Drugs of the Future 1998, 23(5): 485-490

CCC: 0377-8282/98

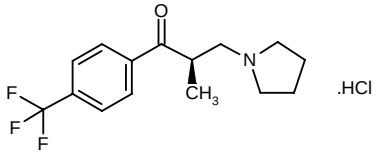
Lanperisone Hydrochloride

Centrally Acting Muscle Relaxant

Rec INNM

NK-433

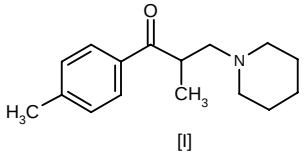
(–)-2(*R*)-Methyl-3-(1-pyrrolidinyl)-1-[4-(trifluoromethyl)phenyl]propanone hydrochloride



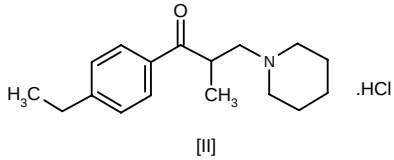
$C_{15}H_{18}F_3NO.HCl$ Mol wt: 321.77

CAS: 116287-13-9
CAS: 116287-14-0 (as free base)

EN: 150006



[I]



[II]

Synthesis

The Grignard reaction of 4-(trifluoromethyl)benzaldehyde (I) with ethylmagnesium bromide in ethyl ether gives 1-[4-(trifluoromethyl)phenyl]-1-propanol (II), which is oxidized with CrO_3/H_2SO_4 yielding 4-(trifluoromethyl)propiophenone (III). The condensation of (III) with pyrrolidine (IV) and paraformaldehyde by means of HCl in refluxing isopropanol affords racemic 2-methyl-3-(1-pyrrolidinyl)-propiophenone (V), which is finally submitted to optical resolution with *N*-acetyl-L-phenylglycine (VI) or D-malic acid (VII) and treated with dry HCl gas (1, 2). Scheme 1.

Description

M.p. 156-9 °C; $[\alpha]_D^{20}$ –45° (c 1.0, MeOH).

Introduction

Centrally acting muscle relaxants with high potency and few adverse effects have been an actively pursued target in the development of therapeutics for the treatment of several pathologies such as gait, hypertonia, lower back pain and shoulder stiffness. Drugs with potent muscle relaxing activity include tolperisone hydrochloride [I] and eperisone hydrochloride [II], two compounds structurally defined by a 2-methyl-3-aminopropiophenone moiety. Even though these compounds display lower potency as compared to agents such as baclofen, diazepam and tizanidine, they are widely used in clinical settings due to their low frequency of side effects. Recent research efforts at Nippon Kayaku, in the search for centrally acting muscle relaxants, have focused on 2-methyl-3-aminopropiophenone-containing compounds. Several interesting candidates and their enantiomers were screened for their biological activity, leading to the selection of NK-433 (lanperisone hydrochloride) for further development (1).

Pharmacological Actions

Administration of lanperisone at 5 mg/kg i.v. to rats produced 40.3% flexor reflex inhibition, with an LD_{50} of 61.1 mg/kg, as compared to the 31.3% and 34.5% inhibition observed with tolperisone hydrochloride and eperisone hydrochloride, respectively. At a dose of 3.5 mg/kg i.v., lanperisone produced 23.6% inhibition of anemic decerebrate rigidity in mice, as compared to 15.4% inhibition with tolperisone and 24.2% inhibition with eperisone; a dose of 50 mg/kg p.o. lanperisone produced 72.9% inhibition of the flexor reflex in this model. The LD_{50} of lanperisone administered orally was calculated to be 800 mg/kg using the Van der Waerden method. At 100

