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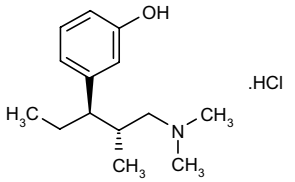
Tapentadol Hydrochloride

Prop INNM; USAN

Analgesic
Mu-Opioid Receptor Agonist
Noradrenaline Reuptake Inhibitor

CG5503
BN200

(–)-(1*R*,2*R*)-3-(3-Dimethylamino-1-ethyl-2-methylpropyl)phenol hydrochloride



$C_{14}H_{23}NO.HCl$
Mol wt: 257.80

CAS: 175591-09-0

CAS: 175591-23-8 (as free base)

EN: 232967

Abstract

Tapentadol is a novel, investigational, centrally acting analgesic with a dual mode of action: mu-opioid receptor agonism and noradrenaline reuptake inhibition. Tapentadol showed analgesic effects in a wide range of animal models of acute, inflammatory and chronic neuropathic pain. Both mechanisms of action were shown to contribute to its analgesic effects. Generally, the potency of tapentadol was between that of morphine and tramadol. The activity of tapentadol resides in a single enantiomer and is independent of metabolic activation. It has no active metabolites, and the main metabolic pathway for elimination of tapentadol is phase II glucuronidation. Thus, tapentadol has a low potential for drug-drug interactions. Preclinical studies suggest a favorable tolerability profile compared to pure mu-agonists. Data from early clinical studies suggest improved gastrointestinal tolerability compared to morphine at doses producing similar efficacy. Phase III clinical trials are currently investigating the therapeutic potential of this innovative compound.

Synthesis

Tapentadol hydrochloride is synthesized by ether cleavage (*e.g.*, conc. HBr) from its corresponding methyl ether (III). Compound (III) can be obtained by several methods, *e.g.*, starting from diethyl ketone, which is transformed under standard Mannich conditions to racemic (I). The Grignard reaction with 3-bromoanisole and subsequent separation of diastereomers (crystallization as HCl salt from 2-butanone with $TMSCl/H_2O$) and enantiomers (HPLC, CS phase) gives (–)-(*S,S*)-(II). Removal of the hydroxy group can be achieved diastereoselectively (under retention) by chlorination with thionyl chloride, followed by treatment with zinc borohydride (from $ZnCl_2$ and $NaBH_4$), leading to (–)-(*R,R*)-(III) (Scheme 1).

Background

Compounds that activate opioid receptors, in particular the mu-opioid receptor (MOR) subtype, have been used for many decades for the treatment of moderate to severe pain (1). However, extensive clinical experience with the prototypical MOR agonist morphine indicates that, although this compound is very effective against acute pain, it may be less effective against chronic pain conditions, especially those of neuropathic or inflammatory origin (2, 3). The finding that chronic pain can lead to MOR downregulation may offer a molecular basis for the relative lack of efficacy of morphine in long-term treatment settings (4). Moreover, prolonged treatment with morphine may result in tolerance to its analgesic effects, most likely due to treatment-induced MOR downregulation and other regulatory mechanisms. As a consequence, long-term treatment can result in substantial increases in dosing in order to maintain a clinically satisfactory analgesic effect. Furthermore, morphine has a limited therapeutic window, as its analgesic efficacy generally coincides with diverse side effects. These side effects are dose-limiting and result in poor patient compliance, especially in the case of chronic pain (5, 6). Nausea and emesis are typical for classical MOR agonists and

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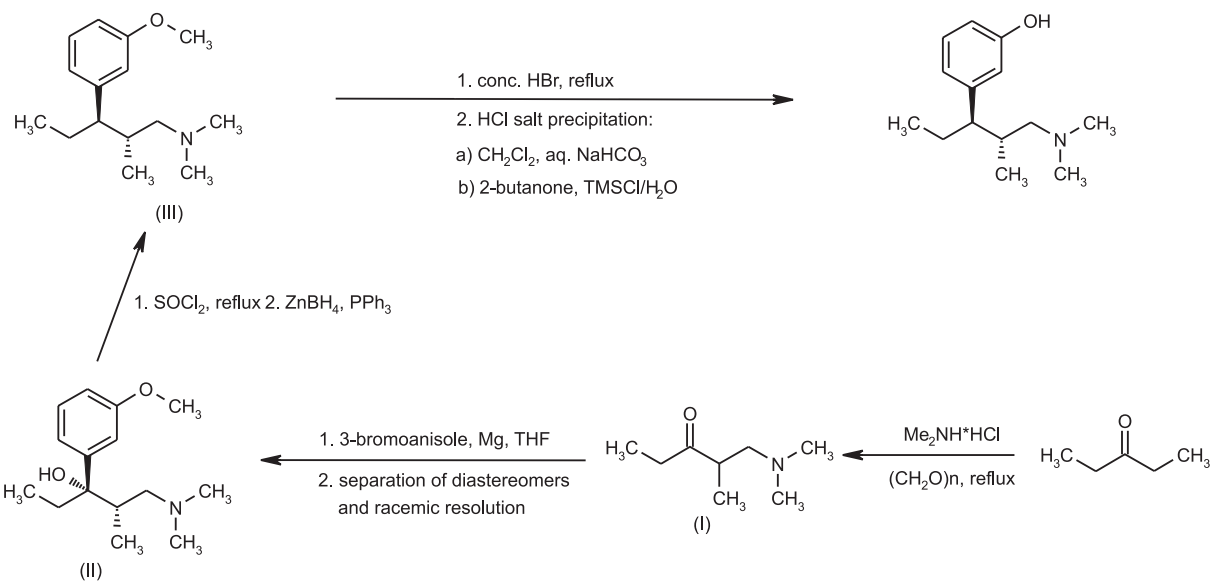
Scheme 1: Synthesis of Tapentadol hydrochloride



