Pharmacology Review: Narcotic Analgesics and the Opiate Receptor in the Horse

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Drugs of the opiate group have been known since the dawn of history as the most effective medication available for relief of pain. Why they are so effective in pain relief has not become clear until recently, and in the last five years our understanding of the mechanism of action of opiate drugs has made major advances.

It is characteristic of opiate drugs, and particularly of their synthetic analogues, that they are pharmacologically active at very low concentrations. Thus, a 4-mg dose of fentanyl in a horse produces a marked increase in motor activity, and 1 mg of etorpine can immobilize a 5000-lb rhinoceros. This type of exquisite sensitivity to a drug has long been interpreted in terms of specific receptors for drug molecules, and the approximate shape of the opiate receptor was deduced from study of the structures of drugs which produced or blocked narcotic effects. It was not until very recently, however, that it became possible to locate these narcotic receptors in the body and to study them in any detail.

Identification of the narcotic receptor was made possible by the introduction of radiolabeled drugs of high specific activity.[9] With these highly radioactive drugs, all one had to do was add a very low concentration of the drug to a nervous tissue fraction, and it could be shown that a portion of the binding had the characteristics expected of binding to the narcotic receptor. More importantly, these receptors would also bind labeled narcotic antagonists, and the narcotic antagonists would displace labeled narcotics from the specific binding sites. Using these simple methods, two laboratories in the United States simultaneously reported identification and localization of opiate receptors in nervous tissue early in 1973.[6]

It was soon discovered that all vertebrates (including the horse)[7] possess these narcotic receptors, and they are found in the brain and spinal cord in areas known to be involved in pain perception or in emotional responses to pain. This then gave rise to the question of why should man and all vertebrates have specific receptors for drugs which are found primarily in the opium poppy? A logical answer to this question is that all vertebrates must also possess endogenous "opiate" molecules, and that the opiate narcotics are a

chance interaction with this system. A search for these "endogenous opiates" was immediately instituted, and they were soon identified as two closely related "opiod" pentapeptides, leucine and methionine "enkephalin."[2] These enkephalins are found in the same areas of the brain as the opiate receptors, but once released from nerve terminals, they are rapidly broken down by the body. Because of this rapid breakdown, they are not very pharmacologically active when given intravenously. However, if given intracerebrally, they produce good analgesia, and, insofar as one can tell with rats, they also produce addiction. More recently, nonmetabolizable analogues of the enkephalins have become available, and these presumably produce all the pharmacological actions of the enkephalins for longer periods.

It has, therefore, become clear in the last few years that opiate drugs act by mimicking the action of the body's own natural "painkillers," the enkephalins. What has been even more interesting is the discovery that the opiate receptor can exist in two configurations, one induced by the narcotic drugs and enkephalins and associated with sedation and analgesia, and another induced by the narcotic antagonists and associated with the analgesic blocking action of the antagonists. These antagonists, which are very potent drugs, can displace analgesics from the narcotic receptor within seconds after their intravenous injection, and completely reverse almost all the pharmacological effects of an opiate drug. Pentazocine, a narcotic drug which gives good analgesia and has a low addiction potential,[5] apparently acts to induce a configuration of the opiate receptor intermediate between these two forms, which likely accounts for its mixture of analgesic and narcotic antagonist activities.

As well as being found in the central nervous system, both the opiate receptors and the enkephalins are found in high concentrations in the gastrointestinal tract. This distribution of opiate receptors accounts for the well-known constipating effects of the opiate drugs, since intestinal tonus is increased and propulsive movements are reduced by this group of drugs. However, the tendency of opiate drugs to increase tonus in the gastrointestinal tract may create problems in the treatment of colic in horses, as increased intestinal tone due to the opiates may increase pain and counteract the analgesic effect of these drugs.

