Rapid development of tolerance to dipyridamole-associated headaches

J. G. W. Theis,¹ G. Deichsel² & S. Marshall^{2,3}

Departments of ¹Clinical Research and ²Biostatistics, Boehringer Ingelheim Pharma KG, Biberach, Germany, and The University of Reading³, Berkshire, United Kingdom

Aims In the Second European Stroke Prevention Study headaches associated with dipyridamole frequently (8% of patients taking dipyridamole or dipyridamole plus acetylsalicylic acid (ASA) *vs* 2% of patients taking ASA or placebo) led to discontinuation of therapy. We have now used data from a recent trial comparing the bioequivalence of two formulations of the fixed combination of 200 mg dipyridamole in an extended release formulation and 25 mg ASA to explore predicting factors for headaches associated with this drug combination.

Methods The bioequivalence trial employed a two-way crossover, randomised, open design. Trial medication was given for two periods of five days separated by a 72 h washout period. Statistical methods were employed to explore the prevalence, the time course, and the relation to individual pharmacokinetic parameters of treatment associated headaches.

Results Headache episodes, being mostly mild and transient, rapidly declined from 67% of the volunteers on the first day of treatment to 3% on the final days of treatment (days 4–5 of the second period). During the first days the prevalence of the headaches peaked 2–3 h after the morning administration, which coincided with the peak of the plasma concentrations of dipyridamole. The occurrence of headaches was not related to interindividual differences of the pharmacokinetic parameters.

Conclusions The rapid decrease in the incidence of headaches over time implies that most patients quickly develop tolerance to dipyridamole-associated headaches. Appropriate information given to the patient when prescribing and dispensing dipyridamole/ASA may reduce early withdrawals from treatment and increase compliance.

Keywords: adverse events, dipyridamole, headaches, stroke prevention

Introduction

The fixed combination of 200 mg dipyridamole in an extended release formulation and 25 mg ASA provides a safe and effective treatment to provide secondary prevention of stroke as demonstrated by the Second European Stroke Prevention Trial (ESPS2) [2, 3]. Considering these benefits it is unfortunate that 8.0% of the patients enrolled in the dipyridamole or dipyridamole/ASA arms of the ESPS2 trial withdrew from treatment because of headaches compared to only 2.1% of the patients enrolled in the ASA or placebo arms [3]. Patients typically withdrew early, in particular between enrolment and the first follow up visit after one month [3].

Recently, minor changes in the production process of the capsules containing the fixed combination of extended release dipyridamole with ASA led to the decision to conduct a bioequivalence trial involving the product which was used in the pivotal clinical study and the commercial product to date. This was an opportunity to further analyse the prevalence, the relation to the pharmacokinetic parameters, and the time course of headaches during dipyridamole/ASA treatment.

Methods

Trial design

This bioequivalence trial employed a two-way crossover, randomised, open design which pharmacokinetically proved bioequivalence between the two formulations

Correspondence: Dr J. G. W. Theis, Clinical Research, Boehringer Ingelheim Pharma KG, D-88397 Biberach an der Riss, Germany. Fax: +49 7351 542178. E-mail: jochen.theis@bc.boehringer-ingelheim.com.

Received 17 August 1998, accepted 30 July 1999.

used. Each treatment period consisted of 7 days. Capsules containing 200 mg dipyridamole extended release formulation and 25 mg ASA originating either from a batch of the ESPS2 study or from a representative production batch were given twice daily at approximately 08.00 h and 18.00 h on days 1 to 4 and in the morning of day 5. All doses were administered with 150 ml tap water.

The second period during which the volunteers received the alternate formulation followed immediately after day 7 of period one. Since the last dose of ASA/extended release dipyridamole was given in the morning of day 5, there was a washout period of 72 h between the last dose of period 1 and the first dose of period 2. This washout period was not sufficient for complete elimination of dipyridamole but was deemed appropriate because determination of pharmacokinetics of the dipyridamole part of the preparation at steady state was the main objective of the study.

