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Pharmacokinetic study of metopimazine by oral route in children

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Abstract

Metopimazine (MPZ) is an antiemetic considered as a currently used drug. In France, it has become the leading antiemetic mediator due to its good tolerance, however, its pharmacokinetics has never previously been studied in children. MPZ was administered by oral route to 8 children with a single dose of 0.33 mg/kg during an endocrine exploration using stimuli well known for its adverse emetic effects. We used biological remnants from sera following an hGH test in order to obtain the MPZ pharmacokinetics. Plasmatic concentrations of MPZ and the active acid metabolite AMPZ, were quantified by HPLC-MS/MS during a 270 min test period. MPZ is quickly absorbed with a median C_{max} of 17.2 ng/mL at one hour and its half-life is 2.18 h. The plasmatic concentrations of AMPZ were higher than MPZ with a median C_{max} of 76.3 ng/mL, a T_{max} to 150 min and its concentration was approximately maintained at 50 ng/mL from 1 to 4 h. The plasmatic concentrations in children are similar to those observed in adults. No adverse effects, nausea or vomiting occurred during the trial. Therefore, these results confirm the MPZ dosage that should be used in children under 15 kg administered as 0.33 mg/kg up to 3 times a day.

Abbreviations

AMPZ, active metopimazine; API, atmospheric pressure ionization; AUC, area under the curve; BMI, body mass index; CTD, common technical document; ESI, electrospray ionization interface; hGH, human growth hormone; LOD, limit of detection; LOQ, limit of quantification; MPZ, metopimazine; MRM, multiple reaction monitoring.

Introduction

Metopimazine (MPZ) has been commercialized for the past 30 years in France and is considered as a currently used drug. This medication is frequently used to treat nausea or vomiting especially during acute gastroenteritis. It is a phenothiazine derivate which is an antidopaminergic D2 receptor antagonist. In France, MPZ is sold under various pharmaceutical forms. Hard capsules, suppositories, injectable solutions and orodispersible tablets are available for adults and a solution or suppositories for children. Different drug administration routes can be chosen to adapt the treatment to the patient's requirements. The transdermal route has been also studied but the low percutaneous absorption of MPZ limits the development of a transdermal form (Bounoure et al. 2008). The drug only acts on *area postrema* receptors and peripheral receptors due to its low brain penetration. Jolliet et al. (2007) showed that MPZ brain penetration is lower than domperidone and metoclopramide, as well as the main MPZ metabolite, the acid metabolite AMPZ which also exhibits a very low blood brain barrier permeability which explains its good tolerance to MPZ.

MPZ is also a medication with a satisfactory therapeutic balance. Herrstedt et al. (1997) reported the MPZ tolerance administered via the oral route at large doses in

adults. These authors concluded that the tolerance remained acceptable at a dose of 180 mg/day 30 mg × 6 and at a higher dose, primary side effect was dizziness caused by orthostatic hypotension.

The low brain penetration is thought to be the reason why MPZ side effects are different from the other phenothiazine compounds. The rare neurologic side effects are sedation, drowsiness and extrapyramidal syndrome which are reversible once the drug is stopped. This possible extrapyramidal adverse event was reported by Herrstedt et al. (1997) in a single patient with a very high dose of 360 mg per day. The α1 adrenergic antagonist activity causes orthostatic hypotension and dizziness. MPZ is also a low muscarinic cholinergic antagonist which can generate urine retention, visual disorder, constipation or dry mouth (Herrstedt et al. 1993). These rare side effects are described in the CTD.

Two recent notices from the French Drug Agency (ANSM) on domperidone and metoclopramide MPZ defined by default as the reference antiemetic medication due to its good tolerance. Currently, metoclopramide is contraindicated for children because of the high proportion of major neurologic side effects such as extrapyramidal syndrome (ANSM 2012). Also, the daily dose of domperidone has been decreased for the elderly people because of a risk of cardiac arrhythmia or sudden death (ANSM 2011).

MPZ pharmacokinetics has been previously studied in adults and a number of series have been reported in the literature. For Herrstedt et al. (1996) the oral bioavailability of MPZ was approximately 22.3%. This low value is due to a liver deamination into MPZ acid. The oral route only increases the area under the curve (AUC) ratio between MPZ acid and MPZ, that is, 13.7 by oral administration and 2.5 by intravenous administration. For these authors the postprandial oral administration of MPZ reduces the AUC of MPZ by 30% (Herrstedt et al. 1990).

