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ORIGINAL COMMUNICATION

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Levodopa and bromocriptine in hypoxic brain injury

Abstract *Background* Postanoxic encephalopathy is frequent in patients presenting with abrupt cardiac arrest or respiratory failure. Little is known about the effectiveness of oral medications on the cognitive and motor consequences. *Objective* To present data suggesting partial improvement after administration of levodopa/benserazide. *Methods* After observing partial benefit in one case, each patient admitted to rehabilitation following brain anoxia was systematically treated with levodopa/benserazide (200/50 to 400/100 mg/day), then bromocriptine (15 mg/day). *Results* In the first patient, brain anoxia was severe, with secondary agitation, quadriparesis, involuntary movements, inattention and communication disorders. Introduction of levodopa/benserazide resulted in reduction of agitation and involuntary movements and improvement of communication, thus facilitating care and rehabilitation efforts. A weaning test resulted in rapid worsening. The four following patients also presented with anoxia of variable severity. Marked improvement was observed in case 2, presenting with agitation, loss of orientation, amnesia, postural disorders, involuntary movements and dysphagia, with a withdrawal test resulting in immediate re-enhancement of symptoms. Modest improvement was observed in patient 3, who had hypokinesia, rigidity, adynamia, impaired attention, and reduced verbal fluency. Patient 4 presented with memory disorders without motor difficulties: mild improvement was observed in daily life and memory tests. In patient 5 who also presented with severe memory disorders, the benefit was absent. In each case, bromocriptine was introduced 3–4 weeks following levodopa, but without additive effect. Both treatments could be interrupted after a few months, without worsening. *Conclusions* Levodopa and benserazide can be of benefit in the few months following brain anoxia, especially on some of the motor disorders and apathy, but the benefit is inconstant and modest on memory disorders. Anoxia could alter dopaminergic mesencephalic systems, which activate the striatal and mediobasal frontal cortex, and these disorders could be partially reversible by medical treatment.

Key words brain anoxia · extrapyramidal disorders · frontal syndrome · amnesia · levodopa · bromocriptine

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Introduction

Improving techniques have made cardiopulmonary resuscitation more and more successful. Consequently, postanoxic encephalopathy has become a rather frequent cause of neurological handicap. Symptoms observed at the acute stage of brain hypoxia are to be distinguished from irreversible deficiencies, which determine the postanoxic encephalopathy, ranging from

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vegetative state to more moderate mental, perceptual or motor disorders. The most frequent deficits include impaired attention and memory [16], frontal lobe dysfunction with marked apathy [12], visual agnosia and cortical blindness [9], involuntary movements, dystonia [2], extrapyramidal rigidity [4], and tetraparesis [9]. Only 3 to 10 % of patients resuscitated from cardiac arrest can resume their former life style [19]. So far, no drug has shown to consistently improve patients' deficiencies and disability. Calcium channel antagonists, superoxydedismutase, barbiturates, GABA-receptor inhibitors have been tested at the acute phase, in order to block the sequence leading to neural damage [19], but without substantial benefit. Little is known about pharmacological treatment of fixed neurologic deficiencies resulting from brain anoxia. While levodopa and dopamine agonists are mentioned abundantly in the treatment of sequelae of traumatic brain injury [7, 8, 10, 11, 17], there are very few accounts of the use of these drugs in postanoxic encephalopathy [15].

The aim of the study was to describe five patients with postanoxic encephalopathy, for which we evaluated the effect of levodopa/benserazide and bromocriptine.

Patients and methods

The first patient was put on a levodopa/benserazide (Modopar®) regimen after several other pharmacological treatments had failed. The positive results led us to propose this treatment systematically to each patient presenting with neurological complications of hypoxic brain injury. Informed consent was obtained from the family. The treatment was always started at a distance from the acute event, and titrated gradually up to 100/25 mg levodopa/benserazide x 3 or x 4/day. The effect of an additional treatment with bromocriptine was evaluated on each patient (5 mg x 3/day).

