GRAND MAL SEIZURE AFTER EXTRADURAL MORPHINE ANALGESIA

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Major advances have been made in our understanding of the sites and mechanisms of action of opioid agents [1,2]. Recent reports indicate that effective and prolonged pain relief can be obtained in man by the injection of small doses of morphine or pethidine into either the subarachnoid [3] or the extradural space [4]. As a result, extradural morphine analgesia is being used increasingly by clinicians [5,6], especially in obstetrics and gynaecology [7]. Side effects attributed to extradural morphine are common, possibly dose-related and include nausea and vomiting, pruritus, urinary retention and (more rarely) early and late respiratory depression [8]. Seizure, a theoretical complication of intraspinal administration of opioids [9], has been reported only once before and it happened after what was probably a high pressure intrathecal injection in a patient with known metastatic breast cancer [10]. We report the case of a patient who developed a generalized tonic-clonic seizure 6 h after the administration of morphine 3 mg into the extradural space.

CASE REPORT

A 30-yr-old woman (gravida 4, para 3), weighing 75 kg, was referred to our department for an elective Caesarean section as an ultrasound scan had shown the presence of twins in the breech position at 37 weeks gestation. The actual pregnancy was free of incident; there was no hypertension, oedema or proteinuria.

At the age of 19 yr the patient had suffered her first grand mal seizure. Investigations did not reveal any brain lesion and she had no family history of epilepsy. From that time, she was treated with phenobarbitone 175 mg daily, and suffered one or two grand mal fits each year up to the age of 26 yr. She had had an uneventful pregnancy terminated by forceps delivery under extradural bupivacaine analgesia at age 29 yr.

It was decided to utilize extradural anaesthesia. Ringer's solution 1500 ml was infused and the patient was placed in the left lateral decubitus position. Using the "loss of resistance" technique, the extradural space was entered at L2–3 with an 18-gauge Tuohy needle and the catheter was advanced 5 cm cranially without difficulty. An aspiration test revealed neither blood nor CSF and 1% lignocaine 2 ml was injected through the catheter. As neither motor nor sensory deficit occurred, a second aspiration test (also negative) was carried out 5 min later and 2% carbonated lignocaine 20 ml (Astra) with freshly added adrenaline 0.1 mg was injected at a rate of 5 ml min⁻¹. The resulting sensory block extended to T5 on both sides. Two male infants (2440 and 2540 g) were delivered with Apgar scores of 8/9/10 and 7/9/10, respectively. A bilateral tubal ligation was performed and a continuous infusion of oxytocin (10 u. in 5% glucose 500 ml over 12 h) was started.

At the end of the procedure and following a negative aspiration test, 3 mg of preservative-free morphine (Vifor, Geneva) was administered in 10 ml of physiological saline via the extradural
catheter. The immediate postoperative period was uneventful. Analgesia was satisfactory, the rate of ventilation was within the normal range and normovolaemia (as assessed by diuresis and central venous pressure) was maintained. Four hours after the administration of the extradural morphine, a slight pruritus of the face and the neck was noted, but this was not severe enough to necessitate medical treatment. Two hours later, without alterations in vital signs or warning symptoms, the patient suffered a generalized tonic-clonic seizure with loss of consciousness. The plasma concentration of phenobarbitone (16.2 \mu g ml^{-1}) was within the therapeutic range and close to that measured at 25 weeks gestation (17.1 \mu g ml^{-1}). An EEG performed 3 days later was characterized by a diffuse and non-specific abnormal tracing.

**DISCUSSION**

Grand mal seizures can be precipitated by a number of factors, including certain drugs and pregnancy [11]. The increase in seizure frequency reported in pregnancy is thought to be the result of a pregnancy-associated alteration in the kinetics of antiepileptic agents, causing a decrease in the plasma concentration. When dosage was adjusted to maintain plasma concentrations in the therapeutic range, no increase in seizure frequency was observed [12]. In this patient, the plasma concentration of phenobarbitone was in the therapeutic range. Furthermore, with the same therapeutic regimen, the patient had suffered no seizure during the previous 4 yr, despite another pregnancy terminated by forceps delivery under extradural bupivacaine analgesia 1 yr before the event reported here.

Experimentally, the intracerebroventricular or intrathecal administration of morphine possesses convulsant properties [13, 14], in contrast to i.v. morphine, which has been used to suppress convulsions in eclampsia [15]. Bromage and colleagues [16] have shown cervical and intracranial spread of morphine injected into the lumbar extradural space in man and have observed a time-lag of approximately 6 h for the drug to reach the brain stem and the fourth ventricle.

The poor lipid-solubility of morphine, with its consequential restriction to CSF, implies a high concentration of free drug. Thus, the CNS irritating properties of morphine may have been enough to initiate a grand mal seizure in a patient whose trigger threshold was already low. The 6-h delay between the administration of the morphine and the onset of seizure in our patient is consistent with the known kinetics of morphine in the CSF [16, 17]. Factors known to induce seizures, such as pain, hyper- or hypoventilation or hypervolaemia, were all absent and cannot be considered contributory factors in this patient. Moreover, the penetration of morphine into the CNS was heralded by the development of pruritus, known to be one of the earliest side-effects of extradural morphine.

Although lignocaine, with its known central nervous system toxicity [18], either alone or by interacting with morphine [19], might have played a role in this patient, the absence of other CNS symptoms of lignocaine toxicity, such as dizziness, auditory and visual disturbances, coupled to the rather long delay between the administration of the lignocaine and convulsions (8 h) [20] argue against such a role.

In conclusion, although extradural morphine administration greatly improves the comfort of the patient after Caesarean section, its administration to epileptic patients might be questioned and should at least be monitored carefully.

**REFERENCES**

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