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Release hallucinations and tiapride

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The authors describe seven patients in whom the administration of tiapride led to the disappearance of visual hallucinatory manifestations with the characteristics of "release hallucinations", the results being maintained throughout the period of treatment. The authors also discuss the mechanism and presumed site of action of the drug.

Key Words: visual hallucinations — blindness — tiapride.

Introduction

The hallucinations described by Cogan as release hallucinations (RH) are caused by the removal of the normal flow of visual impulses to the occipital cortex, with the consequent release of the endogenous cerebral activity of the visual system. They therefore appear after damage to the anatomical structures which collect and send the images of the outside world to the specific primary sensory area, where they become localised only in that part of the visual field which has become blind [6, 7, 18, 24].

These are prevalently complex visual hallucinations occurring some time after sensory deprivation. They may remain indefinitely, as is often the case in elderly patients who have become completely blind, or with Charles Bonnet syndrome [3, 8, 22, 23, 25-27]; or they may spontaneously resolve after a variable period of time, particularly in cases of campimetric deficits caused by cerebrovascular lesions [1, 2, 12, 14, 15, 18].

Such hallucinatory manifestations include very clear colourful images, rich in detail and completely silent, of people, animals or objects. They may be stationary, or move from the periphery to the centre of the visual field: and they are destined to disappear if the patient moves his eyes in an attempt to look at them more closely. The appearance of RHs is constantly encouraged by particular stimuli affecting the undamaged part of the visual field (e.g. lighting changes, the face of the person being spoken to, a live television screen, etc.), but darkness does not seem to have the same considerable effect that it has in hallucinatory situations of other origins. Whether animate or not, the figures tend to repeat themselves in a stereotype fashion, each of them always appearing in the same form down to the smallest detail. However, over the course of time, they may appear in numerous varieties following one another in sequence or appearing in alternation.

Sometimes, the image is unpleasant and causes distress or a strong dislike, but it never gives rise to fear or terror.

Patients often show amazement at their unusual experience, particularly at the beginning; only later becoming irritated by the permanence of an intrusion which, regardless or the situation in which it appears, is always considered unreal and rightly regarded as an artificial product of their own brains.

Although they disappear if an improvement in sight occurs, such as after cataract surgery [23], RHs are generally considered to be resistant to any therapeutical treatment and, in practice, this refractoriness has even been incorporated in the definition of the syndrome [18].

However, our experience indicates that tiapride is capable of constantly suppressing such hallucinations, and that its effects is highly dose-dependent: a full dose of 300 mg per day leads to their certain disappearance; lower doses, even though they can also sometimes completely abolish the phenomenon, may only reduce the frequency of the episodes.

Nevertheless, tiapride does not affect the course of RHs, which tend to return unchanged in appearance and frequency when its administration is discontinued.

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Clinical cases

Case No. 1

Over a period of a few years, a 78-year old woman who was already severely myopic in both eyes presented twice with detachment of the right retina, and consequently completely lost her sight in the corresponding monocular field.

About one year later, she began to report visual hallucinations in that part of her visual field which had become blind. These hallucinations alternated between animals (mainly horses), miniature prophet-like figures with white beards moving in a long procession which unwound vertically as if they were making a daring mountain ascent, and small and kindly-looking human faces. Finally, five years after their onset, an amazingly beautiful blue doll was frequently induced by a lighted television screen. The doll would appear at the side of the television and disappear whenever the patient tried to look directly at it; more rarely, it also appeared in the evening when the living room lamp was on.

Although many different drugs had been used over the years, from neuroleptics (particularly haloperidol) to antiepileptics (carbamazepine) and to benzodiazepines, none of them had had any effect on the clinical picture. Tiapride treatment was begun as a trial and, surprisingly, led to the complete suppression of the hallucinations at a daily dose of 150 mg, which has so far been well tolerated and not caused any disturbances. Three years later, this result is fully confirmed; periodic attempts to reduce the dose have constantly led to the reappearance of the same blue doll under the same conditions as before.

Consciously lucid, and fully oriented in time, space and with respect to the people around her, the patient has always regarded these curious visions as abnormal and unreal, even while tolerating their appearance. Only the blue doll bothered her, because the brightness of the colour was a disturbance when she was watching television.

