Should codeine still be used for post-craniotomy analgesia?

The traditionally held belief that craniotomies are not as painful as other surgical procedures is increasingly being questioned. Pain following this type of surgery is now considered to be a greater problem than previously thought. De Benedittis et al (1996) showed that 60% of post-craniotomy patients suffered pain and in two thirds of these, pain intensity was moderate to severe especially in the first 48 hours after surgery.

There has been a conventional reluctance to use strong opioids to treat post-craniotomy pain. Opiate-related side effects of sedation, respiratory depression, nausea and vomiting are particularly undesirable in this patient group who require continued monitoring of conscious level, neurological status and control of intracranial pressure.

A survey by Roberts (2005) revealed that in the majority of the 33 neurosurgical centres in the UK, intramuscular codeine phosphate was the principal first-line analgesic post-craniotomy with only three centres using morphine routinely.

Codeine is a pro-drug

Historically codeine has been the favoured opioid following neurosurgery. Sedation, respiratory depression and pupillary constriction are thought to be less than with other opioids, although this may reflect the ceiling effect of the small doses used.

Codeine is a pro-drug and is metabolized mainly in the liver where it undergoes O-demethylation to form morphine, N-demethylation to form norcodeine, and partial conjugation to form glucuronides and sulphates of both the unchanged drug and its metabolites. O-demethylation into morphine accounts for 10% of codeine clearance and is thought to be mainly responsible for the analgesic effect. This step is carried out by the genetically polymorphic enzyme cytochrome P450 2D6 (CYP2D6), also known as debrisoquine or sparteine hydroxylase.

Individuals from different ethnic groups exhibit considerable variability in the functional capacities of their expressed CYP2D6 enzymes. About 7–10% of Caucasians lack any CYP2D6 activity while 1–3% of Middle Europeans and up to 29% of Ethiopians are ultrafast metabolizers (Cascorbi, 2003). Poor metabolizers who lack CYP2D6 activity gain little or no analgesia from codeine while the ultrafast metabolizers (the result of CYP2D6 gene duplication) may experience severe side effects from increased levels of the active metabolite. Furthermore, commonly prescribed drugs can affect the activity of CYP2D6 enzymes: potent inhibitors are quinidine, some selective serotonin-reuptake inhibitors and neuroleptics, while enzyme inducers include dexamethasone and rifampicin.

Morphine *vs* codeine

The study by Goldsack et al (1996) comparing intramuscular injections of codeine phosphate 60 mg with morphine 10 mg showed neither drug caused respiratory depression, sedation or pupillary constriction in patients following intracranial surgery. Morphine was also found to be the more effective analgesic beyond 60 minutes.

A more recent study of post-craniotomy patients by Sudheer et al (2007) found patient satisfaction was better with morphine patient-controlled analgesia than with intramuscular codeine. Pain scores at 4, 12 and 18 hours post-operation were significantly lower in the patient-controlled analgesia group compared with the intramuscular codeine group. There was also no difference in sedation and respiratory depression between the groups as in the study by Goldsack et al (1996).

Unlike codeine, morphine has the additional advantage that it can be given in titrated intravenous doses thus avoiding the need for unpleasant intramuscular injections.

Conclusions

The perceived advantages of codeine have made it the analgesic of choice after craniotomy. But almost all of its analgesia is provided by its conversion into morphine, a process dependent on the genetic make up of the individual, and which can be influenced by other drugs. Importantly, the side-effect profile of codeine and morphine is similar at equipotent doses. Therefore instead of relying on an unpredictable pro-drug, it is reasonable to use the active metabolite, morphine, which can be easily titrated to effect and which has been shown to be the superior analgesic in this group of patients. **BJHM**

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Anaesthetic and critical care dilemmas are coordinated by Dr John Orr and Dr Annie Hunningher, Research Fellows at the Centre for Anaesthesia, UCL, London Ideas for future dilemmas can be sent to Rebecca Linssen bjhm@markallengroup.com