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Señor

SUPERINTENDENTE DE INDUSTRIA Y COMERCIO

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

E. S. D.

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO



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Ref:	Expediente No.	08-105.545
	Patente de Invención:	COMBINACIÓN FARMACÉUTICA
		QUE COMPRENDE 3-(3-
		DIMETILAMINO-1ETIL-2-METIL-
		PROPIL)-FENOL Y PARACETAMOL
	Solicitud Internacional:	PCT/EP2007/003632
	Titular:	GRÜNENTHAL GmbH

RECURSO DE REPOSICIÓN CONTRA LA RESOLUCIÓN NO. 81127
DE 27 DE DICIEMBRE DE 2012, NOTIFICADA POR FIJACION EN
LISTA DE 2 DE ENERO DE 2013, DESFIJADA EL 2 DE FEBRERO
DE 2013.

HUMBERTO RUBIO CAMACHO, mayor de edad, domiciliado en Bogotá, D.C., con la Oficina 506 de la Carrera 7 No. 74-64 de ésta ciudad, Abogado en Ejercicio, portador de la Tarjeta Profesional No. 50.007 expedida por el Consejo Superior de la Judicatura, actuando en carácter de apoderado de la sociedad **GRÜNENTHAL GmbH**, domiciliada en Zieglerstrasse 6, 52078, Aachen, Alemania; reconocido por su despacho y encontrándome dentro de la debida oportunidad procesal, por medio del presente escrito interpongo **RECURSO DE REPOSICIÓN** contra la Resolución No. 81127 de 27 de Diciembre de 2012, notificada por fijación en lista el 2 de Enero de 2013, desfijada el 2 de Febrero de 2013; con el propósito que sea revocada y en su lugar proferir otra, en que se **OTORGUE** el privilegio de la Patente de Invención denominada: **"COMBINACIÓN FARMACÉUTICA QUE COMPRENDE 3-(3-**

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DIMETILAMINO-1ETIL-2-METIL-PROPIL)-FENOL Y PARACETAMOL", conforme a lo siguiente:

1. MOTIVOS DE INCONFORMIDAD.

Base de la Negativa

- 1.1.** Mediante la Resolución objeto del presente recurso, su Despacho niega el privilegio de patente de invención denominada: **"COMBINACIÓN FARMACÉUTICA QUE COMPRENDE 3-(3-DIMETILAMINO-1ETIL-2-METIL-PROPIL)-FENOL Y PARACETAMOL"** solicitado por mí representada la sociedad **GRÜNENTHAL GmbH**; al considerar que no cumple con los requisitos dispuestos en la legislación comunitaria vigente.
- 1.2.** La División de Nuevas Creaciones decidió negar el derecho de patente de invención por no cumplir con el requisito de nivel inventivo, y que de conformidad con el estado de la técnica, la solicitud de estudio resulta obvia. Se puede establecer con la simple lectura de la Resolución que esa división de ninguna manera considera la inversión, la importancia y el alcance del objeto de la presente solicitud y a pesar de tener novedad y nivel inventivo decide negarla, haciéndose una interpretación equivocada.
- 1.3.** Nos permitimos respetuosamente indicar que no compartimos la interpretación realizada por el examinador con respecto a los documentos citados, en los cuales se fundamento el rechazo de la presente solicitud, interpretación equivocada teniendo en cuenta los siguientes argumentos:

NIVEL INVENTIVO.

El examinador fundamenta su rechazo a la presente invención por falta de nivel inventivo en vista del documento D1 (Medve et al.) y documento D2 (ES2115298T3 correspondiente a DE4426245A1, citado en el Reporte de Búsqueda Internacional de la presente solicitud PCT).

La línea de razonamiento del Examinador se basa esencialmente en que D1 divulga que una combinación de tramadol y acetaminofen (también conocido como paracetamol) sería obvio el reemplazar el tramadol por (1R,2R)-3-(3-Dimetilamino-1-etil-2-metil-propil)-fenol para mejorar la actividad analgésica del paracetamol y para reducir los efectos secundarios de la composición farmacéutica al eliminar el tramadol.

Mi representada manifiesta respetuosamente que no está de acuerdo con la posición del Examinador por las siguientes razones:

D2 se relaciona con derivados de 1-fenil-3-dimetilamino-propano con actividad farmacológica.

