Oral Topiramate in Neonates with Hypoxic Ischemic Encephalopathy Treated with Hypothermia: A Safety Study

Luca Filippi, MD, Chiara Poggi, MD, Giancarlo la Marca, Pharm Sc, Sandra Furlanetto, Pharm Sc, Patrizio Fiorini, MD, Giacomo Cavallaro, MD, Angela Plantulli, MD, Gianpaolo Donzelli, MD, and Renzo Guerrini, MD

Objective To investigate whether topiramate associated with mild or deep hypothermia in asphyxiated term infants is safe in relation to the short-term outcome.

Study design We report on 27 consecutive asphyxiated newborns who were treated with whole body hypothermia and 27 additional consecutive newborns with hypothermia who were co-treated with oral topiramate, once a day for 3 consecutive days, at 2 different doses.

Results Newborns were divided in 6 groups according to the depth of hypothermia and the association with higher or lower topiramate dosage. A statistical comparison of the groups identified some differences in biochemical and hemodynamic variables, but no adverse effects attributable to topiramate were detected. There were no statistically significant differences in the groups in short-term outcomes, survival rate at discharge, or incidence of pathologic brain magnetic resonance imaging.

Conclusion Although the number of newborns in this study was limited, the short-term outcome and the safety data appear to support the evaluation of topiramate in clinical trials to explore its possible additive neuroprotective action. *(J Pediatr 2010;157:361-6)*.

See editorial, p 351 and related articles, p 367 and p 499

Neonatal hypoxic-ischemic encephalopathy (HIE), caused by perinatal asphyxia, is one of the leading causes of cerebral palsy, the incidence of which has remained essentially unchanged in recent decades despite improvements in perinatal practice and neonatal care.[1] Topiramate (TPM), an anticonvulsant agent widely used in adults and children,[2,3] has multiple mechanisms of action, including an inhibitory effect on glutamate receptors. TPM has neuroprotective properties against hypoxic ischemic brain damage, both in vitro and in animal models, and was included in neuroprotective strategies for ischemic stroke[4-11] and neonatal hypoxic-ischemic cerebral injury.[12]

Several studies have demonstrated the therapeutic effects of whole-body or selective head cooling to treat asphyxiated newborns.[13-15] Consequently, mild hypothermia is recommended for the treatment of moderate degrees of encephalopathy.[1] Deep hypothermia may also be safe and neuroprotective.[16] Although TPM logically would be expected to enhance the neuroprotective effects of hypothermia in HIE, no trial has tested this combination treatment.[1] Hypothermia can reduce drug clearance, thereby affecting the pharmacokinetics of drugs.[17] In an earlier pilot study, we assessed the effects of mild or deep hypothermia on TPM pharmacokinetics in neonates with HIE. We observed a slow absorption and elimination of TPM.[18] We now report the safety profile of TPM in neonates treated with hypothermia in a retrospective comparison with newborns treated with hypothermia only.

Methods

We studied asphyxiated newborns admitted in 2 neonatal intensive care units (NICUs; A. Meyer University Children's Hospital, Florence, Italy, and Carlo Poma Hospital, Mantua, Italy) from November 2004 to August 2009. Newborns admitted before May 2007 were treated only with deep (temperature 30-33°C) or mild

aPTT	Activated partial thromboplastin time
DH	Deep hypothermia
DH-highTPM	Deep hypothermia and high topiramate dose
DH-lowTPM	Deep hypothermia and low topiramate dose
HIE	Hypoxic-ischemic encephalopathy
MH	Mild hypothermia
MH-highTPM	Mild hypothermia and high topiramate dose
MH-lowTPM	Mild hypothermia and low topiramate dose
MRI	Magnetic resonance imaging
NICU	Neonatal intensive care unit
TPM	Topiramate

From the Neonatal Intensive Care Unit, Department of Critical Care Medicine, "A. Meyer" University Children's Hospital, Florence, Italy (L.F., C.P., P.F.); Department of Pharmacology, University of Florence, Florence, Italy (G.I.M.); Department of Pharmaceutical Sciences, University of Florence, Florence, Italy (S.F.); Institute of Pediatrics and Neonatology, Fondazione IRCCS Ospedale Maggiore Policlinico, Mangiagalli e Regina Elena, University of Milan, Milan, Italy (G.C.); Neonatal Intensive Care Unit, "Carlo Poma" Hospital, Mantua, Italy (A.P.); Department of Pediatrics, "A. Meyer" University Children's Hospital, Florence, Italy (G.D.); and Department of Neurology and Neurosurgery, "A. Meyer" University Children's Hospital, Florence, Italy (R.G.)

The authors declare no conflicts of interest.

