Addiction to apomorphine: a clinical case-centred discussion

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ABSTRACT

Aim To report the case of a patient, who in the context of an anti-Parkinsonian therapy, developed addiction to apomorphine. **Methods** Clinical case description. **Results** Apomorphine is a dopaminergic agonist that acts directly on D2 receptors. It has been used in alcoholism, male sexual dysfunction and with diagnostic and therapeutic purposes in Parkinson's disease (PD). **Conclusions** The present work describes the case of a woman with PD who developed a loss of control over the consumption of apomorphine that resulted in a significant impairment of her functioning. PD patients with high frequency develop different psychiatric symptoms. Conversely, anti-Parkinsonian drugs also generate psychiatric symptoms that can be experienced by the patient as pleasant sensations ('alerting', 'awakening', 'activating', hypomania and hypersexuality). In spite of this, addiction to these drugs in patients with PD is a very rare phenomenon. Currently, the prescription of apomorphine has been extended to patients with erectile dysfunction, which may increase the prevalence of addiction cases or of severe psychiatric symptoms.

Keywords Addiction, anti-Parkinsonian drugs, apomorphine.

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HISTORY OF THE USE OF APOMORPHINE

Apomorphine is a drug synthesized originally in 1869 [1]. Before its current indications were defined during the 1940s and 1950s, its use became popular. The English psychiatrist John Yerbury Dent (1888–1962) became renowned for the use of apomorphine in pathologies such as alcohol or opioid deprivation, and for what he called 'troublesome morning sickness in the pregnant woman, puerperal mania, or menopausal distress . . .'. Through the research on the effects of this drug, Yerbury Dent elaborated interesting hypotheses about the physiological mechanisms likely to be involved in addictions [2–4].

In a paper published in the *British Journal of Addiction* under the heading 'Letter from a master addict to dangerous drugs', the well-known American writer William Burroughs (1914–97) described the advantages of treating the symptoms of opioid deprivation from his personal experience as an addict [5]. In the introduction of his book *Naked Lunch* he stated: 'The vaccine that can relegate the junk virus to a land-locked past is in existence. This vaccine is the apomorphine treatment discovered by an English doctor whose name I must withhold . . . The apomorphine cure is qualitatively different from other methods of cure . . . I can say definitely that I was never *metabolically* cured until I took the cure' [6].

Apomorphine is a dopaminergic agonist that acts directly on dopaminergic D2 receptors with an affinity 100 times higher than dopamine (DA) [7]. It is used for diagnostic and therapeutic purposes in Parkinson's disease (PD), male sexual dysfunction and alcoholism [8,9].

PARKINSON'S DISEASE AND APOMORPHINE

PD is a neurological disorder with motor, sensitive, sensorial, psychiatric and cognitive symptoms derived from a deficiency in DA in the nigrostriatal system [10,11]. During the 1960s Birkmayer and Hornykiwiecz started, with success, the administration of a dopamine precursor, levo-3,4 dihydroxyphenylalanine (L-Dopa), to control the symptoms of disease. Nevertheless, once its use became ubiquitous, two important clinical problems became evident: (a) the induction of dyskinesias; and (b) motor fluctuations, i.e. the sudden and unexpected manifestation of

periods with loss of the clinical response and intense acute exacerbation of symptomatology, known as 'off' states [12]. The latter brought about the search of new therapeutic alternatives, and initiated the use of dopaminergic agonists. These have been used for more than 30 years to control PD. Currently, there are several studies available in which apomorphine, either as intermittent subcutaneous rescue injections or as continuous infusion, has been shown to be efficient to reverse 'off states', decreasing dyskinesias and improving motor indicators [1,9,13,14].

CASE REPORT

Mrs M is a 69-year-old female, divorced, with one daughter. She had worked as a secretary but had to retire due to PD, which was diagnosed at the age of 52 years. Six months before admission, she presented severe muscle stiffness upon waking, rest tremor of the upper limbs, a choking sensation and severe distress, which she attributed to her inability to stand, walk and even feed herself. Due to the progressive loss of efficacy of different anti-Parkinsonian drugs, apomorphine therapy, 5 mg subcutaneously (s.c.) (one ampoule) was started. With such indications, the patient experienced a fast improvement of off states. Upon waking a drug ampoule was administered, and the patient perceived a fast decrease of muscular stiffness and tremor and a dramatic decrease of the choking sensation, thus being able to stand without problems. Mrs M experienced no nausea or vomiting with the use of the drug. She also indicated that she experienced a notable improvement of mood, disappearance of distress, a sensation of general well-being, pleasure and agility. The patient managed to maintain herself in good condition during the day with the above-mentioned dose combined with oral anti-Parkinson medication. Two weeks after initiating the therapy, she perceived that the intensity and duration of the drug effect decreased progressively and therefore, with no intervening medical indication, the patient increased the morning dose to 2 ampoules. The situation recurred and upon completing 1 month of treatment, the patient was administering herself 2 ampoules every 12 hours.