Estos compuestos ejercen un efecto analgésico y son apropiados para el tratamiento del dolor severo sin aumentar los efectos secundarios por los que son conocidos los opioides y ellos no debiesen manifestar los efectos secundarios que ocurren en algunos casos de tratamiento con tramadol, por ejemplo, náuseas y vómitos (D2, pág. 2, líneas 34-38). Los compuestos se destacan por un pronunciado efecto analgésico, que es significativamente más intenso comparado con el tramadol (D2, pág. 2, líneas 39-42) y pueden ser usados como ingredientes activos en drogas, preferiblemente como

ingrediente activo en drogas contra el dolor. D2 divulga la preparación de (1R,2R)-3-(3-Dimetilamino-1-etil-2-metil-propil)-fenol (D2, ejemplo 24).

Uno de los objetivos de la presente invención es el encontrar una combinación farmacéutica apropiada para el tratamiento del dolor y que preferentemente manifieste menos efectos secundarios indeseados comparados a sus componentes individuales, al ser administrados en dosis efectivas.

- 1.4.** Los inventores de la presente invención han encontrado sorprendentemente que una combinación particular de (1R,2R)-3-(3-Dimetilamino-1-etil-2-metil-propil)-fenol y Paracetamol muestra un efecto sinérgico (supra-aditivo) (presente invención, según WO 2007/128413, pág.13]

En el general conocido en el estado del arte que dos drogas pueden o no interactuar entre sí al ser administradas a un paciente. Si la interacción ocurre, ésta puede ser negativa, por ejemplo, en relación a la toxicidad. Sin embargo, la interacción puede llevar a un efecto aditivo o supra-aditivo.

Un efecto supra-aditivo puede ser observado cuando las drogas interactúan en una forma que mejora o magnifica uno o más efectos de tales drogas.

En cualquier caso, el comportamiento global de tal combinación de dos o más drogas al ser administradas a un paciente no puede ser predicho con confiabilidad a partir del comportamiento de los componentes individuales. La capacidad de dos drogas para mostrar un efecto supra-aditivo es determinada por sus propiedades fármaco-dinámicas y farmacocinéticas y

es, por ejemplo, función de las características fisicoquímicas de los compuestos de la droga y sus formas de acción en el cuerpo del paciente. Por lo tanto, se requiere de análisis farmacológico para evaluar si cierta combinación de drogas muestra una interacción favorable y posiblemente un efecto supra-aditivo.

Una vez que se encuentra que cierta combinación de drogas interactúa favorablemente con otra, se puede asumir razonablemente que para un experto en la materia que intercambie una de estas drogas por otra droga que tiene propiedades fisicoquímicas similares, por ejemplo, una estructura molecular similar, y que ejerce sus efectos beneficiosos a través de la misma forma de acción, por ejemplo, a través del mismo tipo de receptor, podría llevar a obtener una combinación que muestre la misma interacción positiva al ser administrada a un paciente.

- 1.5.** D2 no da ningún indicio de que los compuestos divulgados en dicho documento puedan ser usados en combinación con paracetamol, ni hace referencia a que una composición que comprende (1R,2R)-3-(3-Dimetilamino-1-etil-2-metil-propil)-fenol y Paracetamol resultaría en un efecto sinérgico (supra-aditivo).

D1 no contiene ninguna referencia a (1R,2R)-3-(3-Dimetilamino-1-etil-2-metil-propil)-fenol, ni mucho menos hace referencia a que podría ser combinado con paracetamol en lugar de tramadol, como se indica.

Los compuestos de fórmula (I) de acuerdo a D2 no contienen la estructura del tramadol. Además, D2 enseña claramente que los compuestos de fórmula (I) tales como (1R,2R)-3-(3-Dimetilamino-1-etil-2-metil-propil)-fenol

no exhiben los efectos secundarios como ocurre en algunos casos en el tratamiento con tramadol. Más aún, los compuestos de fórmula (I) son distinguidos por un pronunciado efecto analgésico, que es significativamente más intenso al ser comparado con el efecto del tramadol.

El objetivo real de D2 no es considerar el tramadol, sino el mejorar el perfil de efectos secundarios y efecto analgésico comparado con el tramadol, al introducir compuestos de fórmula (I) que difieren estructural y farmacológicamente del tramadol. En relación a ello, un experto en la materia no habría considerado las enseñanzas de D1 que trata únicamente con tramadol en combinación con acetaminofen, es decir, los mismos compuestos de los que se busca mejorar el perfil farmacológico y que son excluidos de D2.

Debido a que los compuestos de fórmula (I) per se ejercen un efecto analgésico significativamente más intenso acompañados de menores efectos secundarios comparados con el tramadol, un experto en la materia no tendría incentivo a buscar un efecto sinérgico debido a que los compuestos de fórmula (I) per se ejercen un alivio del dolor con menores efectos secundarios. Un experto en el arte no tendría un incentivo especial de considerar las enseñanzas de D1 ya que este usa tramadol, que es precisamente el compuesto que D2 deja fuera.