 10.1016/j.jpeds.2010.04.019

(temperature 32-34°C) whole-body hypothermia and were the historical control group (deep hypothermia [DH] and mild hypothermia [MH] groups). Newborns admitted subsequently received combined therapy with mild or deep hypothermia and TPM at 2 different doses (deep hypothermia and high topiramate dose [DH-highTPM], deep hypothermia and low topiramate dose [DH-lowTPM], mild hypothermia and high topiramate dose [MH-highTPM], and mild hypothermia and low topiramate dose [MH-lowTPM] groups).

Infants were treated with whole-body hypothermia within 6 hours of birth, and it was continued for 72 hours when these criteria were fulfilled: (1) gestational age ≥36 weeks and birth weigh ≥1800 g with at least 1 of the following: a) Apgar score ≤5 at 10 minutes; b) persisting need for resuscitation, including endotracheal intubation or mask ventilation 10 minutes after birth; c) acidosis (pH <7.0, base deficit ≥16 mmol/L in umbilical cord blood, or in umbilical cord blood or arterial, venous or capillary blood arterial, venous, or capillary blood) within 60 minutes from birth; (2) moderate to severe encephalopathy, consisting of altered state of consciousness (irritability, lethargy, stupor, or coma) and ≥1 of the following signs: a) hypotonia, b) abnormal reflexes, including oculomotor or pupil abnormalities, c) absent or weak suck, d) clinical seizures. Exclusion criteria were congenital abnormalities, congenital viral infections, or evidence encephalopathy other than HIE. Outborn patients were initially cooled to 35°C at the birth hospital, avoiding heating and using ice packs during the transfer to NICU.

In 1 of the 2 centers (Mantua), neonates were cooled by applying ice packs to the head and body or by using a cooling blanket (NIG 2, Iemmi Medical Srl, Mantua, Italy). In the other center (Florence), a cooling blanket (Blanketrol III, Hyper-Hypothermia System, Cincinnati Sub-Zero, Cincinnati, Ohio) with an esophageal probe was used to induce hypothermia; the esophageal temperature was lowered with the blanket's servomechanism. Rectal temperature was monitored with a rectal probe connected to cardiomonitor (Viridia 24C, Hewlett-Packard Company, *Palo Alto*, *California* or Infinity Delta, Dräger Medical System, Telford, Pennsylvania). After 72 hours of hypothermia, the newborns were gradually re-warmed to 36.5 to 37.0°C for 6 to 12 hours (0.5°C/h). Vital signs were continuously monitored during hypothermia.

TPM was administered with an orogastric tube as enteric-coated granules mixed with water on arrival in the NICU, when the cooling was begun (T_0), once a day for the first 3 days of life, for a total of 3 doses per patient. Initially, newborns received 5 mg/kg once a day (in the DH-highTPM and the MH-highTPM groups). This schedule was validated by monitoring that TPM plasma levels were maintained at the upper limits of the reference range.[18] Subsequently, newborns received 5 mg/kg on the first day and 3 mg/kg on the following 2 days, to have lower TPM plasma values (in the DH-lowTPM and the MH-lowTPM groups). TPM plasma concentrations were measured on dried blood spots, as previously reported.[18]

For the first 9 patients, plasma TPM concentrations were evaluated starting from 48 hours of hypothermia, before the administration of the third dose of TPM (T_{48}) and at $T_{48.5}$, T_{49}, $T_{49.5}$, T_{50}, T_{52}, T_{54}, T_{56}, T_{60}, T_{64}, $T_{68,}$ and T_{72}. To better define drug levels, in the following 18 patients plasma TPM concentrations were measured at the beginning of hypothermia, before the first dose of TPM (T_0), and at $T_{0.5}$, T_1, $T_{1.5}$, T_2, T_4, T_6, T_8, T_{12}, T_{16}, T_{20}, and T_{24} (before the second dose), at T_{26}, T_{30}, T_{34}, T_{40}, and T_{48} (before the third dose), and at $T_{48.5}$, T_{49}, $T_{49.5}$, T_{50}, T_{52}, T_{54}, T_{56}, T_{60}, T_{64}, $T_{68,}$ and $T_{72.}$ In 5 newborns treated with MH-highTPM, concentrations were also measured after 12 and 24 hours of heating.

Respiratory and hemodynamic variables (respiratory rate, oxygen saturation, fractional inspired oxygen, systolic, diastolic and mean arterial pressures, heart rate) were recorded before hypothermia and then at hours 0, 6, 12, 18, 24, 30, 36, 42, 48, 54, 60, 66, and 72 of hypothermia, and after re-warming. These blood tests were planned at T_0, T_{24}, T_{48}, and T_{72} and 24 hours after re-warming process (T_{96}): blood gas analysis (corrected for body temperature), serum electrolyte level, liver and renal function tests, creatine-kinase level, creatine-kinase MB isoenzyme level, lactate dehydrogenase level, troponin IC level, complete cell blood count, C-reactive protein level, procalcitonin level, and coagulation tests. To evaluate whether TPM can modify the cellular oxidation reduction potential through the inhibition of carbonic anhydrase isoenzymes,[19] we performed at 24 and 48 hours of hypothermia, respectively (after 1 and 2 doses of TPM), a redox status study with measurements of plasma lactate, pyruvate, ß-hydroxybutyrate, and acetoacetate levels on deproteinized arterial blood with spectrophotometric assay (COBAS FARA; Roche, Basel, Switzerland).[20]

