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Bilateral Wada test: Amobarbital or propofol?

J. Curot [a,c,*], M. Denuelle [a], T. Busigny [c], G. Barragan-Jason [c], M. Kany [b], P. Tall [b], F. Marlat [a], N. Fabre [c], L. Valton [a,c]

[a] Service de Neurologie et d'Explorations Fonctionnelles Neurologiques, Unité "Chirurgie de l'épilepsie", Centre Hospitalier Universitaire de Toulouse, Hôpital Rangueil, 1 avenue du Pr Jean Poulhès TSA 50032, 31059 Toulouse, France
[b] Service de Neuroradiologie Diagnostique et Thérapeutique, Centre Hospitalier Universitaire de Toulouse, Hôpital Rangueil, 1 avenue du Pr Jean Poulhès TSA 50032, 31059 Toulouse, France
[c] CERCO – Centre de Recherche Cerveau et Cognition UMR 5549 – CNRS (Centre National de la Recherche Scientifique), Pavillon Baudot, Centre Hospitalier Universitaire de Toulouse, Hôpital Purpan, Place du Dr Baylac, 31059 Toulouse, France

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ABSTRACT

Purpose: The Wada test is still the gold standard procedure to predict language and memory deficits before temporal lobe epilepsy surgery. As amobarbital was no longer available, our aim was to validate propofol as an alternative.
Method: We retrospectively studied 47 patients who underwent a bilateral intracarotid procedure, performed with amobarbital (18), or propofol (29), between 2000 and 2010 during the preoperative evaluation of temporal lobe epilepsy.
Results: The number of patients experiencing an adverse event (mostly transient disturbance of consciousness or benign ocular symptoms) during both injections did not differ significantly between amobarbital and propofol. Hemispheric dominance was successfully determined in 96.5% patients with propofol vs. 94.4% with amobarbital for language, and in 72.4% under propofol vs. 77.7% under amobarbital for memory with no significant difference between groups.
Conclusion: Propofol can be used for the Wada test with an efficacy and safety comparable to amobarbital.

1. Introduction

The Wada test traditionally consists of a selective intracarotid injection of a fast acting barbiturate drug, generally sodium amobarbital, which transiently inhibits the ipsilateral cerebral hemisphere, in order to isolate the contralateral hemisphere and assess its activity. The original aim of this intracarotid procedure (ICP) developed by Dr Jung Wada in 1960[1] was to confirm the hemispheric lateralization of speech during preoperative evaluation of some refractory epilepsies in order to predict a risk of aphasic sequela. The test was extended to the study of hemispheric localization of memory functions, especially before considering anterior temporal lobectomy, in order to prevent the risk of global amnesic syndrome as in patient HM.

Nowadays, the traditional Wada test needs to be re-evaluated because amobarbital is no longer available in many countries[3] and other anesthetic drugs with different pharmacokinetic characteristics are currently used.[4]

There is still no consensus on a single substitute for amobarbital. One of the most widely used alternatives is propofol. Bazin and colleagues[5] were the first to describe the use of propofol to perform ICP and propofol ICP has now been reported in several studies,[6–10] where it appears to be as effective and well tolerated as the amobarbital procedure.

In 2004, 12 propofol ICP were compared to 55 amobarbital ICP.[7] ICP was successfully performed for language in 12 patients and for memory in 9 with propofol, in comparison to 52 language lateralization and 41 conclusive memory assessments using amobarbital. Only minor adverse effects (AE) were observed (laughing in one patient, and head and eye version in another).

In 2005 a study evaluated all AE, apart from the well-known cardiovascular effects, induced by intravenous propofol injection[8] during ICP in 58 patients and proposed a classification of AE in three severity grades (see Fig. 1). AE were reported for one third of patients with propofol. Magee et al.[10] recently reported AE in 29.1% of unilateral propofol ICP with no significant differences in number and type of AE compared with amobarbital.

Nevertheless it is difficult to draw definitive conclusions from these studies because of the small number of patients (at most 25 propofol ICP[9]), the heterogeneity of affections (only a specific cohort of epileptic patients[10]) and absence of standardized

* Corresponding author at: CERCO – Centre de Recherche Cerveau et Cognition UMR 5549, Pavillon Baudot, CHU Toulouse, Hôpital Purpan, Place du Dr Baylac, 31059 Toulouse, France. Tel.: +33 06 78 93 33 84.
E-mail address: curot@cerco.ups-tlse.fr (J. Curot).