appear directly after the start of treatment. Nausea and emesis are normally transient in the first week of treatment, but have a negative impact on patient compliance in this early treatment phase. Further side effects typical of morphine and other MOR agonists are constipation, mental clouding and respiratory depression, the latter being a rare but life-threatening event. Moreover, prolonged use of opioids results in physical dependence and may lead to addiction. Taken together, these points indicate that there is a significant medical need for safer and more tolerable opioids with an improved efficacy profile in chronic pain therapy.

Since the isolation of morphine two centuries ago, numerous derivatives have been synthesized, with the primary aim of separating analgesic effects from unwanted effects (7-9). However, the cloning of the MOR and the use of transgenic mice lacking this receptor (10, 11) indicated quite convincingly that both the analgesic efficacy and the unwanted effects of morphine and its analogues are mediated by the same receptor (*i.e.*, the MOR). This strongly suggests that a dissociation of analgesia from these unwanted effects can not be achieved with a selective MOR agonist.

An alternative approach to improve the therapeutic usefulness of opioid analgesics is to combine MOR activation with an additional mechanism of action aimed at enhancing analgesic efficacy. Such an additional analgesic mechanism may result in an opiate-sparing effect, thereby attenuating the unwanted effects of MOR activation. Activation of the noradrenergic descending pain-inhibitory pathway can be considered a candidate for such an additional mechanism. Compounds that inhibit the reuptake of noradrenaline (NA) are effective analgesics, particularly against chronic pain conditions in which opioids are considered to be less effective or problematic due to their side effects (12-15). This mode of action was shown to be particularly effective in neuropathic pain (16). It was also demonstrated that such compounds can potentiate the analgesic effects of morphine (17, 18).

The concept of combined mechanisms of action was realized for the first time with the introduction of tramadol, a compound that produces MOR activation and inhibition of serotonin (5-HT) and NA reuptake (19-21). Tramadol is a racemate with active metabolites (22), each of which has a different profile of activity. NA and 5-HT reuptake inhibition mainly reside in the (–)- and (+)-enantiomer of the parent compound, respectively, whereas MOR activation resides in the (+)-enantiomer of *O*-desmethyl-tramadol, and to a lesser degree in (+)-tramadol itself (23). Interestingly, it was shown that systemic administration of either (–)- or (+)-tramadol in humans induces analgesia (24, 25), leading to the suggestion that a noradrenergic mechanism may contribute to the analgesic profile of racemic tramadol. In addition, it was found that the analgesic efficacy of tramadol was less pronounced in subjects who showed a reduced capability to form the (+)-*O*-desmethyl metabolite ("poor metabolizers"), as compared to subjects who produced relatively high levels of the metabolite. This indicates that the MOR-active metabolite contributes significantly to the analgesic profile of tramadol (26). Therefore, it was postulated that both enantiomers and the *O*-desmethyl metabolite are necessary for the full analgesic profile of tramadol (27, 28).

It can be argued, however, that inhibition of 5-HT reuptake contributes less to the analgesic profile of tramadol than MOR activation and NA reuptake inhibition.

First, it is highly likely that the analgesic efficacy of (+)-tramadol is (at least in large part) mediated by the (+)-*O*-desmethyl metabolite, which relatively potently activates the MOR. Second, and more importantly, it was found that while tramadol-induced analgesia is partially blocked by co-administration with either the MOR antagonist naloxone or the NA receptor antagonist yohimbine, it was completely abolished by combined administration of both antagonists (26). Also, preclinical and clinical evidence with selective 5-HT reuptake inhibitors, selective NA reuptake inhibitors and mixed 5-HT/NA reuptake inhibitors indicates that analgesia is more readily obtained by NA reuptake inhibition than by 5-HT reuptake inhibition (14, 16, 29, 30).