Patient 1

A 25 year-old woman, sustained a cardiac arrest secondary to Coxsackie myocarditis on January, 2000. During the following weeks she suffered severe vigilance disorders. She was admitted to rehabilitation two months later. Vigilance normalised gradually. Attention and communication were difficult for her. Tetraparesis remained severe with diffuse hypertonia. Complex involuntary movements were observed involving the four limbs and the trunk. MRI was considered normal, and Single Photon Emission Computed Tomography (SPECT; HMPAO) revealed severe and diffuse hypoactivity, more marked in the frontal cortex, with a significant reduction in the anteroposterior perfusion ratio. Medications were introduced sequentially, such as muscle relaxants, antispastic (baclofen), anticholinergic (tropatepine) and antiepileptic drugs (gabapentine, carbamazepine), and morphine. They were either ineffective, or had to be discontinued because of side effects. Seven months after the cardiac arrest (August 2000) the patient was put on levodopa/benserazide, 50/12.5 mg x 4/day. After one day, involuntary movements and agitation were reduced, and this improvement was even more obvious in the following days. This resulted in the patient being more alert and communicative. The dosage was titrated gradually and divided into five doses (400/100 mg/day). Within one month, spoken language and oral feeding were restored, and the tracheostomy tube was removed. Antiemetics had to be added because of nausea. A weaning test was performed. Involuntary movements and agitation were rapidly re-enhanced and the initial dosage was restored. Later (May 2001), bromocriptine was added (5 mg x 3/day), without additional benefit. Twenty months after the cardiac arrest, the patient returned home (September 2001). Alertness and communication were good. Involuntary movements had disappeared. Tetraparesis remained important, as well as memory disorders. The patient was still severely dependent (Functional Independence Measure, FIM = 35/126). Levodopa/benserazide and bromocriptine were gradually weaned (September, 2001), without changes in deficits and behaviour.

Patient 2

A 50 year-old man suffered ventricular fibrillation and cardiac arrest on August, 2000. The cardiovascular evolution was favourable. Vigilance disorders were observed in the first few weeks. Later on, the occurrence of behavioural disorders and hallucinations justified the administration of risperidone, 2 mg x 3/day. The patient was admitted two and a half months later in the rehabilitation department. Examination showed moderate right hemiparesis, retropulsion and motor hyperactivity. Subsequently elements of an extrapyramidal syndrome became evident with hampered alternating movements, hypomimia and festinating gait. There was no tremor or rigidity. The patient suffered dysarthria and severe dysphagia, with sialorrhoea and drooling. He was also incontinent. There was a marked lack of drive, reduced attention, utilisation behaviour, perseverations, and amnesia. The MMSE score was 9/30. The patient was highly dependant in daily living (FIM = 52/126). On magnetic resonance imaging, moderate cortico-subcortical atrophy and signal heterogeneity in the lentiform nuclei were observed. A SPECT study (HMPAO) revealed bilateral fronto-temporo-parietal hypoactivity, with reduced anteroposterior perfusion ratio. During the two following months, the mental status slowly improved, but the motor disorders remained relatively severe and stable. Risperdone was withdrawn in December, 2000.

In February 2001, the extrapyramidal signs were unchanged and a therapeutic test with levodopa was carried out. One hour after the absorption of 50/12.5 mg of levodopa/benserazide the extrapyramidal signs were diminished, the patient was able to perform alternating movements and sialorrhoea was less prominent. He was then put on levodopa/benserazide 50/12.5 mg x 4/day. After a few days, there was a significant improvement of attention, communication and motor disorders, such as hampered alternating movements, festinating gait, sialorrhoea and dysphagia. A withdrawal test of levodopa/benserazide resulted in immediate symptoms re-enhancement. Because of orthostatic hypotension the dosage of levodopa/benserazide could not be increased. One month later (March 2001), treatment with bromocriptine, 15 mg/day, was initiated, without clear benefit. Bowel and bladder continence were restored, as well as salivation and swallowing, and oral feeding could be resumed. Treatment with bromocriptine was later interrupted (June, 2001), without clinical worsening. The patient was able to turn home on April 2001. On follow-up visits, he was totally autonomous in daily activities (FIM = 125/126). Physical examination was normal, even in complex motor activities. He still showed mild difficulties in learning and solving problems. The MMSE score was 26/30. Treatment with levodopa/benserazide was withdrawn in January, 2002, without change in the neurological and functional status.