A total of 36 healthy volunteers (mean age 33 years, range 19–54 years), 18 male and 18 female were enrolled in the trial. Due to this relatively large number, the healthy volunteers were divided into two cohorts. After the first cohort of 16 volunteers had completed the two treatment periods of the study, the second cohort of 20 volunteers started taking the trial medication.

The trial was performed in an ambulatory setting. The volunteers reported to the Human Pharmacology Centre each morning to have blood samples taken, to take the medication under supervision and to eat a standardised breakfast before they were allowed to return home or to work. The evening dose was taken at home. Compliance was assessed by having the volunteers call the pharmacokineticist immediately after substance intake. In the morning of day 5 the volunteers were admitted to the Human Pharmacology Centre to obtain a pharmacokinetic profile at steady state.

The study was approved by the ethics committee of the Regional Medical Society Baden-Württemberg.

Exploratory analysis of factors possibly associated with the headaches

The healthy volunteers were advised to spontaneously report any adverse events. In addition, once daily each volunteer was asked the standardised question: 'How do you feel'. Any reported adverse events were stratified according to the WHO System Organ Class and rated according to severity (1=mild, awareness of a sign or symptom which is easily tolerated; 2=moderate, discomfort enough to cause interference with usual activity; 3=severe, incapacitating with inability to do work or usual activity). Only reported headaches which were considered part of the 'Central Nervous System Disorders'

according to WHO System Organ Class were included in this analysis. Therefore one reported adverse event of headaches which was recorded in the context of influenza-like symptoms (WHO System Organ Class 'Body as a Whole—General Disorders') was not included.

It was hypothesised that the headaches may be related to one or more of the following predictors: the achieved serum concentrations of dipyridamole (AUC_{ss} and $C_{max,ss}$) in each individual volunteer, the treatment with one of the two tested drug formulations (treatment), the sequential treatment periods (period) or one of the two patient cohorts (cohort). The cohorts were included to account for potential external factors, i.e. specific climatic conditions.

For statistical analysis the reported episodes of headaches were tabulated and compared with respect to treatment, period and cohort. To investigate a possible association of the headaches with the two pharmacokinetic parameters $C_{max,ss}$ and AUC_{ss} or the treatment formulation or period, a non parametric analysis according to Akritas *et al.* [1] was performed as follows: Dependent outcome variable of the model was the product of the severity of the headache episodes and their duration (hours). This product was chosen as the outcome variable because it reflects two components of the headaches that are a measure of subjective discomfort. The following variables were used as possibly explanatory, independent variables: Period (whether the headaches were reported during the first or second treatment period), treatment (whether the headaches were reported during treatment with ASA/extended release dipyridamol from the ESPS2 batch or the representative production batch), and the two pharmacokinetic parameters, $C_{max,ss}$ and AUC_{ss} of each individual.

Additionally, the effects of period, cohort and period $\times$ cohort interaction on highest headache severity during either period were assessed by fitting logistic models for ordered categories (syn.: proportional odds models) to the frequency data in table 1 using SAS PROC LOGISTIC. Basic model assumptions are that headache severity is a continuous variate which is, however, observable only on a four category scale, i.e. none, mild, moderate and severe. Thresholds separating the categories and the change of the distribution of severity categories of period 2 relative to period 1 are estimated in logistic units [4].

Finally, the headaches quantified as described in the results section were determined for each treatment day and tabulated for comparison.

Only the first 4 days of each period were analysed to avoid introduction of confounding factors related to the admittance of the healthy volunteers to the Human Pharmacology Centre on day 5 of each period and the repeated blood sampling on that day.

Results

During the entire trial at least one episode of headaches was reported by 72% of the volunteers. These headaches were mostly mild (Table 1) and transient (69 out of a total of 82 episodes lasted for less than 12 h). All patients recovered fully from the headache episodes. Two volunteers of the first cohort elected to withdraw from treatment on the first and second days of the first period, respectively, because of severe headaches. One subject from the second cohort discontinued the trial at the end of the first period because of an adverse event which was not related to the trial medication.

