DISCREPANCY BETWEEN THE DEVELOPMENT OF TOLERANCE TO BUPIVACAINE IN EXTRADURAL AND SPINAL ANAESTHESIA IN RABBITS

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SUMMARY

We gave equal groups of rabbits seven extradural (500 µg kg⁻¹) or intrathecal (250 µg kg⁻¹) injections of bupivacaine, at 24-h intervals. A decrease in the duration of motor block was observed after the extradural injections. The intrathecal injections exerted a reproducible effect. An additional regimen was tested in which five doses of bupivacaine 125 µg kg⁻¹ were administered intrathecally after a loading dose of 250 µg kg⁻¹, when the animals showed partial recovery from the previous dose; there was no decrease in the effect. The absence of tolerance to intrathecal bupivacaine implies that tachyphylaxis to extradural local anaesthetics results from a decrease in availability of the drug to the neural target, rather than a diminution in effect at the site of action. (Br. J. Anaesth. 1993; 71: 450-452)

KEY WORDS


Tachyphylaxis to local anaesthetics has been described widely when different routes of administration are used, including extradural injections [1]. However, in several studies the development of tolerance has not been confirmed after continuous or repeated spinal administration of local anaesthetics [2, 3]. As the indications for extradural and spinal analgesia in many cases are similar, we designed this study to examine and compare the existence and extent of tolerance to a local anaesthetic in the extradural and spinal spaces. Local anaesthetic action, evaluated by estimation of motor block duration, has been assessed after repeated intrathecal and extradural injections of bupivacaine in rabbits.

METHODS AND RESULTS

Seven injections of bupivacaine were administered to two equal groups of male rabbits (2.8–3 kg; n = 6) extradurally (group I; bupivacaine 500 µg kg⁻¹) or intrathecally (group II; bupivacaine 250 µg kg⁻¹) at 24-h intervals via chronically implanted catheters. Cannulations were performed using modifications of techniques described elsewhere [4, 5]. The period between administration of the drug and restoration of the animal’s ability to move freely was defined as the duration of motor block.

We found a significant gradual decrease in the duration of the motor block produced by repeated extradural injections (group I) commencing from the fourth injection (P < 0.05 between the 3rd and 4th days; P < 0.01 between 4th–5th, 5th–6th and 6th–7th days) (fig. 1). In contrast, animals treated by repeated intrathecal injections of the anaesthetic (group II) exhibited similar periods of motor block throughout the 7 days of the study (fig. 1).

As tolerance to repeated intrathecal injections of bupivacaine at 24-h intervals was not found, an additional study was undertaken, in which bupivacaine was injected before the animal exhibited complete recovery from the effect of the previous dose. Six rabbits (group III) received bupivacaine 250 µg kg⁻¹ followed by five doses of 125 µg kg⁻¹. These doses were administered as soon as the animal supported the back of the body using four limbs (showed partial recovery from the block). The period between injection and restored ability of the animal to stand, still exhibiting ataxia, was referred to as the duration of maximum motor block. The repeated intrathecal injections of bupivacaine at short intervals (each injection was administered before complete recovery from the effect of the previous dose) exerted a similar maximum motor block (fig. 1).

COMMENTS

Tachyphylaxis to extraduraly administered local anaesthetics has been described in humans [1]. Tachyphylaxis to spinal administration of local anaesthetics has also been assumed, based on two types of evidence [1]. The first was the finding of a reduction in the duration of analgesia produced by successive subarachnoid injections of lignocaine in patients with crural gangrene caused by vascular occlusion. This reduction was attributed to tolerance. However, an alternative explanation, relating the reduction in effect to an increase in pain because of progression of the pathological process, may be...
anatomical structures affect drug distribution in spinal compared with caudal anaesthesia, the legitimacy of this evidence is doubtful.

Analysis of results obtained by Kroin and colleagues, who used continuous subarachnoid administration of bupivacaine in dogs for 16 weeks, did not show a decrease in motor block [2]. Successful analgesia of 7 months duration, achieved by bupivacaine in a patient with a spinal tumour, has been reported [3]. In the present study, repeated spinal injections of bupivacaine at 24-h intervals produced reproducible effects. Repeated injections of the drug before full recovery from the previous dose also did not show any reduction in effect.

A decrease in effect after repeated extradural administration of local anaesthetics may occur because of a fibrosis around the catheter. Formation of connective tissue in the extradural space was reported in rats [5]. Moreover, a study in cancer patients after prolonged spinal administration of bupivacaine and morphine revealed formation of adhesions mostly in the extradural space [6]. Obviously, this mechanism cannot account for the reduction in anaesthetic efficacy when short intervals between injections were used. A decrease in the duration of block has been reported when local anaesthetics were administered extradurally shortly after the reduction of the effect of the previous injection [1]. However, in the same work it was shown that after three or four injections the reduction in anaesthetic efficacy did not continue. Moreover, if repeated injections were given before the end of the effect of the previous dose, it resulted in augmentation of effect [1]. We speculate that frequent extradural injections of anaesthetic solutions may increase the amount of extracellular and intracellular fluid in the area of injection or decrease the buffering capacity and pH of the surrounding tissue. This may reduce the availability of the drug to nerve cells, causing a reduction in effect. Hence, repeated extradural administration of local anaesthetics may display different patterns of effect:

1. Initial diminution as a result of decreased drug availability to nerve cells because of changes in pH and accumulation of fluids around the area of injection.

2. Initial augmentation because of anaesthetic accumulation when administered before elimination of the residual drug from the nerve cells.

3. Delayed diminution after a few days because of formation of adhesions around the catheter.

The basis for tolerance could be a reduction either in the effect at the receptor level or in the fraction of anaesthetic reaching the neural target. The molecular mechanism of anaesthetic action on neural tissue is similar for both spinal and extradural anaesthesia. The difference in the development of tolerance between the routes of administration implies that tachyphylaxis to local anaesthetics results from a decrease in drug availability, rather than alteration in the effect at the site of action.

REFERENCES


