 doi:10.1111/j.1468-1331.2010.03113.x

Rufinamide in refractory childhood epileptic encephalopathies other than Lennox–Gastaut syndrome

G. Coppola[a], S. Grosso[b], E. Franzoni[c], P. Veggiotti[d], N. Zamponi[e], P. Parisi[f], A. Spalice[g], F. Habetswallner[h], A. Fels[h], A. Verrotti[i], A. D'Aniello[a], S. Mangano[l], A. Balestri[b], P. Curatolo[m] and A. Pascotto[a]

[a]*Clinic of Child Neuropsychiatry, Second University of Naples, Naples;* [b]*Department of Pediatrics, Pediatric Neurology Section, University of Siena, Siena;* [c]*Child Neuropsychiatry Unit, Bologna University, Bologna;* [d]*Department of Child Neurology and Psychiatry, C. Mondino Institute, University of Pavia, Pavia;* [e]*Pediatric Neurology Department, G. Salesi Hospital, Ancona;* [f]*Chair of Pediatrics, Second Faculty of Medicine, Sapienza University;* [g]*Department of Pediatrics, First Faculty of Medicine, Sapienza University, Sapienza;* [h]*Clinical Neurophysiology Unit, Cardarelli Hospital, Naples;* [i]*Department of Pediatrics, University of Chieti, Chieti;* [l]*Child Neuropsychiatry, Palermo University, Palermo; and* [m]*Pediatric Neuroscience Unit, Tor Vergata University of Rome, Rome, Italy*

Keywords:
epileptic encephalopathies-childhood, refractory seizures, rufinamide

Received 12 February 2010
Accepted 7 May 2010

Background: To report on the first multicenter Italian experience with rufinamide as adjunctive drug in children, adolescents and young adults with refractory childhood-onset epileptic encephalopathies other than Lennox–Gastaut syndrome.
Methods: Thirty-eight patients (19 males, 19 females), aged between 4 and 34 (mean 13.7 ± 8.3, median 12.5), all affected by different types of childhood-onset refractory epileptic encephalopathies other than Lennox–Gastaut syndrome, were treated with rufinamide as adjunctive drug for a mean period of 11.4 months (range 3–26 months).
Results: Fifteen of 38 patients (39.5%) had a ≥50% seizure reduction in countable seizures. Complete seizure freedom was achieved in one of these patients (2.6%). Three patients (7.9%) had a 25–49% seizure reduction, whilst seizure frequency remained unchanged in 15 (39.5%) and increased in five patients (13.1%). Eleven patients (28.9%) reported adverse side effects. Vomiting was reported in five patients (13.1%); drowsiness, decreased appetite and irritability with migraine manifested in other four patients. They were transient and mild in all cases.
Conclusion: Rufinamide may be an effective and well-tolerated adjunctive drug for the treatment of refractory childhood-onset epileptic encephalopathies other than Lennox–Gastaut syndrome. Rufinamide was most effective in patients with drop-attacks and (bi)frontal spike–wave discharges.

Introduction

Rufinamide is a structurally triazole-derivative (1-[2,6-difluorophenyl)methyl]-1hydro-1,2,3-triazole-carboxamide) novel antiepileptic drug, structurally unrelated to the existing antiepileptic drugs, and approved by the Food and Drug Administration for the treatment of Lennox–Gastaut syndrome in patients aged 4 and over, and for the treatment of partial seizures in adults and adolescents.

The proposed mechanism of action is the limitation of excessive sodium-dependent action potential firing [1,2]. Rufinamide has a broad efficacy spectrum in rodent seizure models of epilepsy [3]. In three randomized controlled trials, rufinamide was effective and safe for the adjunctive treatment of partial seizures in adults and adolescents [4,5], as well as for the treatment of generalized seizures associated with Lennox–Gastaut syndrome [6].

To the best of our knowledge, data regarding rufinamide' efficacy in childhood epileptic syndromes other than Lennox–Gastaut syndrome and partial epilepsy are not so far available. In their heterogeneous study population, Kluger *et al*. [7] report on 12 patients treated with rufinamide and affected by myoclonic-astatic epilepsy (3), Dravet syndrome (2) and unclassified generalized epilepsy (7). The purpose of this study is to report on the first multicenter Italian experience with rufinamide as add-on drug in children and

Correspondence: G. Coppola, MD, Department of Psychiatry, Clinic of Child Neuropsychiatry, Second University of Naples, Italy, Via Pansini 5 80131 Naples, Italy (tel.: +39 081 5666695; fax: +39 081 5666694; e-mail: giangennaro.coppola@unina2.it).

adolescents and young adults with childhood-onset refractory epileptic encephalopathies other than Lennox–Gastaut syndrome.

