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ORIGINAL REPORT

Postpartum Intracranial Haemorrhage in Normotensive Users of Bromocriptine for Ablactation

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SUMMARY

The authors describe three cases of severe intracranial haemorrhage, associated with marked blood pressure elevation, which occurred between the 6th and 10th days postpartum in women taking bromocriptine for ablactation. All of these patients were young, normotensive and apparently healthy during the pregnancy. These incidents probably present the 10–12th reported cases of gross intracranial bleeding among users of bromocriptine in the puerperium. The results suggest that early diagnosis and prompt surgical intervention may improve the outcome for this rare but potentially catastrophic postpartum complication. © 1998 John Wiley & Sons, Ltd.

KEY WORDS — intracranial haemorrhage; craniotomy; vasospasm; ergot derivatives; bromocriptine

INTRODUCTION

Shortly after its introduction into obstetric practice in 1980, as an effective suppressor of milk production, bromocriptine mesylate (Parlodel, Sandoz Pharmaceutical Corp., East Hanover, New Jersey)[1] became a routine medication in the United States and elsewhere for women who did not wish to breast feed their infants. Perceived, initially, as an innocuous vasodilator, it was several years later that, as a result of untoward drug reactions reported to the Food and Drug Administration (FDA)[2] and case reports published in the medical literature,[3–12] the profession became aware of serious and even life-endangering potential side-effects associated with pharmacologic ablactation using this hydrogenated ergot derivative. As the documented cases increased in number and scope, it became possible to establish, eventually, six major, even if often overlapping, categories of bromocriptine-related severe side-effects:[11,12]

I. Cerebral oedema with convulsions resembling postpartum eclampsia.
II. Cerebral arterial occlusion.
III. Mental derangement occasionally presenting as pure puerperal psychosis.
IV. Intracranial haemorrhage.
V. Myocardial infarction.
VI. Circulatory failure caused by cardiac dysrhythmia.

With growing awareness of physicians and even the general public of the possibility of serious untoward sequelae deriving from milk suppression with bromocriptine, the number of cases identified at the bedside as likely drug-related side-effects, increased exponentially in recent years. In the same process, there has been a comparable increase in the number of medico-legal inquiries in the United States, in connection with serious postpartum complications among women who had used bromocriptine for ablactation.[11,12] It was in this process

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that, from various parts of the country, within a short period of time, three recent, as yet unpublished, cases came to our attention, each of them belonging to the fourth category (IV) of bromocriptine-associated severe vascular complications early in the puerperium. All of them involved massive intracranial haemorrhage; a manifestation which, to our knowledge, has only been reported nine times thus far.[9–14]

CASE REPORTS[a]

Case 1

The patient was a 29-year-old white married resident of one of the eastern states of the USA. She was a healthy mother of two children without significant personal medical history, apart from smoking half a pack of cigarettes per day. Her family history included hypertension, heart disease and stroke among first and second degree relatives.

The third pregnancy of the patient was uneventful and resulted, in December 1993, in the birth of a healthy, mature child at 37 weeks gestation. Postpartum, she received Parlodel (2.5 mg) to be taken twice a day for 15 days as well as oxycodone hydrochloride (5 mg) and acetaminophen (500 mg) tablets. She also received amoxicillin, a broad spectrum penicillin derivative, for an upper respiratory tract infection. The mother left the hospital 2 days postpartum.

The patient was re-hospitalized eight days after her childbirth on account of increasingly severe headache which, since the previous night, spread into her neck. She also experienced photophobia. On admission, the blood pressure was 192/100 mmHg, the pulse rate 104 per minute and the temperature 37.7°C. A neurological examination found nuchal rigidity. A spinal tap revealed gross blood staining of the cerebrospinal fluid. The CT scan showed evidence of subarachnoid haemorrhage. A four-vessel angiogram in the arterial and venous phases showed no abnormality. There were no aneurysms, arterial–venous malformations or evidence of arthritis demonstrated. At this point, the patient was transferred to a tertiary care centre.

Early next day, a repeat CT scan demonstrated extensive bihemispheric subarachnoid haemorrhage with blood contained in the convexity of the brain and the parasagittal sulci, predominantly in the frontal areas. There was also evidence of right frontal cortical haematoma at and above the lateral ventricles and a dense clot in the associated sulcus. The examination also showed local cerebral oedema around the haematoma. By this time, a neurological examination revealed decreased muscular strength in the left lower extremity. The patient appeared somnolescent and, somewhat later, lethargic.

For the hypertension, the mother was given nifedipine sublingual tablets. She received care in the intensive care unit. Serial CT scan examinations showed increasing intracerebral bleeding. Meanwhile, the mental status of the patient deteriorated. Therefore, 48 after her admission, she underwent a craniotomy. Large amounts of clots and fluid were removed during the operation. No evidence of aneurysm was detected either in the preoperative X-rays or in the course of the surgical procedure.

