A Death Knell for Codeine for Acute Pain after Craniotomy?

Can. J. Neurol. Sci. 2011; 38: 390-391

Unrelieved acute pain has been identified in a variety of post-operative settings.[1] Specifically, a recent review of acute and chronic pain after craniotomy concluded that both are frequent and under recognized with several risk factors and that there is a need for further research regarding mechanisms, predictors, prevention and treatment.[2] Inadequate acute pain management may be a factor in persistent post-operative pain.[3,4] Fear of sedation in neurosurgical patients may have led to the widespread use of an analgesic that is thought to cause less sedation but which is often pharmacologically inactive and does not relieve pain in many patients. In others this drug may be excessively soporific. Both extremes of effect are because of pharmacogenetics.

In this issue of the Journal, Hassouneh et al[5] have reported an important survey of acute pain management after craniotomy in Canada. A significant finding is that codeine was the first choice of drug for pain relief in 59% of instances. Further, they found that the need for a second opioid was significantly higher among codeine prescribers compared to morphine (which was used as a primary choice in 38% of instances). Side effects were frequent including sedation (27%) despite the frequency of the use of codeine. The authors discuss alternative drugs. Strikingly, the neurosurgeon respondents reported a high level (90%) of satisfaction with their current choice of analgesic. Nonetheless, they described their practice as resulting from personal preference or protocols rather than evidence-based. No account is available in this survey of the outcome of pain relief but the authors refer to other reports indicating significant moderate to severe pain and low patient satisfaction after craniotomy. Rating pain may be problematic in neurosurgical patients with communication difficulties but non-verbal ratings can be used. Responses from neurosurgical colleagues in Quebec to a French language questionnaire were 20% versus an overall participation rate of 66%.

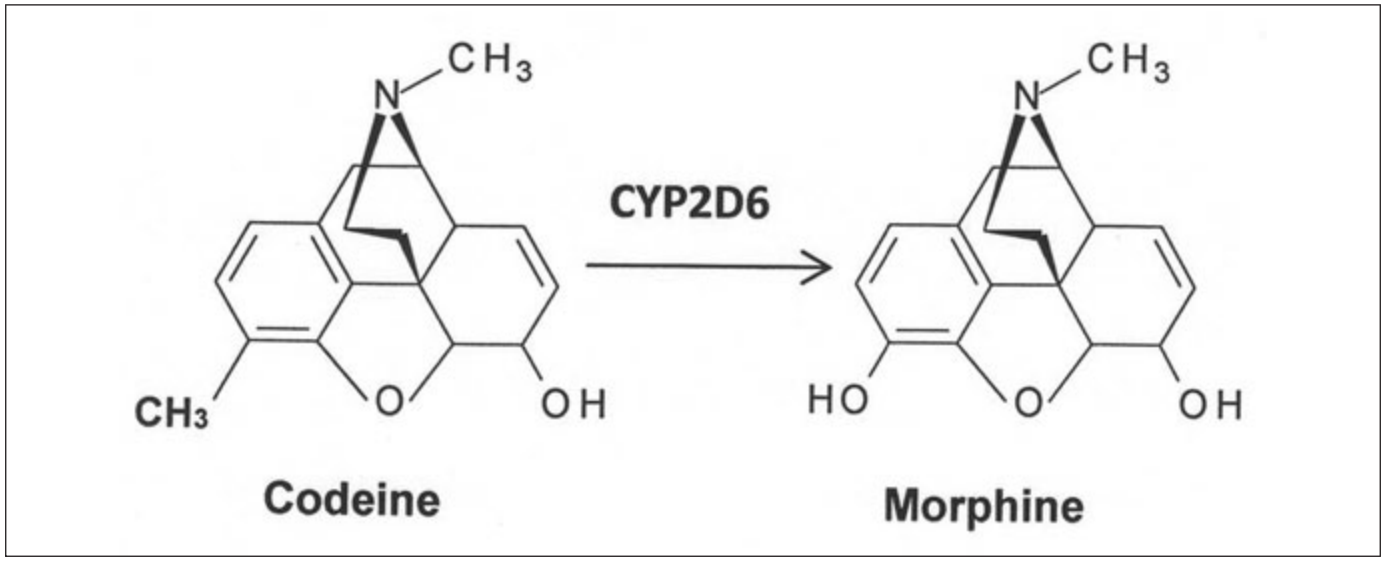

Figure: *the metabolism of codeine to its active metabolite morphine via cytochrome P450 (CYP) and the enzyme CYP 2D6 (courtesy of Maree Smith[8])*

