

## The effect of chronic toxicity of pethidine on the spinal cord: an experimental model in rabbits

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### Abstract

The aim of this study was to evaluate the toxicity of chronic spinal analgesia with pethidine in a rabbit model. We introduced epidural catheters in twenty New Zealand white rabbits, divided into two groups, and we administered 0.5 mg/kg pethidine or the same volume of normal saline through the catheters, for three consecutive days. Throughout the experiment, the animals were evaluated in terms of neurological status using the Tarlov score. After the rabbit's euthanasia, 4 μm sections of spinal cord stained with Hematoxylin–Eosin were analyzed by a pathologist blinded to the study for neurohistopathological changes. The results were statistically analyzed with Prism 5 software for Windows. No significant differences were noticed between the two groups in as far as body temperature ( $p=0.295$ ) and weight ( $p=0.139$ ) were concerned. In the group of animals, which received epidural pethidine, nine rabbits showed histological changes suggestive for neurotoxicity at the lumbar level of the spinal cord. These findings were significantly different compared with the control group which received only saline (no microscopic lesions revealed;  $p=0.0006$ ). When combining the data from both groups or using the pethidine group alone, there was a significant correlation between the presence of neurological injury (Tarlov score) and the presence of the histopathological lesions in the spinal cord ( $r=-0.709$ ,  $p=0.0002$  and  $r=-0.635$ ,  $p=0.013$ , respectively). Based on our findings, the chronic epidural administration of pethidine in rabbits induces moderate to severe histological changes on the spinal cord, but further investigations are needed to make a definitive statement about the histological effect of pethidine on the neurological tissue.

**Keywords:** rabbit, neurotoxicity, pethidine, epidural, spinal cord.

### Introduction

The progress in understanding the neuropharmacology of spinal cord processing of nociceptive input has resulted in an increased interest in the use of spinal drugs in anesthesia and especially in pain management [1]. Intrathecal and epidural opioids were first administered to human subjects in 1979, and since that time, they have been proven to provide effective and prolonged analgesia [2]. Pethidine is a phenylpiperidine opioid agonist analgesic, first synthesized in 1939, with anticholinergic, noradrenergic, and serotonergic effects [3, 4].

For its unique quality to combine both analgesia with local anesthetic effect, pethidine has been used in neuraxial anesthesia in general, obstetric, urologic and orthopedic surgery [5] and pain management in patients with chronic non-malignant pain [6] and intractable cancer pain [7].

Lipid solubility of opioids is a very important determinant of their pharmacokinetics following neuraxial administration [8].

For hydrophilic drugs, the intrathecal route is favored, because the therapeutic cerebrospinal fluid concentration is obtained with the administration of small doses [9]. If the drug is lipophilic the advantage of the epidural route is the diffusion through the spinal meninx [10].

The intrathecal or epidural application of receptor-specific drugs like spinal anesthetics may induce injury to the spinal cord and central nervous system through several mechanisms: decrease in neuronal blood supply by high concentrations of the solutions, long duration exposure to anesthetics and the use of adjuvants [11].

Pethidine is metabolized in the body by two-different pathways. The most clinically significant pathway is N-demethylation by the hepatic cytochrome P450 system to normeperidine, a non-opioid active metabolite. Normeperidine has half the analgesic potency of pethidine, but two to three times the potency of a central nervous system excitatory agent. Anxieties, shaky feelings, delirium, nervousness, hyperreflexia, tremors, twitches, multifocal myoclonus, and generalized seizures are some of the neurotoxicity effects of this metabolite [12]. It is

difficult to predict which individuals will experience neurotoxic effects and how severe the reaction will be.

Except the incidence of adverse effects increasing in a dose dependent manner [13], neuraxial administration of pethidin in dose lower than 1 mg/kg did not show any clinical significant manifestation of local neurotoxicity in human studies. However, some reports in which pethidine was used neuraxial describe neurological complications, but in one, the complication can not be attributed to pethidine itself [14].

Also, spinal pethidine has undergone no published preclinical animal neurotoxicity testing [15].

In humans, spinal pethidine has been reported as an effective drug for surgical anesthesia without any noted clinical neuropathology, but no formal neurotoxicity testing has been undertaken [5].

Currently there is a debate regarding pethidine's unique and dangerous side-effects profile, which is why pethidine has lost the confidence of many medical organizations [10].

In this study, we evaluated the toxicity of chronic spinal analgesia with pethidine in a rabbit model.

## ☒ Materials and Methods

### Animals and study design

The experiment protocol used was reviewed and approved by the Institutional Animal Ethics Committee, being in accordance with the Romanian laws.

