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NEUROPROTECTIVE EFFECT OF GACYCLIDINE
A multicenter double-blind pilot trial in patients with acute traumatic brain injury

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SUMMARY: **Neuroprotective effect of gacyclidine. A multicenter double-blind pilot trial in patients with acute traumatic brain injury**

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The aim of this study was to assess the safety and efficacy of intravenous (IV) injections of gacyclidine, a novel NMDA receptor antagonist, for neurological and functional recovery following acute traumatic brain injury. This multicenter, prospective, randomized, placebo-controlled, double-blind study compared four parallel groups. Two IV doses were administrated (placebo, 2×0.005mg/kg, 2×0.001mg/kg, 2×0.02mg/kg): the first dose was given within 2 hours following the trauma, and the second dose 4 hours after the first. Fifty-one patients were enrolled and 48 studied between March 1995 and June 1997 in France. Evaluation criteria for safety were physical examination, cardiovascular parameters, blood chemistry, hematology, ECG, and neuropsychological changes monitored after medication. Primary evaluation criteria for efficacy was the Glasgow coma scale complemented by the initial CT-scan and Glasgow outcome scale, motor deficiencies, neuropsychological changes, and functional indenpendence at D90 and D365 or endpoint. Intracranial pressure (ICP) monitoring was not taken into account because all the clinical centers participating in this study did not use this technique in daily practice during the inclusion period.

RÉSUMÉ : **Étude de l'effet thérapeutique de la gacyclidine. Essai pilote multicentrique en double aveugle chez des patients victimes d'un traumatisme crânien grave**

Le but de cette étude était d'évaluer la sûreté et l'efficacité de l'injection intraveineuse (IV) de gacyclidine, un antagoniste de récepteur NMDA, sur le rétablissement neurologique et fonctionnel dans les traumatismes crâniens graves en phase aiguë. Cette étude prospective, randomisée, avec groupe placebo, en double aveugle, a comparé quatre groupes de patients. Deux doses IV ont été administrées (placebo, 2 × 0,005 mg/kg, 2 × 0,001 mg/kg, 2 × 0,02 mg/kg): la première dose a été donnée à moins de 2 heures suivant le traumatisme, et la deuxième dose 4 heures après la première. L'étude a été menée en France, 51 patients ont été inclus et 48 ont été effectivement étudiés entre mars 1995 et juin 1997. Les critères d'évaluation pour la securité étaient l'examen clinique, les paramètres cardiovasculaires, le ionogramme sanguin et la numération formule sanguine, l'ECG, et l'évaluation neuropsychologique après traitement. Les critères initiaux d'évaluation d'efficacité du traitement étaient le Score de Glasgow, associé au scanner cérébral initial, le Glasgow Outcome Scale, les modifications neuropsychologiques, les déficits moteurs, et l'indépendance fonctionnelle à J90, J365 ou à la fin du suivi. Le monitoring de la pression intra-crânienne (PIC) n'a pas été prise en considération, en effet tous les centres participant à cette étude n'employaient pas cette technique dans la pratique quotidienne durant la période d'inclu-

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Twelve patients died during the follow-up period, none of these deaths being related to the drug. Serious adverse events (181) were reported by most of the patients with no significant differences between groups. Only 10 of these adverse events were considered to be drug-related. Safety-related laboratory tests did not show any relevant changes. Concerning efficacy, the predefined prognostic factors (initial CT-scan score, initial Glasgow Coma Scale and occurrence of low systolic blood pressure during the first 24 hours) largely determinated the patient's outcome. When the prognostic factors were taken into account together with the dose level in a logistic regression model, gacyclidine showed a beneficial long-term effect and a best dose-result in the 0.04mg/kg treated group. Data obtained in this clinical trial appeared sufficient to warrant a European multicenter study on gacyclidine using the same evaluation criteria and ICP monitoring.

Key-words: *clinical trial design, traumatic brain injury, gacyclidine, N-methyl-D-aspartate, NMDA, neuroprotection, favorable outcome, Glasgow outcome scale.*

sion de patients. Douze patients sont décédés pendant la période de suivi, aucun de ces décès n'était lié à la gacyclidine. Les événements défavorables sérieux (181) ont été rapportés chez la plupart des patients sans différence significative entre les groupes. Seulement 10 complications ont été considérées comme des effets secondaires au traitement par gacyclidine. Les dosages en laboratoire pour la sécurité du produit n'ont montré aucun changement significatif. Pour ce qui concerne l'efficacité, les facteurs pronostiques prédéfinis (score Scanner initial, score de Glasgow initial, et épisode de pression artérielle systolique basse pendant les 24 premières heures) déterminaient nettement l'évolution du patient. Quand les facteurs pronostiques ont été pris en considération ainsi que le niveau de dose dans un modèle logistique de régression, la gacyclidine a montré un effet bénéfique à long terme, avec de meilleurs résultats dans le groupe de patients ayant reçu une dose de 0,04 mg/kg. Les résultats de cette étude clinique justifient une étude européenne multicentrique en utilisant les mêmes critères d'évaluation, et la mesure de la pression intra crânienne.

Traumatic brain injury (TBI) is an important cause of morbidity and mortality in most countries. In France, most TBI patients are under 35 years old (two men for one woman). Moreover, TBI accounts for 60% of accidental deaths, and sequelae are often severe, leading to major neurological and psychological impairment seriously compromising the social and professional future of the patient [20]. Despite the considerable number of neuroprotective pharmacological agents developed and taken forward into phase III clinical trials in severe head injury, none of these clinical trails performed to date has shown convincing evidence of efficacy in a large population of TBI patients [1, 7, 14, 29, 36, 43]. Therapeutic strategies are thus limited to surgical draining of hematomas, control of post-traumatic edema and global care of the vital functions. The initial lesion, compromising either the brain stem or the cerebral hemispheres, is rarely immedialtely complete and definitive, but worsens during the following hours [17, 32, 35].

Secondary injury after TBI involves complex neurobiological, cellular and molecular reactions leading to a variable degree of neurological impairment [13, 32, 33]. Excitatory amino acids, acetylcholine, endogenous opioids, catecholamines, serotonin, free radicals, cytokines, platelet activating factors, steroids, magnesium, ion channels, are some of the physiological compounds participating in the pathophysiology of the secondary injury [32, 33, 40]. The severity of a traumatic brain injury (TBI) is apparently correlated with the increase in the extracellular amino acid concentration [10, 13]. Overstimulation of glutamate receptors, especially the N-methyl-D-aspartate subtype (NMDA receptors), is beleived to initiate cellular processes leading to a neurodegenerative effect. Activation of specific receptors induces an increased neuronal influx of cations (Na+ and Ca2+) via specific ion channels [28, 32] but NMDA-mediated toxicity is mainly due to the influx of extracellular Ca^{+}, and Ca^{2+} homeostasis dysregulation [3, 26].

