BUPIVACAINE TOXICITY IN ASSOCIATION WITH EXTRADURAL ANALGESIA FOR CAESAREAN SECTION

J. THORBURN AND D. D. MOIR

SUMMARY
Evidence of central nervous system toxicity was noted in two patients undergoing extradural analgesia for Caesarean section. There was no cardiovascular depression and both patients recovered rapidly. The patients had received total doses of bupivacaine plain solution of 357.5 mg and 356.25 mg, respectively and the relationship of these to the clinical signs of bupivacaine toxicity is discussed.

Bupivacaine toxicity has been reported infrequently and the majority of cases have been the result of accidental and unsuspected intravascular injection. Some controversy exists regarding the relationship between neurological and cardiovascular toxicity: the hypoxia of the former may result in or add to the latter. Cardiovascular toxicity is quite refractory to treatment and requires prolonged resuscitation. We report two cases of bupivacaine toxicity after extradural analgesia during labour.

CASE REPORT

Case 1
A primigravid patient, aged 22 yr and weighing 72.7 kg, was admitted following the spontaneous onset of labour some 3 h previously. Two hours after admission, lumbar extradural analgesia was instituted, using 0.375% bupivacaine plain solution. Over the next 8 h 30 min, bupivacaine 69 ml was injected in divided doses, with good effect (total dose of 258.75 mg). At this point, the decision was made to deliver the patient by Caesarean section under extradural anaesthesia. This required extension of the blockade. Despite effective pain relief, extension proved difficult, and during the next hour, the patient received 9 ml of 0.375% and 13 ml of 0.5% bupivacaine plain through the catheter. Twenty minutes after the last injection, without any warning or symptoms, there was a sudden onset of a grand mal convulsion, lasting some 90 s, accompanied by the rapid onset of deep cyanosis. Recovery was also rapid and complete, within a further 30 s. No cardiovascular abnormalities occurred and the arterial pressure remained unchanged. General anaesthesia was induced, and delivery undertaken. There were no untoward sequelae and the infant was delivered in good condition.

The total dose of bupivacaine administered was 357.5 mg over a 10-h period, and of that, 98.5 mg was administered in the last 60 min.

Case 2
A primigravida aged 23 yr and weighing 54.9 kg, was admitted following the spontaneous onset of labour. Two hours after admission, extradural analgesia was instituted, using 0.375% bupivacaine plain solution. Pain relief was effective, and over the next 9 h, the patient received bupivacaine 35 ml in divided doses. Twenty-five minutes after “topping up”, 0.5% bupivacaine solution was injected to extend the block for Caesarean section. It proved rather difficult to achieve the required extent, and over a period of 70 min, 0.5% bupivacaine 45 ml was injected. The block was satisfactory although, following delivery (some 20 min following the last top up), the patient was noted to become drowsy. Suddenly she convulsed and transient cyanosis developed. Recovery followed rapidly, and diazepam was injected i.v. No sequelae ensued, the arterial pressure remained stable, and the subsequent course of the operation was uneventful.

A total dose of bupivacaine 356.25 mg plain solution had been administered over a 9-h period, 225 mg within the last 70 min.

DISCUSSION

The characteristics of the two patients were similar. Both had effective continuous extradural analgesia of similar duration. The presence of effective pain relief with standard “top-up” volumes, and the timing of the onset of convulsions which would coincide with the peak blood concentrations following...
ing extradural injection of bupivacaine, almost certainly exclude the possibility of intravascular injection.

Moore and colleagues (1978) noted generalized systemic toxic reactions in 15 of 11,080 patients receiving bupivacaine, but 13 of those resulted from intravascular injection, and in 1982 Moore, Thompson and Crawford reported a further five toxic reactions (four from intravascular injection), associated with hypoxia and acidosis. The characteristics of the toxic reactions of the two patients reported here and those described by Moore are similar and quite at variance with the suggestion by Albright (1979) that refractory cardiovascular collapse is likely to follow neurological systemic bupivacaine toxicity. Studies have suggested that the dose of bupivacaine causing convulsions is similar to the lethal dose in mice (de Jong and Bonin, 1980), but in dogs the lethal dose is considerably greater than that required to produce convulsions (Avery et al., 1981; Lui et al., 1982). Species and methodological differences may account for this, as the dogs were ventilated, but not the mice. Avery and his colleagues (1981) have shown that mild hyperkalaemia will decrease the plasma concentration of bupivacaine required to produce cardiovascular collapse. However, there was no evidence of metabolic upset in the patients described. Thus, attempts must be made to limit the dose of bupivacaine administered.

Moore and colleagues (1977), have been critical of the maximum dose recommended by the manufacturer, and claim that, provided intravascular injection is avoided, bupivacaine has a wide margin of safety and stringent dose limitations have restricted its use. The package insert in the U.K. recommends a maximum dose of 2 mg kg\(^{-1}\) for an adult weighing 65-70 kg in a 4-h period, and this is less than that received by both our patients. There is no doubt that considerably greater doses than those recommended by the manufacturer have been used to provide anaesthesia for Caesarean section (Thorburn and Moir, 1980), but the risk of convulsions carries considerable danger to the mother and the fetus.

The use of more dilute solutions decreases the plasma concentration of bupivacaine (Tucker et al., 1972), and the more usual concentration used at the Queen Mother's Hospital, Glasgow for pain relief in labour is 0.25% bupivacaine plain solution. No patient receiving this solution has shown evidence of generalized systemic toxic reactions.

With the increased popularity of extradural anaesthesia for Caesarean section, and the belief that it is perhaps safer than general anaesthesia, there is an understandable reluctance to undertake general anaesthesia in a patient whose extradural block is inadequate, but for whom the injection of further bupivacaine (which would exceed the manufacturer's recommended maximum dose) might create adequate blockade. This temptation should be resisted, the evidence presented here suggests that the total dose of bupivacaine injected should not be greater than that recommended by the manufacturer. It may be an advantage to use the more dilute solutions of bupivacaine to provide pain relief in labour, as this will decrease the total dose, and pain relief may still be adequate (Thorburn and Moir, 1981). The risks will then relate mainly to the use of larger volumes of more concentrated solutions for Caesarean section.

REFERENCES
périnéale pour une césarienne. Il n'y a pas eu de dépression cardiovasculaire et les deux patientes ont récupéré rapidement. Les patientes avaient reçu des doses totales de bupivacaine en solution non adrénalinée, respectivement de 357,5 mg et de 356,25 mg et la relation entre ces doses et les signes cliniques de toxicité est discutée.

**TOXICITÉ DE LA BUPIVACAÏNE EN ASOCIACION CON ANALGESIA EXTRADURAL EN OPERACIONES CESAREAS**

Se observaron pruebas de la toxicidad en el sistema nervioso central en dos pacientes sometidas a una analgesia extradural con fines a operaciones cesáreas. No hubo depresión cardiovascular y ambas pacientes se recuperaron rápidamente. Las pacientes habían recibido dosis totales de bupivacaina en solución llana de 357,5 mg y de 356,25 mg respectivamente y se discute de la relación de éstas con las señales clínicas de toxicidad de la bupivacaina.