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Grade 3	hypotension, hypertension, increased muscle tone with twitching and tonic posture or rhythmic movements, disturbance of consciousness
Grade 2	confusion, head and eye version, involuntary movements, tremor
Grade 1	eye pain, lacrimation , face contortion, headache, laughing, apathy, shivering, sweats, warm feeling

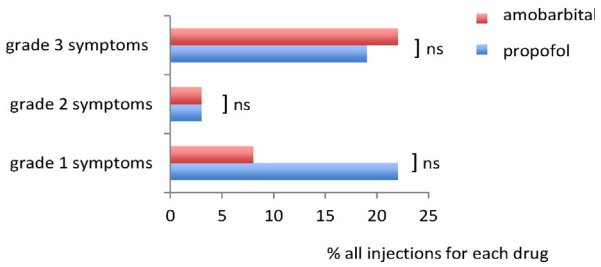

Fig. 1. AE considering all ICP, according to classification adapted from Mikuni et al.[8] ns: non significant. *The following AE were already described in Mikuni et al.'s classification[8]: eye pain, lacrimation, face contortion, shivering laughing and apathy (grade 1), confusion, head and eye version and involuntary movements (grade 2), increased muscle tone with twitching and rhythmic movements or tonic posture (grade 3). We added symptoms not reported in Mikuni's study: headache, sweats and warm feeling (grade 1), tremor (grade 2), disturbance of consciousness, and significant arterial hypotension or hypertension (grade 3). Grade 1 symptoms: we observed no significant difference between amobarbital and propofol during first ($\chi^2_1 = 0.721$, $p = 0.396$), second ($\chi^2_1 = 2.715$, $p = 0.099$) or both injections ($\chi^2_1 = 3.118$, $p = 0.077$). Grade 2 symptoms: we observed no significant difference between amobarbital and propofol during first injections ($\chi^2_1 = 0.033$, $p = 0.855$). No grade 2 symptoms were observed during second injections with either drug. Grade 3 symptoms: we observed no significant difference between amobarbital and propofol during first ($\chi^2_1 = 0.033$, $p = 0.880$), second ($\chi^2_1 = 0.559$, $p = 0.455$) or both injections ($\chi^2_1 = 0.146$, $p = 0.702$).

protocols. Not only do propofol doses vary across centers but also only one unilateral ICP is usually performed, although it has been demonstrated that bilateral ICP has a better prognostic value in predicting both post-operative verbal memory and verbal intelligence quotient.[11]

For all these reasons, standardization and validation of propofol use are needed, especially in bilateral ICP. We sought to contribute to this by retrospectively reviewing the complete series of epileptic adult patients who underwent ICP in our center. Our purpose was to make a detailed comparison of the technical characteristics and tolerance of bilateral ICP with propofol and amobarbital. We are aware that noninvasive techniques are currently being developed with the potential effect of making the Wada test obsolete.[12,13] Despite this context, we are convinced that ICP still has indications and that it is important to discuss which drug to use for the procedure.

2. Method

2.1. Population

We retrospectively reviewed all data from 51 patients (26 women) aged 18–57 years (mean age = 34.6 ± 10), who had undergone an ICP between 2000 and 2010 during preoperative evaluation of refractory epilepsy at the University Hospital of Toulouse, France. All patients had a comprehensive assessment, including neurological examination, neuropsychological testing, routine MRI, surface EEG and video. ICP was carried out as part of the patients' clinical care. Each patient received detailed information about the objectives and course of the procedure, and gave informed consent in the usual way.

We used amobarbital in 18 patients (from 2000 to 2003), then, at the beginning of the shortage of amobarbital in France, methohexital in 3 patients (2003). We very quickly stopped using methohexital because duration of action of the drug was too short, and propofol has been employed since then. Thirty patients have had propofol ICPs since 2004.

2.2. Procedure

Selective catheterization of the internal carotid artery (ICA) was performed by an interventional neuroradiologist (PT or MK), using a transfemoral approach. An angiography of the intracranial circulation was performed before each anesthetic injection to study its distribution territory. Selective ICA anesthesia was performed with the same procedure for both sides in each patient. The cerebral hemisphere to be operated on was first anesthetized. Blood pressure, heart rate and oxygen saturation were monitored non-invasively throughout the procedure. EEG recording (sampled at 256 Hz, bipolar montage, 10 channels, reference between Cz and Pz electrodes), started several minutes before the anesthetic injection and continued several minutes after the return of baseline clinical and EEG signs. It was read on line by an electroencephalographer (MD or LV). Before injection, a baseline state was obtained for EEG, visual fields, hand strength and cognitive functions. Patients were instructed to maintain arms and hands up, and to count aloud. While they counted to ten, the anesthetic solution was slowly injected manually through the catheter directly into the ICA (see Table 2). The injection was stopped when effective anesthesia was confirmed, as soon as hemiparesis was observed. Hand strength, sensitivity, visual field and language were evaluated periodically before the start of the test, after every minute and at the end of the test. A memory retention test was done after recovery had been verified through complete normalization of EEG and a neurological examination. The second hemisphere was evaluated about 30 min after the first.

