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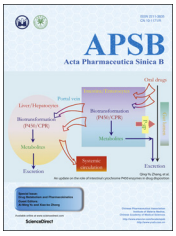

ORIGINAL ARTICLE

Effect of age on the pharmacokinetics of polymorphic nimodipine in rats after oral administration

Wenli Liu[a], Xiaona Wang[a], Ruilian Chen[a], Kaixuan Zhang[a], Yao Li[a], Yi Li[a], Duanyun Si[b], Junbo Gong[a,*], Dianshu Yin[c], Yongli Wang[a], Zhenping Wei[a,*], Mingshi Yang[d]

[a]*School of Chemical Engineering and Technology, Tianjin University, Tianjin 300072, China*
[b]*State Key Laboratory of Drug Delivery Technology and Pharmacokinetics, Tianjin Institute of Pharmaceutical Research, Tianjin 300193, China*
[c]*Pharmaceutical Research Institute, Shijiazhuang No. 4 Pharmaceutical Company, Shijiazhuang 052165, China*
[d]*Faculty of Pharmaceutical Science, University of Copenhagen, Copenhagen, Denmark*

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Abstract The previous investigation has proved that their existed pharmacokinetic difference between the different crystal forms of the polymorphic drugs after oral administration. However, no systemic investigations have been made on the change of this pharmacokinetic difference, resulted either from the physiological or from the pathological factors. In this paper, we used polymorphic nimodipine (Nim) as a model drug and investigated the effect of age difference (2- and 9-month old) on the pharmacokinetics after oral delivery in rats. As the results shown, for L-form of Nim (L-Nim), the $AUC_{0-24\,h}$ in 2-month-old rats was 343.68 ± 47.15 ng · h/mL, which is 23.36% higher than that in 9-month-old rats. For H-form of Nim (H-Nim), the $AUC_{0-24\,h}$ in 2-month-old rats was 140.91 ± 19.47 ng · h/mL, which is 54.64% higher than that in 9-month-old rats. The $AUC_{0-24\,h}$ ratio between H-Nim and L-Nim was 2.44 in 2-month-old rats and 3.06 in 9-month-old rats. Since age difference could result in unparallelled change of the absorption and bioavailability of the polymorphic drugs, the results in this experiment are of value for further investigation of crystal form selection in clinical trials and rational clinical application of the polymorphic drugs.

*Corresponding authors. Tel.: +86 22 27890336.
E-mail addresses: junbo_gong@tju.edu.cn (Junbo Gong), zpwei2000@sina.com (Zhenping Wei).

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1. Introduction

According to the previous investigation, the *in vivo* absorption and bioavailability of polymorphic drugs may be different due to the crystal form modification, which usually result in the change of the physical and chemical properties[1–3]. Wang et al.[4] reported that after oral administration of A and B polymorphs of *m*-nisoldipine to rats, the area under the plasma concentration-time curve (AUC) of *m*-nisoldipine B was 1.17-fold higher than that of A, the maximum plasma concentration (C_{max}) and the time to reach a C_{max} (T_{max}) values showed statistically significant differences between *m*-nisoldipine A and B. They concluded that the crystal form could influence the rate and extent of absorption and bioavailability of *m*-nisoldipine. Du et al.[5] investigated the *in vitro* and *in vivo* correlation of Forms I, II and III of agomelatine, and found that the agomelatine polymorphic forms with faster dissolution rates *in vitro* would increase the rate and extent of oral absorption *in vivo*.

So far, numerous works have proved the physiological and pathological effects on the absorption and elimination of non-polymorphic drugs. These influencing factors generally refer to age, diabetes, nephropathy and hepatopathy[6–9]. Considering the factor of age, possible reasons for these pharmacokinetic changes are diverse and complex. Natural developmental maturation and aging of gastrointestinal tract, liver and renal could lead to different changes in drug absorption, metabolism and clearance, and transport and elimination[10–14]. A recent population pharmacokinetic study showed statistically significant differences in carbamazepine pharmacokinetics between elderly and relatively young epileptic patients[15]. Tarral and Merdjan[16] noted the prolonged elimination half-life of oral minodronic acid in elderly subjects and they concluded that it could be due to the reduced renal function. As Zhou et al.[17] reported, the higher exposure of minodronic acid in the elderly subjects could be attributed to the reduction of renal blood flow, glomerular filtration rate and the bone uptake of the elderly.

