# Fluanison-Fentanyl Anaesthesia in the Rat

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*A mixture of fluanison, 10 mg/ml and fentanyl, 0.2 mg/ml, commercially available as Hypnorm® has been used in rats. Judged by the practical experience over five years it seems that this combination offers an anaesthesia which in certain respects is superior to that of barbiturates in the rat. It is faster, depresses less autonomic reflexes and there seems to be fewer complications both during and after the anesthesia. The most serious unwanted effect is depression of respiration, but it was only observed at high doses.*

The term neuroleptanalgesia has been used to describe an anaesthesia caused by the combined action of morphine-like analgesics and neuroleptic agents. Neuroleptanalgesia has been successfully applied in man since the early sixties. For the use in animals a combination of fluanison, a neurolepticum, and fentanyl citrate, an analgeticum (Hypnorm®) has been available for some years. However, it seems that on the whole its use has been restricted to the dog, though it can be a useful anestetic in other species too. In this study observations will be described obtained in the rat. The study is based on practical observations over more than 5 years. It will show that Hypnorm offers several advantages over barbiturates which suggest a more extensive use of it. The study is not intended to be a pharmacological description of its effects, since the observations have been collected while the analgeticum was used as a mean to study other physiological parameters.

## Methods

A combination of 10 mg fluanison and 0.2 mg fentanyl dihydrogen citrate per ml solution (Hypnorm®) has been used in white albino rats (Sprague Dawley and Wistar) ranging from 200—500 g weight. During the anaesthesia different kinds of surgery ranging from simple sutures of the skin to intracranial surgery have been made. The drug has been used either alone or in combination with Mebumal sodium, 60 mg per ml (Mebumal®), fentanyl citrate (Leptanal®) and gallamine triethiodide (Flaxedil®). The doses of Hypnorm used have been fairly standardized, about 0.25 ml to a 300 g rat and 0.30—0.35 to a 400 g animal. Lower doses were used for minor surgery. The standard combination of Mebumal and Hypnorm has been 0.20—0.25 ml of each to a 400—450 g rat. Leptanal was only used after previous administration of Hypnorm for extended anaesthesia. When this was done Flaxedil was given in addition. All drugs except Flaxedil which was given intravenously were injected intramuscularily (i.m.).

## Results

Hypnorm injected in the dose described above gives in the rat an anaesthesia which within 5 min is

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deep enough to allow even large surgical operations. All reactions to pain are abolished, the muscle strain is very much depressed and the animal is in a cataleptic stage. After about 30 min the first signs of return of consciousness may be observed. However, despite this surgery can be continued for about another 15 min. If regarded necessary, about 0.10 ml Hypnorm can be given i.m. This should be made as soon as possible after the first sign of recovery has been observed. It will keep the rat sufficiently anaesthtized for another 30—45 min.

With regard to the effects of Hypnorm on physiological parameters, the incidences of respiratory depression, the major problem with morphine-like types of analgesics, are low in the rat. Further, the tendency of defecation commonly seen in the dog, is rarely seen and of no problem in the rat. The arterial blood pressure is well maintained and circulatory insufficiency seems to be no problem during Hypnorm anaesthesia. The temperature control deteriorates and the body temperature should be controlled. Vestibular reflexes and other reflexes like swallowing, capability to keep the respiratory airways open as well as other unconditional reflexes remain though they are depressed. This is considered as one of the large advantages of this type of anaesthesia, and may depend on the fact that, centrifugal neural activity from the CNS to the periphery remains to a much larger extent than during barbiturates, which in certain nerves completely abolishes all centrifugal activity (*Hellekant* 1971). The postoperative recovery offers another main advantage in comparison with that of barbiturates, because the animals are never completely reflexless. Thus they rarely die from insuffocation and can be returned to their cages immediately after surgery. The only precaution we have used is to put the rats on a piece of soft paper tissue in the cage.

It was initially mentioned that Hypnorm sometimes was combined with Mebumal. This combination is useful for several reasons. Firstly, these drugs apparently have a synergistic effect. Therefore lower doses of each can be used. Secondly the time for induction and duration of their effects differ. After i.m. administration the anaesthesia of Mebumal has a slower onset but lasts longer than that of Hypnorm. Thirdly, their effects on the CNS differ. The Mebumal acts as a hypnotic agent and affects cortical levels which among other things gives relaxation of muscle tonus and abolishes reflexes to which Hypnorm adds its analgetic effects.

The relationship between the amount given of these drugs can and shall be adjusted to the situation. For more short lasting surgery with more rapid recovery wanted, more Hypnorm and less Mebumal are given and for longer lasting, deeper anaesthesia more Mebumal and less Hypnorm are administered in certain situations, when the experiment demanded that the centrifugal activity from the CNS was left unaffected as much as possible, the anaesthesia was maintained with fentanyl alone (Leptanal) or partly Leptanal and Hypnorm. In these cases the rats were given gallamine

triethiodide (Flaxedil) i.v. or i.p. and then put on artificial respiration. Flaxedil has a curariform action and competes with acetylcholine for the motor receptor sites on cross-striated muscles. It has no analgetic effect but judged by the general status of these rats and their blood pressure this combination seemed adequate.