Based on pre-clinical data, it appears that systemic administration of NMDA receptor antagonists such as MK-801, thienylphenxyclidine (TCP) and gacyclidine, attenuates the long-term neurological deficit in experimental models of central nervous system injury [9, 11, 12, 25, 38]. NMDA receptors have therefore become an excellent therapeutic target in experimental acute central nervous sytem trauma [40]. Gacyclidine (GK11, (Pip/Me 1- [1-2-thienyl)-2methylcyclohexil] piperidine) a compound synthesized by Kamenka [18], and developed by Beaufour-Ipsen pharmaceutical (France), is a molecule structurally derived from TCP [38, 39]. *In vitro*, gacyclidine has been shown to be neuroprotective against acute glutamate toxicity to neurons of the cortex [2, 5, 6, 23, 24, 34, 39], and *in vivo*, against nerve agent poisoning in monkeys [21, 22], and spinal cord injury in rodents [11, 12], strongly suggesting a therapeutic indication in neurotrauma. Moreover, negative side effects and toxicity seen with order NMDA receptor antagonists such as TCP and MK-801 (psychomimetic effects, neuronal vacuolization), are absent at the dose of gacyclidine efficient for neuroprotection [15].

Concerning safety, a phase I clinical study conducted in 60 volunteers (Beaufour-Ipsen pharma, internal report), showed maximum tolerated doses of 0.04mg/kg for a single IV injection. The dose of 0.02mg/kg repeated after a 4-hour interval showed a good safety profile similar to one single injection. No serious adverse events were noted with gacyclidine treatment and no significant blood anomalies were detected at any dose. Systolic and disatolic blood pressure and heart rate were transiently increased with the treatment, but normal ECG traces were obtained at all doses. Signs of drowsiness were noticed at 0.01mg/kg and stupor at 0.05mg/kg. Generally speaking central side effects appearing rapidly and transiently in a dose-dependent manner. Nevertheless, no major peripheral effects were seen. Finally, the compound showed a short distribution time with a long elimination half-life and excellent pharmacodynamic cerebral bioavailability.

The present work is considered as a pilot study whose aims are to assess safety of these different doses of gacyclidine in patients with severe TBI when the drug is administrated within two hours of the trauma, to determine whether there is a trend in favor of any activity of gacyclidine after TBI and to carry out an evaluation of the sample size for a new study in this indication.

MATERIALS AND METHODS

PATIENT SELECTION

The trial was performed between April 4, 1995, and June 26, 1996, in TBI patients initially managed by the Mobile/Emergency Medical Unit (SAMU or SMUR). Patients were included in the study if: (I) they were aged between 18 and 65 years; (II) their weight was less than 110 kg; (III) the injury consisted of a closed cranial trauma or a trauma associated with a skull base fracture with a tear in the dura mater; (IV) they were treated as soon as possible, within 2 hours following trauma; and (V) the initial Glasgow coma scale (GCS, Teasdale 41 and Jennett, 1974) ranged 4 to 8 inclusive.

Patients were excluded if any one of the following criteria was fulfilled: (I) associated life-treatening lesion with probably survival of less than 24 hours; (II) multiple trauma liable to interfere with the neurofunctional assessment, (III) lesions that existed before the trauma and liable to interfere with the neurological assessment; and (IV) patients unlikely to understand the French language or with a residence location incompatible xith their long-term follow-up.

The study was approved by the French ethical committee and designed in accordance with French regulations. The investigators were responsible for providing information to persons who were suitable candidates for the study. Since the patient was in a coma, information was given to his or her family and included the objectives, methodology, and duration of the study, as well as the potential risk and benefits of the studied drug. Due to the seriousness of the craniocerebral traumas and the need to adminster the drug as rapidly as possible, it was decided, in agreement with French regulations, that the patient's consent could be obtained after the administration of the compound. Similarly, in critical emergency situations, the consent of the patient's family was requested as soon as possible. Patients were asked to give their consent once they recovered consciousness. They were free to stop their participation in the study at any time without any consequence on the quality of their medical care.

STUDY DESIGN AND TEST DRUG ADMINISTRATION

The study was designed as a multicenter, prospective, randomized, double-blind, placebo-controlled trial comparing four parallel groups of patients who received each placebo or gacyclidine 0.01mg/kg, 0.02mg/kg, or 0.04mg/kg in a one-day treatment (0.1 ml/kg of the reconstituted freeze-dried product or placebo per injection). The total dose was administered as soon as possible after the trauma. The latest injection was given by the SAMU or the SMUR within two hours of the trauma, the second injection being given four hours after the first. The 4-hour interval was judged to be clinically relevant as it was long enough to avoid additive side effects and short enough to assume effective blocking of the L-glutamate cascade. Patients were assigned to their treatment group using a pre-established randomization list, balanced by blocks of 4 patients and by study center using a centralized randomization procedure (Randovox® system, GECEM, 71, rue Desnouettes, 75015 Paris, France). Whatever the dose of gacyclidine in the bottle, it always contained the same amount of freeze-dried product; placebo had the same aspect as the active compound.

Concerning prior and/or concomitant therapies, the following treatments were prohibited throughout the study: NMDA inhibitors, free radical inhibitors such as lazaroids, super oxide dismutase, or their derivatives, and high-dose corticosteroids. In addition, the following treatments were prohibited during the first 48 hours after TBI but tolerated thereafter: calcium-channel blockers, free radical inhibitors such as vitamins C and E and N-acetylcysteine, and low-dose corticosteroids. Finally, ketamine was prohibited during the first 8 days after TBI but tolerated thereafter. Proscribed drugs concerned only drugs used for emergency treatment of the cranial trauma and did not take into account drugs previously taken by the patient.

PHYSICAL EXAMINATION AND LABORORY TESTS

The patient's condition was assessed by the SAMU or SMUR prior to his or her inclusion before the first drug injection (D0 pre-treatment), on arrival at the hospital (D0 post treatment), then on D1, D3, D5, D7, D14 (±1 day), D21 (±1 day), D30 (±3 days), D90 (±3 days), D180 (±7 days), and D365 (±7 days).

Safety and efficacy of gacyclidine were assessed by various clinical and laboratory variables. Clinical safety was assessing as follows:

— monitoring of vital signs (systolic blood pressure SBP, diastolic blood pressure DBP and heart rate HR) every 15min after each injection of the product, for 90min;

— recording of any adverse events, whether related or not to the drug under study, throughout the study;

— clinical laboratory safety: differential blood cell count and platelet count, serum levels of sodium, potassium, chlorine, calcium, urea, creatinine, glucose, aspartate aminotransferase, alanine aminotransferase, alkaline phosphatase, free bilirubin, and blood gases. These laboratory tests were carried out at the investigator's usual laboratories (a central laboratory was not used);

— EEG and neuropsychological changes throughout the study.

Efficacy was assessed using the following parameters:

— Glasgow outcome scale (GOS) score (5-level scale: good recovery, moderately disabled, severely disabled, vegetative state, death) at D90 and D365 or at endpoint [16];

— neurological-cause deaths at D90 and D365 or at endpoint;

— motor deficiency assessed by the neurological examination at D90 and D365 or at endpoint;

— assessment of the patient's functional independence using a 19-items scale at D90 and D365 or at endpoint;

— assessment of the patient's neuropsychological condition by means of a standardized questionnaire at D90 and D365 or at endpoint;

— changes in CT-scan images by means of the Marshal and Marmarou scale *(table I)*, to classify the lesion found at D0 [31].