Currently, to our knowledge, no study has been published regarding MPZ pharmacokinetics in children. The aim of this study was to validate the currently used pediatric dosage of 0.33 mg/kg 3 times a day in children under 15 kg.

Materials and Methods

Study population

The study was conducted within the framework of the national constitution for organic collection. It received its authorization from the Ministry of Higher Education and Research and was registered under number 201161469 DC. The biological collection was obtained from organic residues remaining after serum human growth hormone (hGH) tests were performed for children explored in a day hospital for assessment of their small size.

The organic residues obtained from these children were used to perform a stimulation test for hGH secretion using two stimuli, betaxolol and glucagon secretory response and assessed over a 4 h period by repeated blood sampling. As the test is known to cause nausea or vomiting, this justified the oral administration of MPZ 30 min before starting the test. Biological collection obtained from organic residues of this exploration of the hGH secretion kinetics, permitted us to also assess the kinetics of MPZ administered orally at the recommended dose in children under 7 years of age.

Study design

Eight children explored at a day hospital for an evaluation of their small size, were included in a biological collection study. There were 4 boys and 4 girls, 2 to 6 years of age with a body mass index (BMI) in kg/m^2 which ranged from 13.5 to 17.5 for boys and 13.7 to 17.9 for girls. After individual child selection all parents received written information regarding the study, and a signed informed consent was obtained as recommended by the Committee for the Protection of Individuals in the North West Region of France.

A complete biological evaluation was conducted to assess the children's small size. The results confirmed a normal liver and kidney function. The hGH secretion test protocol results were as follows: Time minus 30 min, oral administration of MPZ (Vogalene®; Teva Laboratory, Courbevoie, France) solution 0.1% at the recommended dosage for the particular age, that is, standard pharmaceutical reference found in the standard French pharmaceutical reference manual common technical document (CTD), that is, 0.33 mg/kg, and a beta blocker (Kerlone® or betaxolol hydrochloride; Sanofi-Aventis, Paris, France) at a dose of 2.5 mg/kg (Herrstedt et al. 1990). Installation of the first venous injection time 0 test administration by intravenous injection of glucagon (i.e., Glucagen®; Novo Nordisk® La Défense - Paris, France) at a dose of 0.03 mg/kg.

Blood samples of 2 mL using a neutral tube as mentioned in this protocol for testing hGH secretion and blood glucose, obtained via the venous route were performed at −30, 0, +30, +90, +120, +150, +180, +240 min and after a snack and control of blood glucose.

Blood samples were immediately sent to the laboratory preserved in ice, centrifuged at 3600 G (4000rpm/min), serum was kept frozen at −20°C until assayed for hGH secretion. The residue recovered after serum dosage was immediately refrozen at −20°C before the assay and its metabolite MPZ. A maximum period of 3 months took

place between the beginning the biological collection and tests performed this series.

Chemicals and reagents

Methanol and acetonitrile, both HPLC gradient grade, were purchased from VWR Chemicals (Fontenay-sous-Bois, France). All other chemicals, formic acid (99%, VWR Chemicals), ammonia solution (25%, Merck, Darmstadt, Germany), ammonium formate (Fluka, Buchs, Switzerland) were analytical grade. Deionized water was purified using the Milli-Q-system from Millipore Corporation (Bedford, MA). Drug-free serum Liphochek® was purchased from Bio-Rad (Irvine, CA). MPZ and its acid metabolite were obtained from Schwarz Pharma (Boulogne-Billancourt, France); stock solutions of each compound were prepared at 1 mg/mL in methanol. Working solutions of MPZ and acid metabolite at 10 μg/mL in methanol and stored at +4°C, were used for standards preparation in drug-free serum at the following levels: 1–10–100 ng/mL. The limit of quantification (LOQ) and the limit of detection (LOD) of this on-line analytical method were, respectively, of 1 and 0.1 ng/mL. Zolpidem-d6 was used as internal standard (LGC Standards, Teddington, Middlesex, UK); a stock solution at 10 μg/mL (stored at −20°C) and a working solution at 10 ng/mL (stored at +4°C) were prepared in methanol.