## Discussion

The results described show that Hypnorm in the rat within 5 min causes an anaesthesia which is deep enough to allow even large surgery but with characteristics which leave some of the reflexes important for survival intact. With regard to the doses of Hypnorm used they were about twice as large as those recommended (Leo), 0.3—0.5 ml/kg b.w. in the dog. However, for minor shortlasting operations the dose can be considerably lowered in the rat too. But we never considered it vital to search for the lowest possible dose. In spite of this the recovery was faster and less complicated after Hypnorm than after Mebumal.

Though this study is not the result of a specific attempt to study the pharmacological action of the drug it seems worthwhile to compare some of our observations in the rat with those obtained in other species. In man neuroleptanalgesia has been used for more than a decade. Its effects on man seem not to differ significantly from those observed here in rat. *Dobkin, Israel & Byles* (1964) report unconsciousness within 5 min after i.v. injection. Since we observed similar time periods after i.m. injection, rate of absorption from the place of injection seem not to be the limiting factor in the onset of anaesthesia in man. The most severe unwanted effect in man seemed to be respiratory depression. This was also the case in the rat. However, their frequency increased when the drug was i.v. injected. After i.m. injection, apnoe was very rare. In man as in rat the effects on the blood pressure seemed equally small. In both species potentiation of the effect of barbiturate occurred. We have not recorded the effects on any metabolic parameter except the blood sugar level. In man an elevation has been reported (*Dobkin, Israel & Byles* 1964). During Hypnorm it seemed not to be significantly changed in comparison with the figures given by others in the unanaesthetized rat (*Altman & Dittmer* 1961). Excitation which occurs in the cat was never observed in the rat and defecation which is observed in the dog was rare and of no problem. From the above it seems that Hypnorm offers a generally anaesthetic alternative with several advantages over Mebumal.

In certain situations this type of anaesthesia seems to be the only alternative. Such a situation seems to be when it is essential that the centrifugal activity from the CNS remains as much as possible. This was the case when we studied the efferent activity to the tongue and the salivary glands in the chorda tympani proper nerve (*Hellekant* 1971). Under barbiturate no efferent nerve impulses could be recorded in the nerve. Fig. 1 shows an example of this effect of barbiturate. The left record was obtained before Mebumal but under Hypnorm anaesthesia.

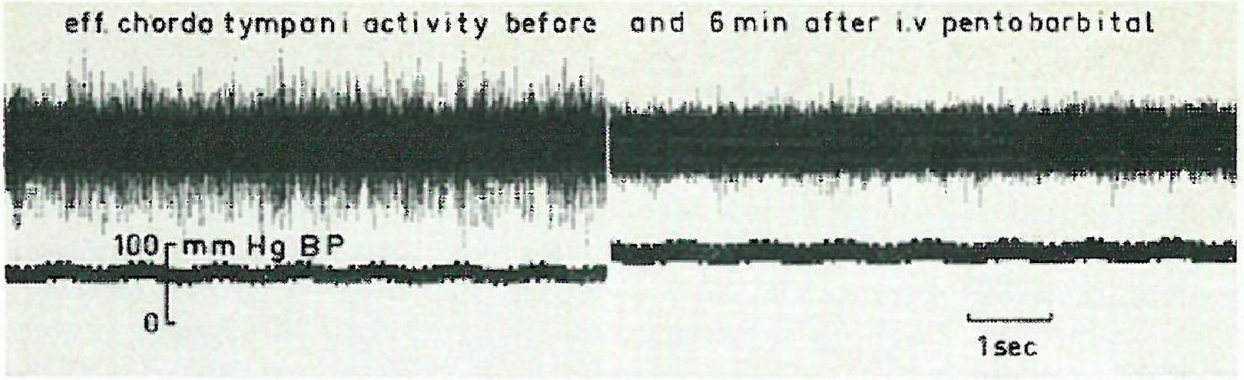


*Fig. 1.* It shows two recordings obtained from the central part of the cut chorda tympani proper nerve of a rat. The left recording was obtained under Hypnorm anaesthesia. It shows a strong spontaneous efferent nerve activity. Immediately after this record 6 mg Mebumal was injected i.v. The right recording was then obtained 6 min after the injection. It shows that barbiturate considerably decreased the efferent nerve activity.

It shows that during this anaesthesia a number of efferent impulses in the nerve could be recorded. Then, 6 min before the right record was obtained 0.1 ml Mebumal (6 mg) was injected i.v. The right part of Fig. 1 shows that this diminished very much the nerve activity. The effect was not the result of deteriorated blood supply to the brain because the systemic blood pressure was well maintained. It even increased after the Mebumal. This is shown in the bottom trace. The efferent activity will continue to decrease for another 10 min but if the animal is kept for a sufficient long time after barbiturate is given and provided the dose is not too large, some of the efferent activity will return.

It should be mentioned that the fluanison component of the Hypnorm also depresses the activity, it is therefore advisable to continue the anaesthesia with only fentanyl citrate. If the aim is to study the efferent activity then in most cases muscle relaxantia must be given after which the animal must be artificially respirated. Judged by the blood pressure and the general status of the animals, this procedure seems to be successful and adequate. In conclusion this discussion suggests that the effects of Hypnorm in the rat are similar and in some cases more favourable than those observed during neuroleptanalgesia in other species. In addition under Hypnorm, impulse activity can be recorded in nerves which under Mebumal are silent.

References

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