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Effect of lipid emulsion infusion on paliperidone pharmacokinetics in the acute overdose rat model: A potential emergency treatment for paliperidone intoxication

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ABSTRACT

Paliperidone prolongs cardiac repolarization in a concentration-dependent manner. Meanwhile, continuous infusion of intravenous lipid emulsion (ILE) has been established as a detoxification therapy for lipophilic drugs. However, this change in pharmacokinetics of various drugs following ILE administration remains to be clarified. Our objective is to clarify the effect of continuous infusion of ILE on the pharmacokinetics of overdosed paliperidone in rats. Paliperidone (20 mg/kg) was administered orally to free-moving male Wistar rats. Continuous infusion (initial loading dose: 4 ml/kg for 10 min, followed by 4 ml/kg/h for 12 h) of ILE or acetated Ringer's solution (AR) was initiated 30 min after paliperidone administration. Plasma concentration profile of paliperidone was monitored for 12 h after administration. The plasma concentration and tissue/plasma concentration ratios of paliperidone were compared between ILE and AR groups. The rat group infused with ILE showed a higher area under the concentration–time curve (mean [S.D.]: 6102 [900.9] *vs.* 3407 [992.1] ng h ml^{-1}, $p = 0.02$) and longer elimination half-time ($t_{1/2}$) (4.1 [0.9] *vs.* 2.2 [0.4] h, $p = 0.02$) compared with the AR group. Tissue/plasma concentration ratios of paliperidone were lower in ILE rats than in AR rats (1.98 [0.70] *vs.* 3.82 [1.47] in the heart, $p = 0.04$; 0.28 [0.29] *vs.* 1.27 [0.58] in the brain, $p < 0.001$). In conclusion, continuous infusion of ILE would reduce tissue distribution and prolonged the $t_{1/2}$ of paliperidone in rats. These results suggest that continuous infusion of ILE has potential as an emergency treatment for acute paliperidone intoxication.

1. Introduction

Paliperidone, the major active metabolite of risperidone, is a new second generation antipsychotic agent for the treatment of both positive and negative symptoms associated with schizophrenia. Paliperidone is readily distributed in the myocardium after administration, is established as a potent human *ether-a-go-go*-related gene blocker, and prolongs cardiac repolarization in a concentration-dependent manner (Titier et al., 2002; Vigneault et al., 2011). Cases of prolonged QT interval and syncope due to paliperidone overdose have also been reported (Catalano et al., 2001; Hough et al., 2011; Nishikage et al., 2002; Vieweg et al., 2013). Therefore, overdose of paliperidone may represent a life-threatening condition.

Intravenous lipid emulsion (ILE) consists of nanometer-sized droplets of triglyceride oils in water, stabilized by phospholipid surfactants (Damitz and Chauhan, 2015). Continuous infusion of ILE has been established as a detoxification therapy for several lipophilic drugs and toxicants (Bertrand et al., 2010: Damitz and Chauhan, 2015). In addition, Fettiplace MR et al. showed that ILE exhibits a rapid scavenging effect in rats, removing bupivacaine from organs including the heart and brain (Fettiplace et al., 2015). However, this change in pharmacokinetics of various lipophilic drugs following ILE administration, especially during the elimination phase, remains to be clarified.

The purpose of this study was to clarify the effect of continuous infusion of ILE on the pharmacokinetics of paliperidone.

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2. Materials and methods

2.1. Animals

A total of 22 male Wistar rats (Japan SLC, Inc., Japan) were included in this experiment. Experimental animal protocols and animal procedures used in this study were approved by the Ethics Review Committee of Mie University School of Medicine.

2.2. Treatments

Ten-week-old male Wistar rats were cannulated in both the carotid artery and jugular vein. At day 2 after cannulation, 20 mg/kg paliperidone (Tokyo Chemical Industry, Tokyo, Japan), setting to cause acute intoxication (European Medicine Agency, 2007), was administered orally by oro-gastric tube under free-moving conditions without anesthetic (paliperidone was dissolved in 0.1 M citric acid-hydrochloric acid buffer solution [pH 2.0] to yield 10 mg/ml). Continuous infusion (initial loading dose of 4 ml/kg for 10 min followed by 4 ml/kg/h for 12 h) of ILE (Intralipos injection 20%, Otsuka Pharmaceutical Factory Inc., Tokushima, Japan) or acetic Ringer's solution (AR, Solacet F, Terumo Corporation, Tokyo, Japan) were initiated 30 min after paliperidone administration. Aliquots (200 µl) of whole blood were collected from the carotid artery at 1, 2, 4, 8, and 12 h after paliperidone administration, 15 µl of 250 µM disodium ethylenediaminetetraacetate was added, and plasma was separated by centrifugation of blood at 14,000 × *g* for 3 min and immediately stored at − 20 °C for later analysis. In a separate experiment, rats were sacrificed 4 h after administration of paliperidone and blood, heart, and brain tissue samples were collected for the determination of paliperidone concentration in its free fraction in plasma and tissue.