2.3. Neuropsychological assessment

All patients underwent neuropsychological testing before ICP to determine the appropriate level of difficulty for the items of the test. The dominant hemisphere for language was determined by the onset of language impairment (speech arrest, dysphasia, delay in understanding and producing comprehensible language) after drug injection into one side but not the other. Speech control was defined as bilateral if language impairment occurred after injection of both sides, and was not defined when no language impairment occurred after injection of both sides.

Memory assessment began approximately 1 min after injection, as soon as anesthesia was both effective and allowed sufficient cooperation from the patient. Memory items were presented in three consecutive parts, in the same order in each part and for each patient (who was instructed to repeat, read or name every item and to memorize them) to assess verbal and nonverbal episodic memory: 3 audio presented words, 3 abstract Figure 3 written words, 3 concrete pictures, a sentence, and two real objects. The memory retention test began 5–10 min after clinical examination and EEG had returned to baseline, usually 10–15 min after the injection.

Free recall and recognition memory were tested by using a three-alternative forced-choice task. Total memory score was obtained by adding one point for each item with good retrieval. An asymmetry score was calculated by subtracting the memory score of the pathological hemisphere from the memory score of the contralateral hemisphere. One hemisphere was considered dominant when there was a gap of more than two points between the total memory scores of the two hemispheres.

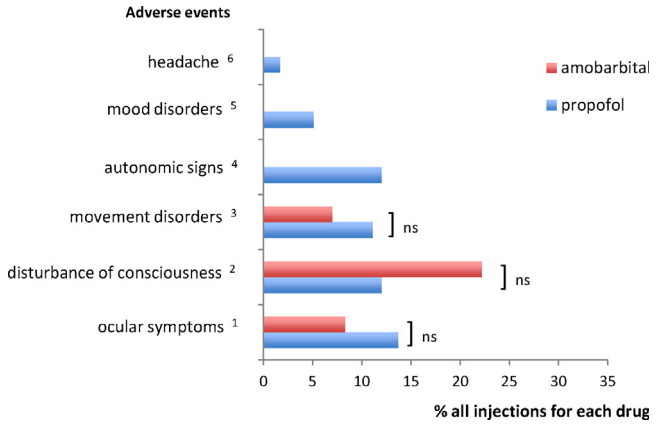

Fig. 2. Details of main adverse events in both groups considering all ICP. ns: non-significant ($p > 0.05$). 1 – Ocular symptoms included eye pain (intraocular or retroocular), lacrimation, itching, flashes. 2 – Disturbance of consciousness: occurred in 7 injections with propofol (mild and brief loss of contact (5 injections), moderate drowsiness lasting 140 s (1 injection) and snoring followed by crying and agitation (1 injection), vs. 8 injections with amobarbital, among which 3 deep drowsiness (2 lasting 120 and 160 s, and 1 shorter followed by agitation). 3 – Movement disorders were contralateral upper limb dystonic attitudes (propofol: 1.7% vs. amobarbital: 2.8% of injections), axial dystonia (propofol: 5.1% vs. amobarbital: 5.6% of injections), trismus (propofol: 0, vs. amorbarbital: 8.3% of injections) and tremor (propofol 1, vs. amobarbital 0 injection). 4 – Autonomic signs included cold or warm feelings in the head, chills, sweats, hypotension ($n = 1$), and a marked hypertension (193/87 mmHg peak) during both injections in 1 patient with chronic hypertension). 5 – Mood disorders included mild euphoria in 3 patients with propofol. They did not disrupt ICP and accurate lateralization for memory and language were obtained for two of the patients. 6 – Headache was observed in 1 patient with propofol. One patient complained about left earache and tingling on the forehead; this occurred during a left injection with poor ICA distribution and reflux in the external carotid artery. As a third injection was necessary for successful assessment of the left hemisphere we excluded this patient from analysis.

2.4. AE reporting system

We considered any AE that could endanger the patient (hemodynamic and vegetative disorders), create discomfort (pain, dysphoria), or hinder the realization of the test (motor disorders and disturbance of consciousness (DoC)). We detailed all AEs (Fig. 2) and rated their severity using Mikuni's classification,[8] adapted for symptoms not reported in his study (Fig. 1).

2.5. Statistical analyses

Comparison of continuous data (i.e. duration of EEG slowing) was computed for each group (amobarbital and propofol) with a univariate ANOVA. Categorical data (i.e. occurrence of an AE) were analyzed using the χ^2 test. Non-parametric tests (Mann Whitney U test) were used to compare doses of each drug that led or did not lead to DoC, because of substantial asymmetry in the sizes of the groups. A p value ≤ 0.05 was considered as the significance threshold for considering groups as different. In one patient in the propofol group, no deficit or EEG slowing was observed during the first injection on the left side. As a third injection was necessary for successful assessment of the left hemisphere we excluded this patient from the analysis. We excluded methohexital procedures from the statistical analyses in order to dichotomize the sample into propofol vs. amobarbital.