The use of codeine in this setting is not unique to Canada.[6] A recent report[7] addresses the problems with the use of codeine. One of the chief difficulties is that codeine is a pro-drug for morphine and requires to be metabolized to morphine to be effective (Figure). As well its pharmacokinetics are unpredictable. This occurs via the cytochrome P450 (CYP) superfamily of enzymes specifically CYP 2D6. About 10% of codeine is metabolized to morphine by this enzyme.[8] There is a broad range of phenotypic diversity between ethnic groups. In brief, the poor metabolizer (PM) phenotype is in the order of Caucasians (7-11%) > African American, Hispanic > Indian > Asian > Chinese, Korean and Japanese (0-1.2%).[8] The

https://doi.org/10.1017/S0317167100011744 Published online by Cambridge University Press

ultrametabolizer (UM) phenotype is in the order of 40% in North Africa (Ethiopia, Somalia, Kenya) >26% in Australasia > 12% in the Middle East >8% in North America > 3% in Europe.[9] Thus in patients of European origin (PM), up to 11% will not metabolize codeine to morphine at all resulting in poor analgesia. However, the UM will produce high levels of morphine, so that up to 40% of patients (Somalia, Kenya, and Ethiopia), 26% from Australasia and 12% in the Middle East will produce large amounts of morphine because of this pharmacogenetics variant issue. This is problematic because impaired sensorium in the UM phenotype may be misattributed to neurological or other causes. This is, of course, an issue in Canada in settings where there are substantial proportions of some of these ethnic groups. Pharmacogenetic susceptibility has been suggested in the death of a breast fed neonate whose UM mother had received codeine and death and anoxic brain injury in two other young children prescribed codeine for pain after tonsillectomy.[7] Young children may be particularly susceptible to ordinary doses of codeine possibly because of immaturity of the blood-brain barrier. The Hospital for Sick Children has removed codeine from its formulary and there have not been significant issues for neurosurgery with this change to the predominant use of morphine (personal communication with James Rutka). Life threatening respiratory depression has also been described in adults.[9] Another issue with codeine metabolism is that a number of drugs which neurosurgical patients may be taking inhibit CYP2D6 and codeine metabolism.

The current article raises a number of questions that give direction for future research. Data are needed about the incidence of unrelieved moderate to severe acute pain in neurosurgical patients in Canada, the frequency of use of a standardized pain measure such as the numerical rating scale (0-10) as a fifth vital sign, patient ethnic demographics, analgesic drugs used and incidence of sedation. It is also important to know the incidence of persistent pain after surgery (craniotomy and other procedures) including incisional pain, (which can be neuropathic) and post-surgery headaches of various types which are a reasonably common occurrence in my practice. These persistent pains are an important issue and better management of acute pain may help to prevent them.

Finally, as an additional incentive for the ongoing evaluation of acute pain after neurosurgery, the Canadian Council on Health Services Accreditation (CCHSA) has included pain assessment and management in the CCHSA standards published in 2005. Criterion 7.4 addresses processes for assessing and managing pain in critical care. Processes addressed in this criterion are available at: http://www.canadianpainsociety.ca/pdf/accreditation_manual.pdf.

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References

1. Apfelbaum JL, Chen C, Mehta SS, Gan TJ. Postoperative pain experience: result from a national survey suggest postoperative pain continues to be undermanaged. Anesth Analg. 2003; 97: 534-40.
2. Flexman AM, Ng JL, Gelb AW. Acute and chronic pain following craniotomy. Curr Opin Anaesthesiol. 2010; 23:551-7.
3. Kehlet H, Jensen TS, Woolf CJ. Persistent postoperative pain; risk factors and prevention. Lancet. 2010; 367:1618-25.
4. White PF, Kehlet H. Improving postoperative pain management. What are the unresolved issues? Anesthesiology. 2010; 112: 220-5.
5. Hassouneh B, Centofani JE, Reddy K. Pain management in post-craniotomy patients: a survey of Canadian neurosurgeons. Can J Neurol Sci. 2011; 38(3):456-60.
6. Roberts GC. Post-craniotomy analgesia: current practice in British neurosurgical units—a survey of post-craniotomy analgesic practices. Eur J Anaesthesiol. 2005; 22(5):328-32.
7. MacDonald N, MacLeod SM. Has the time come to phase out codeine? CMAJ. 2010; 182:1825.
8. Smith MT, Muraldharan A. Pharmacogenetics, International Association for the Study of Pain (IASP) clinical updates, XVIII, Issue 8, September 2010 (www.iasp-pain.org).
9. Madadi P, Koren G. Pharmacogenetic insights into codeine analgesia; implications to paediatric codeine use. Pharmacogenomics. 2008; 9:1267-84.