The postoperative recovery was satisfactory. Therefore, with the final diagnosis of resolved subarachnoid and intracerebral haemorrhage, the patient was discharged from the institution on the 5th day after her surgery. She was left with a speech defect and impaired mental function, particularly in the areas of computation and solving of problems. In addition, she had persistent sensory loss on the left side of her body.

Case 2

The patient was a 20-year-old Caucasian resident of one of the southern states of America. She was described in the records as a small and slender (45 kg) white woman whose background included two previous childbirths. The first pregnancy was complicated by mild pregnancy-induced hypertension. For milk suppression, the patient took Parlodel postpartum, apparently without untoward effect. The second gestation involved no hypertension. However, it resulted in the premature delivery of a non-viable child with polycystic kidneys.

The pregnancy under current consideration was uncomplicated. The baseline blood pressure level[15] of the mother was 101/66 mmHg and it remained at the same range until the birth of a mature and healthy child at term. For ablactation, the mother received Parlodel (2.5 mg) tablets to be taken twice a day for 15 days. Ten days after her discharge, early in January 1994, the woman required re-hospitalization as an emergency. Her history

[a] All cases were reported to the FDA with full names of the affected individuals, the exact times of the events and the names and locations of the hospitals involved.

revealed she had developed episodes of headache at home. These evolved, eventually, into what she described as the worst headache of her lifetime. At the time of her arrival, she was conscious. Apart from a mild systolic blood pressure elevation (140/80 mmHg), she had normal vital signs. However, within an hour, marked hypertension developed with peak systolic and diastolic levels of 163 mmHg and 102 mmHg respectively. She appeared pale and her skin was dry. During the evaluation, it was noted that her right pupil became dilated. Subsequently, a CT scan confirmed the suspicion of intracerebral haemorrhage. Without delay, a right front-temporal craniotomy was performed. The operation revealed a massive right frontal intracerebral haemorrhage which extended into the ventricles. The procedure involved removal of the intraparenchymal blood and right frontal ventriculostomy. No aneurysm or vascular malformation was noted during the operation.

With intensive use of life supporting measures, the patient improved postoperatively. However, despite vigorous medication, her hypertension continued for a further 2 weeks with peak levels of 190 mmHg systolic and 100 mmHg diastolic pressures. Eventually, she remained wheelchair-bound and required help with self care. Her mental deficits included the cognitive areas of function as well as impairment of memory, judgement and problem solving.

Case 3

Also a resident of one of the southern states, the patient was a 31-year-old white mother of two healthy children. Following another normal pregnancy and labour, in July 1994, she gave birth to a mature baby boy. Apart from a few mild blood pressure elevations at the time of the performance of an epidural anaesthesia (peak level of 140/90 mmHg), the parturient was normotensive throughout the perinatal period. As a routine postpartum order, she received Parlodel (2.5 mg) to be taken twice a day for 15 days along with ibuprofen (800 gm) tablets six-hourly during the first 24 hours after delivery. The mother left the hospital in good condition 48 h following her childbirth. However, 3 days later she returned to her physician complaining of severe headache with the pain spreading into her spine, vomiting and impaired hearing. A neurological consultation was sought. With the suspicion of cerebral aneurysm and pituitary apoplexy, the consultant referred her to a regional centre. By that time, she displayed aphasia, dysarthria and impaired sensorium. There was a difference between the sizes of her pupils and her left eye tended to deviate laterally. Her blood pressure increased from 170/100 mmHg shortly after the admission to 260/150 mmHg a few hours later. As the condition of the patient deteriorated, a CT scan was performed. It showed evidence of intracranial haemorrhage.

An emergency craniotomy revealed large blood clots in the subdural space over the left parietal cortex. The brain was found markedly swollen. The clots were removed and the dura was then closed.

Two days after the surgery a four-vessel arteriogram showed a normal left internal carotid artery and the absence of vascular malformation. A patent superior sagittal sinus was noted. A magnetic resonance angiography 5 days later still showed a patent superior sagittal sinus with no evidence of thrombus. There was a question about a small arterial–venous malformation in the right temporal lobe. There was evidence, however, of a left parietal–occipital intracerebral haematoma and of a left subdural haematoma.

Soon after the above outlined examinations, there appeared clinical evidence of re-accumulation of blood in the subdural space. On this account, 9 days after the first procedure, a second surgical exploration was performed. Following the removal of some 150 ml of dark blood, the dura was closed completely. The patient made a good postoperative recovery. She was left, however, with significant long range deficits, including difficulty with independent walking, diplopia and impaired mental abilities. The latter included problem solving as well as delayed response to commands and stimuli.