Materials and methods

Patients were recruited in a prospective, add-on, open-label treatment study from eleven Italian centres for paediatric and adolescent epilepsy care. The patients were selected according to the following criteria: (i) age 4 and over; (ii) childhood-onset epileptic encephalopathies, the so-called catastrophic epilepsy syndromes other than Lennox–Gastaut syndrome, refractory to at least three previous antiepileptic drugs (AEDs), alone or in combination; (iii) more than one seizure per month in the last 6 months; (iv) use of at least one other AED, but no more than three, at baseline; (v) informed consent from parents and/or caregivers, who had to be able administer the study drug and record seizures in a diary. Moreover, female patients of child-bearing age were required not to be pregnant and to be using an adequate form of contraception.

Exclusion criterion included progressive neurological or systemic disease. Patients with significantly abnormal liver, kidney and blood laboratory values were also excluded, as were those who were considered to be unlikely to comply with the study requirements.

Besides enrolling rufinamide-naïve subjects, study sites that had previously started patients on rufinamide had the option of enrolling patients who had completed at least 6 months of maintenance treatment and met the study inclusion and exclusion criteria.

Pseudo-seizures were excluded by means of video-electroencephalographic recordings (EEGs) recordings and/or long-term monitoring EEGs. CT and MRI were performed in all cases. The number of the seizures was recorded by parents and/or caregivers at home and at school. Seizure frequency, type and duration were recorded in an epilepsy diary to be kept and reviewed at each follow-up visit. All seizures were classified according to the International League against Epilepsy Revised Classification of Seizures [8], whilst diagnostic criteria for Lennox–Gastaut syndrome were based on the International League Against Epilepsy classification [9]. There was an initial observation period of 6 months (baseline) that could be shortened to 3 months if seizures occurred almost daily. After the observation period, rufinamide was added to the baseline therapy at the starting dose of 10 mg/kg body wt, evenly divided in two daily doses and then titrated by 10 mg/kg per day approximately every 3 days up to a maximum of 1000 mg/day in children aged ≥4 with a body weight <30 kg. If baseline therapy included valproic acid, rufinamide could be titrated up to a maximum of 600 mg/day, because of the significantly reduced clearance, especially in children, of rufinamide in combination with valproic acid [10]. In patients more than 30 kg body wt, rufinamide could be titrated up to 1800 mg/day if body weight was comprised between 30.0 and 50.0 kg, up to 2400 mg/day for body weight of 50.1–70.0 kg, and up to 3200 mg for body weight of more than 70.1 kg.

During titration and maintenance periods, anticonvulsant drug daily doses including rufinamide could be changed whenever necessary depending on clinical and adverse side effects. Rescue drugs were allowed if necessary. EEG, adverse effects and blood levels of concomitant anticonvulsant drugs were monitored in all the patients. Patients were followed on a weekly basis during the titration period, either by means of visits to the clinic or by telephone. Patients subsequently visited the clinic at 3-month intervals during the maintenance treatment, with a monthly follow-up by telephone between visits to the clinic whenever necessary. Blood chemistry and liver and kidney function were carefully assessed at each time interval. Parents/caregivers were informed of the potential clinical adverse effects to refer to the clinician.

Efficacy was assessed by comparing the frequency of countable seizures at baseline (4 weeks before rufinamide therapy) with the frequency in the last 4 weeks of observation.

The response to treatment was monitored in terms of reduction of seizure frequency, in relation to the baseline phase, using the following categories: (i) seizure control (100% seizure remission); (ii) 50–99% decrease in number of seizures; (iii) 25–49% decrease in number of seizures; (iv) worsened when the seizure rate increased.

The Institutional Review Board from each epilepsy unit approved the study; no support was received from pharmaceutical companies.

Statistical evaluation was performed by means of a two-tailed Wilcoxon rank test for non-parametric data and the Fisher's exact test. Data were expressed as mean ± SD and median values. Significance was set at $P < 0.05$.