All safety and efficacy assessments were performed under the responsability of the following teams: SAMU ou SMUR, Intensive Care units, Neurosurgery units and Rehabilitiatation units. *Table II* summarizes the flow-chart of the study.

Steering and safety committees

Independent brain trauma specialists (Emergency Medecine, Neurosurgery, Neuroradiology, Instensive Care, Rehabilitation) composed the study steering committee and the study safety committee. The steering committee was responsible for close monitoring throughout the entire study. Each patient's essential datum was reviewed blindly by the steering committee. Thus, the reality of the cranial trauma was reassessed on the basis of the history and results recorded in each case report form (CRF) and on copies of the CT-scan images obtained from the investigators (Marshal and Marmarou 30 classification; see *table I*). The safety committee was responsible for close monitoring of the study from a safety point of view. They reviewed blindly every severe adverse event that occurred during the study. They assessed the quality and completeness of the case description and the relationship of the event with the compound injected.

Statistical analysis

The statistical analysis was mainly descriptive. For all continuous data recorded at inclusion, descriptive statistical tables were drawn up registering the frequency, the number of missing values, the mean value and standard deviation, the median value, and the maximum and minimum values for each treatment group. For discrete data, contingency tables were drawn up entering the frequencies and percentages of each class level for each treatment group. A p-level, corresponding to 0.05 was considered to be statistically significiant.

Concerning safety analysis, all adverse events (Aes) were listed. Incidences of Aes were determinated by group and by severity or drug-relatedness taking into account all Aes that appeared within 30 days of the last drug administration. For clinical laboratory safety, all results were listed by parameters with low (L) and high (H) values flagged. Thus, tables with the number and percentage of patients with a low, high, or within normal range results at each assessment compared with baseline values, were given.

Efficacy analysis was performed including prognosis factors as covariates. The prognosis factors were previously defined by the steering committee and were taken into account in the analysis of the 5-level

Table I. — Marshall and Marmarou CT-scan score.

Tableau I. — *Score tomodensotométrique de Marshall et Marmarou.*

Diffuse injury I (no visible pathology)	No visible intracranial pathology seen on CT-scan
Diffuse injury II	Cistern are present with midline shift 0-5 mm and/or: — lesion densities present — no high- or mixed-density lesion>25 cc — may include bone fragments and foreign bodies
Diffuse injury III (swelling)	Cistern compressed or absent with midline shift 0-5mm, no high- or mixed-density lesion > 25 cc
Diffuse injury IV (shift) — evacuated mass lesion — non-evacuated mass lesion	Midline shift>5 mm — no high- or mixed-density lesion>2 cc, any lesion surgically evacuated — high- or mixed-density lesion>25cc, not surgically evacuated

TABLE II. — Study flow-chart.
TABLEAU II. — *Diagramme de l'étude.*

	D0 pre-treatment	*D0 post-treatment*	*D1*	*D3*	*D5*	*D7*	*D14*	*D21*	*D30*	*D90*	*D180*	*D365*
Clinical examination	X[1]	X	X	X	X	X	X	X	X	X	X	X
Neurologic examination, + Glasgow	X	X	X	X	X	X	X	X	X	X	X	X
Inclusion and exclusion criteria	X											
Circumstances of accident	X											
Clinical laboratory	X	X	X	X	X	X	X	X	X			
Injection of gacyclidine	X[2]	X[3]										
Early follow-up (post-injection)	X	X										
Medical history		X										
Previous/concomitant treatments		X	X	X	X	X	X	X	X	X	X	X
CT-scan		X		X[4]	X[4]	X[4]	X[4]			X		X
ECG	X[5]	X	X	X		X	X	X	X			X
EEG				X[6]	X[6]				X			
Informed consent (patient's family)		X										
Patient identification		X										
Adverse events		X	X	X	X	X	X	X	X	X	X	X
Glasgow Outcome Scale									X	X		X
Neuropsychological testing									X	X		X
Functional independence									X	X		X
Clinical global impression												X

[1] With estimation of the body weight. [2] Within 2 hours after the accident. [3] Four hours after the first injection. [4] One between D3 and D5 and one between D7 and D14. [5] Monitoring on scope. [6] At any time between D3 and D5.

GOS score on day 90 (primary efficacy criterion) and the 2-class outcome on day 90: initial Glasgow coma score, Marshal and Marmarou CT-scan score at inclusion, occurrence of the low SBP (<90mmHg) at any time during the injury day, injection of vasopressor drugs during the injury day, existence of inflammation signs on injury day determined either by high white blood cell count (>12G/l) and/or fever (>38°C), time interval between the accident and the first injection of the study drug.

RESULTS

Fifty-one patients were randomized in the study during the 14-month time interval. Fifty patients were included for the purposes of the study, since one patient did not receive the drug because he was under 18 years old. Moreover, the steering committee decided to exclude two patients with no evidence of brain trauma and no follow-up visit after inclusion (one belonging to the placebo group and one to the 0.01mg/kg group). Thus, the results are presented on 48 patients distributed as follows:

— 12 from the placebo group,
— 11 from the 0.01mg/kg group,
— 13 from the 0.02mg/kg group,
— 12 from the 0.04mg/kg group.

Patients had a median age of 30 years (range: 18-64) and a median weight of 70 kg (range: 55-105). Male patients predominanted in the study (only 2 women). This was explained on one hand by the initial exclusion of women in the protocol (their inclusion being allowed only 6 months after the beginning of the recruitment), and on the other hand by the higher prevalence of accidents leading to cranial trauma in men. Demographic characteristics are summarized in *table III*. At inclusion, there was no statistically significant difference between groups for any demographic datum. The emergency medical unit (SAMU) arrived on the accident site within 30min in 66.7% of the

TABLE III. — Patient characteristics.
TABLEAU III. — *Caractéristiques de la population.*

	Placebo (n=12)	*0.01mg/kg (n=11)*	*0.02mg/kg (n=13)*	*0.04mg/kg (n=12)*
Age±SD	27 ± 2	37 ± 4	31 ± 4	36 ± 4
Weight (kg) ±SD	74 ± 3	73 ± 4	69 ± 2	76 ± 3
Height± SD	176 ± 2	175 ± 2	173 ± 3	176 ± 2
Mechanism of injury, n and (% of group)				
Public thoroughfare accident	10 (83)	8 (73)	9 (69)	6 (50)
Fall	2 (17)	2 (18)	3 (23)	5 (42)
Other	0	1 (9)	1 (7)	1 (8)

cases (32/48), and within the first hour in 93.8% of the cases (45/48). Despite a relative faster intervention in the 0.04mg/kg group that in the placebo group, no significant differences were noticed between groups.