Se hace evidente a partir de D2 que los compuestos de fórmula (I) tales como (1R,2R)-3-(3-Dimetilamino-1-etil-2-metil-propil)-fenol ejercen un perfil farmacológico (farmacodinámico y farmacocinético) diferente al compararlo con el tramadol usado en la combinación de acuerdo a D1. Esto puede ser derivado fácilmente a partir de lo divulgado en D2, en que los efectos

analgésicos de los compuestos de fórmula general (I) son más pronunciados y con menores efectos secundarios comparados con el tramadol.

El examinador es de la opinión que el compuesto (1R,2R)-3-(3-Dimetilamino-1-etil-2-metil-propil)-fenol sería análogo al tramadol. Sin embargo, este claramente no es el caso como puede ser apreciado en detalle a partir de los documentos de referencia Tschentke et al and Raffa et al que se adjuntan en esta respuesta.

Al respecto, se debe tener presente que el tramadol ejerce una única acción farmacológica que es diferente de aquella que ejercen los compuestos de fórmula (I) de acuerdo a D2 y, por lo tanto, difieren de los compuestos de la composición farmacológica de acuerdo a la presente invención.

- 1.6.** Para ilustrar los diferentes perfiles farmacológicos, farmacodinámicos y farmacocinéticos, se comparan tramadol y (1R,2R)-3-(3-Dimetilamino-1-etil-2-metil-propil)-fenol (indicado como tapentadol) de acuerdo a lo siguiente:

El tapentadol de acuerdo a lo utilizado en la presente invención ejerce una actividad analgésica con un modo de acción dual: antagonismo del receptor μ -opioide (MOR) e inhibición de la recaptación de noradrenalina (NA). Además muestra mayor potencia al ser comparado con tramadol.

La actividad del tapentadol reside en un único enantiómero y es independiente de la activación metabólica. No tiene metabolitos activos, y la principal vía metabólica para su eliminación es la glucurunidación fase II que es mediada por enzimas de la superfamilia UDP-glucuronosiltransferasa que resulta en la desactivación de la señal farmacológica. Las vías metabólicas fase I, que son mediadas, entre otros, por enzimas citocromo P-450, juegan un rol menor en la biotransformación de tapentadol y, por lo tanto, tienen bajo potencial para interacciones entre drogas, tal como se

presenta en el trabajo de Tzschentke et al (Tzschentke T. M. et al. Tapentadol Hydrochloride. Drugs of the Future 2006, 31, 1053-1061). Otro artículo científico reciente que describe en detalle las diferencias funcionales y mecánicas de tapentadol y tramadol es el trabajo de Raffa et al. Ambos documentos se acompañan como referencia junto a la presente respuesta.

En contraste, el tramadol ejerce su actividad analgésica a través del antagonismo con MOR, de la inhibición de la recaptación de noradrenalina y de la inhibición de la recaptación de serotonina (5-HT). El tramadol se usa como racemato con metabolitos activos, cada uno de los cuales tiene un perfil de actividad diferente. Por lo tanto, el tramadol muestra activación pro-droga. La inhibición de la recaptación de NA y 5-HT reside principalmente en los (-)-enantiómeros y (+)-enantiómeros de la composición parental de tramadol, respectivamente, mientras que la activación de MOR reside en el (+)-enantiómero de O-desmetil-tramadol. El metabolito MOR-activo contribuye significativamente al perfil analgésico del tramadol. Tanto los enantiómeros de tramadol y su metabolito O-desmetil son necesarios para el perfil analgésico del tramadol. Las vías metabólicas fase I juegan un rol importante en la biotransformación del tramadol, y por lo tanto pueden ser objeto de interacciones droga-droga relevantes clínicamente (ver Tzschentke et al.).

Al comparar la acción farmacológica de tapentadol con la de tramadol, es especialmente importante enfatizar que los diferentes mecanismos de acción de (1R,2R)-3-(3-Dimetilamino-1-etil-2-metil-propil)-fenol residen en la misma molécula, así la relación relativa de los mecanismos no cambia en el tiempo. En el caso del tramadol, sin embargo, los diferentes mecanismos de acción residen en diferentes moléculas (enantiómeros, metabolitos) y, por lo tanto, la contribución relativa de estos mecanismos cambia a medida que el

tramadol se somete a biotransformación. Además, el tapentadol tiene un inicio de acción más rápido comparado con el tramadol debido a que no es activado por enzimas metabólicas y cruza la barrera sangre-cerebro rápidamente.