Therefore, it appears that the combination of MOR activation with NA reuptake inhibition should provide an improved and potent analgesic with high efficacy against acute and chronic pain conditions and an improved side effect profile compared to classical MOR agonists. In order to establish this novel pharmacological concept, an extensive synthesis program was initiated at Grünenthal, with the aim of combining MOR activation and NA reuptake inhibition in one chemical entity (*i.e.*, "dual mode of action" concept).

The present paper reviews the preclinical and early clinical profile of tapentadol, one of the molecules resulting from this program that combines the dual mode of action in a single chemical entity, without active metabolites. The compound shows a broad analgesic profile in animal models of acute and chronic pain. In addition, it has a lower propensity to produce tolerance and physical dependence, and it may have an improved therapeutic window compared to morphine.

Preclinical Pharmacology

Tapentadol was characterized as a MOR agonist and NA reuptake inhibitor. The compound showed K_i values of 0.1 and 0.5 μM in a rat MOR binding assay and a rat synaptosomal NA reuptake assay, respectively. Affinity for the other opioid receptor subtypes (*i.e.*, kappa-opioid receptor [KOR], delta-opioid receptor [DOR] and ORL1 receptor [NOP]) was at least approximately 1 order of magnitude lower (Table I). The affinity of morphine at the MOR was about 50-fold higher than that of tapentadol. At the recombinant human MOR, both tapentadol and morphine had a somewhat lower affinity than at the rat MOR (K_i = 0.54 and 0.023 μM, respectively).

Tapentadol was characterized in a GTPγS assay with human recombinant MOR as a MOR agonist (EC_{50} = 0.67 μM). MOR agonism was confirmed in a guinea pig ileum assay. In this test, electrically induced twitch contractions of the ileum were inhibited with an IC_{50} value of 1.49 μM, an effect that was antagonized by the MOR antagonist naloxone.

In addition to its MOR-agonist effect, tapentadol was found to inhibit the reuptake of NA, as assessed in isolated rat brain synaptosomes, with a K_i value of 0.5 μM. In contrast to its NA reuptake-inhibitory properties, the reuptake of 5-HT was only weakly inhibited (K_i = 2.4 μM) and dopamine and choline uptake was not affected to any relevant degree (Table II). To ascertain that the results measured in the synaptosomal uptake assay represented the appropriate neurotransmitter reuptake systems, binding assays with rat and human transporters were also performed. The results of these assays confirmed the data obtained with the functional reuptake systems.

Further assessment of the target selectivity of tapentadol was performed in a screening profile including more than 50 neurotransmitter receptors, reuptake transporters, ion channels and enzyme systems, including cyclooxygenases. These studies indicated that tapentadol showed submicromolar affinity for muscarinic M_1-M_5 receptors (K_i = 0.47-1.19 μM). Interaction with the muscarinic receptor was further assessed in the acetylcholine-induced guinea pig ileum contraction assay. The

Table I: Comparison of the affinity of tapentadol and morphine at various opioid receptor subtypes, as assessed in binding assays using rat brain membranes (MOR, KOR, DOR) or human recombinant receptors (NOP).

Compound	K_i value (μM)			
	MOR	KOR	DOR	NOP
Tapentadol	0.1	0.9	1.0	> 100
Morphine	0.002	0.17	0.08	> 100

MOR: mu-opioid receptor; KOR: kappa-opioid receptor; DOR: delta-opioid receptor; NOP: ORL1, or nociceptin receptor.

Table II: Comparison of tapentadol and desipramine with respect to neurotransmitter reuptake inhibition, as assessed in rat brain synaptosomes.

Transmitter	K_i value (μM)	
	Tapentadol	Desipramine
Noradrenaline	0.5	0.001
5-HT	2.4	1.4
Dopamine	NE	ND
Choline	39	ND

NE: no effect (5% inhibition at 1 μM); ND: not determined.

results indicated that the compound has weak anticholinergic activity (pA_2 = 6.2).

The *in vivo* functional relevance of NA and 5-HT reuptake inhibition by tapentadol was examined by means of microdialysis probes implanted into the ventral hippocampus of freely moving rats. While morphine at doses of up to 10 mg/kg i.p. did not affect extracellular levels of NA and induced a small increase (approx. 70% above baseline) in extracellular 5-HT levels, tapentadol at doses of up to 10 mg/kg i.p. produced a large, dose-dependent increase in extracellular NA levels (approx. 450% above baseline at 10 mg/kg i.p.) and a much smaller increase in extracellular 5-HT levels (approx. 130% above baseline at 10 mg/kg i.p.). These *in vivo* data correlate well with the *in vitro* data obtained in NA and 5-HT reuptake systems and confirm a much more pronounced functional role of NA compared to 5-HT.