Clinical Course and Concomitant Treatments

A central venous line was placed in all patients. Fluid intake was started at 60 to 70 mL/kg and increased by 10 to 20 mL/kg each day, on the basis of changes in body weight and serum electrolyte levels. Minimal enteral feeding was allowed with human milk from the first day of life. In case of respiratory failure, newborns were supported with patient triggered ventilation. Neonates in whom seizures developed were treated with phenobarbital (loading dose, 20 mg/kg; followed by 1.5-2.5 mg/kg every 12 hours). In case of hypotension, defined as a mean arterial blood pressure <40 mm Hg, single or multiple normal saline boluses were administered (10-20 mL/kg), and dopamine, dobutamine, or norepinephrine was progressively added when blood pressure did not increase.

Magnetic Resonance Imaging and Ultrasound Scanning

Brain magnetic resonance imaging (MRI) was planned within the first week of life. Brain lesions were classified as isolated lesions of white matter, basal ganglia, and thalamus with or without involvement of posterior limb of the internal capsule, cortex, or various combinations of the earlier lesions.[21] Ultrasound scanning of the abdomen, for detection

of renal stones and ophthalmologic assessment of the anterior eye segment, was performed within the first week of life.

Statistical Analysis

We tested 5 groups including at least 5 neonates each, but not including 1 neonate who was given the DH-lowTPM regimen. The variables investigated were continuous or categorical. The results were expressed as numbers (percentages) for categorical variables, as means plus or minus SD for continuous normally distributed data, and as medians and ranges for non-normally distributed data. For non-normally distributed data, comparisons were performed with the Kruskal–Wallis test. This test can be applied when the underlying population distributions are unknown, and it requires a minimum of 5 subjects per group. It addresses the null hypothesis that there is no treatment effect against the general alternative hypothesis that at least 2 treatment effects are not equal.[22,23] To assess the possible dependence in the different treatments and the dichotomous variables, the χ^2 test for k × 2 tables was used. The null hypothesis was accepted with a P value >.05.[23] The Kruskal-Wallis tests were performed with the Statistical Software Program.[24] Dichotomous variables were processed with a public domain epidemiologic analysis program (Epi Info, version 6.01; Centers for Disease Control and Prevention, Atlanta, Georgia). The study was approved by the local ethics committees. Written informed consent was obtained from both parents of all enrolled newborns.

Results

Four newborns (2 treated with hypothermia only and 2 treated with MH-highTPM dose) were not included in the analysis because the data were incomplete; 1 newborn with a congenital inborn error of respiratory chain was also excluded. Newborns reported in an earlier study were included.[18] Twenty-seven newborns were treated with whole-body hypothermia only (15 on DH, and 12 on MH). Of the 27 additional newborns treated with TPM and hypothermia, 10 constituted the DH-highTPM group, 1 constituted the DH-lowTPM group, 6 constituted the MH-highTPM group, and 10 constituted the MH-lowTPM group. Demographic and obstetric data are shown in Table I. Respiratory assistance, hemodynamic support, and number of neonates treated with phenobarbital are presented in Table II.

Plasma TPM concentrations were measured from the beginning of hypothermia, before the first dose of TPM (T_0), in 4 newborns in the DH-highTPM group, in the newborn treated with DH-lowTPM, in 3 newborns in the MH-highTPM group, and in all 10 newborns in the MH-lowTPM group. For all the remaining newborns, TPM levels were measured starting from T_{48} (immediately before the third dose; Figure). The Figure also reports TPM concentrations after 12 and 24 hours of re-warming measured in 5 newborns of the MH-highTPM group.

Two newborns in the DH group, 1 newborn in the DH-highTPM group, and 1 newborn in MH-lowTPM group died during the hospitalization. With the χ^2 test, the hypothesis of contingency between mortality and treatment was rejected ($P = .61$). The statistical analysis of the measured variables (biochemical, hemodynamic, and respiratory) showed no significant differences in the 5 groups before the beginning of hypothermia. During hypothermia, only the variables reported in Table III were statistically different with Kruskal-Wallis tests. After 1 day of hypothermia, pH, base excess, and bicarbonate levels were lower in the DH and DH-highTPM groups. However, in the following days these differences disappeared, and no consistent metabolic acidosis was detected in newborns with TPM and hypothermia. For coagulation profile, after one day of hypothermia, activated partial thromboplastin time (aPTT) and D-dimer levels were higher in the DH group, and the fibrinogen level was lower in the DH and DH-highTPM group. These differences persisted for the second and third day of treatment, but were not present after 1 day of re-warming. Systemic arterial pressure values were different in the 5 groups at T6, 12, and 72 and after re-warming, with higher values for the MH-highTPM and MH-lowTPM groups. The comparison of the redox status after 24 and 48 hours of hypothermia was not different (Kruskal-Wallis test). However, a decrease of lactate and pyruvate levels from 24 to 48 hours (with stable and normal lactate to pyruvate ratio) was observed in all groups.