Patient 3

A 54 year-old man suffered respiratory distress syndrome in September 2000. Vigilance was altered over six weeks. On admission in the rehabilitation department (January 2000), an extrapyramidal syndrome was observed, with marked hypokinesia, and rigidity of limbs and neck with cogwheeling phenomenon, producing a festinating gait with inability to walk unassisted. There was also major hypophonia, psychomotor asthenia and apathy. Language was impaired with

reduced speech fluency. Neuropsychological testing showed perceptuo-motor slowing (visual reaction time) and dysexecutive syndrome (Trail Making Test Form B). On the Grober and Buschke memory test [5], free recall of words was severely impaired. Daily life activities required important help (FIM = 50/126). CT- showed moderate cortico-subcortical atrophy, bilateral lacunar hypodensities in the centrum semiovalum and bilateral pallidal hyperdensity; these lesions were confirmed by MRI. A SPECT study (HMPAO) revealed bilateral hypoperfusion in the prefrontal cortex and heterogeneous perfusion of both frontal lobes and the left temporal lobe.

Five months after the hypoxic brain injury (February 2001), there was no clinical progression and a treatment with levodopa/benserazide 50/12.5 mg x 4/day was initiated. One week later, there was no significant improvement, and the dosage was raised to 100/25 mg x 4/day. At that time, symptoms became gradually less important. The patient regained a certain degree of initiative. Attention was improved as well as executive control (Trail Making Test B) and free recall (Grober and Buschke memory test). Rigidity was minimal. Performing alternating movements was slow but possible, postural reflexes were partially restored and the patient could walk slowly without assistance. Hypophonia was unchanged. The patient was less dependant in daily life activities (FIM = 91/126). Bromocriptine (15 mg/day) was added, without additional benefit after five weeks, and was thus discontinued. Ten months after the hypoxic brain injury the patient returned home, nearly autonomous (FIM = 101/126) but still suffering from a loss of drive, discrete amimia, reduced automatic movements of the upper limbs, slight slowness of gait and minor rigidity. The MMSE score was 28/30. Levodopa/benserazide was progressively interrupted (July, 2001), without clinical worsening.

Fig. 1 HMPAO SPECT study in patient 2. Severe hypoperfusion in both frontal regions.

Patient 4

D. P., a 41 year-old man sustained a cardiac arrest as a result of ventricular fibrillation on March 2001. He was admitted one month later to the rehabilitation department. At that time, mild apathy, disorientation in time and place and amnesia (anterograde more than retrograde) were observed, but physical examination was normal. On the Grober and Buschke test, the deficit was severe on both free recall and recognition (table 1). The Rey Complex Figure was copied correctly but the memory reproduction was severely deficient (12/36). On the Signoret Memory Battery [18], both verbal and visual memories were impaired. Attention (Stroop Test) and executive functions (Wisconsin Card Sorting Test) were normal. A CT-scan showed no anomaly. The SPECT study (HMPAO) revealed multiple zones of cortico-subcortical hypoperfusion in both hemispheres, predominating in both frontal regions. Eight weeks after the cardiac arrest (May 2001), the clinical condition was unchanged. A treatment with levodopa/benserazide was initiated, and raised up to 100/25 mg x 3/day. Subjective signs of improvement were noted by both the family and the medical team, such as increased motivation and drive, breaking in more easily in a conversation and taking more initiatives. Neuropsychological testing carried out after two weeks showed improvement for the Grober and Buschke test (immediate cued recall and recognition), and the memory scores of the Signoret Memory Battery (BEM 144). A third series of tests was carried out after one week on bromocriptine 5 mg x 3/day (July, 2001). Performance was relatively stable for the Grober and Buschke memory test and the BEM 144, but discretely better for the Rey Complex Figure test. Improvement was even more evident two months later. Levodopa/benserazide and bromocriptine were progressively weaned (September, 2001). The performance in tests did not decline, and even improved (BEM 144). The patient was discharged on October 2001. He was fully independent (FIM = 125/126), well oriented, but his memory was still partially impaired.

