Pizotifen in deafferentation pain

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Summary: Deafferentation pain is known usually to be resistant to both narcotic and non-narcotic analgesics. Four cases of this condition are reported here in which benefit was obtained with pizotifen, a 5-hydroxytryptamine antagonist. Further controlled clinical studies are required to verify this observation.

Introduction

Deafferentation pain is defined as pain that occurs in an area of diminished or abnormal sensation.¹ The anatomical site of origin of such pain can be either peripheral, such as in post-herpetic neuralgia, or central, as observed in patients with pain due to thalamic syndrome following a stroke. The mechanism of deafferentation pain is poorly understood and the patients usually do not derive benefits from narcotic or non-narcotic analgesics.² Tricyclic antidepressants and anticonvulsants are often prescribed in this condition for pain originating both peripherally and centrally, sometimes with limited benefit. Transcutaneous nerve stimulation or nerve block may relieve pain in patients with pain originating peripherally,³ but such therapy is usually available in a specialized pain clinic. The opioid antagonist, naloxone, has been reported to be effective in alleviating thalamic pain.⁴ This drug is known to have adverse effects on the cardiovascular system, such as cardiac arrhythmia,⁵ and is therefore potentially hazardous for the elderly patients. Although a recent study indicates that naloxone is probably safe to use if the dose is increased step by step over several weeks,⁴ this drug needs to be administered intravenously.

I report here on the beneficial effect of pizotifen,⁶ a 5-hydroxytryptamine (5-HT) antagonist, in 4 elderly patients with deafferentation pain.

Case reports

Case 1

An 83 year old female patient with previous history of transient ischaemic attacks was admitted following an

acute stroke and left flaccid hemiplegia. She made no significant neurological progress and was eventually transferred to a continuing care ward. Four to five weeks after her stroke, she developed persistent burning excruciating pain over the hemiplegic upper limb, left side of the neck and face, associated with hyperaesthesia and occasional involuntary movements of left arm. Her pain was worse following touch or slight change of posture, for example, during routine nursing care. Conventional analgesics (such as morphine, non-steroidal anti-inflammatory drugs, local analgesic spray, tranquillizers and antidepressants) failed to produce any relief. She developed visual hallucinations and became confused following 2 weeks' treatment with 75 mg imipramine daily.

It was decided to try pizotifen which was initially prescribed at a dose of 1.5 mg as a bedtime medication. Within one week's treatment, she was reported to be sleeping better at nights and shouting less from pain during washing/dressing in the mornings. In view of her previous intolerance to imipramine, after 2 months' treatment, the dose of pizotifen was cautiously increased to 1.5 mg twice daily, with further improvement of her symptoms. Intensity of her pain appeared to be increased after 4 months' medication. The dose was increased to 1.5 mg thrice daily, again with symptomatic improvement.

Although she never became completely free from pain, with this regime she was able to tolerate physiotherapy and the usual nursing procedures better than before. She also appeared to be more cheerful and sociable. No obvious side effects were observed.

Her condition remained stable when this regime was continued for another 2.5 months, but after that the intensity of pain again increased. As pizotifen is not a recognized therapy for thalamic syndrome, her analgesic drug regime was altered without much success by another clinician, after this author's departure from that hospital.

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Case 2

A 77 year old hypertensive female patient was admitted following a stroke. She had dense right hemiplegia and predominant expressive dysphasia, and also had some sensory aphasia. She developed persistent pain on the hemiplegic side approximately 2–3 weeks after the acute episode. Actual description of pain and associated symptoms were difficult to assess because of severe aphasia. Her symptoms were considered to be worse in the morning, as she looked as if she was in pain and was uncooperative with the staff involved in rehabilitation.

Initially, in view of lack of motivation, unhappy appearance and disturbed sleep, the possibility of depression was considered, but she showed poor response to an antidepressant drug therapy for 4 weeks. She appeared to be persistently in pain and was reluctant to change her posture. Analgesics such as codeine and paracetamol were of no benefit. The possibility of thalamic syndrome was considered and pizotifen (0.5 mg twice daily) was introduced. The dose was slowly increased within the next 2 weeks to 3 mg daily, with some improvement. She appeared to be comfortable, looked happier than before, and was more cooperative with the nursing staff, but made no significant neurological progress. Her condition remained reasonably stable on pizotifen (3 mg/day) for a period of 2.5 months. She was discharged home with various nursing and social supports. Lofepamine 70 mg was added before discharge as the possibility of an underlying depression was difficult to exclude.

It was also difficult to comment on whether slight improvement in her mood observed after discharge from hospital was due to change of environment or related to lofepramine therapy. However, with this regime she remained well and it was possible to withdraw medication (both pizotifen and lofepramine) without any setback after 4 months' treatment at the out-patient clinic.

Case 3

A 76 year old man was admitted, having fallen off his motorcycle. He had sustained right shoulder dislocation which was successfully manipulated at the Casualty Department, but he required hospital admission for right upper limb monoplegia. Nerve conduction studies confirmed brachial plexus injury. Not only had he no significant functional ability in the right upper limb, but he was also in agony due to severe pain. He derived no relief even from intramuscular morphine, and this drug made him severely constipated. Pizotifen 1.5 mg thrice daily was started with dramatic improvement in pain within 48 hours. It was possible to discharge him home 3 weeks after admis-

sion. He made slow but steady neurological progress and physiotherapy continued at a day hospital. Since he was never completely free from pain, after 2.5 months therapy, pizotifen was replaced by soluble aspirin. He suffered from recurrence of increase in severity of pain. Pizotifen (4.5 mg daily) was reintroduced with considerable relief of pain and improvement in mental attitude. He has been on this regime now for 6.5 months. No obvious side effects have been observed.