Case No. 2

At the onset of stroke, an 83-year old woman with arterial hypertension presented with left ipsilateral hemianopia following an ischemic lesion in the right temporo-occipital region. Some weeks after the stroke, and fully aware of their unreality, she began to report the appearance of hallucinations in the left half of her visual field. These hallucinations consisted of marching soldiers, strange human faces, animals of varying dimensions, and the head of a normal-sized cow. This last constantly appeared whenever the patient saw the face of the person she was speaking to, projecting itself onto the right shoulder of her interlocutor in the left half of her visual field.

Until her death for cardiac causes three years later, the patient remained lucid and oriented, and was capable of abolishing or reducing the frequency of the hallucinatory manifestations by taking tiapride at daily doses of between 150 and 300 mg; any discontinuation of the drug led to the return of the abnormal visions.

Chronic administration of tiapride caused a slight accentuation of a pre-existing and isolated modest Parkinsonian-type tremor in the right arm when the patient was at rest, without any other extrapyramidal signs.

Case No. 3

Some months after a cerebral toxoplasmosis with a favourable outcome after specific therapy, a 26-year old man with AIDS presented with bilateral chorioretinitis due to cytomegalovirus, with complete loss of visus in the right eye and minor impairment in the left. Some weeks later, he began to see a deformed and horrible-looking face in his blind monocular field for many hours during the day. The face did not disappear even when he instinctively closed both eyes. Although he was perfectly aware that the image did not exist, and that it originated in his own brain, the patient appeared depressed and dismayed by the presence of this figure which made his life even more trying.

As in the preceding cases, the therapeutic result of the daily administration of tiapride 150 mg was spectacular, and it was maintained without any dose changes and without side-effects until the death of the patient about eight months later.

Case No. 4

Two years after her visual deficit had become more marked, a 76-year old woman with bilateral glaucoma, completely blind in the left eye and with severely impaired vision in the right, began to report the sudden appearance of human figures with grotesque caricature-like faces and gaudy, multicoloured clothes. Mainly appearing in the evening or at night, the figures were generally adults preceded by children, who silently approached her bed and moved towards her; whenever she tried to look at them, they disappeared. The figures were always different in appearance and size on the various occasions in which they manifested themselves and, although she never had any doubts as to their unreality, they made the patient apprehensive, particularly when she woke at night. During the day, the hallucinations consisted exclusively of animals (particularly cats), which the patient could see motionless by the side of different household objects.

A daily dose of tiapride 300 mg completely abolished both the diurnal and nocturnal hallucinatory manifestations. Approximately two years later, any

attempt to suspend the drug caused the figures to reappear. A daily maintenance dose of 150 mg appeared to be sufficient to suppress the images but, after some months of treatment, it led to the onset of a shaking of the head and arms which was indistinguishable from essential tremor, clearly accentuated by emotion and controlled with only 250 mg of Primidone.
No other disturbances have been observed.

Case No. 5
In the period immediately following surgery, a 62-year old woman presented with a left temporo-occipital ischemic lesion, residual right upper quadrantanopia and, after some weeks, hallucinatory manifestations of enormous faces on the ceiling of the bedroom. The faces were like those of fountain gargoyles with their mouths wide open, and appeared in the blind part of her visual field. Although the patient considered them unreal, she still found them unpleasant. A daily dose of tiapride 300 mg immediately led to the suppression of the pathological event; various attempts to suspend the drug showed that the hallucinations remained potentially present for another six months, after which they disappeared definitively, allowing the therapy to be discontinued without any kind of side-effect being observed.

Case No. 6
An 86-year old woman with bilateral cataracts and a consequent severe visual deficit, but with sufficiently sound intellectual functions, began to report the appearance of visual hallucinations several times during the day. The hallucinations consisted of groups of young people who came suddenly into her room and moved quickly as though they were dancing. They appeared in an infinite variety of attitudes and forms, causing distress by the suddenness of their appearance and their brightly coloured clothing.
The daily administration of tiapride 150 mg immediately led to the disappearance of the visions, a result which has been maintained for six months. The drug is excellently tolerated and no side-effects have been observed.

