{2} + 1\right), & \text{if } n_1 n_2 \text{ is odd} \end{cases}$$

The lower and upper limits for the $(1 - 2\alpha) \cdot 100\%$ distribution – free confidence interval for $\theta = \mu_T - \mu_R$ are given by:

$$L_w = D[w(\alpha)] \text{ and } U_w = D[w(1 - \alpha) + 1]$$

where $D[w(\alpha)]$ and $D[w(1-\alpha)+1]$ are the $[w(\alpha)]$ th and $[w(1-\alpha)+1]$ th order statistics of $D(1), D(2), \dots, D(n_1 n_2)$.

It was applied the method for AUC. We can calculate for each subject the following:

$$d_i = \ln(AUC_T^i) - \ln(AUC_R^i) = \ln\left(\frac{AUC_T^i}{AUC_R^i}\right) = \ln r_i \quad \text{and}$$

$$\frac{d_i + d_j}{2} = \frac{\ln r_i + \ln r_j}{2} = \ln \sqrt{r_i r_j}$$

In fact the method calculates the geometric means of ratios for all possible pairs of subjects, *id est* for $\frac{N(N+1)}{2}$ pairs, including the pair (R, R), for the same subject. The values of geometric means were ordered. The inferior and superior limits for the 90 % confidence intervals are found in Wilcoxon tables.

The T/R ratio for the subject number 1 is $\frac{AUC(T)}{AUC(R)} = \frac{293}{338} = 0.87$

We further need the geometric means of the pair of ratios. For the first subject combined with itself it results $\sqrt{0.87 \cdot 0.87} \approx 0.87$.

For subject 1 combined with subject 2, it results $\sqrt{0.87 \cdot 1.03} \approx 0.94$.

For the entire group of 39 subjects there are $\frac{N(N+1)}{2} = \frac{39 \cdot 40}{2} = 780$

combinations. From tables associated with Wilcoxon distribution can be found that ranks are included with 90% confidence between 251 and 508. The respective ranks belong to values 1.02 and 1.24. Consequently,

$$CI^{90} \text{ is } (1.02, 1.24)$$

i.e. the formulations are therapeutic equivalent.

Conclusions

Application of cross-over comparative studies in testing therapeutic equivalence have the advantages of a greater power of statistical tests following compensation of intervariabilities.

Comparison of the therapeutic effects of analgesic compositions pain curves in an interval after administration to patients suffering of headaches could be undertaken based on comparison of pain curves.

Integration of areas under the pain curves led to a global endpoint AUC which could be compared using parametric and nonparametric methods from the statistical tests for evaluation of bioequivalence.

If the 90 % confidence interval for the ratio of means of areas under the curve was included in the interval 80 – 125 %, the products were considered as therapeutically equivalent.

The results of all applied tests indicated a therapeutic equivalence of the formulations, in spite of the fact that concentrations of active components in Algopirin[®] tablets are less than half of the doses in Excedrin[®].

From a global, “efficacy plus safety”, point of view, Algopirin[®] can be considered as an alternative treatment to Excedrin[®] at least in the case of patients with gastric and hepatic sensibility.

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