infants[5] undergoing similar surgical procedures. Anaesthesia consisted of either isoflurane 0.2% or nitrous oxide 70% in oxygen. The tracheas were extubated in 23 of 25 patients in the operating room. A similar experience in 14 neonates and infants was reported by Murrell *et al.* using lumbar epidural anaesthesia combined with general anaesthesia.[6] Although the spinal block allows the epidural catheter to be placed without concern for patient movement, both caudal[7] and lumbar epidural catheters[8] can be placed in the awake neonate, if necessary.

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REPLY

We did encounter one episode of unexpectedly high spinal blockade after dosing the epidural catheter.[1] This has occurred several times in our experience after caudal anaesthesia without previous lumbar puncture. Possible causes include high epidural blockade vs direct or indirect subarachnoid injection of local anaesthetic. Several factors argue against transport of local anesthetic through a hole in the dura. The tip of the epidural catheter is located in the mid to low thoracic area and local anaesthetic is injected 60–90 min after lumbar puncture. In addition, the pressure differential between the subarachnoid and epidural spaces does not favour flow into the subarachnoid space.

We agree that both caudal and lumbar epidural blocks can be performed in awake infants. However, we feel that performance of the blocks is easier in the non-struggling anaesthetised child. We have observed, in both adults and children, that subarachnoid block provides a denser block to begin surgery. The epidural catheter is very effective at supplementing and prolonging the original subarachnoid block.

We do not believe that intubating the trachea is necessary for these cases. Induction of general anesthesia, laryngoscopy and placing an endotracheal tube is not a guarantee against aspiration. Our goal is to allow the child to remain appropriately alert with intact airway reflexes. There are times when either the infant's surgical status or level of consciousness, requires endotracheal intubation and general anaesthesia. However, our contention is that an awake, responsive, and spontaneously breathing infant is the best physiological infant monitor.

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Is intrathecal midazolam safe?

To the Editor:

I read with many interests the laboratory investigation done by Bahar *et al.*[1] who concluded that intrathecal midazolam in rats provides "segmental spinal anaesthesia sufficient to permit laparotomy" and concluded that "this 'balanced anaesthesia,' ... could find wide application in abdominal and lower limb surgery."[1] The authors cannot be unaware of intrathecal midazolam effects in patients scheduled for intraabdominal surgery published by investigators at Leeds University.[2] Hypertension was experienced after manipulations of the peritoneum and the bowel and when the colon was handled.[2] Thus, there is evidence that intrathecal midazolam alone cannot provide surgical anaesthesia in man.

Wide clinical use of spinal injections of new drugs raises the question of its lack of neurotoxicity. Bahar et al[1] state positively and quote several reports of neurotoxicological assessments of intrathecal midazolam in animals. From the cited reports, one cannot conclude a lack of toxicity since high incidences of neurotoxic

lesions (nerve root demyelination and Wallerian degeneration) were observed in all groups.[3] However, others have studied the neurotoxicity of intrathecal midazolam.[4,5] We first observed a high incidence of lesions in rabbits,[4] and our findings were confirmed by Svensson *et al.*, who characterised the nature of the toxicity.[5] It is not possible to promote intrathecal midazolam in man since neurotoxicity has been reported in rabbits[4] and in rats.[5] Even if neurotoxicity of epidurally administered drug is attenuated, we must keep in mind that the risk of unintended intrathecal injection of epidurally administered agent is not negligible.

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REPLY

We are pleased to respond to Malinovsky's criticism of our study.[1] We have just completed a neurotoxicity study on intrathecal midazolam in the same animal model which awaits acceptance for publication. We examined whether midazolam injected intrathecally, alone or combined with fentanyl, on 15 occasions over one month produced neurotoxic injury as judged by the animal's neurological behaviour and by histological examination, by light microscopy, of the excised spinal cord and paraspinal tissues on sacrifice after five weeks. The white matter showed a spongiose appearance, but no evidence of demyelination. The neurones of both the anterior and posterior horns of grey matter showed cytoplasmic vacuolation of varying degree, but no differences in these changes were observed among groups that received midazolam alone, midazolam plus fentanyl, and those given intratheal lidocaine alone or fentanyl alone. After each intrathecal injection all animals recovered fully and remained awake, mobile and ate and drank normally. They continued to do so until the end of the study five weeks later.

The sophisticated neurotoxicity studies by Malinovsky et al.[2] and by Svenson et al.[3] employing morphometric and ultrastructural endpoints after chronic subarachnoid midazolam injection, showed subtle changes in the midazolam group of animals, compared with those who received saline or lidocaine. None of the animals presented obvious neurological impairment or behavioural disturbances.

We fully endorse Yaksh's admonition that it is necessary to rule out potential neurotoxic effects of novel drug combinations in laboratory animals before administering such combinations to patients.[4]

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Protamine and its cardiovascular effects

To the Editor:

Backman, Gilron and Robbins' case report makes for interesting observation.[1] They rightly discount the mechanism of acute cardiovascular events following protamine injection as due to a vaso-vagal reaction via reinnervation but, rather, suggest the possible causes as reflex decrease in sympathetic output secondary to stimulation of mechano-receptors, reduced sino-atrial node perfusion, or possible cardiac ischaemia.

Although the cause of the well reported cardiovascular events are uncertain, animal models have indicated possible mechanisms of action. Protamine has been shown to interfere with mitochondrial respiration *in vitro*[2] and, in dogs, reduces *in vivo* oxygen