HPLC-MS/MS system

The column-switching HPLC-MS/MS system consisted of an 1525 Micro Binary Pump (pump 1 for washing solvent; Waters, Milford, MA), an Alliance 2795 HPLC pump (pump 2 for elution mobile phase; Waters), a sample injection valve with 100 μL sample loop (Rheodyne, Cotati, CA), a 10-port valve allowing switching or direct injection (valve 1; Rheodyne), a six-port switching valve (valve 2; Rheodyne), and a Quattro Micro™ API tandem mass spectrometer (Waters) equipped with an atmospheric pressure ionization (API) electrospray ionization interface (ESI) and controlled by computer through MassLynx software (Version 4.2; WATERS SAS, Guyancourt, France). The extraction column was an Oasis HLB (2.1 × 20 mm; 25 μm, Waters). The reversed-phase analytical column was an Atlantis C18 (2.1 × 150 mm; 3 μm, Waters). The wash solvent for sample extraction and enrichment, delivered by pump 1 at 2 mL/min, was Milli-Q water fortified with 0.2% ammonia. The mobile phase for sample elution and separation, delivered by pump 2 at 0.3 mL/min, consisted of 20 mmol/L ammonium formate aqueous solution adjusted to pH 2.8 with formic acid (solvent A) and acetonitrile/solvent A (90:10, v/v) [solvent B]. Analysis cycle time including solid phase extraction and chromatographic separation was 6 min. Detection was operated in positive ionization mode. The probe capillary voltage was 3.2 kV; the source block and desolvation temperatures were 120°C and 450°C, respectively. Cone voltages, collision energies, as precursor and product ion transitions, optimized for MPZ and its metabolites, and zolpidem-d6 are presented in Table 1. Quantitative measurements were carried out by HPLC-MS/MS in the multiple reaction monitoring (MRM) mode.

Sample preparation

100 μL of serum was diluted to 1:200 in water and zolpidem-d6 solution was added with final concentration of 1 ng/mL. After vortex-mixed, 100 μL of the mixture were injected in the on-line HPLC-MS/MS system.

Clinical study

Pharmacokinetic assessment

Pharmacokinetic study was conducted on PK Solution Software (Summit Research Services, Montrose, CO) using a separate system to determine the main pharmacokinetics parameters of MPZ. These parameters were calculated using the median concentration. Pharmacokinetic modeling is performed using a noncompartmental method. The AUC_{∞} is determined by trapezoid rule. C_{max} is the maximum observed concentration (from data) and T_{max} is the time at maximum observed concentration. The half time is the time required for the concentration to diminish by one-half obtained from first-order kinetics on elimination phase. Clearance and Vd are based on the AUC.

The method was validated over the concentration range of 5–500 ng/mL for MPZ and AMPZ. The LOD evaluated over three runs with duplicates from three different samples and defined as the lowest concentration

Table 1. HPLC-MS/MS parameters for metopimazine and its metabolites, and internal standard (zolpidem-d6).

Molecule	Precursor (m/z)	Production (m/z)	Cone voltage (V)	Collision energy (eV)
Metopimazine	446.1	**141.0**	42	36
	446.1	126.0	42	28
	446.1	169.1	42	28
Acid metabolite	447.1	**142.0**	42	38
	447.1	170.1	42	26
	447.1	98.9	42	56
Sulfoxide metabolite	462.1	69.8	40	42
	462.1	**98.0**	40	28
	462.1	141.2	40	28
Zolpidem-d6	314.3	263.2	45	28

Bold indicates quantification.

producing a peak eluting within ±0.1 min of analyte retention time for the lowest calibrator with signal-to-noise ≥3:1 was 1 ng/mL for MPZ and 1.5 ng/mL for AMPZ. The LOQ also evaluated in the same manner, and defined as the lowest concentration that met LOD criteria with signal-to-noise ≥10:1 was 5 ng/mL for MPZ and 7 ng/mL for AMPZ. The intra- and inter-day precision of the method at three concentrations were 1.0–4.6% and 1.6–5.8% for MPZ and 1.2–5.1% and 1.9–7.0% for AMPZ while the intra- and inter-day % accuracy were 99.0–93.8% and 101.8–107.0% for MPZ.

The stability of these compounds was established in a series of stability studies. A drug-free plasma pool was spiked with MPZ and AMPZ at three different concentrations (10–30–60 ng/mL and 20–75–150 ng/mL). The pools were kept at −20°C and analyzed after three periods, 1, 2, and 3 months. All the results ranged between 89% and 107%. The stability data show that there were no stability-related issues that might cause problems to the PK study.

Table 2. Median pharmacokinetic parameters of metopimazine in children (n = 8).