The analgesic properties of tapentadol were investigated in various pain models in mice, rats, rabbits and dogs. These experiments were performed with different routes of administration, including intravenous (i.v.), intraperitoneal (i.p.), oral (p.o.), intracerebroventricular (i.c.v.) and intrathecal (i.t.) routes, and employed a wide range of pain stimuli, including thermal, tactile, chemical and electrical modalities. The pain tests consisted of models of acute nociceptive pain (tail-flick, hot-plate, tooth pulp stimulation and phenylquinone-induced writhing models), acute and persistent inflammatory pain (yeast and formalin models), visceral pain (colorectal distension and mustard oil-induced visceral pain), chronic mononeuropathic pain (chronic constriction injury [CCI] and spinal nerve ligation [SNL] models) and chronic polyneuropathic pain (vincristine and streptozotocin models). Tapentadol induced effective analgesia in all models (analgesic ED_{50} values compared to morphine are shown in Table III), indicating that it is an analgesic with activity against acute and chronic pain of diverse etiology.

Tapentadol also showed analgesic activity when administered centrally (either i.c.v. or i.t.), suggesting that tapentadol-induced analgesia is (at least partially) centrally mediated. Investigations with tapentadol glucuronide, the major metabolite of tapentadol, in the tail-flick test in mice showed that the glucuronide is devoid of analgesic activity. This supports the notion that tapentadol has no active metabolites.

Interestingly, despite its 50-fold lower MOR affinity compared to morphine, tapentadol was only 2-3 times less potent than morphine after systemic administration. This consistent finding across different models may be due to a better brain penetration of tapentadol, but also suggests that the NA reuptake-inhibitory property of tapentadol potently interacts with its MOR-agonist property, resulting in more potent analgesia than would be expected solely from its MOR agonism.

To further substantiate the dual mechanism of action of tapentadol, the extent to which its analgesic properties could be blocked by the MOR antagonist naloxone and by the NA receptor antagonist yohimbine was examined. In the rat formalin test, it was found that tapentadol-induced analgesia was reduced by pretreatment with either antagonist, indicating that both opiate and noradrenergic mechanisms are involved in its analgesic effect

Table III: Overview of the analgesic activity of tapentadol[1] and morphine[1] in various animal models of acute and chronic pain.

Pain model	Route of application	ED_{50} value (mg/kg)	
		Tapentadol	Morphine
Tail-flick (mouse)	i.v.	4.2	1.4
	p.o.	53.4	18.9
	i.c.v.*	65.0	0.4
Tail-flick (rat)	i.v.	2.2	1.1
	i.p.	10.0	5.8
	p.o.	121	55.7
Tail-flick (dog)	i.v.	4.3	0.7
Hot-plate 48° C (mouse)	i.v.	3.3	1.3
Hot-plate 58° C (mouse)	i.p.	27.7	8.5
Phenylquinone-induced writhing (mouse)	i.v.	0.7	0.4
	p.o.	31.3	4.7
	i.c.v.*	18.4	0.08
Tooth pulp stimulation (rabbit)	i.v.	3.1	2.3
Formalin (phase II) (rat)	i.p.	3.8	0.8
Yeast model (rat)	i.v.	2.0	0.9
	i.p.	10.1	5.6
	i.t.*	56.8	1.9
Colorectal distension-induced visceral pain (rat)	i.v.	5.5	3.5
Mustard oil-induced visceral pain (rat)	i.v.	1.5	1.0
Spinal nerve injury neuropathy (rat)	i.p.	8.3	2.9
Chronic constriction injury neuropathy (rat)	i.p.	13.0	13.8
Vincristine polyneuropathy (rat)	i.p.	5.1	3.4
Diabetic polyneuropathy (rat)	i.p.	8.9	3.0

*Dose in μg/animal. [1]All drug doses for preclinical and clinical testing are for the hydrochloride salt.