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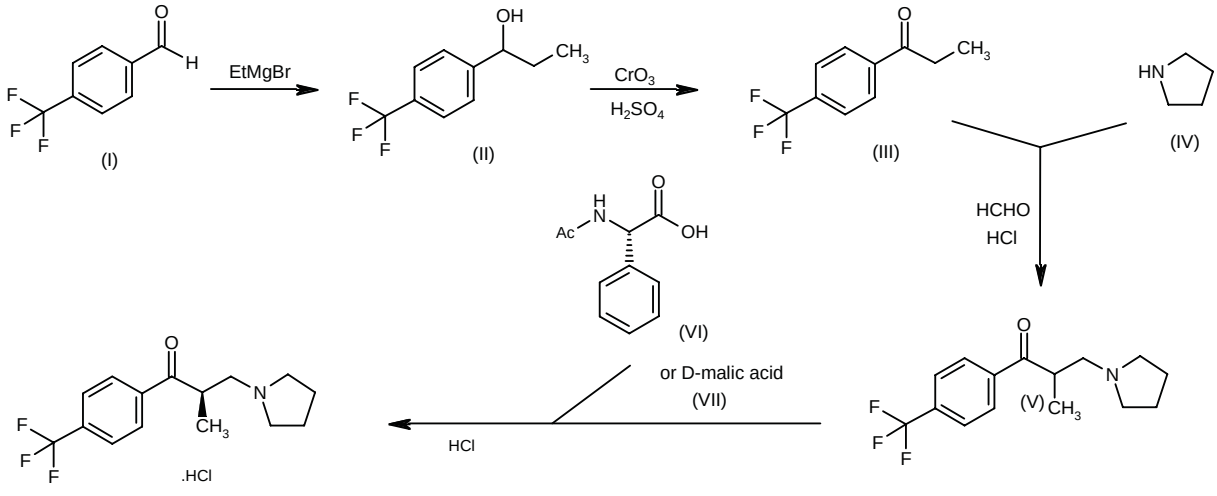
Scheme 1: Synthesis of Lanperisone Hydrochloride



mg/kg p.o., lanperisone produced a 65-70% decrease in the amplitude of the flexor reflex as compared to baseline values, while tolperisone and eperisone had no effect (1).

Lanperisone administered at doses of 10 mg/kg i.v. and p.o. inhibited the mono- and polysynaptic ventral root reflex potentials in anesthetized rats by 40% and 60%, respectively, while eperisone at a dose of 10 mg/kg i.v. inhibited the mono- and polysynaptic reflex potentials by 60% and 80%, respectively. The dorsal root reflex potential in anesthetized cats and spinal (anesthetized and spinalized) cat preparations was inhibited by lanperisone at a dose of 10 mg/kg i.v. by 60% and 40%, respectively. Intravenous administration of lanperisone (10 mg/kg) depressed the flexor reflex mediated by group II afferent fibers by 70% in anesthetized rats, as did oral administration of the drug at a dose of 50 mg/kg. Lanperisone doses of 25 mg/kg p.o. produced a slight inhibition of the patellar reflex in anesthetized cats, while the flexor reflex was dose-dependently suppressed by 60% and 80% after administration of lanperisone at 12.5 and 25 mg/kg p.o., respectively. Facilitation of the flexor reflex mediated by group II afferent fibers induced by intrathecal administration of noradrenaline in anesthetized spinal rats was suppressed significantly by lanperisone at a dose of 50 mg/kg p.o. Spinal reflexes were inhibited by approximately 50% by LPS-9, a metabolite of lanperisone, after a dose of 10 mg/kg i.v. These observations imply that lanperisone is a nonselective inhibitor of spinal reflexes, and that the mechanism of spinal reflex depression induced by lanperisone involves the inhibition of the descending noradrenergic tonic facilitation within the spinal cord (3).

In rats, lanperisone doses of 10 mg/kg i.v. inhibited the tonic vibration reflex in the masseter muscle with a maximum inhibition of 70%. Maximum inhibition by eperisone was comparable to that obtained with lanperisone, but eperisone-induced inhibition was shorter in duration. The jaw opening reflex was depressed significantly by lanperisone (10 mg/kg), although maximum inhibition did not exceed 25%. Eperisone (10 mg/kg i.v.) also inhibited the jaw opening reflex with a magnitude and time course similar to that of lanperisone. At 10 mg/kg i.v., lanperisone inhibited the tonic periodontal masseteric reflex in a dose-dependent manner, displaying a maximum inhibition of 90% immediately after administration. Eperisone at 10 mg/kg i.v. inhibited this reflex with a magnitude similar to that of lanperisone, reaching maximum values of 90% after 10 min, but the inhibition was eliminated much faster than that produced by lanperisone. Intragastric administration of lanperisone suppressed the tonic periodontal masseteric reflex at doses of 25 mg/kg or higher, although maximum inhibition was observed much later than with intravenous administration. Eperisone at doses of 100 mg/kg or lower did not affect the reflex following intragastric administration, but increasing the dose to 200 mg/kg produced significant reflex depression. IC_{50} values for lanperisone and eperisone when administered intragastrically were reported to be 54 and 168 mg/kg, respectively, indicating that lanperisone was approximately 3-fold more efficient than eperisone using this route of administration. These results suggest that lanperisone inhibits masticatory muscle reflexes controlled by the γ motor system, and may therefore be a therapeutic agent for the treatment of the temporomandibular joint syndrome in humans (4).