According to the above investigations, the oral bioavailability of different crystal forms in healthy subjects might vary upon the physiological status. However, so far, little work has been done on the investigation as how the physiological factors influence the pharmacokinetics of the polymorphic drugs. Nim has high permeability and poor solubility, which belongs to Class II of the Biopharmaceutical Classification System[18]. Moreover, Nim is a kind of polymorphic drug presenting two different crystal forms, including H-Nim and L-Nim. As Grunenberg et al.[18] reported, H-Nim, a meta-stable form, is a racemic compound that exhibits a characteristic melting point at 124 °C, while L-Nim, a stable form, is a conglomerate that melts at 116 °C.

In this experiment, the effect of age on the pharmacokinetic properties of polymorphic drug was investigated in rats of 2- or 9-month old with Nim as a model polymorphic drug. The work may help us to choose the suitable crystal form of the polymorphic drugs in their dosage form design, clinical trial, as well as the rational clinical application.

2. Materials and methods

2.1. Materials

H-Nim (99.3%) was kindly supplied by Ruikang Pharmaceutical Co., Ltd. (Zhengzhou, China). L-Nim was prepared by recrystallization of H-Nim in diethyl ether in our laboratory. Methanol and acetonitrile of HPLC grade were purchased from Tianjin Jiangtian Chemical Technology Co., Ltd. (Tianjin, China). Diethyl ether was obtained from Real & Lead Chemical Co., Ltd. (Tianjin, China). All other reagents used were either of analytical or chromatographic grades. Nitrendipine as an internal standard was purchased from National Institutes for Food and Drug Control (Beijing, China).

2.2. Preparation of polymorphic Nim

H-Nim was sieved and the received powder with a particle size between 120 and 150 μm was used for further investigation.

L-Nim was prepared by recrystallization of H-Nim in ethyl ether. Generally, 1.0 g H-Nim was dissolved in 50 mL of ethyl ether at 30 °C to get a solution and then the solvent was evaporated by manually stirring with a glass rod in a draft cupboard in a water bath at 25 °C until a faint yellow powder was received. The obtained L-Nim was then stored in a desiccator for 24 h. The received L-Nim was sieved and the received powder with a particle size between 120 and 150 μm was used for further investigation.

2.3. Characterization of H-Nim and L-Nim

2.3.1. X-ray diffraction (XRD)

An X-ray diffractometer (X'Pert Pro, PANalytical B.V., Netherlands) with Cu-Kα radiation of wavelength 1.5406 Å (40 kV, 40 mA) was employed to study the crystalline form of H-Nim and L-Nim. The samples were then analyzed over a 2θ range of 2–35° with a scanning rate of 8°/min and step size of 0.02.

2.3.2. Differential scanning calorimetry (DSC)

Thermal analysis was carried out using a differential scanning calorimeter (DSC 1/500, Mettler-Toledo, Switzerland) for H-Nim and L-Nim. Samples in sealed aluminum pans were scanned from 25 to 150 °C with a heating rate of 10 °C/min under a dry nitrogen purge.

2.4. In vitro dissolution study

The dissolution of H-Nim and L-Nim in the medium of simulated gastric fluid (SGF, pH = 1.2 HCl) at 37 ± 0.5 °C were investigated with the paddle method at the rotation speed of 50 rpm using a dissolution apparatus (Type RC806, Tianda Tianfa Technology Co., Ltd., Tianjin, China). Thirty mg of drugs were dispersed into 250 mL of the dissolution medium. At the determined time points, a 5 mL aliquot of sample was withdrawn and filtered through 0.22-μm membrane filter. The filtered samples were finally assayed by UV spectrophotometry at 238 nm (UV765, Shanghai Precision Scientific Instrument Co., Ltd., China). Each test was conducted in triplicates. The concentration of Nim was calculated relative to a Nim reference of $y = 0.0592x + 0.0058$ with r^2 (correlation coefficient) value of 0.9998 (x is the concentration of Nim in μg/mL and y is the absorbance).

2.5. Pharmacokinetic study

Male Sprague–Dawley rats were obtained from the center for experimental animal reproduction, Academy of Military Medical Sciences, Tianjin, China. All animals received care in compliance with the guidelines outlined in the Guide for the Care and Use of