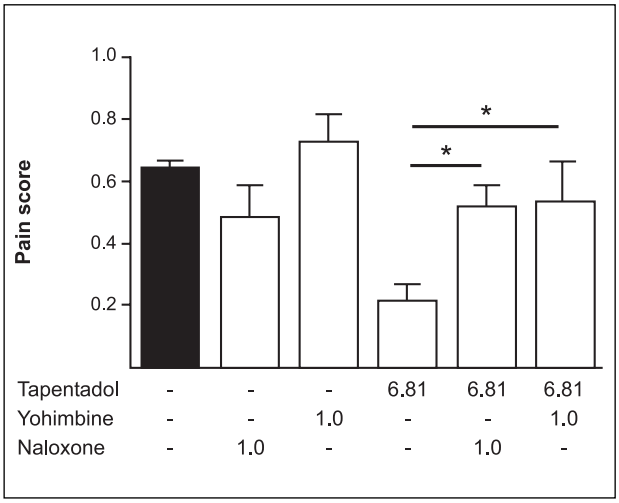


Fig. 1. Antagonism of tapentadol-induced analgesia by the MOR antagonist naloxone and the α_2-adrenoceptor antagonist yohimbine in the formalin test. The figure shows the pain score (according to a rating scale) during phase II of the test. n=10 rats per group.*p < 0.05 *versus* tapentadol treatment. "-" indicates administration of vehicle. Data are shown as mean + S.E.M.

(Fig. 1). Further experiments performed in the SNL model of neuropathic pain demonstrated that the analgesic effect of tapentadol was more sensitive to antagonism by yohimbine than to antagonism by naloxone, whereas the reverse was true for morphine. Taken together, these findings suggest that a prominent part of the analgesic activity of tapentadol in chronic pain states results from its NA reuptake inhibition.

The development of tolerance to the analgesic effects of tapentadol and morphine (at equieffective doses) was investigated in two different pain models in rats —the tail-flick test of acute nociception and the CCI model of chronic neuropathic pain. In both models, tolerance development was considerably delayed with tapentadol compared to morphine (duration of treatment until complete tolerance had developed in the tail-flick and CCI models: tapentadol, 51 and 27 days, respectively; morphine, 21 and 10 days, respectively). These findings may be of relevance for the treatment of chronic pain, because in clinical practice with classical opiates, dose increases may be required due to opioid tolerance.

Physical dependence liability was assessed after precipitated withdrawal (naloxone-precipitated jumping and body weight reduction in mice and rats, respectively) and after spontaneous withdrawal following 3-4 weeks of treatment (diverse withdrawal symptoms in rats). In each model, tapentadol induced less physical dependence than morphine (data from the naloxone-precipitated withdrawal model are shown in Fig. 2).

Pharmacokinetics and Metabolism

In mice, rats and dogs, tapentadol was absorbed rapidly (t_{max} = 0.5-1 h) after p.o. administration. The absolute bioavailability was low and ranged from 3% in dogs to 8% in rats. In male Wistar rats, the mean half-life in plasma was 0.5 h after i.v. administration of 7 mg/kg, but it was clearly longer (> 2 h) after p.o. administration of 300 mg/kg. The clearance was 228 ml/min/kg and the volume of distribution was 10.4 l/kg after i.v. administration. In dogs, the mean terminal disposition half-lives were 0.87 and 3.7 h, respectively, after i.v. and p.o. dosing. The volume of distribution after i.v. administration was 10.9 l/kg and the clearance amounted to 145 ml/min/kg. Protein binding was low in all animal species tested, and ranged from 11% in rabbits to 19% in rats. Comparable protein binding of 19% was found in human plasma.

After p.o. administration of 150 mg/kg [^{14}C]-labeled tapentadol to male Sprague-Dawley rats, the fraction of the radioactive dose recovered in the urine was 69% and that in the feces was 26%, amounting to essentially complete elimination within 48 h. In female rats, approximately 94% of the radioactivity was excreted via urine and 5% via the feces. The high proportion of the dose recovered in urine implies a high extent of absorption of 69-94% of the dose. After oral dosing in male beagle dogs (20 mg/kg), 81% of the dose was recovered in the urine and 18% in the feces within 48 h.

The main metabolic pathway for the elimination of tapentadol in animals and man is phase II metabolism. Glucuronidation was found in mice, rats, dogs and humans; sulfation occurred to a minor extent only in dogs and humans. Phase I biotransformations occurred to a lesser extent, and included hydroxylation of the aromatic ring system with subsequent conjugation and *N*-demethylation, followed by conjugation. *In vitro* investigations on the interaction of tapentadol with cytochrome P-450 enzymes and studies with human hepatocytes indicated no potential for inhibition or induction. Rapid and extensive tissue distribution was found in rats, with kinetics paralleling the conditions in plasma. Radioactivity clearly crossed the blood-brain barrier.

In healthy subjects, tapentadol is rapidly absorbed after a single oral dose, reaching peak serum concentrations within 1-2 h. The calculated pharmacokinetic parameters after i.v. and p.o. administration are summarized in Table IV.

