Comparative Bioavailability of Two Oral Nimodipine Formulations after Administration to 24 Healthy Volunteers

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Abstract

Objective and Study Participants: To investigate the comparative bioavailability of two oral 30mg film-coated tablet formulations of nimodipine, Brainal® (test formulation) and Nimotop® (reference formulation) after replicate administration of a single 60mg dose (2 × 30mg) of both formulations to 24 healthy volunteers.

Results: The data obtained in this study demonstrated the bioequivalence of the two formulations when the individual bioequivalence approach, which takes into account both the intraindividual and the interindividual variances, was applied. The assessment of individual bioequivalence was based on the result of the upper 90% one-sided confidence limits: 2.47 for maximum plasma concentration (C_{max}) and 2.77 for area under the plasma concentration-time curve (AUC_{0-∞}), both lower than the critical value, F_{cr} = 4, thus showing the bioequivalence between the two formulations.

Conclusion: The results indicate the bioequivalence and good tolerability of both nimodipine formulations. The application of the individual bioequivalence approach shows the bioequivalence of the two nimodipine formulations.

Nimodipine, isopropyl-2-methoxyethyl-1,4-dihydro-2,6-dimethyl-4-(3-nitrophenyl) -3,5-pyridine dicarboxylate, is a dihydropyridine calcium antagonist that has been shown to dilate cerebral arterioles and increase cerebral blood flow in animals and humans.[1] It acts by inhibiting the contractile process in the vascular smooth muscle via blockade of the slow Ca^{2+} channels in the cell membrane. Because of its special selectivity for brain blood vessels, it is used mainly in the prevention and treatment of the delayed ischaemic neurological deficits that frequently occur in patients with subarachnoid haemorrhages (SAH). In most clinical trials the treatment regimen has consisted of an intravenous infusion of 1 to 2 mg/h for up to 14 days followed by a period of oral therapy of 45 to 60mg every 4 hours for up to 7 days.

Nimpodipine has been assessed in patients diag-
nosed with Alzheimer’s disease, senile dementia of Alzheimer type, primary degenerative dementia, multi-infarct dementia and related disorders such as ‘impaired brain function in old age’. [2]

Nimodipine is rapidly absorbed after oral administration and extensively metabolised in the liver by dehydrogenation of the dihydropyridine ring and demethylation of the methoxy group at position 3 either before or after the formation of a pyridine analogue. Subsequent metabolism involves ester hydrolysis and hydroxylation of a methyl group. Following a single oral dose of 14C-labelled nimodipine to healthy volunteers, about 50% of the dose was excreted in urine over 4 days. This was almost exclusively in the form of metabolites, as no unchanged nimodipine nor pyridine analogue of nimodipine was detected. [1] Binding to plasma proteins is 98%.

The pharmacokinetic parameters of nimodipine show a very high intra- and intervariability when it is administered via the oral route. Substantial differences are found among different formulations and for a particular formulation when used in different studies. [3] After a single oral dose of 60mg in capsules to healthy participants, peak plasma concentrations of 59 μg/L to 127 μg/L (mean: 80 μg/L) were attained in about 0.7 hours (within 0.25 to 1 hour). The mean terminal half-life of nimodipine after a single dose of 60mg to healthy volunteers ranged from 3 to 11 hours. Thus, studies carried out with healthy volunteers after a single dose of 60mg nimodipine showed maximum concentration (Cmax) values of 116.5 ± 74.3 μg/L when the product was given as a solution and 20.6 ± 11.8 μg/L when it was administered as tablets. [4] In these studies, the plasma levels of nimodipine were determined by gas chromatography and electronic capture detection (GC-ECD).

Nimodipine release from different tablet formulations is highly variable and depends greatly on the qualitative-quantitative composition and on the experimental conditions followed during the manufacturing process. The only way to assess the quality, efficacy and tolerability of a given formulation (e.g. Brainal®) is to correlate the in vitro dissolution profile with the kinetic results obtained in healthy volunteers versus a reference formulation by applying a proper design.

This paper describes a comparative bioavailability study of two oral nimodipine formulations (Brainal®, manufactured by Laboratorios Andrómaco, and Nimotop®, manufactured by Bayer, used as the reference product) administered to healthy volunteers as a single dose according to a replicate design: participants received both test (T) and reference (R) formulations on two occasions following two sequences: TRRT or RTTR.

**Study Participants and Methods**

**Study Population**

Twenty-four normal healthy caucasian male volunteers, all belonging to the ASTER Clinical Research Center, Paris, France, volunteer non-smokers panel, were enrolled in the study. The participants were aged between 18 and 35 years, and their weight was within 15% of the ideal body-weight of the scale proposed by the Metropolitan Insurance Company.

All participants underwent a prestudy medical examination, ECG recording, and haematological and urinalysis in the 2 weeks prior to the clinical start.

The study was approved on 24 October 1997 by the Ethics Committee of the Ambroise Paré Hospital (92100 Boulogne) ‘Comité Consultatif de Protection de Personnes dans la Recherche Biomédicale’. All participants gave written informed consent before participation.

**Study Design**

This study was open for the clinical part, and blind for the analytical part. The clinical part was carried out at ASTER according to a randomised 4-way crossover study in a replicate design. Participants received both T (two 30mg film-coated Brainal® tablets) and R (two 30mg film-coated Nimotop® tablets) treatments as a replicate administration of the two treatments according to a 4-pe-