Twenty New Zealand white rabbits (12 males and eight females), weighing 2.1–4.4 kg at the time of surgery, were used in the study. Based on a physical examination, all rabbits were considered to be *American Society of Anesthesiologists* (ASA) Grade 1 (normal healthy patient).

All animals were kept in approved facilities, had free access to food and water and were individually housed in a 12 hours light: dark cycle during the entire experimental period.

For the placement of the epidural catheter, xylazine (5 mg/kg, Xylazine Bio 2%, Bioveta, Czech Republic) was injected intramuscularly as a premedication into all rabbits. For the induction of general anesthesia, ketamine (40 mg/kg, Vetased, S.C. Pasteur Filiala Filipești S.R.L., Romania) was injected also intramuscularly into all rabbits.

Under general anesthesia, the rabbits were fixed in the prone position to facilitate the surgical procedures of epidural catheter implantation. After physical and chemical antiseptia, local anesthesia with 1% lidocaine, the catheterization was performed using a set for continuous epidural anesthesia (Perifix 451 Filter Set, Braun Melsungen AG, Germany). We performed a midline skin incision between the fifth and sixth lumbar spinous processes. The muscles between the two spine processes were separated by blunt dissection and the sixth lumbar spine process was removed with a Rongeur to expose the ligamentum flavum. Then the polyethylene catheter was directly inserted through the slit in the ligamentum flavum into the epidural space. The 22G polyethylene catheters were advanced 8 cm towards the

cephalous, the absence of blood or cerebrospinal fluid confirmed the correct position of the catheters. The external part of the catheter was tunneled subcutaneously along the back to the neck and connected to a capped connector partially implanted into the skin of the neck.

Finally, the lumbar incision was closed (3–0 silk) and enrofloxacin was administered (5 mg/kg intramuscularly, Enrofloxacin 5%, S.C. Pasteur Filiala Filipești S.R.L., Romania). After full recovery from general anesthesia, to confirm the location of the epidural catheter, a test dose of 0.5 mL lidocaine 1% was injected epidurally. The exhibition of a reversible segmental sensory and motor blockade was considered as the evidence of correct positioning of the catheter. After this procedure, rabbits were individually housed. Motor and sensory function and behavior changes were evaluated and recorded.

The rabbits were divided randomly into two groups, 12 in pethidine group and eight in normal saline group. On the second, third and fourth day of the study, in both groups we slowly injected through the epidural catheter 0.5 mL of solution containing 0.5 mg/kg pethidine (Mialgin, Sicomed S.A./Zentiva, Bucharest, Romania) in group P and normal saline for group NS. To flush the catheter, we injected an additional 0.2 mL normal saline. Seven days after the insertion of the spinal catheter, rabbits were euthanatized with thiopental (50 mg/kg intravenously, Thiopental sodium, E.I.P.I.C.O. MED S.R.L. Romania). Before cardiac arrest and under anesthesia, rabbits were perfused with 5 mL of mixture of 2% glutaraldehyde and 1% formaldehyde in a 0.1 mol/L phosphate buffer through the epidural catheter.

### Clinical evaluation

Rabbits were evaluated for neurological status during the entire experiment using the Tarlov score [16]. The animal's temperature was assessed before the start of the treatment.

### Histological examination

During necropsy, a segment 1 cm long on each side of the catheter tip was removed from the lumbar region of the spinal cord, and fixed in 10% phosphate-buffered formalin for 24 hours and embedded in paraffin wax, cut in 4  $\mu$ m sections, and stained with Hematoxylin–Eosin (HE).

From each animal, five slides were analyzed with an Olympus BX51 microscope with Olympus SP350 digital camera. "Cell B" basic imaging software (Olympus) was used for semiautomatic counting of the degenerative and inflammatory parameters.

Sections were analyzed by a pathologist blinded to the study for neurohistopathological changes including neural damage, chromatolysis and coagulative necrosis, gliosis, myelin sheath loss, infarction, subpial lymphocytic infiltration and leukodiapedesis.

Histology was graded as normal (grade 0) – without changes; mild (grade 1) – myelin pallor, myelin loss, axonal swelling, central chromatolysis of neurons and subpial lymphocytic infiltration; severe (grade 2) – the changes mentioned as mild plus infarction, gliosis and leukodiapedesis [17].

