ANALGESIA

Flower power

Opioids such as morphine are still considered to offer the most effective form of pain relief, despite having adverse effects such as addiction, tolerance, depression of breathing, nausea and chronic constipation. Alternative, efficacious and safe analgesic agents are therefore still sought. Now, reporting in *Nature Chemistry*, Micalizio and colleagues describe the synthesis of conolidine, a non-opioid analgesic that might offer pain relief without having these adverse effects.

Conolidine is a C5-nor stemmadenine that is found in the bark of the tropical flowering shrub *Tabernaemontana divaricata*, which has been used for a long time in traditional Chinese, Ayurvedic and Thai medicines to treat fever and pain. Many indole alkaloids have been isolated from this plant and implicated in analgesia, but this is the first study to report the therapeutic effects of conolidine.

Investigation of the biological properties of conolidine had not been possible until now because of its scarcity; it is isolated from the stem bark of the shrub with a yield of just 0.00014%. However, despite its challenging structure, Micalizio and colleagues have managed to synthesise (±)-conolidine, (+)-conolidine and (–)-conolidine from the commercially available pyridine in just nine steps with an overall yield of 18%.

To investigate the potential analgesic effects of synthetic conolidine *in vivo*, the authors injected 10–20 mg per kg intraperitoneally into C57BL/6J mice and examined their responses to various painful stimuli. Unlike opioids, conolidine did not promote antinociception to acute thermal stimulation; however, like morphine and other analgesics, it prevented a writhing response in a visceral pain model, and reduced nocifensive behaviours in a tonic and persistent pain model.

Interestingly, conolidine showed no affinity for the μ-opioid receptor and it did not alter locomotor activity in an open field test, which suggests that conolidine does not increase dopamine levels (a characteristic of all addictive substances). Although conolidine's mechanism of action is unclear at present, these findings suggest that it works through a different signalling pathway to opioids and could therefore lack their unwanted side effects. The ability to easily synthesize this compound in large quantities is greatly advantageous for further testing in neuropathic pain models and for developing a formulation that can be administered orally.

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ORIGINAL RESEARCH PAPER Tarselli, M. A. *et al.* Synthesis of conolidine, a potent non-opioid analgesic for tonic and persistent pain. *Nature Chem.* **3**, 449–453 (2011).