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A case of naloxone reversed acute coma after a single nefopam intramuscular administration. A link with opioids is sustained by naltrexone-sensitive nefopam analgesic effect in mice.

S Fedrizzi[1], F Minetti[2], I Dubuc[3], PE Gancel[4], S Mantoulet[2], C David[1], E Roupie[4], A Coquerel[1,5].
[1]University hospital, Pharmacology 14033 Caen, France, [2]Faculty of Medicine, 14032 Caen, France, [3]Faculty of Medicine & pharmacy, 76183 Rouen, France, [4]University hospital, Emergency Dpt 14033 Caen, France, [5]Inserm U 1075, University of Caen 14032, France

Nefopam is a well-known analgesic drug widely used since 1976. It is supposed to act within the central nervous system in a non-opioid dependent manner. Among the common reported side effects the main are tachycardia, blood pressure increase, atropinic symptoms and convulsions, malaise or sedative effects. We report a case of an acute and profound central depression after a unique 20 mg intramuscular (IM) administration of nefopam rapidly reversed by 0.4 mg of naloxone IV. Since the mechanisms of nefopam analgesia are still discussed, we tested mice on the hot plate test, with addition or not of 2 mg/kg of naltrexone.

Clinical report: a 40 years old man had an acute abdominal pain. He had no antecedent and did not take any medication. The diagnosis of renal colic is no doubt with the clinical exam. Firefighters were called to drive him to the hospital emergency. The physician administered 2 tablets of phloroglucinol per os and injected a bulb of 20 mg IM of nefopam (Acupan ®). During the transport (10-15 minutes), the patient became unconscious with a Glasgow score 7. He was dramatically hypotonic and progressively lacked of spontaneous breathing but was not intubated. He had no tachycardia, nor convulsion. He displayed a sudden resuscitation after a single injection of naloxone (0.4 mg IV), Transiently he relapsed in a drowsiness with a decreased respiratory frequency (9/min) which disappeared after a short perfusion of naloxone. The patient reported he remembered he was unable to move during the ambulance ride. This severe side effect with near death experience is not described in the drug dictionaries and the only 4 fatal cases previously reported are related to voluntary intoxications. In the French pharmacovigilance bank we found only 2 two cases with vegetative breakdown and loss of consciousness: (i) a 67 years old male who had history of a carcinoid tumor operated and was treated by somatostatin plus lisinopril for hypertension. During a painful episode of occlusion, he received 20 mg of nefopam IV. He had loss of consciousness and coma during 2 h, spontaneously regressive; (ii) a 78 years old male who had hypothermia (32.7°C) without feeling cold or shivering and a 6 Glasgow score. He received for post-operative pain a single morphine dose and a perfusion of nefopam (80 mg/24 h). He recovered in 6 hours.

The literature shows pro and cons for an opioid link in the nefopam effect. Using tail-flick test in mice Piercey and Schroeder (1981) concluded that nefopam was a non-narcotic centrally analgesic because its effect was unaffected by naloxone pretreatment (0.5 mg/kg, ip). But, Gray et al., (1999) using abdominal constriction assay and tail immersion test in mice have suggested an opiodergic component in nefopam antinociceptive effects. Thus, we tested mice on hot-plate (55°C) with nefopam (30 mg/kg, IP) or saline (in presence of naltrexone [NTX] (2mg/kg, SC) or saline. The NTX alone did not modify the jump latency (32.4 ± 2.0 versus 40.0 ± 5.4 s) while it reversed the increased latency induced by nefopam (64 ± 8.8 versus 131.6 ± 15.5 s; $p<0.01$). We concluded (i) the rare vital failures induced by nefopam have to be reversed by naloxone (ii) in mice, the opioid effect of high dosage nefopam is clear because antagonized by NTX. Further studies are needed to explore whether or not the release of endogenous opioids is the main source of this unexpected effect.