The absolute oral bioavailability of 32% is comparable to that of morphine. The clearance of 1531 ml/min after i.v. administration equals the liver blood flow (1400 ml/min). Dose linearity could be shown after i.v. and p.o. administration of tapentadol in the dose range of 10-80 mg and 75-200 mg, respectively. Steady state after oral administration 4 times daily was reached after approximately 25-30 h. The mean accumulation factor was 1.8, which was determined primarily by the dosing interval and apparent terminal half-life of tapentadol. Basic pharmacokinetic parameters of tapentadol did not change during multiple dosing. A mass balance study with [^{14}C]-labeled tapentadol demonstrated that more than 98% of the radioactivity was recovered in the urine during 48 h. Fecal excretion was negligible (~ 1%).

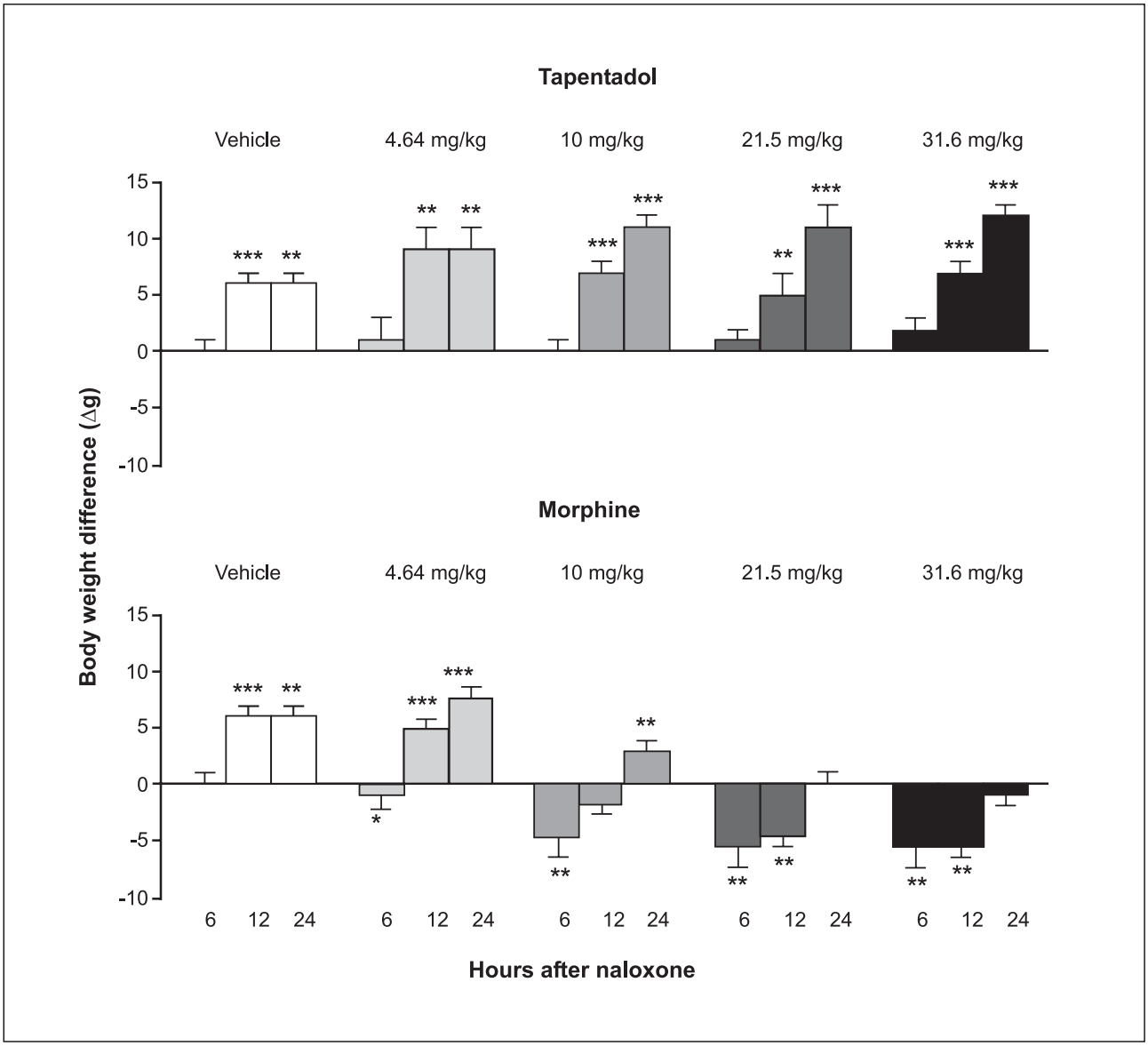


Fig. 2. Comparison of the physical dependence liability of tapentadol and morphine in rats. Data show the effects of naloxone-precipitated withdrawal on body weight measured 6, 12 and 24 h after t.i.d. treatment with tapentadol or morphine during 3 weeks. n=12 rats per group.*$p < 0.05$, **$p < 0.01$, ***$p < 0.001$ *versus* last day of the treatment regimen. Data are shown as mean + S.E.M.