The 2 injections of gacyclidine were given to all the patients except 3 (6.3%, 2 patients in the placebo group and 1 patient in the 0.01mg/kg group). The theoretical maximal delay of the 2 hours between the accident and the first dose of gacyclidine was respected in 75% of the cases, whereas 100% of the patients were treated within 2.5 hours of the trauma. The second dose of gacyclidine was administrated within 4 $^{1}/_{2}$ hours of the first for almost all the patients (91.1% excluding the 3 patients who did not receive the two doses, 1 patient of the 0.02mg/kg group who was medicated within 5 hours after the first dose and 1 patient of the 0.04mg/kg group who was medicated after 6 hours after the first dose).

Forty-seven patients (97.9%) were immediately in a comatous state when the physician arrived at the accident site, while the 48th patient went into a coma 70min after the trauma. As required by the protocol, none of the patients had a cerebral wound (only one patient showed a wound at the right ear level). Concerning other TBI signs, 20 patients had an orbital hematoma (41.7%), 16 an ottorrhagia (33.03%), 10 an epistaxis (20.08%), 3 an ottorhea (6.3%), and none had rhinnorrhea. Forty-two patients were intubated prior to transportation by the mobile unit (97.5%), 41 patients were sedated (87.2%) and volume expanders were used in 24 patients (50%). Associated lesions were found on the face (45.8%), on the spine (4.2%), on the thorax (25%), on the abdomen (8.3%), or on the limbs (39.6%).

Seventeen patients underwent a surgical procedure on injury day (37%), with a median delay between the accident and the procedure of less than 6 hours (287 min): 5 for evacuation of a subdural haematoma, 3 for evacuation of an extradural haematoma, 1 for evacuation of another hemorrhagic collection and 8 for other reasons.

Table IV summarizes the initial status of the studied patients.

SAFETY AND TOLERABILITY

Twelve patients died during the follow-up period, none of these deaths being related to gacyclidine but were considered to be a consequence of the trauma.

Forty-four patients (91.7%) experienced at least one adverse event during the follow-up period: 11 in the placebo group (11/12, 91.7%), 10 in the 0.01mg/kg group (10/11, 90.9%), 13 in the 0.02mg/kg group (13/13, 100%), and 10 in the 0.04mg/kg group (10/12, 83.3%). No significant diffrence of the incidence of Aes was found between groups ($p = 0.53$). Serious Aes were reported by 36 patients during 1-year follow-up period independently of the treatment group (non-significant difference). The most frequently reported events were general disorders (22.9% of the Aes), respiratory disorders (18.8%), and central nervous system (CNS) disorders (12.5%).

Moreover, most patients complained of at least one adverse event within 30 days of administration of the drug (90%): respiratory disorders (30%), general disorders (26%), urinary disorders (24%), liver and biliary disorders (22%), infectious complications (22%), CNS disorders (20%), musculoskeletal disorders (12%), gastrointestinal disorders (12%).

Drug-related Aes, i.e. liver and biliary disorders, were reported in 10 patients (2 from the placebo group, 2 from the 0.01mg/kg group, 2 from the 0.02mg/kg group and 4 from the 0.04mg/kg group). Only two serious Aes were drug-related according to the investigators: one case of acute pancreatitis in the placebo group and one case of

TABLE IV. — Initial patient status after injury and degree of significance of the differences between groups (p value).
TABLEAU IV. — *Statut initial des patients après le traumatisme et degré de significativité (valeur p) des différences entre les groupes.*

	Placebo (n=12)	*0.01mg/kg (n=11)*	*0.02mg/kg (n=13)*	*0.04mg/kg (n=12)*	*p value*
Glasgow Coma Scale score					**0.45**
4	2	3	1	2	
5	3	3	3	0	
6	2	2	3	4	
7	4	2	4	5	
8	1	1	2	1	
Initial CT-scan score					**0.83**
1	0	2	3	1	
2	6	4	1	4	
3	4	2	6	4	
4	2	2	3	3	
Occurrence of low SBP (%)	1 (8)	4 (36)	3 (23)	4 (33)	**0.39**
Occurrence of low MBP (%)	1 (8)	5 (45)	7 (54)	6 (50)	**0.08**
Use of vasopressor drugs (%)	2 (17)	5 (45)	7 (54)	2 (17)	**0.10**
Occurrence of inflammation (%)	9 (75)	4 (36)	11 (85)	7 (58)	**0.08**

severe hypotension in the 0.04mg/kg group that began on the day of gacyclidine administration.

No relevant drug-related clinical laboratory abnormalities were reported during the study except for 10 patients with elevated liver enzymes. Nevertheless, no significant diffrences were noted between groups concerning the distribution of these high laboratory values.

Concerning vital signs (SBP, DBP and HR) monitored within 90min after medication, no significant difference was found between groups at any time point (15, 30, 45, 60, 75 and 90min). Similar results were found after the second dose of gacyclidine. Moreover, no significant variations were seen within each group concerning blood pressure values during the follow-up period after medication (D0) *(table V)*.

Finally, no serious ECG abnormalities were reported during the 30-day period that followed the administration of gacyclidine.

TABLE V. — Systolic blood pressure (mean±SD) following administration of gacyclidine at the injury day.
TABLEAU V. — *Pression artérielle systolique (moyenne ± écart-type) après administration de gacyclidine, le jour du traumatisme.*

	15min	*30min*	*45min*	*60min*	*75min*	*90min*
First injection						
Placebo	134.2 ± 5.2	136.1 ± 7.5	127.4 ± 6.0	129.9 ± 7.0	127.6 ± 5.8	131.2 ± 6.7
0.01 mg/kg	143.6 ± 10.9	120.7 ± 7.6	111.4 ± 114	123.9 ± 10.2	113.4 ± 17.4	107.6 ± 17.6
0.02 mg/kg	116.4 ± 9.2	140.4 ± 7.1	139.5 ± 5.8	129.1 ± 6.0	130.3 ± 5.5	130.8 ± 5.6
0.04 mg/kg	128.1 ± 10.3	133.1 ± 12.0	127.4 ± 9.2	136.3 ± 15.5	124.6 ± 13.5	134.9 ± 8.7
Second injection						
Placebo	124.6 ± 5.3	130.0 ± 4.8	125.7 ± 4.4	132.4 ± 4.5	133.9 ± 4.1	133.7 ± 3.9
0.01 mg/kg	118.1 ± 6.4	119.1 ± 12.0	129.3 ± 7.2	115.0 ± 11.0	113.4 ± 13.0	120.9 ± 11.4
0.02 mg/kg	119.9 ± 6.0	116.2 ± 5.3	118.2 ± 6.2	117.8 ± 5.2	122.3 ± 7.8	122.3 ± 6.1
0.04 mg/kg	114.6 ± 11.4	119.1 ± 9.9	118.8 ± 9.4	132.3 ± 8.1	118.4 ± 8.8	116.9 ± 9.8

TABLE VI. — Glasgow outcome score at 90 days and at the end point (365 days).