The effects of lanperisone on decerebrate rigidity were evaluated in rats and mice in order to assess the clinical potential of the compound for the treatment of human spasticity. Intravenous administration of lanperisone at 10 mg/kg depressed γ rigidity by 50%, while an oral dose of 100 mg/kg produced a peak depression of 70%. IC_{50} values for lanperisone, eperisone and tolperisone in rat α rigidity preparations were 6.3, 8.4 and

9.3 mg/kg, respectively, following intravenous administration. Lanperisone (5 mg/kg i.v.) also blocked muscle spindle discharges produced by pinna pinching in rats, implying that lanperisone inhibits γ activity, while the effect produced by eperisone on muscle spindle discharges was similar to that produced by lanperisone. Furthermore, this inhibition was observed after administration of a lower dose than that necessary to evoke a significant α rigidity depression (2.5 mg/kg i.v.), suggesting that this effect is involved in the preferential depression of γ rigidity. Since oral administration of lanperisone depressed α as well as γ rigidity, it was suggested that the drug has ameliorating effects on spasticity caused by γ hyperactivity and spasticity without hyperexcitability of the γ motor neuron. Lanperisone at 50 and 100 mg/kg p.o. had no effect on morphine-induced Straub tail reaction in mice or the muscle tone of normal animals in the traction test, although a dose of 200 mg/kg p.o. depressed the Straub tail reaction in 6 out of 8 animals. These observations indicate that lanperisone selectively affects muscle tone in decerebrate animals without affecting the excessive muscle tone in animals treated with morphine or in untreated animals. Eperisone and tolperisone showed pharmacological profiles practically identical to that of lanperisone. Tolperisone slightly inhibited muscle spindle discharges, while eperisone did not exhibit peripheral activity. Inhibitory effects of tolperisone and eperisone on α and γ rigidity were comparable to lanperisone when administered i.v., while lanperisone administered orally was at least 3-fold more potent than both tolperisone and eperisone. Eperisone and tolperisone did not affect the Straub tail reaction induced by morphine through excessive excitation of the sarcococcygeus dorsalis muscle. These results indicate that lanperisone and tolperisone mainly depress the excessive muscle tone of γ rigidity as compared to the muscle tone induced by morphine in the Straub tail reaction. The results from the γ rigidity experiments indicate that lanperisone may have potent ameliorating effects in the treatment of human spasticity (5).

The effects of lanperisone on muscle tone of experimental rigidity and spinal reflexes were compared to those of eperisone and tolperisone in rats. Lanperisone (5-10 mg/kg i.v. and 25-200 mg/kg p.o.) reduced muscle tone of the forelimbs of rat anemic decerebrate rigidity and intercollicular decerebrate rigidity with potency equal to that of tolperisone and eperisone when administered intravenously, and with a 3-fold greater potency than tolperisone and eperisone when administered orally. Lanperisone was, in addition, twice as efficient as tolperisone and eperisone in protecting against tonic extensive convulsions. In anesthetized rats, neither lanperisone nor eperisone affected neuromuscular transmission at 200 mg/kg p.o. or muscle spindle afferent discharges at 10 mg/kg i.v. Lanperisone (5-10 mg/kg i.v., 25-200 mg/kg p.o.) inhibited the flexor reflex in the tibialis anterior muscle with potency equal to that of eperisone and tolperisone when administered intravenously, and with 4-fold higher potency when administered orally. Both lanperisone (6.3-25 mg/kg p.o.) and eperisone (25-50 mg/kg p.o.) inhibited the patellar and flexor reflexes in intact cats. Inhibition produced by lanperisone of the patellar reflex was slightly stronger than that produced by eperisone, while lanperisone inhibition of the flexor reflex was at least 4-fold stronger and longer-lasting than the inhibition produced by eperisone. Patellar reflex inhibition by lanperisone and eperisone in spinal cats was comparable to the inhibition produced by the two compounds in intact cats, although flexor reflex inhibition by lanperisone was notably less than that observed in intact cats. The reduction of inhibition in spinal cats versus that in intact cats was minimal in the case of eperisone. The results indicate that lanperisone may have clinical utility as a centrally acting muscle relaxant for the treatment of spasticity, with benefical effects on hpertonia of muscles and hyperflexia (6).