DISCUSSION

All diagnoses having been confirmed by neuroimaging and craniotomy, the above described three cases represent proven episodes of catastrophic intracranial haemorrhage in young and healthy mothers who took bromocriptine for ablactation at the time of the accident. The course of the events, in all of these cases, showed several features that have been described as characteristic of bromocriptine-related puerperal vascular accidents:[8,10,12]

1. All incidents occurred between the 6th and 10th days postpartum; well within the usual

time (4th to 15th days) for bromocriptine-related reactions.
2. All episodes were preceded by severe headache.
3. All of the cerebral bleeding episodes were accompanied by marked hypertension.

Interestingly, none of these patients had hypertension during the pregnancy. This fact adds to the evidence indicating that preexisting chronic or pregnancy-induced hypertension is not a*sine qua non* for bromocriptine-induced vasospasm.[10,11]

Although the first reported cases of bromocriptine-related severe side-effects involved cerebral accidents,[3] apart from an episode of pituitary gland haemorrhage,[16] our literary search found no case of severe intracranial bleeding prior to the publication of one such case by one of us in this journal in 1994.[9] Since that time, the relevant database has expanded.[10–14] It is of interest that, whereas preexisting hypertension predisposes for bromocriptine-related side-effects,[17,18] the patients described here had no previous blood pressure elevation. A matter of further interest is the fact that none of the mothers included in this report took any drug with significant vasoactive propensities, other than bromocriptine, prior to the occurrence of intracranial bleeding. It deserves attention, furthermore, that all of them were young women, free of significant predisposing factors for intracranial haemorrhage.

The old literature and recent studies coming from developing countries refer to a substantially increased incidence of cerebral accidents in the perinatal period.[19] In contrast, contemporary investigations conducted in economically developed communities found only minimal increase, not exceeding 50%, in the rates of stroke and intracranial haemorrhage during pregnancy and postpartum, as compared to women of similar ages in the general population.[19,20] About one-half of all such cases occurred in women suffering from chronic or pregnancy-induced hypertension, a complication which afflicts about 6% of all gravidas.[21] Taking these factors into account, it appears that the intrinsic risk of an intracranial haemorrhage for the normotensive patients described here, was about the same as for non-pregnant women of similar ages in the general population.

The risk of a cerebral accident has been estimated as about 1 out of 20,000 pregnancies.[20] Since none of the available statistics tried to identify patients treated with ergot derivatives among the victims of haemorrhagic cerebral accidents, the role of these pharmacologic agents in the aetiology of this complication cannot be quantitated. It deserves mention, however, that 'cerebral angiopathy' caused by ergot alkaloids has been considered a causative factor for the occurrence of stroke in the puerperium.[22] Such medication was given frequently postpartum in the distant past but only rarely in contemporary obstetric practice.[23] Along with the currently prevailing aggressive treatment of gestational hypertensive complications, this circumstance may account for the apparent reduction in the recent rates of cerebral accidents during pregnancy and in the puerperium.[19,20]

The events described here are consistent with the hypothesis that, as a delayed effect, bromocriptine has powerful vasoconstrictive propensities in some individuals so predisposed.[10,11,18] Apparently, the manifestations of this reaction may be diverse. However, they generally resemble those caused by other ergot derivatives, including the by now almost forgotten clinical picture of ergotism.[23] Whereas an untoward reaction to bromocriptine appears to be more prevalent among women with preexisting hypertension than in others,[17,81] the cases described here, as well as some others,[10,11] suggest that the predisposing factors may be various and insidious. The specific mechanism by which bromocriptine may cause intracranial haemorrhage in some postpartum women is not certain. A likely pathogenesis would be related to its ability to induce hypertension even in previously normotensive individuals. Hypertension is a major risk factor for other types of pregnancy-associated intracranial bleeding, including both intracerebral haemorrhages related to eclampsia or hypertension alone and subarachnoid haemorrhage from ruptured arteriovenous malformations or aneurysms.[24] A similar pathogenesis has been proposed for cocaine-associated intracerebral bleeds, whereby the use of cocaine induces blood pressure elevation which then leads to intracerebral haemorrhage.[25]

The fast increasing number of reports pertaining to bromocriptine-related vascular accidents prompted the FDA to reconsider its approval for the use of bromocriptine for milk suppression postpartum.[26] The manufacturers elected to co-operate, thus bromocriptine is no longer used in the United States for the prevention of breast engorgement postpartum.

Women in the puerperium may be especially prone to develop undesirable side-effects from bromocriptine. However, similar sequelae have

been reported in non-obstetric patients also.[27] It appears desirable, therefore, to administer bromocriptine, for all indications, with due consideration to its rare but potentially serious side-effects. In the cases included in this report, early diagnosis and surgical intervention were probably instrumental in mitigating the long range impact of intracranial bleeding. Awareness of a potential relationship between the administration of vasoactive drugs peripartum and ensuing vascular accidents may contribute both to the prevention and the early diagnosis and prompt treatment of similar episodes.

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