	T_{max}	C_{max}	Half time	Clearance	Volume of distribution
MPZ	60 min	17.2 ng/mL	2.18 h	86 mL/min	16.28 L

Median pharmacokinetic parameters of metopimazine in children (n = 8).

Results

Children received a single dose of 0.33 mg/kg of MPZ by oral route according the recommended dose of the CTD. The MPZ median pharmacokinetics parameters are shown in Table 2. MPZ given by oral route is quickly absorbed with a T_{max} of 1 h and C_{max} 17.2 ng/mL (6.4–92.2). The half time was 2.18 h with a clearance of 86 mL/min and a distribution volume of 16.28 L. The plasmatic concentrations of MPZ for each child are shown in Figure 1. These plasmatic concentrations seem to be close to concentrations in adults. The comparison between the MPZ pharmacokinetic parameters in adults and children is shown in Table 3. Herrstedt et al. (1990) showed that the median C_{max} was 43 ng/mL [14–69] for an oral dose of 20 mg and 59 ng/mL [28; 182] for an oral dose of 40 mg. The doses used by Herrstedt et al. are higher than the CTD which recommends a dose ranging from 15 to 30 mg per day in one or two doses.

MPZ is metabolized by the liver into MPZ acid. This active metabolite appears at the same time as MPZ due to a first pass metabolism. AMPZ plasmatic concentrations for each child are represented in Figure 2. The

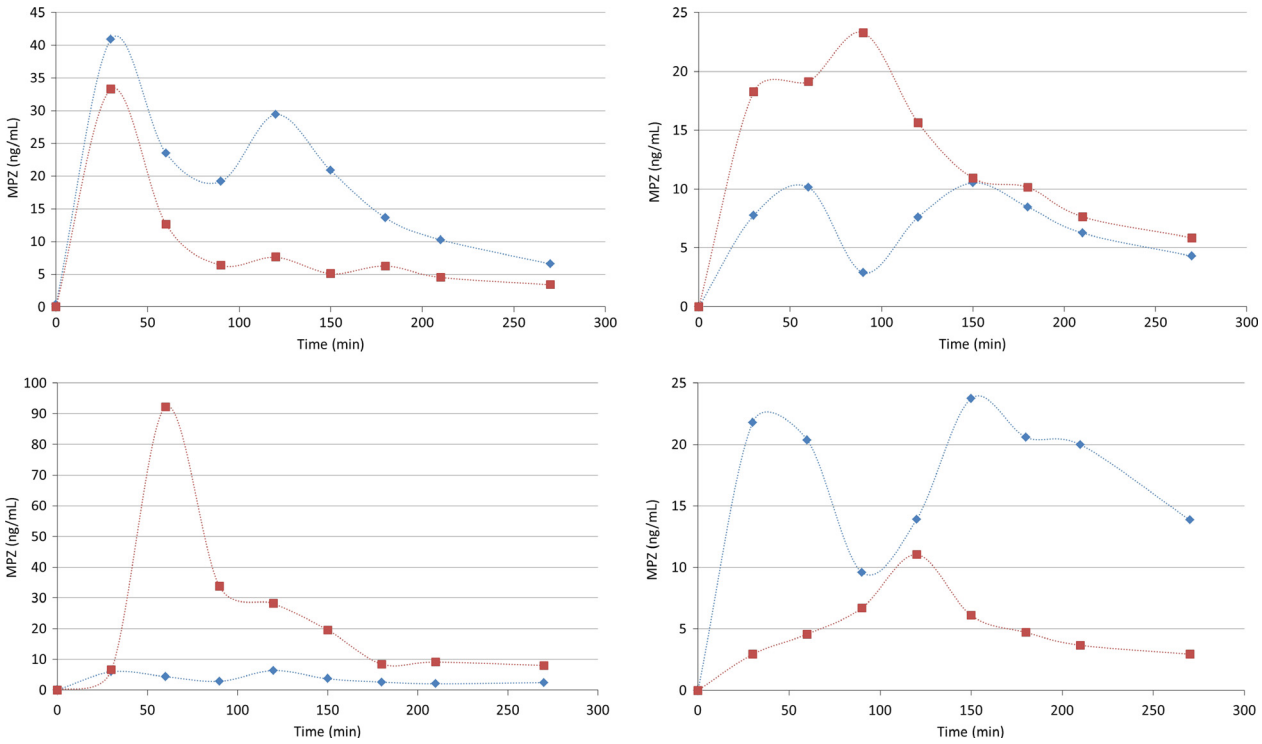

Figure 1. Plasmatic concentration of metopimazine in eight children.

