Failure of oral administration of single rising doses of bromocriptine to produce acute antiparkinsonian effects

The optimal dose of bromocriptine in the treatment of Parkinson's disease has remained controversial. While most investigators have used daily doses of about 40 mg several reports have since claimed success with oral dose regimes of less than 20 mg. For another antiparkinsonian research group has recently confirmed the puzzling finding that with a fast introductory regime higher doses of bromocriptine are needed than with a slower titration schedule to produce similar degrees of clinical improvement in de novo patients with Parkinson's disease.

We have studied the acute anti-Parkinsonian effect of single rising doses of bromocriptine in an open experimental study in seven patients admitted to hospital with fluctuating Parkinson's disease (three females, four males; mean age 57.7 (41-69) years; mean duration of disease 10.9 (8-18) years; mean daily dose of levodopa 1014 (500-1400) mg plus peripheral decarboxylase inhibitor (PDI). All but two had never been treated with bromocriptine.

In one patient concomitant bromocriptine (30 mg/d) was discontinued one day before the study while a second had received bromocriptine (40 mg/d) as an adjunct to levodopa over a 14 months period until one year previously. All showed a predictable wearing-off pattern in response to oral levodopa and during the study period the first daily dose of 200 mg of levodopa was taken at 8 am after a minimum drug free period of eight hours and one hour after a standard hospital breakfast. On alternate days this morning dose was replaced by single rising doses of bromocriptine following the dose schedule depicted in the figure, and oral domperidone (20 mg) was added if nausea and/or hypotension had occurred at the previous dose level. Efficacy assessments of levodopa or bromocriptine test doses were performed using the motor score (section 111) of the Unified Parkinson's disease Rating Scale (UPDRS) beginning 30 minutes before dosing with half-hourly ratings until acute drug effects had worn off or up to a maximum of four hours.

The results are shown in the figure. While 200 mg of oral levodopa led to a mean 50% reduction of the UPDRS motor score, usually within 30 to 45 minutes, there were no acute anti-Parkinsonian effects following any of the single oral doses of bromocriptine employed in this study. The only exception was the patient to whom bromocriptine had been given as a chronic treatment for up to one year before the study. The patient experienced an acute improvement of a coarse resting tremor and moderate peak dose chorea 120 minutes following a single 12.5 mg dose of bromocriptine and lasting for 115 minutes.

Using a similar single rising dose substitution model, acute anti-Parkinsonian effects have been demonstrated for the non-ergot dopamine agonist PHNO and also for the ergot derivative CQA 209-291, which is structurally related to bromocriptine. The lack of effect of bromocriptine seen in this majority of patients in this study may indicate that the doses employed were subthreshold for anti-Parkinsonian efficacy.

In this, however, remarkable that several clinical studies have demonstrated the effectiveness of bromocriptine monotherapy with chronic administration at doses of between 12.5 and 25 mg/d, that is, daily doses in the range of the upper dose levels employed in this single dose trial. A possible explanation for this apparent discrepancy might be that bromocriptine is capable of inducing delayed effects with chronic treatment, possibly via modulatory effects on central dopamine receptors. Such delayed effects have been noted in one patient in this study (case 7, who received combined treatment with bromocriptine until 24 months before the start of the study). He complained of increased severity of levodopa-induced dyskinesias on the days following bromocriptine challenges of 10, 15, 20 and 25 mg and experienced enhanced dyskinesias for another 12 days after the patient's last exposure to bromocriptine in the study when receiving his pre-study daily levodopa regime. But even this patient failed to show acute anti-Parkinsonian effects from single bromocriptine doses as high as 25 mg.

Other reasons for the observed failure of single bromocriptine doses to induce acute effects could lie in the pharmacokinetics of the drug. Thus the extensive first pass effect of bromocriptine means that only about 8% of an oral dose is available to the systemic circulation, and its high lipophilicity could further reduce the free concentration of bromocriptine in the extracellular space. Only after saturation of the lipid compartment following repeated dosing might active biological concentrations be attained within the soluble compartment. Accordingly bromocriptine exerts acute effects in the Urgeseldt rat model only following high oral doses of above 9 mg/kg, with repeated dosing response latencies of a given dose decrease with simultaneous augmentation of efficacy (R Markein, personal communication). Whether such pharmacokinetic properties of bromocriptine or pharmacodynamic receptor changes in the CNS form the pathophysiological basis for the different dose requirements with "fast" versus "slow" introductive regimes of bromocriptine remains unclear.

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Neurovascular paralysis in *vipera aspis* envenomation: pathogenetic mechanisms

Vipera aspis is the most common agent of snake envenomation in Italy and Western Europe.¹ Its bite affects coagulation and causes a shock syndrome with severe cardiovascular failure.

Neurotoxicity, clinically characterised by external ophthalmoplegia, is uncommon (two cases out of 205 patients bitten by vipera aspis² and difficult to explain because overt neurotoxic substances have not been detected in vipera aspis venom.³ Our case suggests that the venom is neurotoxic.