Results

Thirty-eight patients (19 males, 19 females), aged between 4 and 34 (mean 13.7 ± 8.3, median 12.5), all affected by different types of childhood-onset refractory epileptic encephalopathies other than Lennox–Gastaut syndrome, were treated with rufinamide as adjunctive drug for a mean period of 11.4 months (range 3–26 months). Six of 38 patients (15.8%) had an observational period of 3 months; five of them discontinued treatment because of inefficacy or adverse events.

Characteristics of the patients, including type of epileptic syndrome, psychomotor development, mental level, neurological examination and CT/MRI findings are summarized in Table 1.

Seizure frequency during baseline phase was the following: ≥1/day in nine patients (23.7%); 1–20/day in 24 (63.2%), and 1–10/month in 5 (13.1%).

Seizure types, often associated in a given patient prior to the start of rufinamide, were the following: focal with/without secondary generalization (23), atonic (13), tonic-clonic (12), tonic/spasms (9), atypical absences (5), myoclonic (3).

Mean age at seizure onset was 2.6 ± 3.4 years (median 1.0). Mean duration of epilepsy was 11.2 ± 7.9 years (median 10.0). The mean number of anticonvulsant drugs tried before rufinamide was 7.8 ± 2.0 (median 7.5). A final mean dose of rufinamide was 37.9 ± 15.7 mg/kg per 24 h (range 20.5–78.2 mg/kg) if combined to valproic acid, and of 36.4 ± 12.7 mg/kg per 24 h (range 7.5–61.5 mg kg) without valproic acid. All patients received concomitant antiepileptic therapy. Valproic acid (55.3%), lamotrigine (26.3%), levetiracetam (23.7%), topiramate (23.7%), clobazam (21.0%), phenobarbital (21.0%) and clonazepam (20.9%) were the most commonly used concomitant antiepileptic drugs (Table 2).

Rufinamide was discontinued in 7 of 38 patients (18.4%) after a mean period of 2.2 months (range 1–5 months), because of adverse side effects and/or increase in seizure frequency.

Table 1 Characteristics of patients (n = 38)

Sex, male/female	19/19
Age, mean ± SD (range)	13.7 ± 8.3 (4–34 years)
Psychomotor development/mental retardation[a]	
Mild delay	6
Moderate delay	9
Severe delay	14
Profound delay	9
Cerebral palsy	
Tetraparesis	11
Spastic diplegia	2
Hemiparesis	4
Hypotonia	1
Ataxia	4
Normal	16
CT/MRI findings	
Normal	14
Brain atrophy	11
Neuronal migration disorder	6
Brain malformation	2
Tuberous sclerosis	1
Aspecific	4
Epilepsy syndrome	
Multifocal encephalopathy with spasms/tonic seizures	22
Multifocal encephalopathy with (bi)frontal spike–wave discharges	11
Dravet syndrome	4
Myoclonic-astatic syndrome	1
Type of seizure[b]	
Focal with/without secondary generalization	23
Drop-attacks	13
Tonic-clonic	12
Tonic/spasms	9
Atypical absences	5
Myoclonic	3

[a]Evaluated by means of Brunet–Lézine test [13] or Terman–Merril scale [14]; [b]often combined in the same patient.

Efficacy

The results are summarized in Table 2. Fifteen of 38 patients (39.5%) receiving rufinamide as adjunctive therapy had a ≥50% seizure reduction in countable seizures after a mean 11.4-month observational period. Complete seizure freedom was achieved in one of these patients (2.6%). Three patients (7.9%) had a 25–49% seizure reduction, whilst seizure frequency remained unchanged in 15 (39.5%) and increased in five patients (13.1%).

As regards the type of epileptic syndrome, a decrease in seizure frequency was recorded in seven of the twenty-two patients (31.8%) with multifocal encephalopathies with spasms and tonic seizures, and in 7 of 11 patients (63.6%) with (bi)frontal spike–wave discharges. One of the four patients with Dravet syndrome had a 25–49% seizure reduction, whilst seizure frequency remained unchanged in one and increased in other two. The only patient with myoclonic-astatic syndrome had a more than 50% seizure decrease.

As regards seizure type, in the group with (bi)frontal spike–wave discharges, 7 of 11 patients (63.6%), all of them with drop-attacks, had a seizure reduction of ≥50%; conversely, in the group without frontal discharges, in which focal and tonic seizures were most frequent, 7 of 22 patients (31.8%) showed a ≥50% seizure decrease.