## Statistical analysis

Normally distributed data were expressed as mean±SD. Non-normally distributed data were expressed as median and interquartile range (25–75<sup>th</sup> percentile). Baseline weight and temperature data of the two groups were compared bidirectionally using a Student *t*-test. Because no differences between the individuals of the placebo group were noticed, a one-sample *t*-test was used, considering the hypothetical value of 4, for Tarlov score, and 0 for no histopathological lesions. To assess the strength of the association between neurological status and the presence of histopathological lesions in the spinal cord, a correlation matrix was used and the Spearman correlation coefficient was calculated and tested unidirectionally for significance. For all analyses, significance was set at a value of  $p < 0.05$ . The software used was Prism 5 for Windows.

## Results

### Neurological outcome

No neurological impairment was found in the control group, which received saline. In five rabbits from the pethidine group, mild neurological changes (Tarlov score 3) characterized by slight motor deficit of the hind limbs were identified.

No significant differences were noticed between the two groups in terms of both body temperatures ( $p=0.295$ ) and weight ( $p=0.139$ ). Neurological deficit (modified Tarlov score lower than 4) was observed in five rabbits receiving pethidine.

At the same time, there was calculated a significant difference in Tarlov score between the control group and the pethidine group ( $p=0.0172$ ).

### Microscopic findings

In the group of animals, which received epidural pethidine, nine rabbits showed histological changes suggestive for neurotoxicity at the lumbar level of the spinal cord. These findings were significantly different compared with the control group which received only saline (no microscopic lesions revealed;  $p=0.0006$ ). When combining the data from both groups or using pethidine group alone, there was a significant correlation between the presence of neurological injury (assessed by Tarlov score) and the presence of the histopathological lesions in the spinal cord ( $r=-0.709$ ,  $p=0.0002$  and  $r=-0.635$ ,  $p=0.013$ , respectively). The lesions were more severe at dorsal horn and peri-ependymal levels compared with ventral horn. The microscopic findings are presented in Table 1.

The gray matter showed different stages of neuronal damage varying from central chromatolysis to coagulative necrosis of neurons and randomly small necrotic areas of nervous tissue invaded by numerous glial cells, foamy macrophages and scattered neutrophils. Vascular damages characterized by endothelial necrosis, thrombosis and vascular infiltration with neutrophils and glial cells were found in one rabbit from the group treated with pethidine. The central canal presented hydropic

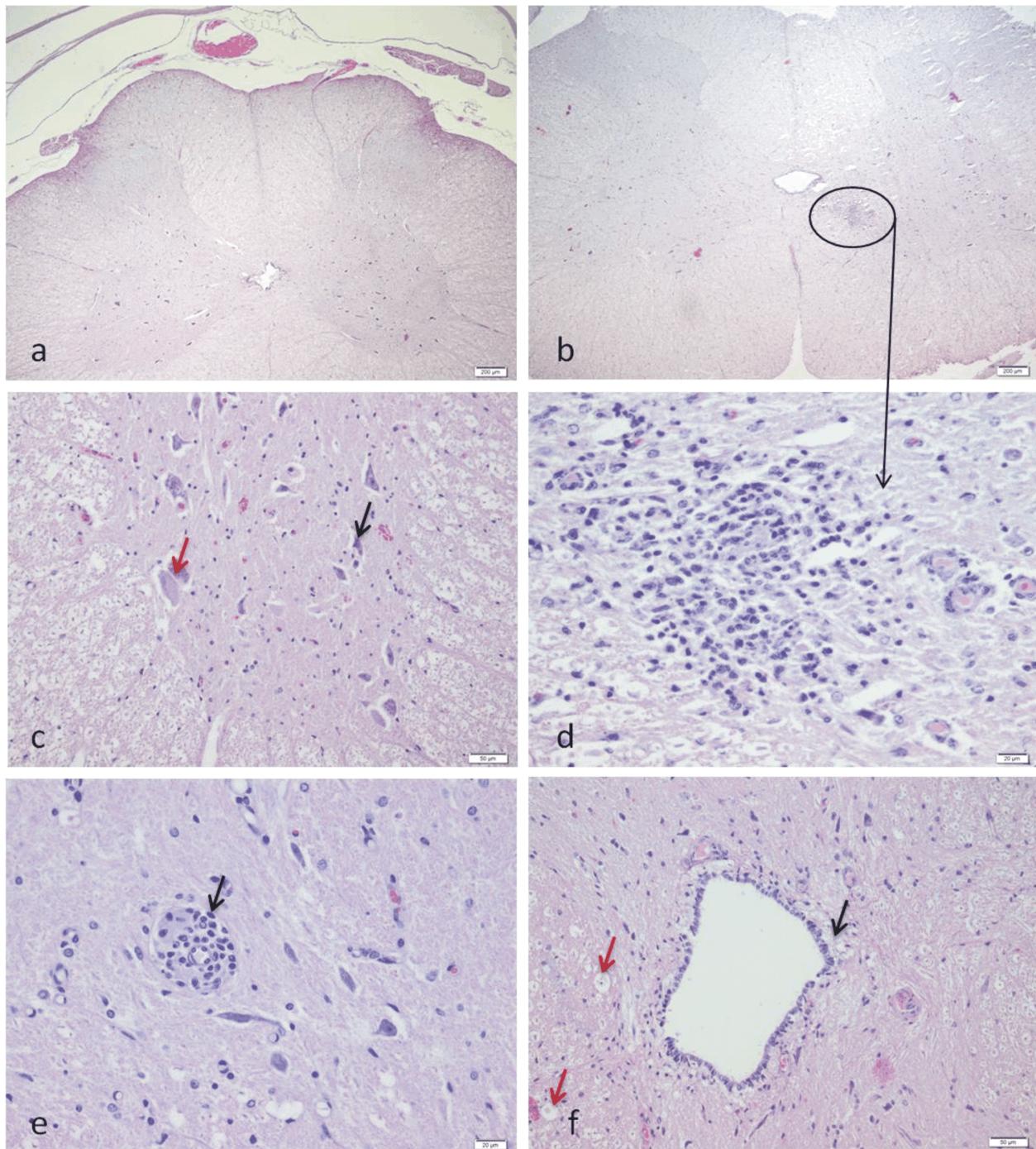
degeneration, necrosis and desquamation of ependymal cells, subependymal edema and discrete leukocytic infiltrate.