With ultrasound scanning of the abdomen, no kidney stones were revealed. The results of ophthalmologic evaluations, performed in 13 newborns in the DH group, in 11 newborns in the

Table I. Demographic and clinical characteristics at admission of newborns in all subgroups

	DH (n = 15)	MH (n = 12)	DH-highTPM (n = 10)	DH-lowTPM (n = 1)	MH-highTPM (n = 6)	MH-lowTPM (n = 10)
Male, n (%)	9 (60.0)	4 (33.3)	6 (60.0)	1 (100.0)	4 (66.7)	5 (50.0)
Gestational age, days, mean ± SD*	276 ± 14	274 ± 18	275 ± 13	278	283 ± 6	272 ± 14
Birth weight, g, mean ± SD	3247 ± 516	3368 ± 768	3294 ± 793	3030	3645 ± 508	2927 ± 550
Cesarean section, n (%)	7 (46.7)	7 (58.3)	5 (50.0)	0 (0.0)	4 (66.7)	6 (60.0)
Stained amniotic fluid, n (%)	5 (33.3)	6 (50.0)	3 (30.0)	1 (100.0)	4 (66.7)	5 (50.0)
Outborn, n (%)	9 (60.0)	8 (66.7)	7 (70.0)	0 (0.0)	6 (100.0)	9 (90.0)
Apgar score, 1 min, mean ± SD	2.7 ± 2.0	3.7 ± 1.8	2.9 ± 2.1	4	1.8 ± 1.7	2.6 ± 1.9
Apgar score, 5 min, mean ± SD	4.9 ± 1.9	5.7 ± 1.5	4.6 ± 2.3	7	2.8 ± 2.2	4.7 ± 1.9
CRIB score[44], mean ± SD	3.5 ± 1.2	3.4 ± 1.7	4.1 ± 1.6	2	3.2 ± 0.8	5.2 ± 2..9
Hr hypothermia started, mean ± SD	3.1 ± 1.8	2.8 ± 1.1	3.6 ± 1.9	1	4.0 ± 1.4	3.3 ± 1.2

*Calculated from maternal menstrual history, from obstetrical data, or with Ballard's score.

Table II. Respiratory assistance and pharmacologic support of infants in all subgroups

	DH (n = 15)	MH (n = 12)	DH-highTPM (n = 10)	DH-lowTPM (n = 1)	MH-highTPM (n = 6)	MH-lowTPM (n = 10)
Mechanical ventilation, n (%)	12 (80.0)	5 (41.7)	7 (70.0)	1 (100.0)	5 (83.3)	8 (80.0)
Hours of ventilation, median (range)	41 (9-246)	96 (4-194)	123 (3-288)	19	96 (77-142)	86 (24-288)
Oxygen supplementation	12 (80.0)	3 (25.0)	5 (50.0)	1 (100.0)	4 (66.7)	6 (60.0)
Hours of oxygen supplementation, median (range)	62 (4-350)	218 (85-300)	106 (3-288)	10	40 (10-70)	31 (6-174)
Dopamine infusion, n (%)	7 (46.7)	6 (50.0)	3 (30.0)	0 (0)	4 (66.7)	7 (70.0)
Days of dopamine infusion, mean ± SD	2.6 ± 0.8	3.2 ± 1.3	4.0 ± 1.0		4.7 ± 1.7	5.2 ± 3.2
Dobutamine infusion, n (%)	6 (40.0)	4 (33.3)	2 (20.0)	0 (0)	2 (33.3)	6 (60.0)
Days of Dobutamine infusion, mean ± SD	2.3 ± 1.0	2.7 ± 1.7	4.5 ± 0.7		3.5 ± 0.7	6.0 ± 2.9
Treatment with phenobarbital, n (%)	14 (93.3)	9 (75.0)	3 (30.0)	1 (100)	6 (100.0)	9 (90.0)

MH group, in 9 newborns in the DH-highTPM group, and in all newborns in the other groups, were normal. Cerebral MRI was performed in 98.1% of the newborns. A higher incidence of isolated lesions of white matter was observed in the MH group, of basal ganglia and thalamus plus cortex was observed in the DH-highTPM group, and of isolated lesions of basal ganglia and thalamus was observed in the MH-lowTPM group. However, the statistical comparisons in newborns treated with or without TPM (χ^2 test) were not different.