Table IV: Summary of pharmacokinetic parameters after a single i.v. infusion and oral administration of tapentadol in 24 fasted male volunteers. Data are presented as mean values and refer to tapentadol (free base).

Parameter	15-min infusion	IR oral
	40 mg	100 mg
AUC (ng.h/ml)	379	314
C_{max} (ng/ml)	243	78
t_{max} (h)	0.26	1.2
$t_{½,z}$ (h)	4.1	4.9
CL (CL/f) (ml/min)	1531	5007
V_z ($V_{z/f}$) (l)	540	2127
F (%)	—	32

IR: immediate release; C_{max}: peak plasma concentration; t_{max}: time to C_{max}; $t_{½,z}$: terminal half-life; CL: total clearance; V_z: volume of distribution; F: bioavailability.

Safety

Tapentadol induced only weak emesis-like behavior in the ferret at doses ranging from 10 to 31.6 mg/kg i.p. Approximately 20% of the animals in both the low- and high-dose groups exhibited emesis with food expulsion. Compared with low doses of morphine (0.125-0.5 mg/kg s.c.), tapentadol was associated with a substantially lower incidence of retches and vomits per animal (Fig. 3), and the duration of these effects was shorter.

The gastrointestinal-inhibitory activity of tapentadol was also relatively weak compared to morphine. In mice, tapentadol and morphine inhibited charcoal transit from the stomach to the cecum with ED_{25} values of 28.1 and 5.9 mg/kg i.p., respectively, and inhibited PGE_2-induced diarrhea with ED_{50} values of 10.3 and 1.1 mg/kg i.p., respectively.

Tapentadol dose-dependently reduced spontaneous respiratory frequency in conscious rats following i.v. bolus injection of 4.64-14.7 mg/kg. In a rat plethysmography model, i.v. tapentadol reduced the respiratory minute volume at 18 mg/kg, but not at 2 and 6 mg/kg. CO_2-induced stimulation of respiratory frequency was less potently inhibited by tapentadol than by morphine (ED_{50} = 0.71 and 0.23 mg/kg i.v., respectively). Tapentadol induced an increase in arterial pCO_2 in rats, but again, with lower potency and efficacy than morphine. Daily treatment with tapentadol or morphine resulted in complete tolerance to the respiratory depressive effect within 22 days, indicating that, with respect to respiratory depression, tapentadol does not show delayed tolerance development compared to morphine (such as that seen with respect to analgesia).

Tapentadol weakly inhibited the I_{Kr} current in Chinese hamster ovary (CHO) cells, with an IC_{50} of 36 μM. The *O*-glucuronide, the *N*-demethyl and the sulfate metabolites of tapentadol were even less active (IC_{50} > 250 μM). Tapentadol slightly shortened the action potential duration at 10 and 100 μM in guinea pig papillary muscle. In isolated spontaneously beating atrial preparations and electrically stimulated papillary muscles of guinea pigs, tapentadol exerted negative chronotropic and negative inotropic effects only at concentrations higher than 100 μM.

In conscious rats, tapentadol (4.64-14.7 mg/kg i.v.) induced transient (10-15 min) increases in arterial blood pressure and heart rate. In anesthetized rabbits, i.v. bolus injections of 1-10 mg/kg tapentadol led to dose-dependent decreases in heart rate and arterial blood pressure and to a negative inotropic effect. Tapentadol did not increase the heart rate-corrected Q-T_c time. In conscious dogs, i.v. infusion of tapentadol at doses of 3, 6 and 9 mg/kg produced dose-related, reversible increases in arterial blood pressure, heart rate and cardiac output. The Q-T time was decreased in parallel to the increase in heart rate. In anesthetized dogs, i.v. infusion of tapentadol at doses of 0.5, 1.5 and 4.5 mg/kg induced a dose-dependent hypotensive effect. Tapentadol did not affect Q-T or Q-T_c times in anesthetized dogs.

Acute toxicity studies were performed in rats and mice after i.v. and p.o. administration. Clinical signs of toxicity included hyperexcitability, irregular respiratory activity and convulsions. LD_{50} values after p.o. administration ranged from approximately 350 mg/kg in mice to > 1000 mg/kg in rats; after i.v. administration, LD_{50} values were approximately 45 mg/kg in both species.

In repeated-dose toxicity studies, tapentadol was administered i.v. and p.o. for 4 weeks to rats and for 2 weeks to dogs. In addition, the toxicological profile was evaluated in long-term studies with a treatment period of 13 and 52 weeks in dogs and 26 weeks in rats. In these studies, treatment-related clinical signs were characterized by CNS-related behavioral disorders, such as fearfulness and increased excitability, or sedation at higher dose levels. Single episodes of convulsions at the maximum tolerated dose (MTD) level and isolated incidences of vomiting were observed in dogs only. There was no indication of specific organ toxicity in either species.