The narcotic analgesics typically produce analgesia, sedation, and respiratory depression in most species, and it is the sedation which leads to their usefulness in the capture of wild animals. In the horse, however, use of some narcotic drugs may be as-
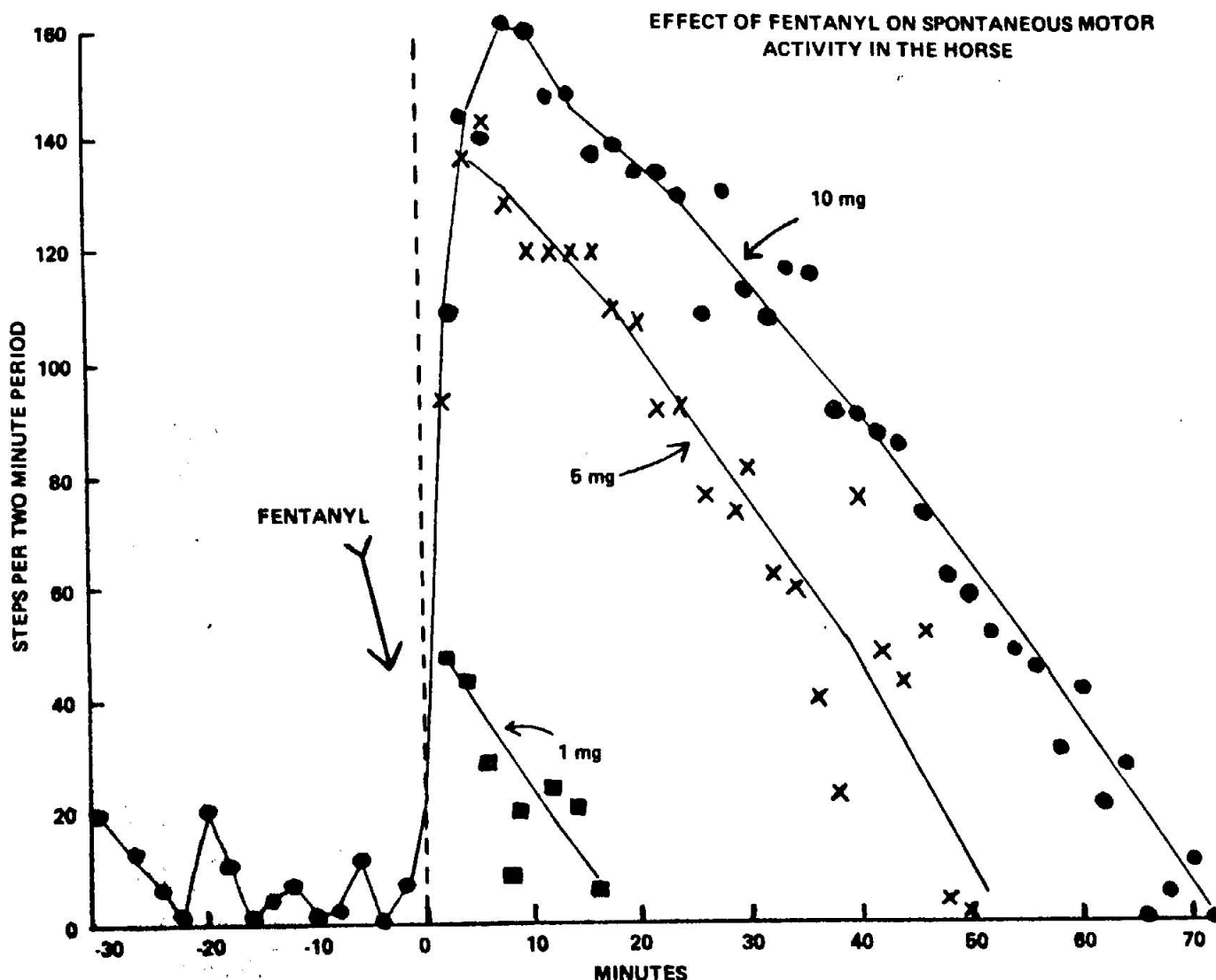
Figure 1—Spontaneous motor activity in the horse after fentanyl. Horses were confined in a partially sound-proofed loose box and observed through one-way glass. Each time the animal lifted its left foot from the ground, a single count was recorded. Data are plotted as counts per two-minute intervals. The solid circles (●‑●) on the left show spontaneous motor activity over a 30-minute control period. At indicated zero time at two-day intervals, this animal was administered 10 mg (solid circles, ●) 5 mg (crosses, ×) or 1 mg (solid squares, ■) fentanyl. The symbols indicate the observed locomotor response to each dose.[7]