TABLEAU VI. — *Glasgow outcome score à J 90 et à la fin du suivi (J 365).*

	Placebo (n=12)	*0.01mg/kg (n=11)*	*0.02mg/kg (n=13)*	*0.04mg/kg (n=12)*
GOS at 90 days				
Death	2	4	4	2
Vegetative state	0	1	1	2
Severely disabled	5	4	1	2
Moderately disabled	0	0	1	1
Good recovery	4	1	6	4
GOS at end point				
Death	2	4	4	2
Vegetative state	0	1	1	1
Severely disabled	1	1	0	2
Moderately disabled	2	3	0	1
Good recovery	6	1	8	5

EFFICACY OR TRENDS IN FAVOR OF GACYCLIDINE ACTIVITY AFTER TBI

Neurological outcome: no significant difference was found among groups when analyzing the raw score of the 5-level GOS scale at day 90, nor when considering the GOS responses pooled into favorable or unfavorable outcome. Moreover, at day 365 no significant difference was found. GOS scores at days 90 and 365 are summarized in *table VI*.

Among the 48 patients, 20 did not complete the study: 12 patients died before the end of the follow-up period (8 neurological deaths and 4 non-neurological deaths) and 8 patients discontinued the study for other reasons as follows:

— 4 in the placebo group: 2 neurological deaths, 2 follow-up losses;

— 7 in the 0.01mg/kg group: 2 neurological deaths, 2 non-neurological deaths, 3 follow-up losses;

— 4 in the 0.02mg/kg group: 3 neurological and 1 non-neurological deaths;

— 5 in the 0.04mg/kg group: 1 neurological death, 1 non- neurological death, 3 follow-up losses.

Log-rank comparison of the product limit estimates of the survical curves, showed no significant diffrences among groups either for all-cause deaths or for neurological-cause deaths. Nevertheless, due to the small number of critical events (deaths), no conclusion could be made about this point.

CT-scan scores according to the Marshall and Marmarou classification (see *table I*) were unevenly distributed between groups but no statistically significant differences were seen ($p = 0.83$). The mean CT-scan score was 2.64. Furthermore, no drug-related signs of ventricular dilatation and/or cortical thickness were found.

The functional independence measure showed no significant difference between groups either at day 90 or at day 365.

As shown below, these poor preliminary results were mainly due to the non consideration of the prognostic factors which largely accounted for the patient outcome and must be taken into account in the analysis of the results. A second statistical analysis was performed including the *a priori* defined outcome prognostic factors including the time interval between the accident and the arrival of the mobile care unit:

a) Stepwise logistic regression of the 5-level GOS score at day 90 (the stepwise procedure led to the selection of 4 successive factors, in addition to the dose level which was forced into the model):

— Marshal and Marmarou CT-scan entered at a significance level of $p = 0.0001$;

— occurrence of low SBP on injury day entered at a significanc level of $p = 0.046$;

— pre-treatment Glasgow coma scale (GCS) entered at a significance level of $p = 0.043$;

— time interval between the accident and the first administration of gacyclidine entered at a significance level of $p = 0.22$;

— dose level entered at a significance level of $p = 0.027$.

— Dose was not a statiscally significant variable ($p = 0.16$). Interpretation of the regression model was hindered by the multiple response levels (i.e. each response level had to be described). Two-class outcome analysis (favorable and unfavorable) which could be interpreted easily was therefore undertaken:

b) Stepwise logistic regression of the 2-class outcome at day 90 (three parameters were retained by the selection procedure):

— Marshal and Marmarou CT-scan entered at a significance level of $p = 0.0032$;

— occurrence of low SBP on injury day entered at a significanc level of $p = 0.048$;

— pre-treatment GCS entered at a significance level of $p = 0.037$.

The corresponding model can be written:

$$\text{log}it\ (p) = \log\ (p/(1-p))$$
$$= 1.70 + (0.07 \times Dose) + (0.75 \times Glasgow)$$
$$- (2.84 \times LowSBP) - (1.39 \times CTscore)$$

where *p* is the probability of favorable outcome (i.e.of good recovery or moderate handicap), *Dose* is the individual treatment dose (inmg/kg), *Glasgow* is the pre-treatment GCS score, *LowSBP* is 1 if low SBP occurs on injury day and 0 if not, and *CTscore* corresponds to the Marshal and Marmarou CT-scan score.

SBP as well as a high Marshal and Marmarou CT-scan score tended to decrease the probability of a favorable outcome. On the other hand, the higher the initial GCS score the higher probability of favorable outcome. Moreover, drug dose also had a positive effect on patient outcome. As shown in *table VII*, based on the logistic model parameters, the proportion of favorable outcome increased 1.34-fold in patients with a radiological score of I and 4-fold in patients with a radiological score of IV. The probabilities were computed for a mean initial GCS score 6 and 25% of patients with low SBP on injury day, which corresponds to the mean results of the present work.

Using the same hypotheses, it was determinated that 44 patients per treatment group would be nesessary to find a statiscally significant difference ($p < 0.05$) between placebo and 0.04mg/kg group assuming a mean radiological score of 2.5. The calculation was performed using the standard formula for comparison of two percentages in a bilateral situation.

Finally, the interpretation of two variables (neuropsychological status and clinical global impression) was hindered by the small size of the cohorts and the complexity of each variable, and therefore results are not shown.

DISCUSSION

Severe TBI is a critical health problem in all countries and a frequent cause of death or a significant factor in approximately half of all trauma-related deaths [32]. Among surviving brain-injured patients, sequelae constitute a very important problem (major physical handicap, severe neuropsychological disorders), which can be ranged from major dependency to neurovegetative status. Apart from the possibility of some improvement when surgery is indicated, and despite real progress in diagnosis, monitoring and resuscitation techniques, existing pharmalogical therapy is largely unsatisfactory [33]. TBI provokes neurological deficits via direct (mechanical disruption of neural pathways) and indirect (secondary or delayed) mechanisms. According to some studies [7], the pathophysiological changes that follow brain injury, related to poor clinical outcome, include immediate and delayed changes in cardiovascular variables (hypotension), cerebral hypoxia and ischemia, metabolic dysregulation, and changes in intracranial pressure (inflammatory factors).

At cellular and molecular levels, one of the main secondary consequences is an increase in extracellular excitatory amino acid concentration (i.e. L-glutamate) [8, 19, 37], which allows the entry of large amounts of calcium into the cells by activating NMDA receptors, and provokes neuronal deaths [3, 4, 26, 28]. Thus, NMDA receptors are a very promising therapeutic target [11, 12, 38]. Among NMDA inhibitors, gacyclidine has shown good promising results in a phase I study (Beaufour-Ipsen pharma, internal report). The decision was therefore taken to study safety and efficacy of the compound in a more advanced clinical trial. Thus, patients were enrolled in a multicenter, randomized, double-blind study comparing four parallel treated groups (placebo, 0.01mg/kg, 0.02mg/kg and 0.04mg/kg).