The headache episodes were equally distributed between the two treatments, 39 occurring during treatment with the production batch compared with 43 during treatment with the ESPS2 batch. They were also distributed evenly between the two patient cohorts, 38 occurred within cohort 1, which contained 16 volunteers (i.e. 2.4 episodes per volunteer), and 44 headaches occurred during cohort 2 containing 20 volunteers (i.e. 2.2 per volunteer).

There was no statistical association between the headaches (quantified by the product of the intensity score 0–3 of the headaches and their duration) and the two pharmacokinetic parameters $C_{\max, ss}$ and AUC_{ss} ($P=0.72$ and $P=0.44$, respectively, determined by a non parametric analysis according to Akritas *et al.* [1]). In contrast, more volunteers experienced headaches during their first treatment period than during their second treatment period (Table 2). The significance of the relation of the periods to the headaches was confirmed by the result of the non parametric analysis ($P=0.0002$ for the variable 'period'), while the sequence of the treatment with the two different formulations of dipyridamole/ASA was not significant ($P=0.43$).

Headache severity was only associated with the explanatory variate period ($P=0.0001$) in the logistic analysis for ordered categories. The model with period as only

explanatory variate for headache severity yields a change estimate of 1.83 logistic units towards 'no'. The antilog $e^{1.83}=6.2$ is an odds ratio. This indicates that the odds of experiencing a certain headache intensity or a lower one in period 2 are 6.2-times the odds of experiencing such a headache intensity in period 1 (Figure 1).

When analysing the headaches on a day by day basis, it became apparent that the headaches rapidly declined within days of the start of the treatment. Headaches (of any duration and intensity) were reported by 67% of the volunteers on the first day of the first period and by 30 to 40% of the volunteers during the second to fourth days of the first period. This drop in reported headaches was even more pronounced if duration and intensity of the headaches were factored in. Interestingly, the decline in headaches continued through the short and incomplete washout phase into the second treatment period (Table 2).

The prevalence of headaches usually peaked 2–3 h after the morning dose (Figure 2). A smaller second peak may be present on days 1–4 about 2–3 h after the evening dose but could not be clearly determined. These peaks in prevalence coincide with the broad peaks in plasma concentrations of dipyridamole at steady state, which were measured approximately 2 h after the dose.

Discussion

It has been known for decades that headaches are a common adverse effect of treatment with dipyridamole [5]. The most likely explanation for the extremely high incidence of headaches in our bioequivalence trial is the health and young age of the trial population. In contrast to elderly patients and especially to stroke patients these young healthy volunteers are likely to have a much higher cerebral vasodilator capacitance [6] allowing for increased vasodilator headaches.

In a bioequivalence trial without a placebo arm it is difficult to determine whether adverse events are related to the trial drug or to other conditions. The fact that the

Table 1 Prevalence of the headaches (mild, moderate, severe) by period and cohort.

	None	Mild	Severity Moderate	Severe	Total
<i>Period 1</i>					
Cohort 1	4 = 25%	3 = 19%	6 = 36%	3 = 19%	16 = 100%
Cohort 2	6 = 30%	11 = 55%	2 = 10%	1 = 5%	20 = 100%
Observed Total	10 = 28%	14 = 39%	8 = 22%	4 = 11%	36 = 100%
Fitted Total	27.2%	40.5%	20.5%	11.8%	100%
<i>Period 2</i>					
Cohort 1	9 = 64%	4 = 29%	0	1 = 7%	14 = 100%
Cohort 2	14 = 74%	4 = 21%	1 = 5%	0	19 = 100%
Observed Total	23 = 70%	8 = 24%	1 = 3%	1 = 3%	33 = 100%
Fitted Total	70.0%	22.9%	5.0%	2.1%	100%

The differences between the periods were statistically significant (see Figure 1).