There were no statistic difference between the characteristics of the responders and non-responders, including age at seizure onset, epilepsy duration and age at rufinamide exposure ($P > 0.05$ at Wilcoxon rank sum test).

Table 3 shows no significant difference as to ≥50% seizure reduction between cryptogenic group and symptomatic group (28.5% vs. 45.8%, respectively; $P = 0.356$ at Fisher's exact test).

Safety and tolerability

Eleven patients (28.9%) reported adverse side effects, whilst taking rufinamide (Table 4). Vomiting was

Table 2 Efficacy and tolerabilty of rufinamide according to age

Age (years)	Number initiating (*n*)	Seizure control	At follow-up (mean follow up 12.3 months)	Seizure etiology	Adverse side effects	Mean number AED	Type of treatment
3–7	9	Seizure free	–		–	C (3.0)	
		50–99%	3 (33.3%)			S (2.0)	
		25–49%	–	S (3)			(VPA); (VPA-LTG);
		Unchanged	4 (44.4%)	C (1) S (3)			PB-LEV-OXC)
		Increased	2 (22.2%)	C (1) S (1)			(TPM); (OXC-ZNS);
							(VPA-LTG-CLOB);
							(PB-CLOB-TPM)
							(VPA-LEV);
							(LTG-CLOB-BRM)
8–12	11	Seizure free					
		50–99%	–		3 (27.3%)	C (2.2)	
		25–49%	4 (36.4%)	C (1) S (3)		S (2.6)	(VPA-LEV); (CLOB-LTG);
		Unchanged	2 (18.2%)	C (2)			(GBP-CNZ-CBZ);
		Increased	4 (36.4%)	C (2)S (2)			(PHT-CNZ-OXC)
			1 (9.1%)	C (1)			((VPA-TPM-CZP);
							(VPA-TPM)
							(VPA-TPM);
							2 (VPA-CLOB);
							(VPA-FBM-CNZ)
							(VPA-TPM)
13–18	9	Seizure free					
		50–99%	1 (11.1%)	C (1)	6 (66.7%)	C (2.7)	(VPA-LEV-CNZ)
		25–49%	3 (33.3%)	C (1) S (2)		S (2.8)	(CLOB-LEV-LTG);
		Unchanged	1 (11.1%)	S (1)			(VPA-ETS); (VPA-LEV)
		Increased	3 (33.3%)	C (1) S (2)			(VPA-LTG-CNZ)
			1 (11.1%)	S (1)			(LEV-NZP-ACZ);
							(PB-LTG-CZP);
							(PB-NZP-VPA)
							(VGB-ZNS-TPM)
>18	9	Seizure free					
		50–99%	–		2 (22.2%)	C (3)	
		25–49%	4 (37.5%)	C (1) S (3)		S (2.5)	(TPM-LTG); (LEV-ZNS);
		Unchanged	–				(PB-CBZ-LTG);
		Increased	4 (50%)	C (1) S (3)			(VPA-CBZ-PB)
			1 (12.5%)	C (1)			(CBZ-CLOB);
							(VPA-TPM-CNZ);
							(VPA-LEV-LTG);
							(PB-CBZ)
							(VPA-CNZ-PB)

C, cryptogenic; S, symptomatic; AED, anti-epileptic drug; VPA, valproic acid; PB, phenobarbital; CNZ, clonazepam; LTG, lamotrigine; ZNS, zonisamide; OXC, oxcarbazepine; CBZ, carbamazepine; LEV, levetiracetam; FBM, felbamate; CLOB, clobazam; TPM, topiramate; PHT, phenitoine; VGB, vigabatrin; ACZ, acetazolamide; BRM, potassium bromide; GBP, gabapentin; NZP, nitrazepam.

reported in five patients (13.1%): in two patients, it appeared during the titration phase and was controlled by decreasing the daily dosage of rufinamide. It was sporadic in the other three.

Drowsiness, decreased appetite and irritability with migraine manifested in four patients; they were transient and mild in all cases.

A seizure worsening was reported in 5 of 38 patients (13.1%), three of them coming from the cryptogenic group, within 1 to 3 months after the start of rufinamide. In four patients, seizures were mainly tonic and/or tonic-clonic; in one patient seizures somewhat changed on rufinamide with respect to baseline.