The good safety observed in the phase I clinical study was confirmed in the present work which showed that: (i) no unexpected drug-related adverse events were reported during the study; (ii) no drug-related deaths occurred among

TABLE VII. — Estimated probability of favorable outcome (based on the stepwise logistic model parameters).
TABLEAU VII. — *Probabilité estimée des résultats favorables (basée sur un modèle de régression logistique pas à pas).*

CT-scan score	*Placebo*	*0.01mg/kg*	*0.02mg/kg*	*0.04mg/kg*	*LF Marshall J Neurosurg, 1991*	*Ratio (0.04mg/kg)/ Placebo*
I	0.67	0.74	0.81	0.90	0.62	1.34
II	0.33	0.42	0.51	0.68	0.35	2.06
III	0.11	0.15	0.20	0.35	0.16	3.18
IV	0.03	0.04	0.06	0.12	0.06	4.00
Probabilities determined for an average initial GCS score of 6 and 25% of patients with low SBP on injury day.						

patients; (iii) no significiant drug-related clinical laboratory anomalies were reported in the 30-day period following medication; and (iv) no significant changes in blood pressure or heart rate were noted after administration of the drug.

During the study, no major side effects of the tested compound were noted by the investigators. Furthermore, the investigators emphasized the good acceptability of the treatment. It was noted that expected side effects observed during the phase I study in healthy volunteers, i.e. increase in heart rate and mean blood pressure (Beaufour-Ipsen pharma, internal report), were not present in TBI patients probably as a consequence of their altered central nervous system regulation. Nevertheless, it has to be pointed out that the stability in blood pressure which remained within normal values during the post-medication period on D0 and can play an important role in clinical outcome, could be interpreted as a positive biological effect of the compound. Finally, none of the reported deaths were related to the medication but rather to the severity and extent of the trauma.

Concerning efficacy, it was established that: (I) the predefined prognostic factors largely determined patient outcome, and consequently that the results cannot be interpreted without taking these factors into account; (II) these factors corresponded to the initial Marshal and Marmarou CT-scan score, the initial GCS and the occurrence of low SBP during the first 24 hours after the trauma; (III) when taken into account together with the dose level in a logistic regression model, it can be concluded that gacyclidine has a beneficial long-term effect on patients with TBI; and (IV) the best dose-result data were found in the 0.04mg/kg treated group but generally speaking the improvement in treated groups varied in a dose-dependent manner.

In the present work, it was considered essential to provide early and coordinated medical care to patients throughout the study. Early medical care included assessment of the GCS at the accident site which was done before the first medication to establish baseline data. The first GCS was of primary importance because many patients were already sedated on admission to the university hospital, preventing any valid coma assessment during the following days. To improve GCS assessment, investigators in all the study centers underwent several training sessions using booklets and videotapes. Nevertheless, it has to be pointed out that optimal GCS exploration is recommended 6 hours after TBI, so we were probably not working in the best conditions of significance.

Twenty-eight of the forty-eight patients eligible for the study were evaluated at one year, the others at their study end-point. Twelve patients died including 8 cerebral deaths related to the initial TBI. Twenty-six patients had a favorable outcome while seven patients had an unfavorable outcome. The outcome of the placebo group was similar to that reported in the literature.

Analysis of the raw data showed that the efficacy of gacyclidine could be masked by the importance of prognostic factors. In fact, these prognostic factors were not homogeneously distributed between the different groups and thier power was of critical relevance due to small sample size. Thus, the use of standard analysis of data to indicate the potential effects of gacyclidine appeared to be inappropriate. Patient outcome was largely and statiscally determined by several well-known prognostic factors (initial CT-scan, initial GCS, post-lesion 24-hour systolic blood pressure). All these elements are crucial in severe TBI and it seems fundamental to take them into account when determining the efficacy of the therapeutic treatment. Indeed, when prognostic factors are taken into account in the analytical model together with the time interval between the accident and the arrival of medical assistance, a more appropriate interpretation of the results becomes possible. The model-adjusted probability of favorable outcome showed that on the average the chances of having a favorable outcome were 2.645-fold better in patients treated with 0.04mg/kg gacyclidine than in patients in the placebo group (the greater the severity of the lesion reflected by the Marshal and Marmarou CT-scan, the higher the difference between the rate of favorable outcome between the 0.04mg/kg treated group and the untreated group) (see *table VII* and *figure 1*).

Investigators performing clinical trials in severe head injury have reached a consensus concerning the relevance of prognostic factors in TBI outcome. In 1979, the Glasgow group ranked the severity of lesions in traumatic brain injuries [41], and in 1992 the importance of anatomical disorders assessed by medical imaging (i.e.CT-scan score) was established and validated [30]. Several neuroprotective agents have shown promising results in experimental models used in preclinical phases but it is now widely accepted than the efficacy of such a compounds is likely to be less in TBI patients [27]. Apart from the above mentioned factors which play a considerable role in patient outcome, one of the major problems of clinical trials is the relative small size of the studied cohorts and consequently the insufficiency of statistical methods to evidence small benefits [27]. It is hoped that further basic and clinical studies in this area will provide important and significant steps towards the develpment of new and effective therapeutic strategies. Nevertheless, based on

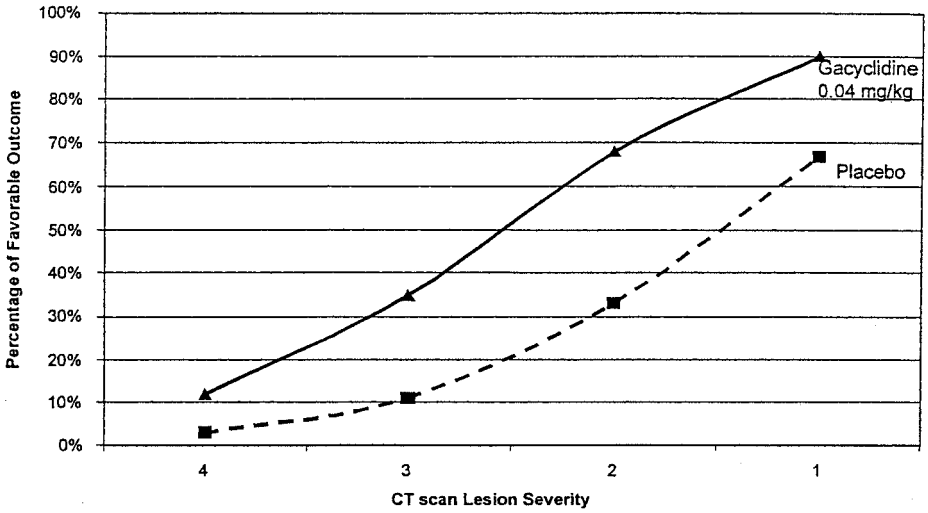

FIG. 1. — Evolution of the estimated percentage of favorable outcomes based on the logistic model between placebo and 0.04mg/kg treated group.

FIG. 1. — *Évolution du pourcentage estimé des résultats favorables basés sur le modèle de régression logistique entre le placebo et le groupe traité à 0,04 mg/kg.*

the available evidence, noncompetitive NMDA receptor antagonits i.e. gacyclidine, appear to be an essential component in their elaboration. Data obtained in this clinical trial appear sufficient to warrant a European multicenter study using the same evaluation criteria.