Discussion

HIE is a leading cause of perinatal mortality and severe neurological impairment. It occurs in approximately 2 to 3 newborns for every 1000 live births,[25] with a mortality rate of 10% for mild HIE and 60% for severe HIE. Approximately 30% of surviving newborns with mild HIE and 100% of surviving newborns with severe HIE have variable degrees of neurological disability.[26] Neuroprotective drugs may enhance the neuroprotective properties of hypothermia for the treatment of HIE.[1] However, there are no studies in asphyxiated newborns.

TPM is an anti-glutamataergic drug mainly used for the treatment of epilepsy,[2,3] which has neuroprotective properties. In neuronal cultures, cell damage induced by oxygen-glucose deprivation[10] or excitotoxic concentrations of glutamate or kainate[27] were consistently attenuated by TPM. In animal models of cerebral ischemia, TPM reduced the severity of cerebral damage either alone[5-8] or with hypothermia.[9] The neuroprotective mechanisms of TPM action appear related not only to glutamate α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) and kainate receptors inhibition,[11,27-30] but also to inhibition of Na^+ channels,[31] high voltage-activated calcium currents,[4] carbonic anhydrase isoenzymes,[32] and mitochondrial permeability transition pore.[19] Hypothermia, conversely, might enhance post-ischemic glutamate reuptake[33], and suppress nitric oxide synthase, oxidative stress, apoptosis, and inflammatory cascades. TPM might therefore additively act on these pathways.

In neonates with HIE, TPM pharmacokinetic properties appear to be modified by concomitant hypothermia.[18] Similarly to other drugs that are poorly metabolized,[34] TPM had reduced clearance with hypothermia, and absorption and elimination processes were slower.[18] Plasma TPM

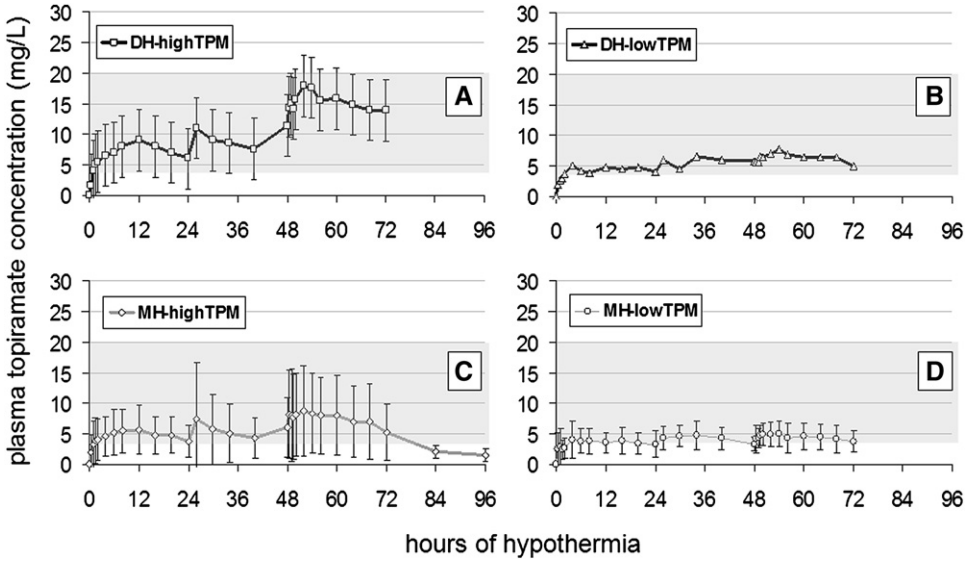

Figure. Plasma TPM concentrations in newborns treated with **A,** DH-highTPM **B,** DH-lowTPM **C,** MH-highTPM **D,** and MH-lowTPM. The *grey area* represents the TPM reference range.

Table III. Variables for which Kruskal-Wallis tests were significant ($P < .05$) and groups for which a significant variable difference was found