In anesthetized spinal rats, lanperisone reduced the facilitation of the group II flexor reflex induced by yohimbine and noradrenaline. Given that noradrenaline mediates the facilitation of the group II flexor reflex through α_1-receptors, these observations imply that lanperisone inhibits α_1-mediated responses in the spinal cord (7).

The effects of lanperisone on bladder contractions induced by electrostimulation of the pelvic nerve were evaluated in rats using cystometrogram. Administration of lanperisone increased bladder capacity and raised the pressure threshold of micturition. Lanperisone produced a stronger inhibition of the pelvic contractions following afferent stimulation of the pelvic nerve than following efferent stimulation of the postganglionic pelvic nerve. These observations indicate that lanperisone inhibits the micturition reflex by acting at the level of the central nervous system (8).

A second study compared the effects of lanperisone on the urinary bladder in anesthetized rats with those of flavoxate, oxybutynin and inaperisone. The inhibition of rhythmic bladder contractions by lanperisone (2.5, 5 and 10 mg/kg i.v.) was equal to that produced by flavoxate and stronger than that induced by inaperisone, while the inhibition produced by oxybutynin was most potent. Contractions of rat bladder strips were blocked by lanperisone after induction by either carbachol or electric field stimulation. The activity of lanperisone on contractions induced by electric field stimulation was comparable to that of flavoxate and inaperisone, but was less potent than that of oxybutynin. Carbachol-induced contractions were inhibited most potently by oxybutynin, followed by lanperisone and inaperisone, and least potently by flavoxate. These results indicate that lanperisone may have clinical potential for the treatment of pollakiuria and urinary incontinence, and that its pharmacological effects on the urinary bladder may be more similar to those of inaperisone than to those of oxybutynin and flavoxate (9).

Toxicity

Toxicity of lanperisone was evaluated in male and female rats given single doses of 263, 395, 593, 889,

1333 or 2000 mg/kg p.o. or 26.9, 35.0, 45.5, 59.2, 76.9 or 100 mg/kg i.v. Oral administration produced various adverse effects including depressed respiration, cyanosis, muscle relaxation, clonic convulsions, sedation and/or prone or lateral position within 30 min after dosing. In addition, transient salivation with foam, reduced eye closure reflex, urorrhea and/or rale and staining around the eyelid and the nose were also reported on the day of administration. However, all side effects were reversed within 1-4 days. Mortality was observed in both male and female rats after doses of 593 mg/kg or higher, and occurred within 5 min to 24 h after drug administration. Animals that did not die appeared to have compromised locomotor activity, paleness, reduced body temperature, emaciation, hunched posture and/or red to brown urine, and died in less than 2 days. Male rats given 395 and 593 mg/kg exhibited reduced body weight, while female rats had only reduced body weight gain. Autopsy revealed liquid material retention and hemorrhage in the stomach, reduced tension in the small intestine and hemorrhage in the urinary bladder. Intravenous administration of the drug produced adverse effects similar to those observed after oral administration. The side effects appeared within 2 h but were not detected thereafter. A dose of 45.5 mg/kg or higher produced death in both sexes within 1 min after administration, although body weight measurements and pathological examination revealed no abnormalities. LD_{50} values after oral administration were determined to be 525 and 569 mg/kg in males and females, respectively, while intravenous administration gave LD_{50} values of 52 mg/kg in males and 49 mg/kg in females, indicating lanperisone does not produce gender-based differences in LD_{50} values (10).

