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FILE: ▪Morphine Withdrawal
▪*Delphinium Denudatum*

HC 010133 -234

Date: June 15, 2003

RE: Study Shows *Delphinium Denudatum* Aids in De-addiction of Morphine

Rahman S, Khan RA, Kumar A. Experimental study of the morphine de-addiction properties of *Delphinium denudatum* Wall. *BMC Complementary and Alternative Medicine* 2002;2:6. <<www.biomedcentral.com/1472-6882/2/6>>

The plant *Delphinium denudatum* Wall. (Jadwar, family; Ranunculaceae) grows in the Himalayas and is widely used in the traditional medical system of India. The roots of this plant are thought to be beneficial for treating fungal infections, brain diseases, toothache, and other conditions. *D. denudatum* appears to have analgesic and astringent effects. A 16th century Persian manuscript mentioned the use of *D. denudatum* for treating opium addiction.

In a previous study, the authors assessed the "de-addiction" properties of *D. denudatum*. They then designed a new study to further explore their initial findings. In this second study, rats were rendered morphine-dependent then denied the drug, causing them to develop withdrawal symptoms. Some of the rats were treated with *D. denudatum* to evaluate its effects on these symptoms.

A total of 48 male albino rats were divided into 6 groups of 8 rats each. Group 1 received saline only, and group 2 received *D. denudatum* only (350 mg/kg twice a day). Group 3 was treated with morphine only. Group 4 received *D. denudatum* (350 mg/kg twice a day) simultaneously with the morphine. Group 5 received *D. denudatum* in a single dose (700 mg/kg) 10 hours after the final dose of morphine. Group 6 received *D. denudatum* in a single dose (700 mg/kg) 10 hours before the first dose of morphine. Morphine was administered by intraperitoneal injection, whereas the saline and *D. denudatum* were given orally (the latter as an alcoholic extract). Rats given morphine (groups 3–6) were rendered morphine-dependent by injecting morphine sulphate in escalating doses (10–100 mg/kg) twice daily for 1 week.

When the rats were in morphine withdrawal (also called morphine abstinence syndrome), their physical dependence was evaluated by observing their behavior. Each rat was observed for various motor and vegetative signs during a 30-minute period 12 hours after the last dose of morphine. The control rats (groups 1 and 2) were also observed in this manner.

The results showed that the control rats in groups 1 and 2 (saline only and *D. denudatum* only, respectively) had similar patterns of behavior. These rats were seen chewing, exploring, yawning, and digging; the frequency of these behaviors was occasional and inconsistent. In contrast, rats in group 3 (morphine only) showed severe morphine withdrawal, characterized by head shakes, teeth chattering, jumping, writhing, wet-dog shakes, eye twitching, squeaking on touch, and hostility while being handled. Group 3 rats also had a multi-fold increase in the frequency of the normal behaviors, such as chewing, that were exhibited by the control rats.

The signs of withdrawal were classified as "counted signs" (the frequency of the sign was counted) or "checked signs" (the presence of the sign was checked). The signs were multiplied by weighing factors and combined to compute an aggregate score. The highest mean aggregate score, 12.9 ± 2.5, was found in group 3 (morphine only). In contrast, the three groups treated with *D. denudatum* in addition to morphine all showed reductions in morphine withdrawal signs. The lowest (best) mean score was 5.8 ± 1.5 (group 5; *D. denudatum* given 10 hours after last morphine dose). The next lowest mean score was 7.2 ± 1.7 (group 4; *D. denudatum* given simultaneously with morphine). The score with the smallest reduction, 10.6 ± 1.9, was found in group 6 (*D. denudatum* given 10 hours before first morphine dose).

In discussing their findings, the authors note that other researchers have found similar patterns of morphine withdrawal signs in rodents. These scientists reported that "certain signs [are] more prominent with less dependence and disappear as the degree of dependence increases, while other signs emerge." The current study showed that all the dosage regimens for administering *D. denudatum* reduced the severity of morphine withdrawal syndrome. The greatest reduction in severity was achieved in rats given *D. denudatum* in a single dose (700 mg/kg) 10 hours after the last morphine dose, which was two hours before the observation period. In this group, the reductions in certain signs (such as writhing and teeth chattering) were significant at $P < 0.001$.

Based on their findings, the authors conclude that *D. denudatum* appears to act on sites in the brain other than the opioid receptors. The main alkaloid present in the *Delphinium* genus, methyllycaconitine, reportedly had blocking activity at the alpha 7-type neuronal nicotinic receptor and also inhibited acetylcholine- and anatoxin-induced whole-cell currents in fetal rat neurons. Other potential mechanisms of *D. denudatum* are discussed, and the authors note that further research is needed in this area.

The results of the current study also indicate that *D. denudatum* has a rapid onset and a long duration of activity. In summary, the authors conclude that treatment with an oral extract of *D. denudatum* achieved striking attenuation of severe morphine withdrawal syndrome in rats. "Thus, the drug may prove to be an alternative remedy in morphine de-addiction," they add.

—Christina Chase, MS, RD

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