Variable	*P* value	Groups
Blood gas analysis at T_{24} of hypothermia		
pH ↓	.023	DH, DH-highTPM
BE ↓	.001	DH, DH-highTPM
HCO_3- ↓	.001	DH, DH-highTPM
Coagulation test at T_{24} of hypothermia		
PTT ↑	.025	DH
Fibrinogen ↓	.001	DH, DH-highTPM
D-Dimers ↑	.001	DH
Coagulation test at T_{48} of hypothermia		
PTT ↑	.019	DH
Fibrinogen ↓	.001	DH, DH-highTPM
D-Dimers ↑	.04	DH
Coagulation test at T_{72} of hypothermia		
PTT ↑	.016	DH
Fibrinogen ↓	.014	DH, DH-highTPM
D-Dimers ↑	.002	DH
Coagulation test after hypothermia		
PTT ↑	.003	DH
D-Dimers ↑	.031	DH
Blood pressure at T_6 of hypothermia		
SAP ↑	.019	MH-lowTPM, MH-highTPM
DAP ↑	.016	MH-lowTPM, MH-highTPM
MAP ↑	.005	MH-lowTPM, MH-highTPM
Blood pressure at T_{12} of hypothermia		
SAP ↑	.022	MH-lowTPM, MH-highTPM
MAP ↑	.008	MH-lowTPM, MH-highTPM
Blood pressure at T_{72} of hypothermia		
SAP ↑	.006	MH-lowTPM, MH-highTPM
DAP ↑	.020	MH-lowTPM, MH-highTPM
MAP ↑	.001	MH-lowTPM, MH-highTPM
Blood pressure after hypothermia		
SAP ↑	.002	MH-lowTPM, MH-highTPM
DAP ↑	.019	MH-lowTPM, MH-highTPM
MAP ↑	.005	MH-lowTPM, MH-highTPM

Down and up arrows (↓ ↑) represent variables decreasing or increasing.
BE, Base excess; *HCO_3^-*, bicarbonate; *PTT*, partial thromboplastin time; *SAP*, systolic arterial pressure; *DAP*, diastolic arterial pressure; *MAP*, mean arterial pressure.

concentrations in newborns treated with deep hypothermia were higher than those of newborns treated with mild hypothermia (**Figure**).

The safety profile of TPM might be different in neonates with HIE treated with hypothermia than for adults receiving chronic therapy for epilepsy. TPM can cause metabolic acidosis, especially in pediatric patients, because of carbonic anhydrase inhibition at proximal renal tubule with renal loss of bicarbonate.[35,36] In as many as 48% of adults and 67% of children with epilepsy treated with TPM, a variable degree of metabolic acidosis develops. However, in most reported cases, bicarbonate levels did not decrease enough to be clinically significant. Only 11% of patients had serum bicarbonate levels <17 mEq/L,[35,37] and symptomatic cases were successfully treated with sodium bicarbonate supplementation.[35] Although this observation is reassuring, metabolic acidosis is severe in neonates with HIE, who have metabolic acidosis because of both asphyxia and renal impairment. In infants, metabolic acidosis usually occurs after 8 to 26 days of TPM treatment, with dosages as high as 8.2 to 26.0 mg/kg/day.[38] In our study, there was a mild and reversible acidosis in newborns treated with deep hypothermia. There was no metabolic acidosis detected in newborns co-treated with MH and TPM.

Inhibition of a specific mitochondrial isoenzyme of carbonic acid anhydrase, as observed after acetazolamide administration, may induce severe metabolic acidosis through inhibition of pyruvate carboxylase activity, with consequent increased lactate to pyruvate ratio and ketosis with low ß-hydroxybutyrate to acetoacetate ratio.[39] In newborns treated with hypothermia and TPM, lactate and pyruvate levels decreased during treatment, and the lactate to pyruvate ratio was normal at 24 and 48 hours, thus excluding impairment of the oxidation reduction status caused by TPM. Therefore, this short course-low dosages treatment schedule did not alter acid-base balance. Similar to other carbonic acid anhydrase inhibitors, long-course TPM therapy was associated with increased risk of nephrolitiasis in adults.[35,36] Abdomen ultrasound scanning was performed in all infants, with no evidence of kidney stones.

Angle closure glaucoma and acute myopia are additional, although potentially reversible, adverse events related to TPM treatment in the pediatric age.[35,36,40] The results of ophthalmological evaluations were normal in these newborns.

Blood chemistry test results showed no relevant differences in the groups. Hemodynamic variables demonstrated higher arterial pressure values at T6, 12, and 72 and after re-warming for newborns in the MH-highTPM and MH-lowTPM groups. This finding might be caused by a lack of homogeneity of the patients. In these 2 groups, the percentage of newborns treated with inotropic drugs and the duration of their use were slightly higher, probably as a consequence of a more severe hypoxic-ischemia, as suggested by the Apgar scores in the MH-highTPM group and Clinical Risk Index for Babies (CRIB) score in the MH-lowTPM group. None of the newborns treated with TPM had hypertension (defined as blood pressure levels persistently >95th percentile for birth weight and gestational age on the basis of available normative data).[41]

Long-term effects on cognitive functions of TPM administration in early life remain to be assessed. In asphyxiated animal models treated with TPM, no cognitive deficit was demonstrated,[10] and in epileptic neonate rodents, TPM appears safer than phenobarbital or benzodiazepines.[42,43] Neuronal death occurred at doses of 50 mg/kg, which are considerably higher than common therapeutic schedules. The gap between effective and neurotoxic doses is greater for TPM than for other antiepileptic drugs,[43] and short-course therapy appears to have few neurotoxic effects. ■

We are grateful to the nursing staffs of the neonatal intensive care units of A. Meyer University Children's Hospital, Florence, Italy, and Carlo Poma Hospital, Mantua, Italy for their assistance in conducting this study.