Table 1 Patient 4

		Series 1 May 14	Series 2 May 28	Series 3 July 20	Series 4 September 7	Series 5 September 24
Grober and Buschke memory test	Version	A	B	A	A	B
	Immediate cued recall/16	11	16	14	15	15
	Free recall/16	2-1-1	3-0-0	2-1-2	2-4-5	3-3-4
	Delayed free recall/16	0	0	2	6	3
	Recognition/16	1	14	10	11	12
Rey Complex Figure	Drawing/36	34	33	36	36	36
	Memory/36	12	13	21	19	29
Signoret BEM 144	Verbal/72	18	34	28	27	47
	Visual/72	24	45	51	47	59
	Total/144	42	80	79	74	106

Series 1: before levodopa/benserazide;
Series 2: 2 weeks after levodopa/benserazide 50/12.5 mg x 3/day;
Series 3: 1 week after bromocriptine 5 mg x 3/day, in addition to levodopa/benserazide;
Series 4: 1 day before withdrawal levodopa/benserazide and bromocriptine;
Series 5: 18 days after withdrawal levodopa/benserazide and bromocriptine.

Patient 5

D. C., a 42 year-old patient abruptly presented with cardiorespiratory arrest (April 2001). He was admitted to rehabilitation two months later (June 2001). By that time, clinical examination revealed discrete motor deficit, combined with disorientation, anomia, dyslexia, visual agnosia, severe long-term episodic and semantic amnesia, and dysexecutive syndrome. A first cognitive assessment showed very severe learning disorders (table 2). The CT findings were normal. The SPECT study (HMPAO) revealed prefrontal hypoactivity and heterogenous fixation in the posterior temporoparietal areas. Levodopa/benserazide was introduced (July 2001), and progressively raised up to 100/25 mg x 3/day. A first reassessment at three weeks showed minor improvement compared to pretherapeutic performance. A brief withdrawal test resulted in no substantial worsening. The therapy was reintroduced, first alone, then in association with bromocriptine, 5 mg x 3/day (August, 2001). Domperidone had to be added because of vomiting. Over the following weeks, the motor and cognitive disorders progressively improved, and this was confirmed by the third memory assessment. Later on, levodopa/benserazide and bromocriptine were interrupted (September, 2001). Further examinations showed that the performance level still improved. Relatively severe cognitive problems were still present on discharge (November 2001), with amnesia and visual recognition disorders. By that time, autonomy was fair in daily living (FIM = 117/126).

Discussion

We presented five patients who sustained hypoxic brain injury and whose symptoms were partially improved by the administration of levodopa/benserazide secondarily associated to bromocriptine, after a relatively long interval from the initial event. In this short series, the endpoints varied widely from one patient to another, but this was due to their clinical disparity. The improvement on levodopa/benserazide was particularly marked on attention impairment and involuntary movements in case 1, on apathy, gait disorder, sialorrhoea and incontinence in case 2, on extrapyramidal rigidity and psychomotor slowing in case 3. It was questionable in patient 4 and especially in patient 5, who both suffered from apathy and memory disorders. In the first one, a discrete benefit was observed in daily living, and memory assessment showed more definite improvement in some of the memory tests. In the second one, no improvement was observed in daily living and memory testing following levodopa/benserazide introduction, and the discrete positive evolution following bromocriptine introduction was similar to what had occurred after the treatment withdrawal. The adverse effects reported during the treatment were orthostatic hypotension in one case and nausea in another, but the treatment needed not be discontinued. Bromocriptine was introduced after a delay, but without additive effect on motor and cognitive functions.

