NORHARMAN - ENDOGENOUS INHIBITOR OF MORPHINE WITHDRAWAL

Cappendijk SLT, [1]Fekkes D, Dzoljic MR, Department of Pharmacology and [1]Psychiatry and Addiction Research Institute, Erasmus University, PO Box 1738, 3000 DR Rotterdam, The Netherlands.

The effects of intraperitoneally administered norharman (ß-carboline) and structurally related ibogaine have been examined on the naloxone-precipitated withdrawal syndrome in morphine-dependent rats. Norharman, similarly to ibogaine, significantly attenuated naloxone-induced withdrawal syndrome in morphine-dependent animals. Both drugs attenuated several withdrawal signs, however, norharman had a more prominent effect, reducing the withdrawal symptoms not affected by ibogaine. These results suggest that norharman, as a physiological constituence of various tissues including brain, may play an important role in the attenuation of withdrawal syndrome.

Methods. Chronic morphine dependence was induced in male Wistar rats (290-330 g) by implantation of pellet (75 mg morphine base/rat, s.c.) under ether anaesthesia (1). Three groups (each 10 morphine-dependent animals) were treated (i.p.) with vehicle (distilled water, 7.2 ml/kg), norharman (20 mg/kg) or ibogaine (40 mg/kg). It has been shown that selected doses of norharman and ibogaine, used in this study are biologically active (2,3). The withdrawal syndrome in morphine-dependent animals was precipitated by naloxone (4 mg/kg, i.p.), 72 h following pellet implantation and 30 min after vehicle or norharman or ibogaine. The observer was "blind" to the treatment order and the withdrawal symptoms were registered during 30 min following injection of naloxone. The withdrawal signs were scored according to the weighting factors described by Neal and Sparber (4). In short, the signs observed during a mild withdrawal syndrome were assigned with 1 (diarrhoea, chewing, grooming, irritability on touch, rearing), whereas the sign rhinorrhoea, observed during severe withdrawal was assigned a 3. All other withdrawal signs (teeth-chattering, wet-dog shakes, penile licking, ptosis and jumping) were assigned by a weighting factor 2.

Results. Norharman (20 mg/kg, i.p.) decreased the locomotion and exploratory behaviour in naive (n=6) and morphine-dependent (n=10) rats, while the ibogaine (40 mg/kg, i.p., n=10) induced a tremor and excitatory behaviour (jumping or violent locomotion on touch). The behavioral effects of norharman or ibogaine lasted no more than 30 min.

Both drugs, norharman and ibogaine attenuated the severity of withdrawal syndrome (Fig. 1). The frequency of several withdrawal signs were significantly attenuated by norharman and ibogaine (Fig. 2 A,C,E,F), or only by norharman (Fig. 2 B,D).

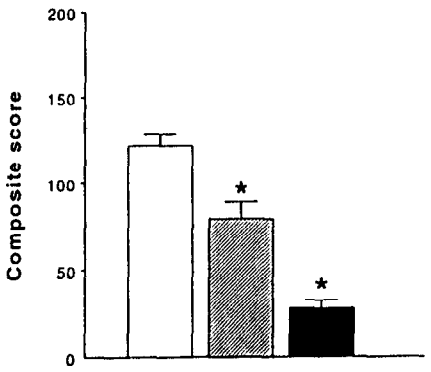

Fig. 1. Effects of norharman and ibogaine on the severity of naloxone-precipitated withdrawal syndrome in morphine-dependent rats. Morphine-dependent rats were pretreated with vehicle (□, 7.2 ml/kg, i.p., n=10), ibogaine (▨, 40 mg/kg, i.p., n=10) or norharman (■, 20 mg/kg, i.p., n=10), 72 h following pellet implantation and 30 min prior naloxone. Data are expressed as composite score, determined by counting the number of all observed withdrawal signs (4), during the 30 min period of abstinence. All data are expressed as mean ± SEM. * Significant decrease of withdrawal syndrome or specific sign (Mann-Whitney *U*-test, $P < 0.05$).

Note that norharman and ibogaine attenuated the severity of withdrawal syndrome.