Submitted for publication Sep 16, 2009; last revision received Mar 26, 2010; accepted Apr 9, 2010.

Reprint requests: Luca Filippi, MD, Neonatal Intensive Care Unit, Department of Critical Care Medicine, A. Meyer University Children's Hospital, Viale Pieraccini, 24 I-50139 Florence, Italy. E-mail: l.filippi@meyer.it.

References

1. Perlman JM. Summary proceedings from the neurology group on hypoxic-ischemic encephalopathy. Pediatrics 2006;117:S28-33.
2. Guerrini R, Parmeggiani L. Topiramate and its clinical applications in epilepsy. Expert Opin Pharmacother 2006;7:811-23.
3. Shank RP, Gardocki JF, Streeter AJ, Maryanoff BE. An overview of the preclinical aspects of topiramate: pharmacology, pharmacokinetics, and mechanism of action. Epilepsia 2000;41(Suppl. 1):S3-9.
4. Costa C, Martella G, Picconi B, Prosperetti C, Pisani A, Di Filippo M, et al. Multiple mechanisms underlying the neuroprotective effects of antiepileptic drugs against in vitro ischemia. Stroke 2006;37:1319-26.
5. Yang Y, Shuaib A, Li Q, Siddiqui MM. Neuroprotection by delayed administration of topiramate in a rat model of middle cerebral artery embolization. Brain Res 1998;804:169-76.
6. Lee SR, Kim SP, Kim JE. Protective effect of topiramate against hippocampal neuronal damage after global ischemia in the gerbils. Neurosci Lett 2000;281:183-6.
7. Edmonds HL, Jr., Jiang YD, Zhang PY, Shank R. Topiramate as a neuroprotectant in a rat model of global ischemia-induced neurodegeneration. Life Sci 2001;69:2265-77.
8. Schubert S, Brandl U, Brodhun M, Ulrich C, Spaltmann J, Fiedler N, et al. Neuroprotective effects of topiramate after hypoxia-ischemia in newborn piglets. Brain Res 2005;1058:129-36.
9. Liu Y, Barks JD, Xu G, Silverstein FS. Topiramate extends the therapeutic window for hypothermia-mediated neuroprotection after stroke in neonatal rats. Stroke 2004;35:1460-5.
10. Noh MR, Kim SK, Sun W, Park SK, Choi HC, Lim JH, et al. Neuroprotective effect of topiramate on hypoxic ischemic brain injury in neonatal rats. Exp Neurol 2006;201:470-8.
11. Follett PL, Deng W, Dai W, Talos DM, Massillon LJ, Rosenberg PA, et al. Glutamate receptor-mediated oligodendrocyte toxicity in periventricular leukomalacia: a protective role for topiramate. J Neurosci 2004;24:4412-20.
12. Choi JW, Kim WK. Is topiramate a potential therapeutic agent for cerebral hypoxic/ischemic injury? Exp Neurol 2007;203:5-7.
13. Gluckman PD, Wyatt JS, Azzopardi D, Ballard R, Edwards AD, Ferriero DM, et al. Selective head cooling with mild systemic hypothermia after neonatal encephalopathy: multicentre randomised trial. Lancet 2005;365:663-70.
14. Shankaran S, Laptook AR, Ehrenkranz RA, Tyson JE, McDonald SA, Donovan EF, et al. Whole-body hypothermia for neonates with hypoxic-ischemic encephalopathy. N Engl J Med 2005;353:1574-84.
15. Eicher DJ, Wagner CL, Katikaneni LP, Hulsey TC, Bass WT, Kaufman DA, et al. Moderate hypothermia in neonatal encephalopathy: efficacy outcomes. Pediatr Neurol 2005;32:11-7.
16. Compagnoni G, Bottura C, Cavallaro G, Cristofori G, Lista G, Mosca F. Safety of deep hypothermia in treating neonatal asphyxia. Neonatology 2008;93:230-5.
17. Tortorici MA, Kochanek PM, Poloyac SM. Effects of hypothermia on drug disposition, metabolism, and response: A focus of hypothermia-mediated alterations on the cytochrome P450 enzyme system. Crit Care Med 2007;35:2196-204.
18. Filippi L, la Marca G, Fiorini P, Poggi C, Cavallaro G, Malvagia S, et al. Topiramate concentrations in neonates treated with prolonged whole body hypothermia for hypoxic ischaemic encephalopathy. Epilepsia 2009;50:2355-61.
19. Kudin AP, Debska-Vielhaber G, Vielhaber S, Elger CE, Kunz WS. The mechanism of neuroprotection by topiramate in an animal model of epilepsy. Epilepsia 2004;45:1478-87.