A 20 year old herpetologist was bitten by a vipera aspis at the distal extremity of the index finger of the left hand. When he was admitted to the intensive care unit (30 minutes later) he was unconscious (Glasgow Coma Scale 7), pale, tachycardic (170 beats/min), tachypnoeic (50 breaths/min), with unattainable peripheral pulses and blood pressure. There was a metabolic acidosis (pH 7.26) and disseminated intravascular coagulation. The left hand was oedematous. Centrifugal venous compression was applied on the left arm. Shock, metabolic failure and disseminated intravascular coagulation syndrome were treated with fresh frozen plasma, albumin, dextran, dopamine and adrenaline, NaHCO₃, and heparin iv infusions. Cardiovascular dysfunction, metabolic balance and consciousness returned to normal within the following three hours.

Neurological examination revealed facial diplegia, pharyngolaryngeal paresis, bilateral ptosis and external ophthalmoplegia, with complete ocular immobility.

The strength of the trunk, limb and respiratory muscles, deep tendon reflexes, plantar and abdominal reflexes, and sensory functions were normal. Symptoms were not modified by iv administration of 10 mg of edrophonium.

Neurophysiological studies of the facial nerves showed a low amplitude muscle action potential (0-9 mV-nv > 3 mv), with normal latency. Repetitive stimulation at low and high frequencies, tetanisation and stimulation with paired stimuli at stimulus intervals of less than 10 ms gave normal responses without muscle action potential defects. Blink reflex showed responses with normal latencies. Similar neurophysiological studies performed on other nerves (median, common peroneal and sural) were normal.

Five days from the onset of the disease the patient improved considerably and after 10 days, neurological examination and neurophysiological tests were normal. He was discharged after 10 days.

The lack of clinical involvement of motor, sensory and cerebellar pathways within the brainstem, together with the normal latency of blink reflex responses in this case, do not suggest an involvement of the brainstem possibly caused by oedema and/or disseminated intravascular coagulation.¹

The biochemical signs and the quick improvement of the clinical picture also lead us to exclude a neuropathic lesion and to hypothesis that a transient functional block of activation of a number of muscle fibres.³ This could be related to three possible mechanisms in particular: 1) a neuromuscular block; 2) a direct action on muscle fibres; 3) a block of depolarisation in the terminal portions of a number of motor nerve fibres.

A neuromuscular block may be related either to a presynaptic site of action of the venom, such as beta-bungarotoxin⁴ and antacetycholinesterase, or to a postsynaptic site of action, like alpha-bungarotoxin.⁵ None of these mechanisms have been detected in vipera aspis and the electrophysiological findings of the reported case are neither consistent with a presynaptic nor a postsynaptic defect of neuromuscular transmission.

A direct myotoxic effect of animal toxin has been related to phospholipase A₂ activity, which has been detected in all viperside venoms so far investigated.⁶ Moreover some authors suggest that some toxins, like cardiotoxin of *Dendroaspis jasminoides*, can induce muscle fibre necrosis with a structural damage of the subneural apparatus. Nevertheless myonecrotic action is shown to be confined to the site of envenomation.

The action of the toxin on the terminal portions of motor fibres could transiently block the conduction of a number of motor fibres by preventing their depolarisation. A lesion in this location is consistent with normal tests of neuromuscular transmission and with the rapid recovery of the amplitude of the muscle action potential as observed in our case. This mechanism has been hypothesised also in the neuromuscular paralysis induced by tick envenomation⁷ and other biotoxins such as tetradoxin.⁸

Why the neurotoxic action of the vipera aspis venom appears to remain strictly localised in cephalic muscles remains unexplained. Peculiar physiological characteristics of cephalic motor units might be an explanation.

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**MATTERS ARISING**

Comparison of two methods for measuring thermal thresholds

In their recent paper,¹ Drs Levy, Abraham and Reid compare two techniques for measuring thermal thresholds in diabetic neuropathy. On the basis of their results they conclude that there is little to choose between the method of limits and the median procedure of psychophysical analysis in the determination of thermal thresholds. We believe that their results and the conclusions based on them are incorrect and a consequence of their experimental design.

When comparing two techniques attempting to measure the same parameter it is imperative that all variables are comparable and strictly controlled since they influence the accuracy of the final results.²³ By their own admission the authors have ignored a number of these variables as follows:

1) The reference skin temperatures for the Sensortek and Marstock methods are different (30°C and 32°C respectively).²³ Neither is in the optimum range 34–35°C at which the variability of the thermal threshold measurements is minimal.⁴²

2) The rate of temperature change in the Marstock technique is fixed. By comparison the rate of temperature change in the Sensor-tek technique, as described by the authors, varies not only during the application of a single stimulus but also during the application of two or more stimuli. This is a source of variability.⁴²⁵

3) In the Sensortek technique two stimuli of different modalities are applied to the skin more or less simultaneously; there is a tactile stimulus (when the thermode is applied to the skin) in addition to the specific thermal stimulus. It is particularly important that a pure thermal stimulus is applied without tactile cues as the latter has been shown to modify thermal sensation.²⁹

4) The duration of application of the thermode is poorly controlled in the Sensortek method. This will influence both the amount and the rate of energy transferred to the receptor zone.

5) The pressure of application of the thermode to the skin is uncontrolled in both techniques. The authors state that the importance of this factor “in clinical testing has not been systematically investigated”. This is incorrect.⁶

6) The lack of calibration of heat transfer at the thermode-skin interface in both techniques does not allow for the variability of the thermal properties of the skin.⁷