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REFERENCES

[1] BAILEY I, BELL A, GRAY J, *et al.* A trial of the effects of nimodipine on outcome after head injury. *Acta Neurochir* 1991 ; *110* : 97-105.

[2] CHAUDIEU I, VIGNON J, CHICHEPORTICHE M, EL HARFI A, KAMENKA JM, CHICHEPORTICHE R. Comparaison entre les sites de fixation de la [^{3}H] phencyclidine (PCP) et de la [^{3}H] (thiényl-2)-1 cyclohexylpipéridine (TCP) dans le système nerveux central de rat. *Eur J Med Chem* 1987 ; *22* : 359-362.

[3] CHOI DW. Ionic dependence of glutamate neurotoxicity. *J Neurosci* 1987 ; *7* : 369-379.

[4] CHOI DW. Calcium-mediated neurotoxicity : relationship to specific channel types and its role in ischemic damage. *Trends Neurosci* 1989 ; *11* : 21-26.

[5] DRIAN MJ, KAMENKA JM, PRIVAT A. In vitro neuroprotection against glutamate toxicity provided by novel non-competitive N-methyl-D-aspartate antagonists. *J Neurosci Res* 1999 ; *57* : 927-934.

[6] DRIAN MJ, KAMENKA JM, PRIVAT A. Non competitive antagonists of N-methyl-D-aspartate prevent spontaneous neuronal death in primary cultures of embryonic rat cortex. *J Neurosci Res* 1999 ; *29* : 133-138.

[7] EUROPEAN STUDY GROUP ON NIMOPIDINE IN SEVERE HEAD INJURY. A multicentre trial of the efficacy of nimodipine on outcome after severe head injury. *J Neurosurg* 1994 ; *80* : 797-804.

[8] FADEN AI, DEMEDIUK P, PANTER SS, VINK R. The role of excitatory amino acids and NMDA receptors in traumatic brain injury. *Science* 1989 ; *244* : 798-800.

[9] FADEN AI, Simon RP. A potential role for excitotoxins in that pathophysiology of spinal cord injury. *Ann Neurol* 1988 ; *23* : 623-626.

[10] FAROOQUE M, HILDERES L, HOLTZ A, OLSSON Y. Changes of extracellular levels of amino acids after graded compression trauma to the spinal cord : an experimental study in the rat using microdialysis. *J Neurotrauma* 1996 ; *13* : 537-348.

[11] GAVIRIA M, PRIVAT A, D'ARBIGNY P, KAMENKA JM, HATON H, OHANNA F. Neuroprotective effets of gacyclidine after experimental photochemical spinal cord lesion in adults rats. Dose-window and time-window effets. *J Neurotrauma* 2000 ; *17* : 19-30.

[12] GAVIRIA M, PRIVAT A, D'ARBIGNY P, KAMENKA JM, HATON H, OHANNA F. Neuroprotective effets of a novel NMDA antagonist, gacyclidine, after experimental contusive spinal cord injury in adults rats. *Brain Res* 2000 ; *874* : 200-9.

[13] GIMENEZ Y, RIBOTTA M, PRIVAT A. Biological interventions for spinal cord injury. *Curr Opin Neurol* 1998 ; *11* : 647-654.

[14] GRUMME T, BAETHMANN A, KOLODZIEJCZYK D, *et al.* Treatment of patients with severe head injury by triamcinolone: a prospective, controlled multicenter trial of 396 cases. *Res Exp Med* 1995 ; *195* : 217-229.

[15] HIRBEC H, GAVIRIA M, VIGNON J. Gacyclidine : a next neuroprotective agent acting at the N-methyl-D-aspartate receptor. *CNS Drug* 2001 ; *7* : 172-198.

[16] JENNETT B, BOND M. Assessment of outcome after severe brain damage. A practical scale. *Lancet* 1975 ; *1* : 480-484.

[17] JONES PA, ANDREWS PJ, MIDGLEY S, *et al.* Measuring the burden of secondary insults in head-injured patients during intensive care. *J Neurosurg Anesthesiol* 1994 ; *6* : 4-14.

[18] KAMENKA JM, CHICHE B, GOUDAL R, *et al.* Chemical synthesis and molecular pharmacology of hydroxylated 1- (1-phenylcyclohexyl) piperidine derivatives. *J Med Chem* 1982 ; *25* : 431-435.

[19] KATAMAYA Y, BECKER DP, TAMURA T, HOVDA DA. Massive increases in extracellular potassium and the indiscriminate release of glutamate following concussive brain injury. *J Neurosurg* 1990 ; *73* : 889-900.

[20] KRAUSS JF, MCARTHUR DL. Epidemiologic aspects of brain injury. Neurol Clin 1996 ; *14* : 435-450.

[21] LALLEMENT G, CLARENCON D, GALONNIER M, BAUBICHON D, BURCKHART MF, PEOC'H M. Acute soman poisoning in primates neither pretreated nor receiving immediate therapy: value of gacyclidine (GK-11) in delayed support. *Arch Toxicol* 1999 ; *73* : 115-122.

[22] LALLEMENT G, MESTRIES JC, PRIVAT A, *et al.* GK11 : promising additional neuroprotective therapy for organophosphate poisoning. *Neurotoxicology* 1997 ; *18* : 851-856.

[23] LEVALLOIS C, CALVET MC, KAMENKA JM, PETITE D, PRIVAT A. Primary dissociated cultures of human brainstem cells: a useful tool of their characterization and neuroprotection study. *Cell Biol Toxicol* 1995 ; *11* : 155-160.

[24] LEVALLOIS C, CALVET MC, KAMENKA JM, PETITE D, PRIVAT A. TCP enhances the survival of human fœtal spinal cord cells in culture. *Brain Res* 1992 ; *573* : 327-330.

[25] LI S, TATOT CH. Effets of MK801 on evoked potentials, spinal cord blood flow and cord edema in acute spinal cord injury in rats. *Spinal Cord* 1999 ; *37* : 820-832.

[26] LU YM, YIN HZ, CHIANG J, WEISS JH. Ca $(^{2+})$-permeable AMPA/kainate and NMDA channels: high rate of Ca^{2+} influx underlies potent of injury. *J Neurosci* 1996 ; *16* : 5457-5465.

[27] MACHADO SG, MURRAY GD, TEASDALE GM. Evaluation of designs for clinical trials of neuroprotective agents in head injury. *Neurotrauma* 1999 ; *16* : 1131-1138.

[28] MAIER CM, SUN GH, KUNIS DM, GIFFARD RG, STEINBERG GK. Neuroprotection by N-methyl-D-aspartate receptor antagonist GCP 40116 : in vivo and in vitro studies. *J Neurochem* 1995 ; *65* : 652-659.

[29] MARSHALL LF, MAAS AIR, MARSHALL SB, *et al.* A multicenter trial of the efficacy of tirilazad mesylate in severe head injury. *J Neurosurg* 1998 ; *89* : 519-525.

[30] MARSHALL LF, MARSHALL SB, KLAUBER MR, *et al.* The diagnosis of head injury required a classification based on computed axial tomography. *J Neurotrauma* 1991 ; *9* : S287-S292.