**Table 1 – Weight and rectal temperature before placement of the epidural catheter; neurological status and histopathological changes of the spinal cord, after seven days**

Rabbit No.	Weight [kg]	Rectal temperature [°C]	Tarlov score*	Histological score
<i>Pethidine group</i>				
64	2.180	38.7	4	0
15	2.425	38.5	4	0
39	2.450	39.3	4	1
35	2.500	40.2	4	1
31	2.510	39.7	3	2
22	2.668	39.8	4	1
16	2.840	39.6	3	1
11	2.849	38.8	3	1
36	2.897	40	3	2
17	2.912	38.4	3	1
68	2.980	38.9	4	1
28	3.077	38.8	4	0
Mean±SD	2.691±0.275	39.225±0.618		
Median (25–75 percentiles)			4 (3–4)	1 (0.25–1)
<i>Control group (saline)</i>				
24	2.120	40.1	4	0
53	2.230	39.1	4	0
51	2.320	38.9	4	0
50	2.980	38.8	4	0
4	3.050	38.1	4	0
69	3.510	38.4	4	0
62	4.300	38.8	4	0
56	4.420	39.2	4	0
Mean±SD	3.116±0.902	38.925±0.595		

\*Tarlov score: (0) paraplegia with no lower-extremity function; (1) poor lower-extremity function, weak antigravity movement only; (2) some lower-extremity function with good antigravity movement but inability to draw legs under body and/or hop; (3) ability to draw legs under body and hop but not normally; (4) normal motor function.

Multifocal white matter damage was observed only in the group treated with pethidine. The changes ranged from swelling of axons to replacement by small and empty spaces (digestion chambers) due to degeneration and phagocytosis. In some cases inside of these new cavities formed is present myelin debris and foamy macrophages or Gitter cells. No lesions induced by trauma including hematoma and presence of bone fragments into nervous tissue were identified in both groups of animals (Figure 1).



**Figure 1** – Light microscopic findings in the lumbar spinal cord of the rabbits. (a) No changes were observed in spinal cord of rabbit from control group, which received only saline (HE staining, scale bar = 200  $\mu$ m). (b) The light microscopic findings of spinal cord in the pethidine treated group revealing severe necrotic foci and inflammatory infiltrate close to central canal (black delimited area) (HE staining, scale bar = 50  $\mu$ m). (c) Central chromatolysis (red arrow) and acute neuronal coagulative necrosis with red, angular and shrunken neuronal cell bodies (black arrow) in the dorsal horn of gray matter (HE staining, scale bar = 50  $\mu$ m). (d) Inflammatory foci characterized by glial cells, macrophages and neutrophils; multiple intravascular hyaline microthrombi (HE staining, scale bar = 20  $\mu$ m). (e) Perivascular infiltrate with glial cells and macrophages in the dorsal horn of gray matter (HE staining, scale bar = 20  $\mu$ m). (f) Periependymal edema (black arrow) and multiple digestion chambers which contain myelin debris and Gitter cells (red arrows) (HE staining, scale bar = 50  $\mu$ m).