3. Results

3.1. Patients

Twenty-nine patients tested with propofol and 18 with amobarbital were analyzed. Demographic or clinical characteristics did not differ significantly between groups (Table 1).

3.2. Tolerance (Figs. 1 and 2)

AEs were observed during 38 ICP in 27 patients (57.4%) of the full sample. All AEs were transient and occurred only during the procedure. We observed AEs in 8 of the 18 patients tested with amobarbital (44.4%) vs. 19 of the 29 with propofol (65.5%). There was no statistical difference between groups ($\chi^2_1 = 2.018$, $p = 0.155$). AEs were observed in 12 out of 36 amobarbital (33.3%) vs. 26 out of 58 propofol injections (44.8%), without statistical difference between groups considering all AEs ($\chi^2_1 = 1.219$, $p = 0.270$). Furthermore, the number of patients with an AE during the first ($\chi^2_1 = 0.735$, $p = 0.391$) and second injections ($\chi^2_1 = 0.510$, $p = 0.475$) did not differ significantly between groups. The two main AEs observed in both groups were DoC and ocular disorders.

3.3. Disturbance of consciousness (DoC)

Level of DoC varied from mild sedation to deep drowsiness. DoC (mostly mild brief loss of contact) was observed in 7 out of 58 propofol injections (12.1%) with similar incidence in first and second injections. With amobarbital, DoC were more severe and more frequent (8 out of 36 injections, 22.2%), and DoC was more frequent during the second injection. However, the number of patients with DoC did not differ significantly between the two groups for first ($\chi^2_1 = 1.403$, $p = 0.236$) or second injection ($\chi^2_1 = 1.236$, $p = 0.266$). All symptoms returned to normal at the end of the procedure. No patient required intensive care. DoC was always associated with the existence of an anterior or posterior communicating artery (PCA), in support of rapid extension of the drug distribution in the brain. Anesthetic doses tended to be higher in ICP with DoC than in procedures without, for both drugs, but the difference was not statistically significant (propofol: 17.2 ± 12.4, vs. 12.1 ± 2.9 mg, $p = 0.415$; amobarbital: 128.7 ± 17.2, vs. 119.2 ± 12.1 mg, $p = 0.118$).

3.4. Ocular symptoms

Mostly ipsilateral to the injection, and always transient, ocular symptoms usually appeared a few seconds after injection and could last for up to 1 min. They predominated with propofol, mostly during the second injection: 8 out of 58 injections (13.7%) with propofol, vs. 3 out of 36 (8.3%) with amobarbital, but without significant difference ($\chi^2_1 = 0.637$, $p = 0.425$). Bilateral glare illusions were noticed and were always associated with a PCA.

3.5. Other AEs

Considering all injections, movement and dystonic disorders were as frequent with amobarbital ($n = 4$; 11.1%) as with propofol ($n = 7$; 12%), ($\chi^2_1 = 0.02$, $p = 0.582$). Pain, mood disorders, and autonomic disorders were only noted with propofol. One propofol injection was accompanied by an increase of epileptic paroxysms on EEG.

There was no significant difference between amobarbital and propofol groups for grade 1, grade 2, and grade 3 symptoms during first and second injections.

3.6. Technical characteristics of injections (Tables 2 and 3)

The first side injected was always the hemisphere including the epileptogenic focus. The delay between first and second injections was similar in both groups (amobarbital: 30.4 ± 5.3, propofol: 35.3 ± 5.7 min). There was no statistical difference between the two groups for duration of slowing EEG ($F_{1,45} = 0.019$, $p = 0.891$), delay of onset of hemiparesis ($F_{1,34} = 2.509$, $p = 0.122$), or duration of

Table 1
Demographic, clinical and anatomical characteristics of patients in amobarbital and propofol groups.

Anesthetic	Amobarbital	Propofol	Statistics	*p* value
Patient (number)	18	29	–	–
Sex				
Men	7 (39%)	17 (58.6%)	$\chi^2_1 = 1.73$	0.198
Women	11 (61%)	12 (41.3%)		
Age (yo. mean ± SD)	37 ± 7	32 ± 10	$F_{1,46} = 2.551$	0.117
Epileptogenic zone side				
Right	10 (56%)	16 (55.1%)	$\chi^2_1 = 0.065$	0.798
Left	8 (44%)	13 (44.8%)		
Epileptogenic zone[b]				
Temporal	17 (94.4%)	29 (100%)		
Frontal	0	0	–	–
Fronto-temporal	1	0		
Etiology of epilepsy[c]				
HS	14 (77.8%)	20 (68.9%)	$\chi^2_1 = 0.431$	0.511
Cavernomas	2	1		
Tumors	1 (DNET)	1 (ganglioglioma)		
Others	1 arachnoid cyst	4 MCD		
		1 sequelae of craniopharyngioma surgery		
		2 cryptogenic		
Handedness[a]				
Right	12 (67%)	21 (72.4%)	$\chi^2_1 = 1.59$	0.452
Left	6 (33%)	6 (20.6%)		
Bilateral		2 (6.8%)		
Language lateralization				
Right	3 (16.7%)	3 (10.3%)	$\chi^2_1 = 1.043$	0.594
Left	14 (77.8%)	25 (86.2%)		
Undetermined or bilateral	1	1		
Memory lateralization				
Right	7 (38.9%)	8 (27.5%)	$\chi^2_1 = 0.345$	0.557
Left	7 (38.9%)	13 (44.8%)		
Undetermined or bilateral	2	8		