[31] MARSHALL LF, MARSHALL SB, KLAUBER MR, *et al.* A new classification of head injury based on computerized tomography. *J Neurosurg* 1991 ; *75* : S14-S20.

[32] MCINTOSH TK. Novel pharmacologic therapies in the treatment of experimental traumatic brain injury: a review. *J Neurotrauma* 1993 ; *10* : 215-261.

[33] MCINTOSH TK, JUHLER M, WIELOCH T. Novel pharmacologic strategies in the treatment of experimental traumatic brain injury. *Neurotrauma* 1998 ; *15* : 731-769.

[34] MICHAUD M, WARREN H, DRIAN MJ, *et al.* Homochiral structures derived from 1- [1- (2-thienyl) cyclohexyl] piperudude (TCP) are potent non-competitive antagonists of glutamate at NMDA receptor sites. *Eur J Med Chem* 1994 ; *29* : 869-876.

[35] MILLER JD, SWEET RC, NARAYAN R, BECKER DP. Early insults to the injured brain. *JAMA* 1978 ; *240* : 439-442.

[36] MURRAY GD, TEASDALE GM, SCHMITZ H. Nimodipine in traumatic subarachnoid haemorrhage : a re-analysis of the HIT I and HIT II trials. *Acta Neurochir* 1996 ; *138* : 1163-1167.

[37] NILSSON P, HILLERED L, PONTEN V, UNGERSTEDT V. Changes in cortical extracellular levels of energy-related metabolites and amino acids following concussive brain injury in rats. *J Cereb Blood Flow Metab* 1990 ; *10* : 631-637.

[38] PENCALET P, OHANNA F, POULAT P, KAMENKA JM, PRIVAT A. Thienylphencyclidine protection for the spinal cord of adults rats against extension of lesions secondary to a photochemical injury. *J Neurosurg* 1993 ; *78* : 603-609.

[39] RONDOUIN G, DRIAN MJ, CHICHEPORTICHE R, KAMENKA JM, PRIVAT A. Non-competitive antagonists of N-methyl-D-aspartate receptors protect cortical and hippocampal cell cultures against glutamate neurotoxicity. *Neurosci Lett* 1988 ; *91* : 199-203.

[40] TATOR CH, FEHLINGS MG. Review of the secondary injury theory of acute spinal cord trauma with emphasis on vascular mechanisms. *J Neurosurg* 1991 ; *75* : 15-26.

[41] TEASDALE GM, JENNETT B. Assessment of coma and impaired consciousness. *Lancet* 1974 ; *2* : 81-84.

[42] TEASDALE GM, MURRAY G, PARKER L, JENNETT B. Adding up the Glasgow Coma Store. *Acta Neurochir Suppl (Wien)* 1979 ; *28* : 13-16.

[43] YOUNG B, RUNGE JW, WAXMAN KS, *et al.* Effects of Pegorgotein on neurologic outcome of patients with severe head injury. A multicenter, randomized controlled trial. *JAMA* 1996 ; *276* : 538-543.

***Appendix.* — Clinical centers participating in this study**
(Emergency Medical Units, University Hospitals, Rehabilitation Centers)

Emergency Medical Units

1. SAMU, Hôpital Nord, 80000 AMIENS — Pr NEMITZ
2. SAMU, CHU Jean-Minjoz, 25000 BESANÇON — Pr NEIDHART
3. SAMU 93, Centre Hospitalier Avicenne, 93009 BOBIGNY — Dr MAGNE
4. SMUR, Centre Hospitalier, 77405 LAGNY — Dr VIDAL
5. SAMU, Centre Hospitalier, 72000 LE MANS — Dr SORET
6. SMUR, Centre Hospitalier Général, 91160 LONGJUMEAU — Dr OUDRAY
7. SAMU, Centre Hospitalier Marc-Jacquet, 77011 MELUN — Dr PORTA
8. SAMU, CHR La Source, 45067 ORLÉANS — Dr GORALSKI
9. SAMU, Hôpital Necker, 75015 PARIS — Pr CARLI
10. SAMU 66, Centre Hospitalier Général Perpignan, 66046 PERPIGNAN — Dr GARCIA
11. SMUR 76 A, Hôpital Charles-Nicolle, 76031 ROUEN — Dr JARDEL
12. SAMU, SMUR de Saint-Denis, 97405 SAINT-DENIS/LA RÉUNION — Dr BOURDE
13. SMUR, Centre Hospitalier, 02321 SAINT-QUENTIN — Dr BERNARD
14. SAMU, Centre Hospitalier Intercommunal, 83056 TOULON — Dr ARZALIER
15. SAMU, Hôpital Trousseau, 37044 TOURS — Dr GIGOT

University Hospitals

1. Neurosurgery, Hôpital Nord, 80000 AMIENS — Pr DELCOUR
2. Neurosurgery, Hôpital Jean-Minjoz, 25030 BESANÇON — Dr GODARD
3. Intensive Care, Hôpital Beaujon, 92210 CLICHY — Pr MARTY
4. Neurosurgery, CHU Bicêtre, 94275 LE KREMLIN-BICÊTRE — Pr TADIÉ
5. Intensive Care, CHU Bicêtre, 94275 LE KREMLIN-BICÊTRE — Pr SAMII
6. Intensive Care, Hôpital Lariboisière, 75010 PARIS — Dr CLAVIER
7. Neurosurgery, CHR La Source, 45067 ORLÉANS — Dr STECKEN
8. Neurosurgery, Centre Hospitalier Général, 66046 PERPIGNAN — Dr BOUSQUET
9. Neurosurgery, Hôpital Charles-Nicolle, 76031 ROUEN — Dr ALIBERT
10. Intensive Care, Hôpital d'Instruction des Armées Sainte-Anne, 83800 TOULON — Pr QUINOT
11. Intensive Care, CHI Font-Pré, 83056 TOULON — Dr DURAND-GOSSELIN
12. Neurosurgery, Hôpital Trousseau, 37044 TOURS — Dr FOURNIER

Rehabilitation Centers

1. Etablissement Hélio-Marin, 62608 BERCK - Dr DANZE
2. Centre de Rééducation Fonctionnelle, 76231 BOIS-GUILLAUME — Pr BEURET-BLANQUART
3. Centre de Rééducation Fonctionnelle de Coubert, 77170 BRIE-COMTE-ROBERT — Dr DESERT
4. Centre Médical Cap-Peyrefite, 66290 CERBÈRE — Dr GALTIER
5. Pavillon Wurtz, Hôpital A.-Chenevier, 94000 CRÉTEIL — Dr MONTAGNE
6. Rééducation Neurologique, Hôpital Raymond-Poincaré, 92380 GARCHES — Pr BUSSEL
7. Centre de Rééducation Fonctionnelle, SAINT-DENIS/LA RÉUNION — Dr GUILLOT-MASANOVIC
8. Centre Jacques-Ficheux, 02410 SAINT-GOBAIN — Dr VIGUIER
9. Service de Rééducation, Hôpital Chalucet, 83056 TOULON — Dr COSTES