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CASE REPORT

Psychostimulants and delirium in patients receiving palliative care

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ABSTRACT

The use of psychostimulants to relieve opioid-induced drowsiness and symptoms of depression in medically ill patients has become increasingly established in North America. The role of psychostimulants in the care of patients receiving palliative care is beginning to be debated in the United Kingdom both in the hospice and hospital setting. Delirium has been well defined and reported as a significant problem in populations of patients receiving palliative care. Two case histories are presented to illustrate the potential benefit of psychostimulants in hypoactive delirium.

KEYWORDS: Psychostimulants, Methylphenidate, Hypoactive delirium, Palliative care

INTRODUCTION

Delirium is a common occurrence for patients receiving palliative care (Breitbart et al., 1995). Estimates of prevalence are clearly dependent on the methods/tools employed to make a diagnosis. Unpublished data from a recent prospective audit of 100 consecutive admissions to St. Columba's hospice in Edinburgh demonstrated a prevalence of delirium of 29%, as defined by the Confusion Assessment Method (Inouye et al., 1990). A point prevalence audit of eight Specialist Palliative Care Units in the East of Scotland involving 120 patients also demonstrated that 29% of inpatients could be defined as having delirium. The majority of patients in each audit were found to have the hypoactive form of delirium. Delirium may be divided into hyperactive and hypoactive subtypes based on psychomotor behavior and level of arousal, principally speed of speech and movement (Lipowski, 1980). The different subtypes have been related to different aetiologies and associated with different clinical pictures, hypoactive delirium being associated with "sicker" patients in one study of admissions to a geriatric unit (O'Keefe & Lavan, 1999) Hypoactive delirium may often be undetected, unless regular formal assessments are made, but can seriously impair quality of life. Relationships with family, staff, and the environment may be compromised through confusion, delusions, or an altered conscious level. This impairs quality of care and symptom control as well as the family's lasting impression of their loved one.

The "standard" treatment for delirium of all subtypes has been the use of psychotropic agents such as the butyrophenones, phenothiazines, or even the benzodiazepines. The use of psychostimulants has been proposed but reported on only one occasion to our knowledge (Stiefel & Bruera, 1991; Morita et al., 2000). The use of psychostimulants to relieve opioid-induced sedation and symptoms of depression in medically ill patients has become increasingly established in North America (Bruera et al., 1989, 1992; Wallace et al., 1995; Pereira & Bruera, 2001). Reported experience with the medical use of psychostimulants in other parts of the world, including the United Kingdom, has been limited.

The psychostimulant methylphenidate had been prescribed for over 50 patients in St. Columba's hospice between 1998 and 2001, principally for

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opioid-induced sedation and depression. The experience with two patients with hypoactive delirium is reported here.

CASE 1

A 65-year-old lady with inoperable gastric adenocarcinoma was admitted to the hospice with nausea, fatigue, and epigastric pain. A CT scan of the abdomen had demonstrated metastatic disease in the spleen, left kidney, and pancreas. She was also a non-insulin-dependent diabetic and was known to have a superficial transitional cell carcinoma of the bladder. Medication on admission comprised transdermal fentanyl (25 μg/h) cyclizine and insulin.

An increase in the dose of fentanyl (to 50 μg/h) invoked symptoms of opioid toxicity that resolved with good pain control after a switch to regular oral morphine.

On day 12 she became less well and was noticeably anxious. On day 13 a diagnosis of delirium was made with the criteria of the CAM fulfilled and with features of a mixed-type (hypoactive/hyperactive) delirium. Investigations revealed normal hematological and biochemical parameters on blood testing and no growth on urine cultures. Neurological examination detected no abnormal focal signs. Although there were no other features suggestive of opioid toxicity the dose of morphine was reduced. Her pain increased accompanied by worsening nausea and vomiting. Pain was relieved by an increase in the dose of morphine and nausea controlled by a continuous subcutaneous infusion of levomepromazine (5 mg/24 h). However, she became increasingly withdrawn and confused, making little or no eye contact and apparently experiencing increasingly frequent hallucinations. Levomepromazine was discontinued with no recurrence of nausea but persistence of delirium. The features of the delirium were more in keeping with a state of hypoactive delirium.

She was commenced on methylphenidate 2.5 mg twice daily. Within $3\frac{1}{2}$ h of the first dose she had become quite animated, eaten a meal, and was beating other patients at cards! After 24 h she was spontaneous in conversation, with no sign of delusions and awake throughout the day. She admitted to having a "memory blank" for the previous week.

The Ritalin dose was increased to 5 mg twice daily but after 5 days of feeling well she refused further methylphenidate because she felt the tablets were making her nauseous. Within 48 h she became withdrawn once again with evidence of hallucinations and verbal aggression. There was no response to haloperidol (5 mg/24 h continuous infusion). After 5 days without methylphenidate her family finally persuaded her to restart treatment at a dose of 5 mg twice daily. She rapidly became calmer and the delirium cleared over the next 48 h. With an increase in dose to 10 mg with breakfast and 5 mg at lunchtime she continued to improve to the point at which she could be discharged into the care of her family at home. She continued on methylphenidate and died peacefully at home, 12 days after discharge.