sociated with a marked component of central nervous system stimulation. Thus, in Thoroughbreds intravenous administration of fentanyl citrate can increase spontaneous locomotion fifteenfold within a few minutes, and the effect can last for up to one hour (Figure 1). These movements are well controlled and coordinated, with the horse rarely stumbling or bumping into objects. It is this narcotic-induced motor activity which apparently has given rise to the use of fentanyl as a stimulant medication in racing horses. It has been suggested that this narcotic-induced motor activity may be related to dopaminergic receptor activation, although the activation appears to be indirect.[3] A logical combination, therefore, to produce sedation, tranquilization, and analgesia in the horse, is a narcotic-

tranquilizer cocktail. This combination, as an etorphine-acepromazine combination, has been commercially available in England for some time, where it is used for the immobilization of horses for minor surgery. The combination may be injected intravenously or subcutaneously, and the onset of action takes from 0.5 to 4 minutes. At this point, the animal goes down and is ready for surgery. When the surgical interference is over, a narcotic antagonist (diphrenorhine) is injected intravenously, and within 30 seconds the narcotic effect is reversed and only the tranquilizing action of acepromazine remains. Because of its rapid action and ready reversibility, this combination of drugs can be very useful in the handling of fractious animals.

The principal side effect seen with this combination of drugs is muscle tremors, presumably associated with the ability of narcotic drugs to produce increased motor activity, and respiratory depression which appears to be inherent in the action of all narcotic drugs. Both of these effects are rapidly reversed by the antagonist, which gives the clinician a good measure of control when using this combination of drugs. Great care, however, should be taken by the clinician not to accidentally inject himself with any of these very powerful narcotic drugs, as accidental self-injection of very small quantities of these drugs has caused deaths among the profession in England.

The relationship between the CNS excitation and muscle tremors induced by narcotics in the horse and their analgesic effects are of considerable importance for the use of this group of drugs in the horse. While some narcotics readily produce marked motor stimulation (Figure 1), others (such as pentazocine) are apparently less effective in this area. A determination of the relationship between these effects and identification of drugs or drug combinations for which the analgesic action is predominant would allow more effective therapeutic use of this group of drugs in the horse.

Another important use of the narcotic analgesics in the horse concerns their use in colic, both to control pain and prevent animals damaging themselves while they thrash about in pain. Their usefulness in this area, however, may be limited. A recent study by Lowe[5] in which he compared xylazine, meperidine, pentazocine, and dipyrone showed that among these only xylazine at the recommended doses gave good relief from symptoms. In an earlier study, Lowe[4] found that high doses of pentazocine (seven times the manufacturer's recommended doses) gave prolonged relief from colic symptoms but produced marked side effects such as muscle trembling and spasms. To judge from this recent work, the usefulness of narcotic analgesics alone in colic may be limited. In addition, it should be kept in mind that the analgesic action of xylazine is limited and that any amelioration of the signs of colic due to this drug are likely to be due to its sedative and muscle relaxant actions, since its analgesic actions are poorly defined.[1]

Recent studies on the pharmacokinetics of pentazocine in the horse have shown that urinary "clearance times" for pentazocine are prolonged, with traces of the drug being detectable in urine for up to six days after a single intravenous dose.[8] Horsemen should be aware of this prolonged clearance time for pentazocine and be careful about use of the drug within a week of racing. Recent studies on the kinetics of fentanyl in the human also suggest that this drug will have a prolonged clearance time in the horse when methods for its detection in the horse become available.

Because the morphine derivatives, and particularly the synthetic narcotics, are very potent drugs, they exist in urine in very low concentrations and their detection there can be difficult. One approach to this problem has been to take the natural narcotic receptor and use it as a drug binding protein in a "radioimmunoassay" type of experiment. Experiments of this type in our laboratory[7] have shown that horse urine contains substantial amounts of unknown materials which can displace narcotic drugs off narcotic receptors. Whether these materials are endogenous enkephalins or not is unclear, but they obviously interact strongly with the opiate receptor, and the possibility of false positives of this type must be borne in mind if radioimmunoassay is ever introduced into routine drug screening for the narcotic analgesics.

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