Table 2 Headaches per day and period.

The table shows indicators for the quantity of headaches on each of the first 4 days of the two treatment periods. The first data column represents the product of headache severity (mild = 1, moderate = 2, severe = 3) and headache duration per day, the second column the duration of headaches of any severity per day and the third column the number of volunteers experiencing any headache per day. The same data are presented on the right side of the table as an indicator of risk per volunteer.

Period	Onset on day	Cumulated severity × duration per day (1)	Cumulated duration of any severity per day (2)	Number of volunteers with any headache per day (3)	Number of volunteers at risk	(1) over volunteers at risk	(2) over volunteers at risk	(3) over volunteers at risk
1	1	512.25	293.25	24	36	14.23	8.15	0.67
	2	185.50	157.00	13	35	5.30	4.49	0.37
	3	93.00	57.00	11	35	2.66	1.63	0.31
	4	83.50	50.25	11	34	2.46	1.48	0.32
2	1	30.75	23.75	8	33	0.93	0.72	0.24
	2	17.00	9.00	2	33	0.52	0.27	0.06
	3	20.00	20.00	4	33	0.61	0.61	0.12
	4	1.00	1.00	1	33	0.03	0.03	0.03

Figure 1 Fitted logistic distributions modelling change of headache severity between periods. Prevalences of worst category of headache experienced by period as obtained by fitting a logistic (syn.: proportional odds) model. The figure displays the shift of the distribution towards 'no headache' in period 2.

trial was performed with two successive cohorts gave us the opportunity to determine whether changing external conditions such as weather changes may have led to a higher prevalence of headaches in one of the cohorts. This was negated by the absence of such differences between the two cohorts.

The two formulations of ASA/extended release dipyridamol were clearly proven to be bioequivalent by this trial. In keeping with this kinetic bioequivalence, the prevalence of headaches was similar during treatment with both of the two formulations. Comparison of the mean time course of the dipyridamole plasma concentrations at steady state with the time course of the prevalence of headaches suggests that the headaches are generally related to the plasma concentrations of dipyridamole. Our analysis did not reveal that individuals with higher values of the two pharmacokinetic parameters $C_{\max,ss}$ and AUC_{ss} were more likely to experience headaches. However, this latter finding needs to be interpreted with caution because of the limitations of the methodology. While the headaches were most prevalent during the initial days of each period, $C_{\max,ss}$ and AUC_{ss} were determined at steady state on the fifth day of each period. Consequently, the finding of a lacking correlation between the pharmacokinetic parameters and the occurrence of headaches is based on the assumption that $C_{\max,ss}$ and AUC_{ss} on day 5 are representative for the pharmacokinetics during the preceding 4 days in each of the individual volunteers.

Interestingly, headaches were reported far more frequently during the first period of treatment than during the second regardless of the sequence of treatment formulations. Moreover, the headaches further declined

Figure 2 Prevalence of headaches during each hour of the trial. Time point zero is the time point of the first dose of the first period. Time point 168 is the first dose of the second period. No drug was taken after the dose at 96 h and before the first dose of the second period (washout period (— / —), which lasted for 72 h). Drug intake was at 0, 10, 24, 34, 48, 58, 72, 82 and 96 h and 168 + 0, 168 + 10 h, etc. For comparison: plasma concentrations of dipyridamole reached steady state after approximately 48 h and showed broad peaks approximately 2 h after the doses.

during each of the periods. In fact, the prevalence of headaches observed after day one of the second period was only slightly higher or even similar to the prevalence of headaches generally reported in a healthy population (13–15% during the last 72 h before questioning [7]) or reported after placebo administration in phase I studies (1.7% [8] and 6.7% [9]).