[a] Handedness was assessed as right, left or bilateral with Edinburgh Manual Dominance Questionnaire (Oldfield, 1971).
[b] 28 patients in propofol group, and 17 in amobarbital group suffered from a pure temporal lobe epilepsy, mainly mesial temporal. Two patients whose epileptogenic zone extended beyond temporal lobe limits were included. One patient in propofol group suffered from a frontal lobe epilepsy.
[c] Etiology was mostly hippocampal sclerosis (HS). DNET: Dysembryoplastic neuroepithelial tumor. MCD: Malformations of cortical development: 3 meningoencephalocele, 1 focal cortical dysplasia, 1 undetermined lesion.

hemiparesis ($F_{1,39} = 0.110$, $p = 0.742$), (Table 2). The order of injection (first or second injection) had no effect on delay of hemiparesis onset ($F_{1,34} = 1.111$, $p = 0.299$), duration of hemiparesis ($F_{1,39} = 0.524$, $p = 0.473$), or duration of EEG slowing ($F_{1,45} = 0.441$, $p = 0.51$). Thus no predominant inhibitory effect of amobarbital or propofol on motor functions was observed. Procedure duration was slightly, but not significantly, shorter with propofol (278 ± 106 vs. 306 ± 114 s with amobarbital; $F_{1,45} = 0.621$, $p = 0.435$). The order of injection had no effect on procedure duration ($F_{1,45} = 0$, $p = 0.994$).

We also compared the drug's effect according to the side of injection (Table 3). No significant difference was observed between propofol and amobarbital groups concerning doses, AE, delay of

Table 2
Comparison of characteristics of procedures with amobarbital and propofol between first and second injections.

	Amobarbital 1st injection	Propofol 1st injection	Amobarbital 2nd injection	Propofol 2nd injection
Dose (M ± SD, mg)[a]	120 ± 14.5[c]	13.75 ± 6.4[b]	122.8 ± 13.2	12 ± 3[b]
Delay of onset of hemiparesis from injection (M ± SD, s)	37 ± 39	27 ± 9	27 ± 25	28 ± 13
Duration of hemiparesis (M ± SD, s)	283 ± 147	342 ± 254	301 ± 127	286 ± 138
Duration of EEG slowing (M ± SD, s)	420 ± 100	431 ± 203	478 ± 157	417 ± 130
Duration of test (M ± SD, s)	301 ± 123	290 ± 150	311 ± 108	279 ± 105
Homonymous hemianopia (% of patients in each group)	38.8%	66.6%	27.7%	53.3%
Visualization of an ACA artery (%)[d]	61.1%	62%	55.5%	68.9%
Visualization of a PCA (%)[e]	77.7%	77.7%	86.2%	68.9%

M ± SD: mean ± standard deviation.
[a] Both drugs were slowly injected in about 10 s. Injection stopped when effective anesthesia was confirmed by the onset of a controlateral facial and upper extremity palsy.
[b] Propofol was dispensed at the concentration of 10 mg/ml. Dilution of propofol consisted in 1.5 mg in 1.5 ml of saline serum for 8 patients (between 2004 and 2005) and in 1.5 mg per 6 ml of saline for the other patients (since 2005). Two patients received two different doses in the left and right ICP.
[c] Amobarbital was injected at a concentration of 20 mg/ml.
The dose of product did not differ significantly between both injections, neither in the amobarbital ($F_{1,17} = 0.702$, $p = 0.414$), nor in the propofol group ($F_{1,29} = 2.661$, $p = 0.114$).
[d] ACA: anterior communicating artery. No significant difference was observed between amobarbital and propofol during first ($\chi^2_1 = 0.004$, $p = 0.948$) and second injections ($\chi^2_1 = 0.865$, $p = 0.352$) in visualization of an ACA.
[e] PCA: posterior communicating artery. No significant difference was observed between amobarbital and propofol during first ($\chi^2_1 = 0.559$, $p = 0.455$) and second injections ($\chi^2_1 = 0.431$, $p = 0.511$) in visualization of a PCA.