Case No. 7
A 67-year old man affected by arterial hypertension for ten years presented with a right ipsilateral hemianopia following a left occipital ischemic lesion.
After six months, he reported the occasional appearance of mutilated figures, simple and repetitive, in the blind half of his visual field. They moved slowly forwards as if to pass the patient after having almost touched his right shoulder. The fact that the patient had spent some time in a military hospital during the war explained the unusual figures.
Some months later, with greater frequency and persistence, but always and only when the patient entered his bedroom, the profile of a very tall man with a moustache started to appear, dressed casually in blue and looking intently at the clock in the room. The figure appeared in the blind half of the patient's visual field, and instantly disappeared if he tried to look directly at it.
Although he considered that it was not real, this last figure caused the patient some distress and made it necessary to begin therapy with a daily dose of tiapride 300 mg. Although treatment led to the immediate disappearance of the hallucinatory manifestations, eight months later, even the smallest reduction in the dose causes the figures to reappear.
The patient has not complained of any disturbances as a result of the protracted administration of the drug.

Discussion

The genesis of RHs is generally attributed to visual sensory deprivation; but old age or another cerebral dysfunction preventing the brain from activating the compensatory mechanisms which might annul the phenomenon are considered equally important [7, 8, 18, 23, 24, 26, 27]. In fact, the appearance of these hallucinations occurs months, years or even decades after the onset of the visual disturbance causing the sensory deprivation, and the patients are elderly [14, 22, 26].
In young cases, a cerebral pathology can be recognised which, in practice, substitutes aging as a favouring factor (AIDS in our Case No. 3).
Nevertheless, sensory deprivation remains the primary cause, and the removal of this deficit (as in the case of cataract surgery) completely annuls RHs [23].
Although the origin of these hallucinations is unknown, their characteristics are very similar to those of hallucinoses due to lesions of the brainstem [9, 13, 20], appearing in the form of bright, highly-coloured, lively images, sometimes picturesque, sometimes stereotypical and repetitive. The patients always consider them abnormal, defining them as dreams which occur when they are awake and with open eyes.
Their pathogenetic mechanism should not be different from that of the hallucinoses caused by brainstem lesions [4, 5, 13, 20], and therefore it may be valid to hypothesise that RHs are indistinguishable from the common hypnagogic hallucinations [4] which are supposed to find them-

selves in an extremely favourable situation for being projected onto the "empty" cortical area created by sensory deprivation while escaping from the inhibitory control mechanisms at the level of the brainstem made inefficient by old age or disease. But although in the case of brainstem lesion hallucinoses such as peduncular and auditory hallucinations, the decisive factor is the existence of a macroscopic cause which removes, without the need for sensory deprivation, whatever impeded dream mechanisms from appearing when people were awake, the scenario in the case of RHs is prevalently functional — to the extent that they are immediately annulled by the restoration of visual function [23].

On the basis of these last considerations, it would appear evident that a pharmacological treatment for RHs is not beyond reach, and we should not be surprised by the spectacular results obtained using tiapride. Tiapride is a drug with an antidopaminergic action at the level of the mesolimbic system [11, 16, 17, 29] which, as is known, represents a functional unity along the large sensory and motorial pathways that is capable of collecting, filtering and transmitting information, and therefore of intervening in the case of any functional imbalance.

Furthermore, tiapride has already proved its efficacy in neurological syndromes in which it is possible to see a loss of equilibrium (either biochemical or between neuronal systems), such as in the case of the involuntary movements of extrapyramidal origin or delirium tremens [16, 19, 28].

The need for the protracted use over time of tiapride in treating RH (an indication which is not currently included among those approved for Seregrile®) is facilitated by the excellent tolerability of the drug, the absence of any important side-effects being widely demonstrated by many authors [16, 21, 28, 29]. The modest disturbances provoked in two of our cases (completely resolved in one) were acceptable to the patients, particularly when compared with the disquieting presence of the hallucinations themselves.

However evident the limitations of an "open" work such as ours, and the fact no tiapride substitution test was carried out using other similar drugs, the obtained results appear to be unequivocal. Consequently, it would seem to be logical to extend the verification of the efficacy of the drug to situations which are more or less similar to RHs, such as the auditory hallucinations of deaf patients [10], or to physiopathologically analogous conditions such as thalamic hyperpathia. On the contrary, in our opinion and for the reasons mentioned above, equally favourable results cannot be expected in peduncular hallucinoses or in the auditory hallucinations caused by lesions of the brainstem.

Sommario

Gli Autori descrivono sette pazienti nei quali la somministrazione di tiapride ha determinato la scomparsa di manifestazioni allucinatorie visive con le caratteristiche delle "Release - hallucinations", con mantenimento del risultato per l'intera durata del trattamento, e discutono l'eventuale meccanismo d'azione del farmaco e la sede presunta del suo intervento.

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