Case 4

A domiciliary consultation was requested for a 72 year old female patient for intractable pain and hyperaesthesia over the left upper face for 4–5 weeks. This she developed following an attack of herpes zoster, involving the ophthalmic branch of the left fifth nerve.

She had no significant relief of pain from various analgesics and developed maculopapular rash following pentazocine. At the time of referral she was taking a cocktail of amitriptyline, meptazinol and chlorpheniramine, in addition to temazepam at night. These drugs made her extremely dizzy and she was unable to stand or walk, and became almost housebound. She was depressed and had no confidence even to attend an out-patient clinic. Prior to the onset of her illness she was independent in all aspects. Her current medication was stopped and her general practitioner was advised to prescribe carbamazepine starting from a dose of 100 mg/day, increasing to 400–600 mg/day, according to her tolerance and response. Although carbamazepine (600 mg/day) partially controlled her pain, she remained dizzy. The dose was therefore reduced to 300 mg/day, which was inadequate to control her pain. Combination of amitriptyline and carbamazepine were without any benefit and increased the side effects. Since carbamazepine at higher dose level produced some symptomatic improvement, it was therefore decided to add pizotifen 1.5 mg thrice daily to 300 mg of carbamazepine. She improved within a week and became asymptomatic within 4 weeks. She was followed up at the clinic. Carbamazepine was discontinued after 3 months and pizotifen after another 7 months' therapy. She remained well without any recurrence.

Discussion

Pizotifen is not a conventional analgesic and is usually recommended for patients with migraine. It was therefore prescribed as a last resort to these four patients who derived no benefit from conventional narcotic and non-narcotic drugs. Two other patients with similar history of drug-resistant post-herpetic

neuralgia are currently receiving this medication but require further observations. Clearly, in order to establish pizotifen's benefit in deafferentation pain, a controlled clinical trial is required.

Thalamic syndrome is typically associated with paresis, hyperaesthesia and involuntary movements.⁷ It is usually due to a vascular lesion. The spinothalamic tract containing afferent pain fibres from the opposite side of the body terminates to the dorsoventral thalamic region. The thalamus is supplied by the thalamogeniculate artery, a branch of the posterior cerebral artery. Vascular lesions in and around this region of the thalamus may produce mild to severe continuous burning pain affecting the opposite side of the face and upper limbs. Both centrally and peripherally acting analgesics have little or no effect.

The first patient had all the classical symptoms of thalamic syndrome, namely severe burning pain, hyperaesthesia and involuntary movements (muscle jerks) of the paralysed limb, neck and face. Typically, she also showed no response to opioid analgesics, non-steroidal anti-inflammatory drugs and tricyclic antidepressants. However, her pain became less severe and hyperaesthesia disappeared within 2 weeks' therapy with pizotifen, a potent 5-HT antagonist. She derived benefit from this therapy for approximately 8.5 months.

The diagnosis of deafferentation pain was not proven in the second patient as she did not present with all the classical features of thalamic syndrome. However, in view of persistent pain on the hemiplegic side and lack of response from conventional analgesics, the diagnosis of thalamic syndrome was probable. She has benefited from pizotifen.

The third patient suffered from excruciating pain due to brachial plexus injury. It was impossible for him to participate in any effective physiotherapy until his pain became controlled following pizotifen therapy. He had no relief of pain from any narcotic or non-narcotic analgesics.

It is, however, unclear whether pizotifen alone would have completely controlled the pain in the fourth patient, but certainly carbamazepine (300 mg) alone was inadequate to control her pain.

Pizotifen is structurally and chemically related to

cyproheptadine and tricyclic antidepressants, and they share many common pharmacological properties. It has weak antihistaminic, anticholinergic, anti-bradykinin effects, as well as mild central sedative and anti-5-HT activities.⁶ Because of its strong anti-5-HT effect, this drug was initially recommended for migraine prophylaxis and indeed is effective in this condition.⁸

The pain and hyperaesthesia in deafferentation pain is known to be resistant even to narcotic analgesics and only limited relief has been observed following psychotropic drug therapy.⁹ The underlying biochemical mechanism of the central pain in thalamic syndrome is unclear, but thalamic nuclei play a significant role in the perception of pain. It is difficult to comment on the mode of pizotifen's analgesic effect in these patients. It could be related to its central anti-5-HT activity¹⁰ or a combination of its antagonistic effects on 5-HT, bradykinin and histamine. Alternatively, it may be due to this drug's specific pharmacological effect on the thalamic nuclei involved with the perception of pain. Similarly, pizotifen's influence at the peripheral neuronal site may be responsible for its analgesic effect in patients with brachial plexus injury and post-herpetic neuralgia.

Whatever may be the mode of action, it is interesting to note that the two patients with thalamic syndrome showed some evidence of increasing tolerance to pizotifen's analgesic effect. Since neither the plasma drug level nor any other pharmacological effect, such as its antagonizing effect on the platelet 5-HT uptake activity¹¹ was monitored, it is difficult to comment whether this was a pharmacokinetic or pharmacodynamic tolerance. Similar tolerance has recently been reported in patients with thalamic syndrome using intravenous naloxone therapy.⁴

Thalamic syndrome is a relatively uncommon complication of stroke and it is therefore difficult to conduct a controlled clinical trial involving patients from only one centre. In a recent report on the effect of naloxone in this condition, the authors quoted only 4 patients.⁴ Obviously, further controlled clinical studies are required to verify pizotifen's beneficial effect in deafferentation pain, a condition for which no oral therapy with proven benefit at present exists.

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