Table 3
Comparison of characteristics of procedures and main adverse events with amobarbital and propofol between left and right injections.

	Left injections			Right injections		
	Amobarbital	Propofol	*p*-value	Amobarbital	Propofol	*p*-value
Delay of onset of hemiparesis from injection (M ± SD, s)	38 ± 39	27 ± 10	0.143	25 ± 26	28 ± 13	0.636
Duration of hemiparesis (M ± SD, s)	290 ± 138	357 ± 229	0.305	292 ± 139	268 ± 170	0.641
Duration of EEG slowing (M ± SD, s)	266 ± 108	293 ± 189	0.578	248 ± 108	230 ± 122	0.622
Duration of test (M ± SD, s)	319 ± 91	311 ± 150	0.841	293 ± 135	257 ± 95	0.288
Homonymous hemianopia (number (%) of injections)	4 (22.2%)	20 (68.9%)	0.003	9 (50%)	16 (55.2%)	0.635
Visualization of an ACA[a] (number (%) of injections)	11 (61.1%)	20 (68.9%)	0.581	10 (55.5%)	18 (62%)	0.658
Visualization of a PCA[b] (number (%) of injections)	13 (72.2%)	24 (82.7%)	0.391	15 (83.3%)	21 (72.4%)	0.390
Adverse events[c] (number (%) of injections)						
Ocular disorders	0 (0%)	3 (10.3%)	0.158	3 (16.6%)	7 (24.9%)	0.504
Movement disorders	3 (16.6%)	2 (6.8%)	0.291	0 (0%)	4 (13.7%)	0.320
Disturbance of consciousness	4 (22.2%)	5 (17.2%)	0.673	4 (22.2%)	2 (6.8%)	0.126
Adverse events[d] (number (%) of injections)						
Grade 1	0	5 (17.2%)	0.077	3 (16.6%)	8 (27.5%)	0.312
Grade 2	1 (5.5%)	1 (3.4%)	0.624	0	1 (3.4%)	0.617
Grade 3	4 (22.2%)	7 (24.9%)	0.586	4 (22.2%)	3 (10.3%)	0.358

M ± SD: mean ± standard deviation.
[a] Anterior communicating artery.
[b] Posterior communicating artery.
[c] Details in Fig. 2.
[d] Adverse events: according to the classification adapted from Mikuni et al.[8] and detailed in Fig. 1.

onset of hemiparesis, durations of hemiparesis or of EEG slowing, or test duration, for left and for right injections. Transient homonymous hemianopia was more frequent with propofol injections (62%) than with amobarbital (33.3%), (first injection: $\chi^2_1 = 4.762, p = 0.029$; second injection: $\chi^2_1 = 2.371, p = 0.124$). We also noticed more homonymous hemianopia during left injections with propofol than with amobarbital ($\chi^2_1 = 8.852$, $p = 0.003$). Visual field was difficult to assess in 2 propofol injections, because of a tonic head and eyes rotation.

3.7. Hemispherical dominance for language, and memory

Duration of language disorders was 471 ± 230 s with propofol vs. 385 ± 194 with amobarbital, and was not significantly different between the two drugs either during the first ($F_{1,21} = 3.361, p = 0.082$) or second injection ($F_{1,25} = 0.083, p = 0.776$).

Problems that could impair ICP interpretation occurred during 14 injections with propofol in 12 patients, for technical reasons (5 injections) or severe AE.[9] Technical problems were: anesthesia too short (2 injections), different doses required for first and second injections,[2] non-selective catheterism with injection partially in the right common carotid.[1] These events were not directly drug-related. AE that could partially hinder neuropsychological assessment were DoC (6 injections), exhilaration[2] and hemineglect.[1] Nevertheless, a definite lateralization could be given for language in all tests and for memory in 8 of these 12 patients. We reported potential interpretation artifacts during 9 amobarbital injections, in 9 patients (50%), mostly related to excessive drowsiness. Language was lateralized for 8 of them, and memory for 6.

Memory could be lateralized for 21 patients (72.4%) with propofol and 14 (77.7%) with amobarbital, without statistical difference between groups ($\chi^2_1 = 0.046$, $p = 0.829$). Hemispheric dominance for language was obtained for 28 patients with propofol (96.5%) and 17 (94.4%) with amobarbital.

4. Discussion

It is not always easy to compare our results with those published previously because many variables can interfere. According to the centers, ICP can be unilateral or bilateral, drug doses are not the same, and the neuropsychological tests chosen for evaluation can vary.

4.1. A specific epileptic cohort

Indications of ICP are scarce and presurgical assessment for epilepsy surgery remains the main indication. We included all the epileptic patients who underwent an ICP in our center between 2000 and 2010, in order to obtain a large, homogeneous cohort allowing the comparison of two groups of ICP, with propofol and with amobarbital. In most previous studies, the interpretation of the tolerance and efficacy of drugs used for ICP could be biased by the heterogeneity of the patients included.