20. Filippi L, Messeri A, Dani C, Pezzati M, Tronchin M, Giani T, et al. Redox status in very-low birth-weight newborns. Biol Neonate 2004;85:210-6.
21. Rutherford MA, Azzopardi D, Whitelaw A, Cowan F, Renowden S, Edwards AD, et al. Mild hypothermia and the distribution of cerebral lesions in neonates with hypoxic-ischemic encephalopathy. Pediatrics 2005;116:1001-6.
22. Kruskal WH, Wallis WA. Use of ranks in one-criterion variance analysis. J Am Stat Assoc 1952;47:583-621.
23. Glantz SA. Primer of biostatistics. 6th ed. New York: McGraw-Hill; 2005.
24. Glantz SA. Statistical software program. Version 6.0. New York: McGraw-Hill; 2005.
25. Robertson CM, Finer NN, Grace MG. School performance of survivors of neonatal encephalopathy associated with birth asphyxia at term. J Pediatr 1989;114:753-60.
26. Shankaran S, Woldt E, Koepke T, Bedard MP, Nandyal R. Acute neonatal morbidity and long-term central nervous system sequelae of perinatal asphyxia in term infants. Early Hum Dev 1991;25:135-48.
27. Angehagen M, Rönnbäck L, Hansson E, Ben-Menachem E. Topiramate reduces AMPA-induced Ca(2+) transients and inhibits GluR1 subunit phosphorylation in astrocytes from primary cultures. J Neurochem 2005;94:1124-30.
28. Sfaello I, Baud O, Arzimanoglou A, Gressens P. Topiramate prevents excitotoxic damage in the newborn rodent brain. Neurobiol Dis 2005;20:837-48.
29. Kaminski RM, Banerjee M, Rogawski MA. Topiramate selectively protects against seizures induced by ATPA, a GluR5 kainate receptor agonist. Neuropharmacology 2004;46:1097-104.
30. Koh S, Tibayan FD, Simpson JN, Jensen FE. NBQX or topiramate treatment after perinatal hypoxia-induced seizures prevents later increases in seizure-induced neuronal injury. Epilepsia 2004;45:569-75.
31. Zona C, Ciotti MT, Avoli M. Topiramate attenuates voltage-gated sodium currents in rat cerebellar granule cells. Neurosci Lett 1997;231:123-6.
32. Dodgson SJ, Shank RP, Maryanoff BE. Topiramate as an inhibitor of carbonic anhydrase isoenzymes. Epilepsia 2000;41(Suppl. 1):S35-9.
33. Zhao H, Asai S, Kanematsu K, Kunimatsu T, Kohno T, Ishikawa K. Real-time monitoring of the effects of normothermia and hypothermia on extracellular glutamate re-uptake in the rat following global brain ischemia. Neuroreport 1997;8:2389-93.
34. Koren G, Barker C, Bohn D, Kent G, Biggar WD. Influence of hypothermia on the pharmacokinetics of gentamicin and theophylline in piglets. Crit Care Med 1985;13:844-7.
35. Walia KS, Khan EA, Ko DH, Raza SS, Khan YN. Side effects of antiepileptics-a review. Pain Pract 2004;4:194-203.
36. Garris SS, Oles KS. Impact of topiramate on serum bicarbonate concentrations in adults. Ann Pharmacother 2005;39:424-6.
37. Philippi H, Boor R, Reitter B. Topiramate and metabolic acidosis in infants and toddlers. Epilepsia 2002;43:744-7.
38. Asconape JJ. Some common issues in the use of antiepileptic drugs. Semin Neurol 2002;22:27-39.
39. Filippi L, Bagnoli F, Margollicci M, Zammarchi E, Tronchin M, Rubaltelli FF. Pathogenic mechanism, prophylaxis, and therapy of symptomatic acidosis induced by acetazolamide. J Investig Med 2002;50:125-32.
40. Wirrell EC. Neonatal seizures: to treat or not to treat? Semin Pediatr Neurol 2005;12:97-105.
41. Fanaroff JM, Fanaroff AA. Blood pressure disorders in the neonate: hypotension and hypertension. Semin Fetal Neonatal Med 2006;11:174-81.
42. Silverstein FS, Ferriero DM. Off-label use of antiepileptic drugs for the treatment of neonatal seizures. Pediatr Neurol 2008;39:77-9.
43. Glier C, Dzietko M, Bittigau P, Jarosz B, Korobowicz E, Ikonomidou C. Therapeutic doses of topiramate are not toxic to the developing rat brain. Exp Neurol 2004;187:403-9.
44. The CRIB (Clinical Risk Index for Babies) score: a tool for assessing initial neonatal risk and comparing performance of neonatal intensive care units. The International Neonatal Network. Lancet 1993;342:193-8.