Table 3. Comparison of median PK parameters between children and adults.

	Adults (Herrstedt et al. 1990)	Children
Dose	20 mg in a single oral administration	0.33 mg/kg in a single oral administration
Median MPZ C_{max}	43 ng/mL	17.2 ng/mL
Median MPZ T_{max}	52 min	1 h
Median AMPZ C_{max}	107.5 ng/mL	73.6 ng/mL
Median AMPZ C_{max}	2 h	2 h 30 min

AMPZ plasmatic concentrations are higher than MPZ with a median C_{max} of 73.6 ng/mL [range 36.9–145.7] and a T_{max} to 150 min. The ratio of C_{max} AMPZ/MPZ is 4.28. These results are in agreement with the study reported by Herrstedt et al. (1990). After a preprandial oral dose of 20 mg, these authors observed a T_{max} of 120 min, a median C_{max} of 107.5 ng/mL for AMPZ and a C_{max} ratio of 1.72. They found a wide range between MPZ and AMPZ serum concentrations. Also, they were higher than the concentrations generally found due to the use of a higher dose rather than that recommended in the CTD. Also, the MPZ and AMPZ concentrations were higher. This result is in accordance with data published in the literature. Herrstedt et al. (1990) also reported a highly significant interindividual variation in MPZ AUC.

Discussion

Due to AMPZ pharmacokinetics a single or double dose per day by oral route is possible in adults. Herrsted et al. showed that after a MPZ administration of 40 mg in six healthy volunteers, the median AMPZ C_{max} of 296 ng/mL was obtained after a T_{max} of 120 min. The mean concentration of AMPZ was always close to 70 ng/mL after 8 h. Moreover, after 8 h, the mean MPZ concentration was not detectable according to the MPZ half-life -time, that is, 2.18 h in this study. Therefore, the extended antiemetic activity was due to the AMPZ. The AMPZ half-life time could not be determined due to the insufficient amount of time available for the study. However, nevertheless AMPZ appears to have a greater half-life -time compared to MPZ and produced by MPZ deamination The AMPZ concentration appeared to be stable during the initial four hours of the trial. In Figure 3, the mean AMPZ concentration was maintained at approximately 50 ng/mL from 1 to 4 h of the study time. AMPZ may also explain the good tolerance of MPZ. Also, MPZ has the lowest brain penetration of any antiemetic drug as compared to domperidone or metoclopramide. Jolliet et al. (2007) assessed the endothelial permeability of MPZ and AMPZ and showed that AMPZ has an