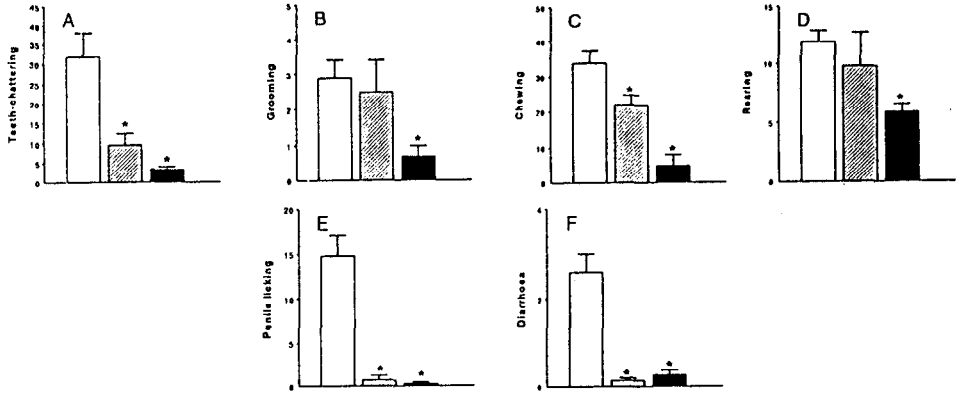

Fig. 2 A-F. Frequency of naloxone-precipitated withdrawal signs in morphine-dependent rats treated with vehicle (□), ibogaine (▨) or norharman (■). For further information see Fig. 1.

Note that norharman and ibogaine significantly attenuated the frequency of several withdrawal signs, while in addition the norharman reduced the grooming and rearing.

Discussion. This study is the first demonstration of anti-withdrawal effect of norharman. A similar effect of ibogaine has been described in previous studies (5,6). Norharman is a physiological substance, while the ibogaine is of plant origin. Both drugs are indole derivatives with psychogenic/hallucinatory properties (7,8).

The precise mechanism of anti-withdrawal effects of norharman or ibogaine is not clear, but some relevant changes in the neurotransmitter systems could be considered. *Opioid system:* norharman is acting as a partial μ-agonist (7), while ibogaine is an agonist of κ-receptors (9). Accordingly, these drugs may displace/prevent the binding of naloxone to opioid receptors, which may lead to an anti-withdrawal effect. *Glutamate system:* norharman and ibogaine have morphine-like properties and recent data show that morphine blocks the glutamate-induced excitation (10,11). Glutamate antagonists prevent morphine withdrawal (1,12) and ibogaine acts as a competitive inhibitor of NMDA (N-Methyl-D-Aspartate) receptors of glutamate (13). Therefore, a blockade of the glutamate receptors could also be considered as an underlying mechanism of anti-withdrawal activity of norharman and ibogaine.

References

1. S.L.T. Cappendijk, R. de Vries and M.R. Dzoljic (1993) *Eur. Neuropsychopharmacol.* 3, 111-116
2. A.M. Morin (1984) *Brain Res.* 321, 151-154
3. S.L.T. Cappendijk and M.R. Dzoljic (1993) *Eur. J. Pharmacol.* 241, 261-265
4. B.S. Neal and S.B. Sparber (1986) *J. Pharmacol. Exp. Ther.* 236, 157-165
5. E.D. Dzoljic, C.D. Kaplan and M.R. Dzoljic (1988) *Arch. Int. Pharmacodyn.* 294, 64-70
6. S.D. Glick, K. Rossman, N.C. Rao, I.M. Maisonneuve and J.N. Carlson (1992) *Neuropharmacology* 31, 497-500
7. M.M. Airaksinen and I. Kari (1981) *Med. Biol.* 59, 190-211
8. N.R. Farnsworth (1968) *Science* 162, 1086-1092
9. D.C. Deecher, M. Teitler, D.M. Soderlund, W.G. Bornmann, M.E. Kuehne and S.D. Glick (1992) *Brain Res.* 571, 242-247
10. W.S. Willcockson, J. Kim, H.K. Shin, J.M. Chung and W.D. Willis (1986) *J. Neurosci.* 6, 2509-2520
11. L.M. Aanonsen and G.L. Wilcox (1987) *J. Pharmacol. Exp. Ther.* 243, 9-19
12. S. Tanganelli, T. Antonelli, M. Morari, C. Bianchi and L. Beani (1991) *Neurosci. Lett.* 122, 270-272
13. P. Popik, R.T. Layer and P. Skolnick (1994) *Psychopharmacol.* 114, 672-674