Intrathecal midazolam: does the benefit truly outweigh the risk?

It was with dismay that I read the article “The effects of intrathecal midazolam on the duration of analgesia in patients undergoing knee arthroscopy” by Nanjegowda et al in the latest issue of SAJAA.¹

The intrathecal use of midazolam has been hotly debated in the literature for over a decade.

Many studies in both animals and humans have shown the analgesic effect of intrathecal midazolam.² It has been used in the management of acute pain, chronic neuropathic pain and spasticity. The mechanism whereby it exerts its analgesic effect is via its agonist action at γ-aminobutyric acid (GABA) receptors, mediating an inhibitory effect on spinal sensory and motor excitability.³

However, the use of midazolam via the intrathecal route remains controversial, and its use off-label, for a reason. Several early animal studies demonstrated histopathological evidence of neurotoxicity, such as neuronal vacuolation, myelin separation and alterations of the blood-brain barrier; other researchers found no damage.⁴

The use of intrathecal midazolam in humans appears safe, in that no overt adverse behavioural or neurological changes have been demonstrated in association with its use. The problem is that the absence of overt acute changes does not necessarily mean the absence of morphological changes in the cord, with potential long-term consequences.⁵

A study published this year in Regional Anesthesia and Pain Medicine found midazolam to be neurotoxic in vitro in various human cell lines.⁴ Midazolam was found to induce apoptosis via mitochondrial activation in a concentration-dependent manner. With increasing concentrations of midazolam, the researchers demonstrated the development of neuronal necrosis.

It is worth noting that drugs such as clonidine and morphine underwent extensive preclinical testing before being approved for intrathecal use in humans.³ This degree of testing has not yet been performed for intrathecal midazolam.

We have, as part of our anaesthetic armamentarium, numerous drugs that provide analgesia; drugs with a long track record of efficacy and safety. Until midazolam has been fully studied, is it really worth exposing healthy patients to a drug that may be neurotoxic, just in order to prolong the time until (safe) rescue analgesia is required?

One other concern would be the issue of patient consent in this study, which the authors do not address. Were the patients informed of the animal evidence of possible neurotoxicity before consenting to inclusion in the study? I have my doubts.

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References