## Discussion

In the current study, the chronic effect of pethidine on the spinal cord morphology was studied in 20 rabbits by neurological and histological investigations.

The local anesthetic effects of opioids raise a high interest given their use in neuraxial anesthetic techniques.

Among phenylpiperidine compounds, pethidine has been successfully used as a sole anesthetic agent providing a segmental motor and sensory block comparable to lidocaine. Sufentanil and fentanyl demonstrated post-operative segmental analgesia probably through a specific opioids receptor-mediated mechanism but both these

two opioids present weaker local anesthetic qualities than pethidine [18, 19].

Pethidine is a lipophilic opioid and has been used for analgesia after short day case procedures. It is known to possess local anesthetic (motor and sensory fiber block) and opioid agonist activity and has been used successfully for intrathecal use as a sole agent in patients with sensitivity to local anesthetics. It is hyperbaric when injected intrathecally, so it may be possible to influence the height of the block with patient positioning. Pethidine is used infrequently because of the relative popularity of other opioids and unfavorable side effects, and also the unknown neurotoxicity profile [20]. Seventy years after pethidine became available, more and more anesthetists believe that it is time to critically challenge its continued use. Numerous drugs of similar vintage have long since been eliminated from anesthetic practice. Pethidine is not a popular drug in pain management, as it provides no advantage over other full agonists, and there are concerns of associated CNS toxicity. There is a lack of data concerning the neurotoxicity of pethidine [15] and additional toxicological data are needed [21].

In our study, the group of pethidine treated rabbits compared to negative control, revealed moderate to severe histological changes of their spinal cord. The lesions were mainly present in the gray matter and were characterized by neuronal degeneration and inflammatory infiltrate with glial cells, neutrophils and foamy macrophages.

It is accepted that vacuolation, demyelinating lesions, neuronal edema and diffuse neuronal degeneration are all strongly suggestive for a direct neurotoxicity of an anesthetic agent [11]. Other studies, on opioid neurotoxicity in animals, demonstrated the lack of neurotoxic effects of spinally administered morphine and sufentanil [22, 23]. Spinal fentanyl in mice has dose-dependent side effects but proved no neurotoxic effects even in high concentration (5000 µg/mL) or in dose 200 times higher than the usual ones [24].

Rawal N *et al.* reported a concentration-dependent occurrence of Nissl bodies' fusion and axonal edema in sheep treated with different and repeated doses of sufentanil for three days [25] but the authors consider that the mentioned effect may be due to a much thinner subarachnoid space in sheep compared with humans. In our study, pethidine was administered epidurally but, considering the structure of duramater, we can suppose that significant amounts of pethidine have passed into the subarachnoid space. In dog and sheep, continuous subarachnoid administration, over 28 days, of morphine and hydromorphone but not fentanyl, is followed by the occurrence of intradural granulomas [26, 27]. None of our study subjects presented epidural mechanical lesions to be attributed to the epidural catheter, probably due to the relatively short time interval in which the catheters were in site, due to a possible protective effect or dura mater itself or due to the pethidine liposolubility – being known that the spinally administered hydrosoluble opioids have a higher risk to induce intrathecal granulomas [28]. Following epidural pethidine, the morphologic lesions are maximal at the level of medullary dorsal horns and periependymal; lignocaine and bupivacaine may induce

neurotoxic lesions on proximal dorsal roots but the occurrence of periependymal lesions is poorly understood.

The presence of histopathological lesions in the spinal cord did not correlate significantly with neurological impairment assessed with the modified Tarlov score. In addition, a significant difference in Tarlov score was observed between the control group and the pethidine group after the administration of the drug. However, according to previous studies [17, 29], the use of Tarlov score to assess neurological impairment in rabbits lacks precision.

This study was primarily designed to evaluate the histological neurotoxicity after chronic epidural administration of the commercial available pethidine in rabbits.

Many anesthetists have used pethidine for decades, possibly without any complications but the pethidine metabolite norpethidine was incriminated for numerous cases of central nervous system toxicity [30]. Nor-meperidine toxicity is not reversed by administration of the opioid antagonist naloxone, which may actually worsen the effects by counteracting the depressant effect of pethidine [31].

## ✚ Conclusions

Based on our findings, the chronic epidural administration of pethidine in rabbits induces moderate to severe histological changes on the spinal cord but further investigations are necessary to make a definitive statement about the histological effect of pethidine on the neurological tissue.

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