A bilateral ICP was performed in all our patients, whereas only a unilateral procedure was performed in certain other studies.[10] In our opinion, a bilateral procedure improves the assessment of post-surgery memory outcome. Even if hippocampal reserve can be evaluated by the hemispheric inhibition ipsilateral to the seizure focus, a better prediction of post-operative verbal memory and IQ, especially when the seizure focus is left-sided, has been demonstrated with the bilateral procedure.[11] In most studies evaluating non-invasive techniques such as fMRI, the comparator is bilateral ICP.[22,25,28]

4.2. Propofol is well tolerated

We performed comparisons between left and right injections as done in previous works, and added comparisons between first and second injections, i.e. injection in the epileptogenic zone side compared to the hemisphere considered as normal, a comparison that has rarely been made in previous studies. One reason for comparing the first and second injections is to ensure the absence of a cumulative effect of the products during the full procedure. In our series, second propofol injections appeared to be as well tolerated as the first.

In accordance with previous studies, no lasting, disabling propofol-related AE was recorded in our study. An AE was observed in 33.3% of amobarbital injections vs. 44.8% of propofol injections, without significant statistical difference between groups. This higher rate of AE in the propofol group than in the amobarbital group was counterbalanced by the low grade of AE (mainly grade 1 according to Mikuni's classification). Our doses of propofol (12.8 ± 5.2 mg) were similar to those used by Mikuni (between 10 and 17 mg).[8] In our study, 58 patients received propofol and 19 experienced an AE (33.3%): 7 (12%) patients experienced grade 3

symptoms, 6 grade 2 (10.3%) and 6 grade 1 (10.3%). In our series, grade 3 symptoms occurred in 11 injections (9 patients, 31%), grade 2 in 3 injections (3 patients, 10.3%) and grade 1 in 17 injections (12 patients, 41.3%). In most of our cases, AE were mild and short-lived, disappeared before the end of the procedure and did not hinder neuropsychological assessment. More severe AEs (grades 2 and 3) were not more frequent with propofol than with amobarbital.

In Mikuni's study,[8] all the grade 3 symptoms consisted of increased muscular tone with twitching or tonic posture. In our series, we found no twitching but a similar rate of tonic postures with propofol (3 of 29 patients) and most grade 3 symptoms were DoC. Using this classification, Magee et al.[10] recently reported AE in 29.1% of unilateral propofol ICP (21.8% grade 1), with no significant differences with amobarbital in number and type of AE. Our results are in agreement with these previous studies, stressing a majority of grade 1 AE with propofol.

It is important to consider DoC because of its potential impact on language and memory. DoC was not reported in Mikuni e tal.'s[8] or Magee et al.'s[10] works. In our cohort, DoC was observed with both drugs, and was more intense with amobarbital. DoC had a low impact on test feasibility. We did not find any correlation between propofol dose and the risk of DoC. Moreover, in Mikati's study,[9] no sedation was noted and only one case of DoC, a confusion with agitation, was reported although the total mean doses of propofol were higher (59.6 ± 40.9 mg), than those used in our series (25.7 ± 9.4 mg). In Mikuni's study, an age older than 55 years, a second dose greater than 10 mg and a total dose greater than 20 mg, were significantly correlated with grade 3 symptoms.[8] None of our patients was over 55 years of age, four experienced grade 3 symptoms during the second injection, two of them had a second dose higher than 10 mg and 3 had a total dose higher than 20 mg.

Transient euphoria was observed in our study only with propofol and not with amobarbital. This AE was observed in 3 patients, independently of the site of injection (3 right and 1 left injections). Laughing has already been reported in 2 patients during a left injection.[7] This transient euphoria may be the result of a specific effect of the propofol molecule or due to a frontal syndrome related to the anesthetic effect. The fact that euphoria is not seen with amobarbital, which has anesthetic effects, pleads in favor of a specific effect of propofol.

In one study,[9] ocular symptoms occurred during injection in all patients, whereas we did not observe this AE in a systematic way. Ocular symptoms could be related to an action on cholinergic transmission and vascular anastomosis between the ICA and external carotid artery systems. In our study, ocular symptoms occurred mainly when propofol was injected too rapidly. So, this uncomfortable AE could be avoided by a slower injection of propofol.

To the best of our knowledge, concurrent EEG monitoring, as done in our series, was performed in only one earlier study.[9] In that study, EEG slowing was observed to be "less remarkable and often milder" with propofol than amobarbital, and one patient presented a seizure with propofol. The high doses (59.6 ± 40.9 mg) used in the study may account for this event. In our series, we found an increase in interictal epileptic activities in one patient but no seizure. No increase of epileptic activities was observed in patients showing DoC.