Of course, it is difficult to distinguish between improvements due to the drug regimen and those due to physical and neuropsychological rehabilitation techniques as well as the natural course. Nevertheless, several elements support the hypothesis of a partial levodopa/benserazide's efficacy: (i) treatment with levodopa/benserazide was initiated at a distance from the hypoxic brain injury (two to seven months), and the clinical evolution was at a standstill during the preceding weeks, especially in the first three cases; (ii) a partial improvement was observed in the hours (patients 1 and 2) or days (patients 3 and 4) that followed treatment onset; (iii) symptoms were re-enhanced after momentary withdrawal of the drug in patients 1 and 2. The positive effect was clearly questionable in patients 4 and 5, who presented with predominating memory disorders. Lastly, in patient 2, part of the extrapyramidal symptoms might have been attributed to the neuroleptic treatment the patient was taking on admission in the rehabilitation unit. However, the symptoms did not diminish after withdrawal of this treatment, even at a distance, and risperidone is considered to produce less extrapyramidal symptoms than other neuroleptics.

Table 2 Patient 5

		Series 1 July 13	Series 2 August, 10	Series 3 September, 11	Series 4 September, 25	Series 5 November, 30
Grober and Buschke memory test	Version	A	B	A	B	A
	Immediate cued recall/16	1	6	9	13	16
	Free recall (3 trials)/16	2-1-1	1-2-1	2-6-4	4-4-4	8-7-10
	Delayed free recall/16	0	0	3	2	10
	Recognition/16	6	7	16	14	16
Rey Complex Figure	Drawing/36	31	32	31	36	35
	Memory/36	1	2	2.5	6	8
Signoret BEM 144	Verbal/72		17	26.5	38.5	37
	Visual/72		17.5	22	37	38.5
	Total/144		34.5	48.5	75.5	75.5

Series 1: before levodopa/benserazide;
Series 2: 3 weeks after levodopa/benserazide 50/12.5 mg x 3/day;
Series 3: 3 week after bromocriptine 5 mg x 3/day, in addition to levodopa/benserazide;
Series 4: 3 days after withdrawal levodopa/benserazide and bromocriptine;
Series 5: 5 weeks after withdrawal levodopa/benserazide and bromocriptine.

The rationale of treating postanoxic encephalopathy with levodopa and dopamine agonists was based mainly on the empirical observation of improvement in the first patient. Involuntary movements decreased significantly and more surprisingly we also witnessed a conspicuous improvement of attention and communication. Muller et al. [15] also reported three patients suffering postanoxic encephalopathy with memory impairment and apathy, who improved on bromocriptine. Other authors have reported similar results in patients presenting with severe traumatic brain injury, particularly improvement of extrapyramidal disorders with rigidity and dyskinesia [7, 10], motivational deficit, frontal lobe dysfunction (divided attention, cognitive flexibility, executive function) [8, 11], and amnesia [14].

The underlying mechanism of levodopa efficacy is questionable. During the acute phase of hypoxic brain injury Gibson et al. [3] have hypothesised a change in the oxygen-dependant metabolism of neurotransmitters such as dopamine. An important point is that dopamine could be a substitute to the dopaminergic circuits affected by the neuronal loss. Dopaminergic neurons depart from the substantia nigra pars compacta in the midbrain and the tegmental ventral area. They are directed partly towards the striatum, and partly towards the cortex, especially the medial frontal lobe, piriform and prepiriform cortex, entorhinal cortex and anterior cingulate cortex [1]. The sensitivity of dopaminergic neurons to hypoxia has been suggested in animal [6], and levodopa treatment helps to restore normal metabolic and cognitive functioning [13]. Interestingly therapeutic withdrawal at a late phase has no clear effect. This point suggests the alterations in the dopaminergic system partially resolve with time.

To conclude, these preliminary observations suggests partial efficacy of levodopa/benserazide on certain aspects of postanoxic encephalopathy, mainly apathy, attention disorders, involuntary movements, extrapyramidal signs, and a less clear effect on memory disorders. Further studies at a larger scale are needed to assess more precisely which symptoms may be alleviated and to determine the optimal dose and duration of treatment.

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