Blood levels of concomitant anticonvulsant drugs were generally not modified by the addition of rufinamide. All the patients had normal laboratory test values during the treatment period.

Discussion

In this prospective, open-label add-on study, rufinamide significantly reduced, after a mean follow-up period of 1 year, the overall seizure frequency in approximately 40% of patients with refractory childhood-onset epileptic encephalopathies other than Lennox–Gastaut syndrome.

Table 3 Response to treatment related to epilepsy type

	Cryptogenic No. of pts (14)*	Symptomatic No. of pts (24)*
Seizure control		
100%	1 (7.1%)*	–
50–99%	3 (21.4%)*	11 (45.8 %)*
25–49%	2 (14.3 %)	1 (4.2%)
Unchanged	5 (35.7 %)	10 (41.7 %)
Increased	3 (21.4 %)	2 (8.3%)

*$P = 0.356$ at Fisher's exact test.

Table 4 Adverse events occuring on rufinamide add-on therapy

Adverse events[a]	No. of patients (11/38) (28.9%)
Vomiting and/or nausea	5 (13.1 %)
Irritability/aggressiveness	2 (5.3 %)
Drowsiness	2 (5.3 %)
Skin rash	1 (2.6 %)
Decreased appetite	1 (2.6 %)
Insomnia	1 (2.6%)
Migraine	1 (2.6%)

[a]Associated in some patients.

To our knowledge, this is the first report on the use of rufinamide as adjunctive therapy for the treatment of the so-called catastrophic epilepsies.

As concerns seizure type, this study confirms rufinamide to be particularly effective against drop-attacks, and, to a lesser extent, tonic and tonic-clonic seizures [6,7].

In the whole, response to rufinamide was less sustained in this study population than in patients with Lennox–Gastaut syndrome (40% vs. 55% as reported by Glauser *et al*. [6] and Kluger *et al*. [7]), whilst it was somewhat better than in adolescents and adults with partial seizures (20–25% as reported by Brodie *et al*. [5] and Kluger *et al*. [7]).

Interestingly, the group of patients with epileptic encephalopathies with (bi)frontal spike–wave discharges and atonic seizures had a higher 50% responder rate (63.6%) compared with the group with epileptic encephalopathies with spasms and tonic fits, originating from other brain areas (31.8%). This may to some extent explain why the overall efficacy of rufinamide in this series appeared to be intermediate between what reported in Lennox–Gastaut syndrome – where rufinamide was particularly effective against atonic seizures – and partial seizures.

Seizure decrease in the only case of myoclonic-astatic syndrome, and seizure recurrence in the four patients with Dravet syndrome are fairly in keeping with Kluger *et al*.[7]. Data regarding these epilepsy syndromes are, of course, small and further studies are warranted.

As shown in Table 2, there was no clear relationship between the clinical response to rufinamide in cryptogenic or symptomatic cases and the baseline AED treatment in the different age groups.

In keeping with pharmacokinetic studies [10], blood levels of concomitant antiepileptic drugs did not significantly change in our patients; furthermore, the dose range of rufinamide' maximal efficacy was substantially comparable to that reported by Kluger *et al*. [7].

Almost similar final mean doses of rufinamide in patients with and without valproic acid as baseline therapy may be somehow related to the early effectiveness of rufinamide, often observed at low to moderate doses. This finding has probably discouraged from adding further dose of rufinamide in some patients.

A systematic assessment of the amount of paroxysmal EEG discharges in wake and sleep recordings whilst taking rufinamide was not performed. Nonetheless, no significant EEG changes were reported in most of the responders.

In our series, after a mean follow-up of 11.4 months, rufinamide was discontinued within 5 months in about 18% of patients. Although our observational study is still ongoing and the follow-up period is not long enough, this preliminary data may somehow support the effectiveness of rufinamide over time. This is in keeping with Kluger *et al*. [11,12], who reported that 41.7% of patients with childhood-onset refractory epilepsy were still taking rufinamide after 18 months of follow-up, with a responder rate of about 38%.

It is noteworthy that seizure worsening on rufinamide has not been reported so far [5–7]. In three patients with Lennox-Gastaut syndrome by Glauser *et al*. [6], status epilepticus appeared 13, 20 and 25 days after the start of rufinamide therapy, respectively. The authors considered the occurrence of the status epilepticus as sporadic and unlikely to be drug related.