To further evaluate oral toxicity, lanperisone was administered to rats by gavage at doses of 5.6, 16.7, 50 or 150 mg/kg/day for a period of 26 weeks. Laboratory examinations after the dosing period revealed fatty changes in hepatocytes in males given doses of 16.7 mg/kg or higher. Serum total protein and albumin levels were higher than in control animals, while triglyceride concentrations were lower in male rats receiving 150 mg/kg. Rats from the 150-mg/kg/day group only demonstrated fatty change in hepatocytes in a 5-week recovery test following drug administration although this change was not as pronounced as the one observed immediately after the administration period. Additional side effects observed included hepatocyte hypertrophy, liver swelling and increased liver weight. Salivation, increased water and food consumption during the administration period, and increased heart, kidney and adrenal gland weights and forestomach hyperkeratosis were also attributed to lanperisone. Females given 150 mg/kg/day displayed increased ovary weight after the recovery period, although the weight increase was not associated with histopathological changes. The observations from the study indicate that the no adverse effect level of lanperisone is 5.6 mg/kg in rats following the described regimen of administration (11).

Clinical Studies

The effects of lanperisone were compared to eperisone in 320 patients with cervical and lower back syndrome in a double-blind multicenter study. Patients received either lanperisone (100 mg b.i.d.) or eperisone (150 mg t.i.d.) for a period of 2 weeks. Final improvement ratio produced by lanperisone was significantly higher than that produced by eperisone in patients with cervical syndrome, while patients with lower back syndrome demonstrated equal improvement ratios after treatment with either drug. Adverse effects were observed in 9.9% of patients treated with lanperisone and in 15.8% of cases treated with eperisone but did not include any serious symptoms. There were no abnormal laboratory results in the lanperisone-treated group. Two cases of laboratory abnormalities were reported in the eperisone-treated group, although their association to the drug was not established. Lanperisone was considered more effective than eperisone in this group of patients and the safety profiles of the two drugs were considered equal. Thus, lanperisone appears to be safe and effective for the treatment of cervical and lower back syndrome involving excessive muscle tension and pain (12).

Lanperisone was evaluated in terms of efficacy, safety and usefulness for the treatment of cervicobrachial syndrome and lumbago in 46 patients given daily doses of 50, 100 and 150 mg divided in 2 administrations per day. Moderate or better improvement was recorded in 46.7, 47.1 and 92.9% of the patients in the groups given 50, 100 and 150 mg/day, respectively. Two adverse reactions were reported in the 150-mg/day group, and there were no abnormal results from clinical laboratory tests. Thus, lanperisone at doses of 50 and 100 mg/day demonstrated a similar efficacy, while the 150-mg/day dose showed a greatly improved efficacy. Safety profiles were similar in all 3 groups, suggesting that lanperisone administered twice-daily is safe for the treatment of cervicobrachial syndrome (13).

The clinical effects of lanperisone for the treatment of lumbago were evaluated at doses of 50, 100 and 150 mg/day in a multicenter double-blind study in 250 patients in order to determine the optimal dose. Moderate or better improvement was reported in 71.0, 64.9 and 73.0% in the groups receiving 50, 100 and 150 mg/day, respectively. Evaluation of improvement in osteoarthritis of the spine, lumbago and osteoporosis after 1 week of treatment showed that moderate or better improvement was documented in 37.9, 48.4 and 58.3% of the patients treated with 50, 100 and 150 mg/day, respectively, while after 2 weeks of treatment, improvement was observed in 75.0, 78.6 and 84.4% of patients in the 3 corresponding dosing groups. Overall safety rating was estimated to be 95.0, 89.2 and 83.9% in the 50-, 100- and 150-mg/day groups, respectively. Side effects were reported in 5% of the cases in the 50-mg/day group, 10.8% in the 100-mg/day group and 12.6% in the 150-mg/day group. Thus, the optimal dose of lanperisone for the treatment of lumbago was determined to be 100 mg/day (14).

When evaluated for the treatment of cervicobrachial syndrome and lumbago involving myotonic pain in 46 patients, lanperisone at a dose of 50 mg b.i.d. demonstrated an improvement rating of 83.3%, while the safety and global ratings were established as 95.2 and 78.6%, respectively (15).