The overall weight of evidence from a battery of *in vitro* and *in vivo* mutagenicity tests demonstrates that

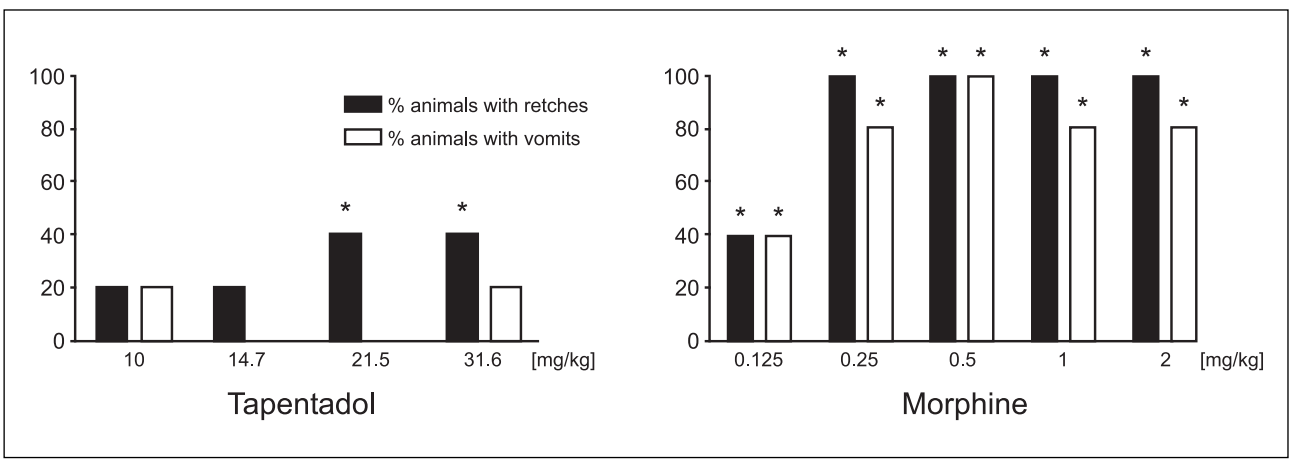


Fig. 3. Comparison of the liability of tapentadol (i.p.) and morphine (s.c.) to induce emesis in ferrets. Data represent the percentage of animals showing retches and/or vomits. n=10 ferrets per group. *p < 0.05 *versus* vehicle control.

tapentadol has no mutagenic potential of relevance for human use. Embryotoxicity studies in rats and rabbits showed that it has no teratogenic properties; male and female fertility was not affected.

Following single and multiple doses in clinical trials, tapentadol exhibited a good safety and tolerability profile. The adverse event profile after single oral doses was well within the expected range for centrally acting substances. The most frequently reported adverse events were nausea, dizziness, vomiting, somnolence, vertigo and headache. At presumed equianalgesic doses, tapentadol appeared to have an improved tolerability profile compared to tramadol and morphine with regard to nausea and vomiting. Multiple doses of 25 and 50 mg tapentadol given every 6 h were also well tolerated. The most frequently reported adverse events in patients treated over 5 days were headache, nausea, dizziness and sleep disturbance.

Following orthopedic surgery, multiple doses of tapentadol of 58 and 116 mg were administered over a period of 4 days. Compared to oxycodone 10 mg, an equianalgesic dose of 58 mg tapentadol showed a more favorable tolerability profile, with a lower frequency of nausea, dizziness, vomiting and constipation. In the case of the more effective higher dose of tapentadol, the frequency of nausea and constipation was lower compared to oxycodone 10 mg, while the frequency of dizziness and somnolence was higher. Tapentadol did not have any clinically relevant effects on laboratory variables, ECGs or vital signs, including respiratory function, pulse rate and blood pressure.

Conclusions

Tapentadol is a novel, orally available, centrally acting analgesic that combines MOR agonism and NA reuptake inhibition in a single molecule, independent of metabolic activation. Its dual mode of action translates into a broad and efficacious analgesic profile, as assessed in a variety of animal models of acute and chronic pain, with both mechanisms of action contributing to its analgesic effects. Moreover, tapentadol has a lower propensity to produce tolerance and physical dependence, and may have an improved side effect profile (in particular, with respect to gastrointestinal side effects) compared to morphine. This is presumably due to its nonopioid component, which results in higher analgesic efficacy than expected from its lower affinity for the MOR. Based on these attributes, it is expected that tapentadol will offer an improved therapeutic option for the treatment of moderate to severe pain.

Source

Grünenthal GmbH (DE).

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