It is remarkable that, after all this time, the patient said she did not use apomorphine because of the improvement in motility, but rather because of the effects of the drug on mood, stating that: (she) 'felt more energy and vitality, was able to open the windows, to watch TV, and then go out shopping'.

Subsequently, the periods of time during which the patient experienced the effects of apomorphine injection decreased progressively. Following the latter, she reported increasing anxiety, sweating of the hands, palpitations and breathing difficulty. All these symptoms disappeared minutes after the administration of the drug dose. The described symptomatology led the patient to increase the frequency and quantity of drug to one ampoule every hour at 6 months of therapy, thus attaining a daily dose of 15 ampoules (75 mg). When the patient left home she always carried three to four ampoules, and stated that: (she) 'was afraid of feeling bad and not being able to administer a dose rapidly'. Initially the injection sites were exclusively on the arms, but with time the abdomen and both thighs were also used as injection sites.

Because in Chile the drug is distributed exclusively in health-care centres, the patient provided distorted information to various physicians in order to obtain the necessary number of prescriptions to maintain a weekly stockpile of 100 doses. In view of the high expenses derived from the purchase of apomorphine the patient dedicated a significant part of her budget to such purpose, thus restricting some other expenses, and even selling some valuable belongings. Years earlier, she had developed a Lorazepam dependence, using doses three times higher than prescribed.

Mrs M was admitted to the Clinical Hospital of the University of Chile in May 2002 for acute respiratory disease. Upon admission the patient had lost weight, her blood pressure was within the normal range and she showed profuse sweating. Marked muscular stiffness and bradykinesia, rest tremor of both hands and expressionlessness were noteworthy. She also showed multiple cutaneous lesions secondary to the injection of apomorphine, located on thighs and abdomen, some of them with haemorrhage and erythema around the puncture site, and clinical signs of infection.

On physical examination upon admission the patient was awake, alert, orientated to time and place and collaborated with the examination; however, questioning was difficult due to the hypotonia and the loss of almost all her teeth, revealing evident personal neglect. She showed no impairment of thought processes and content, nor alterations of perception. She had had marked mood disturbance during approximately the last 2 months, with anxiety during most of the day, with a slight decrease during the few minutes following the administration of apomorphine. The patient had initial insomnia responding to the use of Lorazepam. Her cognitive performance was within the adequate range for her age.

DISCUSSION

The clinical case is presented of a patient who received a prescription of apomorphine for the treatment of PD, and who developed dependence on the substance according to the criteria of the *Diagnostic and Statistic Manual of Mental Disorders* , fourth edition (DSM-IV-TR) [15].

Addiction drugs generate a rewarding effect and a loss of control upon consumption. These drugs consist of molecules of various natures, and it is hypothesized that the increase in dopaminergic activity at the mesolimbic–cortical level constitutes a final common pathway accounting for its pharmacological effects [16]. Anti-Parkinsonian drugs provoke this effect and are therefore likely to cause addiction.

Patients with PD suffer from psychiatric symptoms that develop not only as a reaction to the chronic disease, but also because of the dysfunction of the dopaminergic system that also involves the mesolimbic–cortical level; among such psychiatric symptoms are depressive mood, hopelessness, apathy and anhedonia. Depression manifests in up to 50% of cases [11,17–20]. On the other hand, anti-Parkinsonian drugs also generate psychiatric symptoms that can be experienced by the patient as unpleasant (hallucinations, confusion, depression) but also as pleasant sensations ('alerting', 'awakening', 'activating', hypomania and hypersexuality) [1,21]. It is interesting to note that, in spite of the sensation of well-being that might be induced by these drugs, and the use of high doses for prolonged periods of time, addiction to them is very rare in patients with PD.

In fact, there are few cases of dependence on apomorphine described in the literature. Courty *et al*. [1] identified such disorder in four patients among a population of 50 apomorphine users. Giovannoni *et al*. [22] reported 15 cases from a population of 364 treated patients. Pezzella *et al*. [23] diagnosed the disease in seven patients through a standardized interview applied to a population of 202 subjects. These patients used higher doses than prescribed originally and continued their use in spite of the manifestation of severe psychic and physical symptoms. Among the psychic symptoms were mood fluctuations, hypersexuality, delusion, compulsions, psychomotor agitation and impulsiveness. Physical symptoms included motor disorders, particularly dyskinesia, which although severe were well tolerated. Drug use was not withdrawn in spite of the impairment of labour and social performances. Cases of dependence on other anti-Parkinsonian drugs have also been reported with a low prevalence [24]. In our population, there have been no other cases described but this may be an underestimation, because diagnostic instruments [22,24] are not used routinely.

There are no criteria enabling us to predict with certainty which users are more likely to develop dependence to a certain substance. Currently, the prescription of apomorphine has been extended to patients with erectile dysfunction. Thus, the drug will begin to be used by a population with different personality traits and in a pleasant context, such as intercourse, which may increase the prevalence of addiction cases or of severe psychiatric symptoms.

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