4.3. Increasing tolerance of propofol in the future

With the increasing use of propofol in ICP, improving tolerance has become a major concern. In one study, administration of 500 mg of intravenous methylprednisolone before propofol injection led to a significant reduction of AE, with a decrease of 92% for serious AE.[14]

Fujii et al. showed that injection of propofol in the middle cerebral artery (MCA), may allow better tolerance,[15] as mild DoC occurred in only 6 of their 17 patients after MCA injection, while 3 out of 4 presented moderate or severe DoC (one fell into a reversible coma) after ICA injection. This indicates that a more restricted site of injection could decrease the rate of severe AE. However these results have to be modulated on account of the small group of patients with ICA injection. In our larger population, with similar doses of propofol, no coma was observed. It must also be stressed that, although MCA injection is suitable for investigating language lateralization, exploration of memory requires ICA injection due to the more extensive area of vascularization.

Finally, while Mikati et al.[9] reported 70% of patients needing more than one dose of propofol, we did not need a second injection in most cases and most ICP gave satisfactory tests with a single injection and low doses of propofol.

4.4. Propofol is as effective as amobarbital

Although the half-life of propofol is shorter than that of amobarbital (2–24 vs. 14–42 h), propofol anesthesia enables a complete neuropsychological assessment with no additional technical constraint. The duration of the test was similar with both drugs. A recent review summarizes various alternatives to amobarbital ICP[4]: pentobarbital, propofol, methohexital and etomidate, and notes that propofol appears to be the best. This is consistent with our experience. We used methohexital in three patients but this drug has such a short duration of action that several injections were necessary and, in one patient, the test was inconclusive in spite of reinjection of the product. Moreover methohexital may significantly increase seizure frequency compared to amobarbital.[16] Homonymous hemianopia, more frequent in our patients with propofol than with amobarbital, may have led to a bias when the cognitive task was performed. However, this AE did not hinder the achievement of the test and was not a limiting factor in the appreciation of the hemispherical dominance for memory and language. We have no explanation other than a possible historical measurement bias (amobarbital ICPs were carried out before 2003, which could explain a difference in data collection). This result should also be weighed against deeper drowsiness with amobarbital, which could also be a limiting factor for procedure achievement.

In Takayama's study[7] using propofol, language could be lateralized in 12 and memory in 9 out of 12 patients vs., respectively, 52 and 41 out of 55 patients for amobarbital. There was no statistical difference between propofol and amobarbital groups for verbal and non-verbal responses. Our results are similar in a larger and more specific population of epileptic patients: we succeeded in finding language (96.5%) and memory (72.4%) lateralization in a similar number of patients, with similar doses of propofol. No statistical difference between verbal and visuo-spatial memory scores was observed in our study. However comparison with other studies is rendered difficult by the difference in the neuropsychological tests used.

4.5. Wada test will remain necessary

Research is currently attempting to develop non-invasive techniques which will eventually lead to ICP being abandoned.[17,18] Functional MRI (fMRI) is the most promising technique and has already replaced ICP in a majority of patients for language lateralization.[19,20] Numerous studies have shown high concordance for language lateralization between ICP and fMRI (about 90%) whatever the studies and the handedness of patients. However, the reliability of fMRI for memory lateralization is based on a small number of surveys.[21–25] Nevertheless, Bonelli et al.[26] recently demonstrated, in a cohort of 72 patients, that fMRI memory activation in the hippocampal regions was predictive of both verbal and visual memory outcome after left or right anterior

temporal lobe resection. However, until fMRI has been validated for memory assessment by multicentric studies and its clinical application, the ICP test is currently necessary for predicting postoperative selective memory deficits in patients with atypical memory assessment (absence of significant memory impairment before surgery, verbal and non-verbal memory deficits, pre-surgical unilateral memory deficit). Moreover, ICP may still have an indication in some refractory epileptic patients in whom fMRI is contraindicated (pediatric patients, low IQ and pacemaker). A recent retrospective analysis of 50 ICP[27] listed its remaining indications: non-compliance for fMRI task due to agitation, mental disablement or perceptual impairment, and inconclusive language activation mapping in fMRI, such as bilateral activation or atypical lateralized activation pattern. This analysis found that fMRI data were inconclusive or not feasible in 29 patients and, for 21 (72%) of them, ICP could specify language lateralization.

5. Conclusion

As the Wada test will remain useful for some years in some specific epileptic populations, discussing the characteristics of the drugs used for this test and proposing a standardized procedure across centers still remains a topic of interest. In conclusion, propofol, despite its shorter half-life, allows a full, conclusive test to be carried out with tolerance and performance equal to those of amobarbital.

Conflict of interest

None of the authors of the manuscript has declared any conflict of interest.

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