CASE 2

A 51-year-old lady with metastatic renal carcinoma was admitted to the hospice with symptoms of poor mobility secondary to lower limb lymphoedema, low mood state, and controlled mixed nocioceptive/neuropathic pain. She had received treatment for depression during the year prior to admission but had discontinued antidepressants several months earlier due to unacceptable sedation as a side effect.

She was known to have chronic mild hypercalcemia and was receiving treatment for hypertension and anticoagulants after a deep venous thrombosis of the lymphoedematous leg.

After a period of assessment and discussion with the patient an antidepressant, paroxetine, was commenced on day 7 of her admission. After she became increasingly withdrawn a diagnosis of hypoactive delirium was made with the criteria of the CAM fulfilled. Investigations revealed a mild normocytic anemia (HB 97 G/L) and a raised calcium (3.05 mmol/l corrected for albumin levels) with no clinical evidence of infection or growth on culture of a urine specimen. An intravenous infusion of pamidronate was complicated by an episode of extreme paranoia and hallucinations. By day 19 she was totally withdrawn, offering no verbal communication, and observation of her behavior suggested she was suffering intermittent hallucinations. Methylphenidate was commenced with an initial trial dose of 2.5 mg and thereafter 5 mg twice daily. After 48 h she was brighter, maintaining eye contact and initiating conversation. The dose of methylphenidate was increased to 10 mg with breakfast and 5 mg with lunch. From day 22 to 30 the delirium cleared completely with accompanying brightening of mood and, perhaps most importantly, she was able to restore family relationships that had suffered during her relatively long history of depression and particularly during the delirium. She requested increasing input from the physiotherapists and managed several trips out with her husband.

On day 80 she developed nausea secondary to a urinary tract infection and was unable to take methylphenidate for 24 h and developed further

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paranoia and hallucinations that resolved after restarting treatment.

The dose of methylphenidate was gradually increased during her stay, titrating against conscious level and mood state, to a dose of 15 mg twice daily. She died from septicemia on day 111.

DISCUSSION

It has been estimated that approximately 50% of cases of delirium occurring in patients receiving specialist palliative care are potentially reversible (Gagnon et al., 2000; Lawlor et al., 2000). Identifying and directing treatment at such causes, if appropriate in the individual situation, remains the optimum management. However, the options for the treatment of "nonreversible" delirium lie principally with neuroleptic agents and particularly those with sedating activity in hyperactive and some incidences of mixed-type delirium. Newer antipsychotics such as risperidone and olanzapine have been reported to be of use in delirium (Passik & Cooper, 1999) and because they tend to be less sedating they may be more useful in the hypoactive form. The potential role of psychostimulants in the management of hypoactive delirium has been recognized but, to our knowledge, only one case history has been published (Morita et al., 2000).

In the United Kingdom there appears to have been a reluctance among physicians working in palliative care to consider the use of psychostimulants in their practice. This may be related to an understandable avoidance, by general psychiatrists, of this class of agents for the treatment of depression. Our experience over a 3-year period has reflected reports in the North American literature of a 45% to 70% response rate for the symptoms of depression (Emptage & Semla, 1996; Masand & Tesar, 1996; Olin & Masand, 1996; Macleod, 1998). We have also employed methylphenidate as an adjunct in opioid-induced sedation, for the treatement of apathy associated with primary brain tumors and even in cancer-related hyperactivity states. Side effects have been few in number and rapidly reversible.

One of the attractions of psychostimulants in patients receiving palliative care is their speed of action, with depressive symptoms often being relieved within 48–72 h (Emptage & Semla, 1996). In the two cases presented here the patients, both clearly suffering significant effects of delirium, were afforded relief within 48 h and in the first case within 4 h of the first dose. Interestingly, both patients discontinued medication for different reasons 5 and 60 days after commencing treatment. In each case symptoms of delirium recurred quickly but responded to reintroduction of methylphenidate therapy.

It has been postulated that the hypoactive form may represent an early stage of delirium that could potentially progress to an agitated state. The evidence for such an evolution is, however, lacking. We were cautious with our dosing schedule for fear of precipitating an agitated delirium but observed no evidence to suggest this.

CONCLUSION

The realization of the high prevalence of delirium in patients admitted to specialist palliative care services has stimulated discussion of the potentially reversible etiologies, frequently drug toxicity, and their investigation and management. However, the management of symptoms of unknown or irreversible etiology has changed little and is largely dependent on the use of antipsychotic agents. The response noted in the two patients reported here encourages further study of the potential of psychostimulants to relieve hypoactive delirium. Furthermore, the potential role of psychostimulants in several aspects of the care of patients with short prognoses warrants further examination and discussion, particularly in the United Kingdom.

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