A second study evaluated lanperisone 100 mg/day divided in 2 doses in 19 patients with cervicobrachial syndrome. Moderate or better improvement was observed in 52.6% of the cases, while overall safety and global usefulness ratings were determined to be 84.2% and 47.4%, respectively. Adverse reactions were reported in only 1 case, and abnormal findings in clinical laboratory tests were not observed. Lanperisone was deemed safe and effective for the treatment of cervicobrachial syndrome (16).

Lanperisone at a dose of 150 mg p.o. b.i.d. was compared to eperisone (150 mg t.i.d.) in patients with spastic paralysis treated during 4 weeks. No significant differences were observed between the two treatment groups as far as final improvement ratio. General improvement and the global improvement ratings for neurological signs and subjective syndrome ratios increased in both groups by the end of the fourth week as compared to evaluation after the second week of treatment. Safety profiles were similar in both groups, and neither abnormal clinical laboratory findings nor adverse effects were detected. The two drugs appeared to be equally useful leading to the conclusion that lanperisone is equivalent to eperisone in terms of efficacy, safety and usefulness for the treatment of spastic paralysis related to cerebral and spinal cord lesions (17).

The efficacy, usefulness and long-term safety of lanperisone (150 mg/day) were evaluated in 55 patients with spastic paralysis treated for 12-24 weeks. The study drug demonstrated an efficacy rate of 37%, as defined by the number of patients showing moderate improvement. Side effects were recorded in 20.4% of the patients and included weakness, lightheadedness and gastrointestinal symptoms such as nausea or vomiting. Overall usefulness of the treatment was established at 28.3%. No abnormalities were detected in clinical and laboratory examinations, and dependency and tolerance did not emerge in any subjects. Thus, lanperisone was deemed to be a safe and effective therapeutic option for patients with spastic paralysis (18).

Subjective effects of lanperisone were compared to those of diazepam and placebo in 12 healthy volunteers in order to evaluate the psychological dependency potential of lanperisone. Subjects given lanperisone (75 mg) did not demonstrate notable somatic symptoms as compared to subjects given placebo, although 1 subject given 150 mg lanperisone demonstrated moderate somatic symptoms. Six subjects in the diazepam group (10 mg) reported moderate or more severe somatic symptoms. Psychological symptoms described as a mild “preference” were reported by 1 subject in the 75-mg lanperisone group, by 2 subjects in the 150-mg lanperisone group, and by 3 subjects in the 10-mg diazepam group, while no subjective effects were observed in the group given placebo, leading to the conclusion that only diazepam was remarkable in “preference”. Thus, subjective effects that may be relevant to psychological dependency potential are more pronounced with diazepam therapy than with lanperisone (19).

The therapeutic effects and safety of lanperisone were assessed in patients with hemiplegia of apopletic secondary disease. Resistance in the ankle joint training machine improved significantly by the second and fourth weeks as compared to baseline values, as did the R index of the pendulum test. Improvements in global ratings and subjective symptoms were determined to be 55.6 and 77.8%, respectively, at the end of the 4 and 8 weeks, while the overall efficacy rate was 50%. Safety and usefulness ratings were calculated to be 66.7 and 41.7%, respectively, and adverse reactions were recorded in 4 cases. Plasma C_{max} values of lanperisone and its active metabolite LPS-9 were reached after 1-4 h following administration and decreased rapidly. The results suggest that lanperisone is a clinically useful antispastic drug (20).

The clinical usefulness of lanperisone for the treatment of temporomandibular joint arthrosis was evaluated in 27 patients. Moderate and marked improvement was seen in 56.0% of the patients treated, and the drug’s usefulness was rated as 52.0%. Twelve patients reported drug-related side effects, although none of them were severe. Thus, lanperisone also appears to be safe and useful for the treatment of temporomandibular joint arthrosis (21).

A granule formulation of lanperisone hydrochloride with improved stability compared to the conventional tablet formulation has been claimed (22).

An NDA was filed in Japan for lanperisone in July, 1995 (23).

Manufacturer

Nippon Kayaku Co., Ltd. (JP).

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