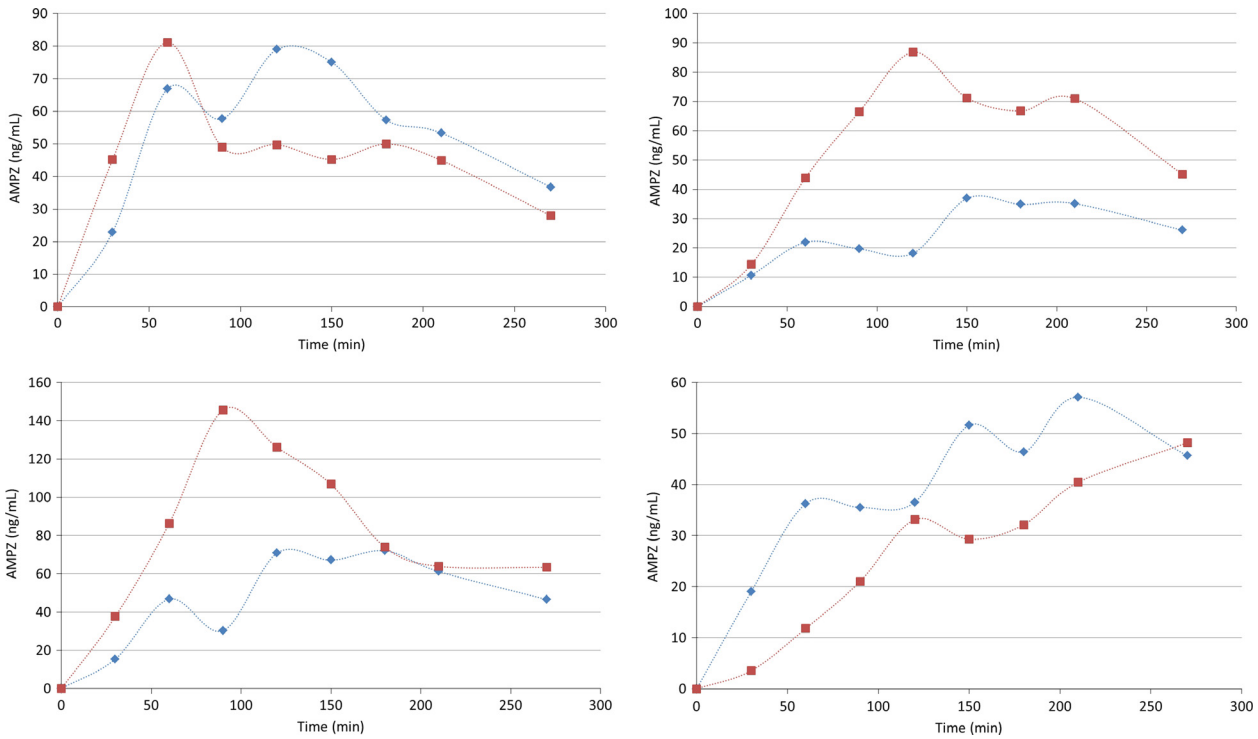

Figure 2. Plasmatic concentration of metopimazine in eight children.

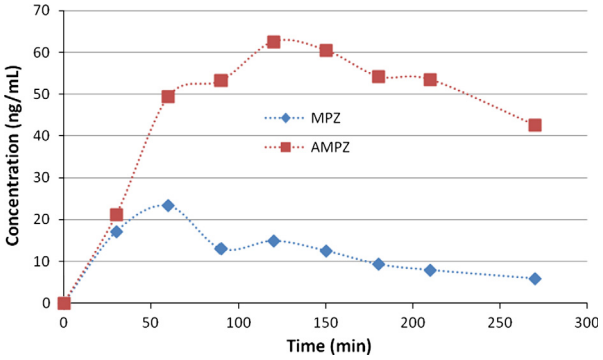

Figure 3. Mean plasmatic concentration of metopimazine (MPZ) and acid of MPZ in children (n = 8).

endothelial permeability of 0.49×10^{-3} cm min^{-1} compared to 9.35×10^{-3} cm min^{-1} for MPZ, 44.9×10^{-3} cm min^{-1} for domperidone.

hGH endocrine investigation

During this trial, children received a large dose of glucagon, the stimuli used for hGH endocrine exploration which provokes nausea or vomiting. The administration of glucagon is known to induce nausea and to be emesis. Dillman et al. (2013) showed that after a glucagon IV administration in 50 children, 48% self-reported nausea and 8% experienced emesis (Colle et al. 1984). In this study, no adverse reaction, nausea or emesis was observed with an MPZ administration of 0.33 mg/kg although nausea reactions were expected in four children. During the hGH stimulation tests, at an administered dosage of 0.33 mg/kg, we were able to obtain the MPZ and AMPZ serum concentration of approximately 10 and 50 ng/mL with important videral variations. No nausea or emesis was observed in any of the eight children studied. However, as we did not use a control group we cannot consider, with certainty, these serum concentrations as being representative of an active concentration. Nevertheless, the results we obtained corresponded to the dosage considered to be effective and considered as a currently used drug, that is, 0.33 mg/kg and according the recommended dose of the CTD. No children tested had growth hormone deficiency.

Conclusion

In France, MPZ is now the recommended antiemitic especially in children due to its good tolerance. Pharmacokinetics in children was unknown prior to this study and the results were similar as compared to adults. The original pharmacokinetics presented in this paper corresponds to the posology per os considered as a currently used drug as being useful and effective in children. Our results are in accordance with the recommended MPZ dosage for children under 15 kg of 0.33 mg/kg with up to three administrations per day. Also it can be considered that the common technical document recommended therapeutic dosage can be adapted for children under 15 kg weight.

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Author Contributions

Eric Mallet was involved in conception, design, writing, editing, and interpretation of the data. Frederic Bounoure was involved in analysis, writing, and editing. Mohamed Skiba was involved in data collection, processing, and interpretation of the data. Elodie Saussereau was involved in data collection and processing. Jean-Pierre Goullé was involved in analysis, interpretation of the data, writing, and editing. Mireille Castanet was involved in editing, interpretation of the data, and was Head of CIC INSERM 204.

Disclosures

None declared.

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