During our trial, a significant increase in seizure frequency appeared in five patients (13.1%) within 1–3 months after the start of rufinamide, and led the drug to be discontinued in all the patients. Interestingly, four of these patients most frequently had tonic and tonic-clonic seizures.

Eight patients from our series underwent implantation of vagus nerve stimulator (7) or callosotomy (1), with no significant results on seizure frequency prior to receiving rufinamide. Four of the seven patients on VNS showed a ≥50% seizure reduction mainly in drop-attacks after a mean follow-up of 6 months (range 4–11 months).

With respect to tolerability, adjunctive therapy with rufinamide was generally well tolerated, according with Glauser *et al*. [6] and Kluger *et al*. [7]. Vomiting, drowsiness, decreased appetite and irritability were

most frequently reported, even combined in some patients. Overall, they were transient and mild in all the patients.

Nonetheless, rufinamide is still an 'orphan drug' only for Lennox–Gastaut syndrome, and it should be used with cautions in other epileptic syndromes.

In conclusion, the present preliminary data reveal that rufinamide may be an effective and well tolerated adjunctive drug for the treatment of refractory childhood-onset epileptic encephalopathies other than Lennox–Gastaut syndrome. Rufinamide was most effective in patients with drop-attacks and (bi)frontal spike–wave discharges. However, further experience is warranted to gain better understanding of the therapeutic potential of this drug in well-defined epileptic syndromes.

References

1. Schmutz M, Allgeier H, Pozza MF, *et al.* Rufinamide (CGP 33101): Broad anti-convulsant spectrum and excellent tolerability in rodents. *Epilepsia* 2000; **41**(Suppl. 8)**:** 159.
2. Arroyo S. Rufinamide. *Neurotherapeutics* 2007; **4:** 155–162.
3. White HS, Franklin MR, Kupferberg HJ, *et al.* The anticonvulsant profile of rufinamide (CGP 33101) in rodent seizure models. *Epilepsia* 2008; **49:** 1213–1220.
4. Pålhagen S, Canger R, Henriksen O, *et al.* Rufinamide: a double-blind, placebo-controlled proof of principle trial in patients with epilepsy. *Epilepsy Res* 2001; **43:** 115–124.
5. Brodie MJ, Rosenfeld WE, Vazquez B, *et al.* Rufinamide for the adjunctive treatment of partial seizures in adults and adolescents: a randomized placebo-controlled trial. *Epilepsia* 2009; **50:** 1899–1909.
6. Glauser T, Kluger G, Sachdeo R, *et al.* Rufinamide for generalized seizures associated with Lennox–Gastaut syndrome. *Neurology* 2008; **70:** 1950–1958.
7. Kluger G, Kurlemann G, Haberlandt E, *et al.* Effectiveness and tolerability of rufinamide in children and adults with refractory epilepsy: first European experience. *Epilepsy Behav* 2009; **14:** 491–495.
8. Commission on Classification and Terminology of the International League Against Epilepsy. Proposal for revised clinical and electroencephalographic classification of epileptic seizures. *Epilepsia* 1981; **22:** 489–501.
9. Commission on Classification and Terminology of the International League Against Epilepsy. Proposal for revised classification of epilepsies and epileptic syndromes. *Epilepsia* 1989; **30:** 389–399.
10. Perucca E, Cloyd J, Critchley D, *et al.* Rufinamide: clinical pharmacokinetics and concentration-response relationships in patients with epilepsy. *Epilepsia* 2008; **49:** 1123–1141.
11. Kluger G, Haberlandt E, Kurlemann G, *et al.* First European long-term experience with the orphan drug rufinamide in childhood-onset refractory epilepsy. *Epilepsy Behav* 2010; **17:** 546–548.
12. Kluger G, Glauser T, Krauss G, Seeruthun R, Perdomo C, Arroyo S. Adjunctive rufinamide in Lennox-Gastaut syndrome: a long-term, open-label extension study. *Acta Neurol Scand* 2010; doi: 10.1111/j.1600-0404.2010.01334.x [Epub ahead of print].
13. Brunet O, Lézine I. *Le Développement Psychologique de la Première Enfance*. Paris: Presse Universitaire de France, 1951.
14. Terman LM, Merrill M. *Stanford-Binet Intelligence Scale: Manual for the Third Revision, Form L-M*. Boston: Houghton Mifflin, 1960.