Before concluding that the observation of the spontaneous, rapid decline in headache prevalence throughout the first days of treatment is drug-related, possible confounding factors need to be excluded. One possible confounding factor may be a general tendency of the healthy volunteers to report adverse events at the beginning of a trial and to become less anxious about such events over time. However, we have never observed such a reporting behaviour at our Human Pharmacology Centre hence making this an unlikely explanation. Another possible confounding factor leading to headaches in clinical trials may be caffeine withdrawal. It has been reported that 52% of volunteers who were used to drinking a moderate amount of coffee experienced a withdrawal syndrome which included headaches upon cessation of consumption [10]. However, being aware that headaches are known to be a common adverse effect of dipyridamole and that caffeine antagonises some of the pharmacodynamic effects of dipyridamole [11], the consumption of coffee was expressly allowed throughout this bioequivalence trial. Consequently, the headaches observed in this trial cannot be attributed to caffeine withdrawal. In conclusion, the most likely explanation for the great and quick decrease in prevalence, duration, and intensity of headaches over time is a rapid develop-

ment of tolerance to this particular adverse effect of dipyridamole.

During the first month of the ESPS2 trial headaches were significantly more frequent in the dipyridamole and dipyridamole plus ASA groups than in the ASA or placebo groups [2, 3]; this difference was not observed at later visits. The drop in headache prevalence in the dipyridamole groups exceeded the rate of headache-related treatment cessation, making the development of tolerance to the dipyridamole-associated headaches the most probable explanation for the decline.

Our analysis clearly demonstrates that the experienced headaches are of transient nature and decline in prevalence, severity, and duration in the vast majority of cases. Appropriate information given to the patient when prescribing and dispensing dipyridamole/ASA may reduce early withdrawal from the treatment and may increase compliance. Hence such action will ensure that the patient at risk of a future stroke will truly experience the prophylactic effect of the fixed combination of extended release dipyridamole with low dose ASA.

References

- 1 Akritas MG, Arnold SF, Brunner E. Nonparametric Hypotheses and Rank Statistics for Unbalanced Factorial Designs. *J Am Stat Assoc* 1997; **Vol.92**, No.437, 258–265.
- 2 Diener HC, Cunha L, Forbes C, Sivenius J, Smets P, Lowenthal A. European Stroke Prevention Study 2: dipyridamole and acetylsalicylic acid in the secondary prevention of stroke. *J Neurol Sci* 1996; **143**: 1–13.
- 3 European Stroke Prevention Study 2: efficacy and safety data. *J Neurol Sci* 1997; **151** (Suppl): S1–S77.

- 4 McCullagh P. Regression Models for Ordinal Data. *J R Statist Soc B* 1980; **42**: 109–142.
- 5 Acheson J, Danta G, Hutchinson EC. Controlled trial of dipyridamole in cerebral vascular disease. *Br Med J* 1969; **1**: 614–615.
- 6 Meyer JS, Terayama Y, Konno S, Margishvili GM, Akiyama H, Rauch RA *et al.* Age-related cerebrovascular disease alters the symptomatic course of migraine. *Cephalalgia* 1998; **18**: 202–208.
- 7 Reidenberg MM and Lowenthal DT. Adverse nondrug reactions. *N Engl J Med* 1968; **279**: 678–679.
- 8 Sibille M, Deigat N, Janin A, Kirkesseli S, Durand DV. Adverse events in phase-I studies: a report in 1015 healthy volunteers. *Eur J Clin Pharmacol* 1998; **54**: 13–20.
- 9 Rosenzweig P, Brohier S, Zipfel A. The placebo effect in healthy volunteers: influence of experimental conditions on the adverse events profile during phase I studies. *Clin Pharmacol Ther* 1993; **54**: 578–583.
- 10 Silverman K, Evans SM, Strain EC, Griffiths RR. Withdrawal syndrome after the double-blind cessation of caffeine consumption. *N Engl J Med* 1992; **327**: 1109–1114.
- 11 Smits P, Straatman C, Pijpers E, Thien T. Dose-dependent inhibition of the hemodynamic response to dipyridamole by caffeine. *Clin Pharmacol Ther* 1991; **50**: 529–537.