2.3. Determination of paliperidone concentration in plasma and tissue

Whole heart and brain samples were combined, diluted 3 fold in normal saline by tissue weight, and homogenized. Concentrations of paliperidone in plasma and whole tissue homogenates were determined using a modification of a previously reported procedure (Olesen and Linnet, 1997). Plasma or whole tissue homogenate (50 µl) was added to 50 µl of 0.6 M sodium carbonate/bicarbonate buffer (pH 10) and internal standard (1 µg/ml risperidone [Tokyo Chemical Industry, Tokyo, Japan]). Hexane (500 µl) was added and sample tubes were gently rotated for 10 min at 4 °C before samples were separated into organic (upper) and aqueous (lower) layers by centrifugation at 14,000 × *g* for 5 min. The organic layer (approx. 450 µl) was transferred to a new microcentrifuge tube and evaporated to dryness under a vacuum at 20–25 °C for 15 min. The residue was dissolved in 100 µl acetonitrile, of which 5 µl was injected into the liquid chromatography with tandem mass spectrometry (LC-MS/MS) apparatus (Eksigent EkspertTM microLC 200 system, Eksigent, Redwood, CA) connected to a quadrupole time-of-flight TripleTOF 5600 mass spectrometer (AB Sciex, Framingham, MA). LC separation was achieved using a HOLO fused-core C18 column (0.5 × 50 mm, 2.7 µm, Eksigent) maintained at 40 °C and with a flow rate of 10 µl/min. The mobile phase consisted of 0.1% formic acid in water (solvent A) and 0.1% formic acid in acetonitrile (solvent B). The gradient used was 30% solvent B for 0.1 min; increased to 90% solvent B in 15 min; returned to 30% solvent B in 15.1 min; and re-equilibrated in 30% solvent B for 5 min. The TOF scan range was 100 to 1250 *m/z* and the declustering potential was 80 V. The MRM transitions monitored (collision energy) of paliperidone and risperidone (internal standard) were *m/z* 427.2 → 207.1 (36 V) and 411.2 → 191.1 (45 V) in positive ionization mode, respectively. The ion spray voltage was 5500 V. The linearity, accuracy, and precision of this assay method were evaluated (expressed as the percentage coefficient of variation [%CV]). Calibration curves were constructed for each paliperidone concentration using ten samples with concentrations ranging from 2.5 to 1000 ng/ml (2.5, 5.0, 10, 50, 100, 250, 500, and 1000 ng/ml). The intra- and inter-day precision and accuracy of the assay were assessed by analyzing control samples with concentrations of 5.0, 10, 50, 250, and 500 ng/ml (intra-day: n = 6; inter-day: n = 3) on the same day and examining the mean values obtained for these samples over 3 days. The limit of quantification was determined by the criteria of relative standard deviation < 20.0%, which was calculated from the intra-day accuracy.

2.4. Determination of free-fraction of paliperidone in plasma

For determination of the free-fraction of paliperidone, blood samples taken 4 h after paliperidone administration were ultrafiltrated using an Amicon Ultra-0.5 10 k filter (Merck Millipore, Massachusetts, USA) at 14,000 × *g* for 10 min. Paliperidone concentration in the filtrate was measured as described for plasma samples, and was defined as the free fraction of paliperidone. The plasma-free fraction was calculated as % of free fraction per total paliperidone concentration in plasma.

2.5. Effect of lipid emulsion on free paliperidone concentration in vitro

ILE was added to pooled serum (L-CONSERA I EX [Nissui Pharmaceutical, Tokyo, Japan]) and serum containing 0, 0.05, 0.1, 0.25, 0.5, or 1.0% lipid emulsion was prepared (n = 3 per sample). Paliperidone was added to the serum samples containing lipid emulsion to a concentration of 500 ng/ml. Samples were ultrafiltrated using Amicon Ultra-0.5 10 k filters at 14,000 × *g* for 10 min. Paliperidone concentration in the filtrate was measured and defined as the free fraction of paliperidone in serum containing lipid emulsion. The serum-free fraction was calculated as % of free fraction per total paliperidone concentration in serum containing lipid emulsion before ultrafiltration. The concentration of triglycerides in serum containing lipid emulsion was measured by GK-GPO free glycerol trap method, which was conducted by SRL Corporation, Japan.

2.6. Pharmacokinetic analysis

Noncompartmental pharmacokinetic analysis was applied to the plasma concentration–time data using the R software package PK (R for Windows, version 3.0.3 [R Foundation for Statistical Computing, Vienna, Austria]) (Jaki and Wolfsegger, 2011). The terminal elimination rate constant (k_{el}) was determined by the linear regression of three data points from the terminal portion of the plasma concentration–time plots. The area under the plasma concentration–time curve (AUC_{0-last}) was calculated using the linear trapezoidal rule up to the final plasma concentration measured ($C_{p\ (last)}$) and extrapolated to infinity using a correction term, namely $C_{p\ (last)}/k_{el}$. Oral clearance (CL_{oral}) was calculated as D/AUC, where D represents the dose administered per kg of body weight. The terminal elimination half-time ($t_{1/2}$) was obtained by dividing natural logarithm of 2 by k_{el}. The volume of distribution (Vd) per bioavailability (F) was obtained by multiplying CL_{oral} by the mean residual time (MRT). MRT was obtained using the following equation:

$$MRT = \int (t \cdot C(t) dT) \Big/ AUC$$

where t and C(t) are time after paliperidone administration and plasma paliperidone concentration at that time, respectively.

2.7. Statistics

Statistical analyses were performed using GraphPad Prism version 5.01 (GraphPad Software, Inc., San Diego, CA). An unpaired *t*-test was used for comparisons between the ILE and AR groups. For the *in vitro* study, Dunn's multiple comparison test was used for comparisons between the serum-free fraction of the six groups, 0, 0.05, 0.1, 0.25, 0.5,