Como se mostró, el tapentadol y el tramadol muestran diferencias significativas en sus perfiles farmacodinámicos y farmacocinéticos. Por lo tanto, el tapentadol de acuerdo a como es usado en la composición de la presente invención no es comparable con la acción farmacológica del tramadol, a pesar de que el examinador considere que ambos compuestos estén relacionados estructuralmente. Es así como un experto en el arte habría sido disuadido de combinar las enseñanzas de ambos documentos.

Para una mejor ilustración de lo mencionado anteriormente, me permito anexar dos documentos: Robert B. Raffa *et al.* – Mechanistic and functional differentiation of tapentadol and tramadol; y Tzschentke *et al.*, Tapentadol Hydrochloride; como referencias a los argumentos señalados anteriormente.

Por lo anteriormente expuesto y demostrado, la presente invención, además de tener novedad, cumple con tener actividad inventiva por sobre lo divulgado en el estado del arte, por lo tanto en forma respetuosa solicitamos revocar la resolución impugnada y en su lugar proferir otra por medio de la cual se otorgue la patente de privilegio de invención denominada: **“COMBINACIÓN FARMACÉUTICA QUE COMPRENDE 3-(3-DIMETILAMINO-1ETIL-2-METIL-PROPI)-FENOL Y PARACETAMOL”**, a favor de GRÜNENTHAL GmbH

2. PETICIONES.

a) Pretensión Principal.

De acuerdo a lo señalado en el transcurso de este recurso, solicito respetuosamente a su despacho, tener en cuenta los argumentos anteriormente propuestos y con base a ello, proceder con la concesión de la Patente de Privilegio de Invención, **“COMBINACIÓN FARMACÉUTICA QUE COMPRENDE 3-(3-DIMETILAMINO-1ETIL-2-METIL-PROPI)-FENOL Y PARACETAMOL”**, a favor de mi representada.

b) Pretensiones Subsidiarias.

- 1). **REVOCAR** la Resolución No. 81127 de 27 de Diciembre de 2012, y en su lugar proferir otra en la que otorguen en forma parcial las reivindicaciones solicitadas, todo de conformidad con los documentos que hacen parte esencial del trámite.
- 2). **REVOCAR** la Resolución No. 81127 de 27 de Diciembre de 2012, y en su lugar proferir otra en la que si su Despacho, no obstante la claridad de la invención, considera que es necesaria alguna precisión, se requiera a mi representada con las explicaciones pertinentes, pues reiteramos que la invención solicitada encaja dentro de las normas vigentes, por lo tanto en aras de los principios de equidad y justicia deberá ser otorgada, como respetuosamente lo solicito.

3. PRUEBAS.

- 3.1. Todos y cada uno de los documentos que reposan en el expediente citado en la referencia y los documentos que estamos anexando.
- 3.2. Resolución No. 81127 de 27 de Diciembre de 2012.

- 3.3. Artículo Robert B. Raffa *et al.*, Mechanistic and functional differentiation of tapentadol and tramadol.
- 3.4. Tzschentke *et al.*, Tapentadol Hydrochloride.
- 3.5. La actuación surtida.

4.- FUNDAMENTOS DE DERECHO.

Las disposiciones legales que invoco como fundamento para promover el presente recurso los artículos 14, 16, 18, y 34 y demás aplicables de la Decisión 486 de la Comunidad Andina, en las normas aplicables del Código Contencioso Administrativo, y en las demás disposiciones vigentes.

5.- OPORTUNIDAD.

La Resolución recurrida fue notificada el 2 de Enero de 2013, por lo tanto me encuentro dentro de la debida oportunidad legal, consagrada en el Código Contencioso Administrativo.

6.- NOTIFICACIONES.

Mí representada y el suscrito recibiremos notificaciones en la Secretaría de su Despacho o en mi Oficina de Abogado, situada en la Carrera 7 No. 74-64 de Bogotá.

Atentamente,



HUMBERTO RUBIO CAMACHO

C.C. 17'192.062 de Bogotá

**T.P. 50.007 Consejo Superior
de la Judicatura**

COD. 4134

EXPERT OPINION

1. Introduction
2. Chemical differentiation of tapentadol from tramadol
3. Pharmacological differentiation of tapentadol from tramadol
4. Metabolic differentiation of tapentadol from tramadol
5. Clinical efficacy
6. Conclusion
7. Expert opinion

Mechanistic and functional differentiation of tapentadol and tramadol

Robert B Raffa, Helmut Buschmann, Thomas Christoph, Gary Eichenbaum, Werner Englberger, Christopher M Flores, Torsten Hertrampf, Babette Kögel, Klaus Schiene, Wolfgang Straßburger, Rolf Terlinden & Thomas M Tzschentke[†]

[†]Grünenthal GmbH, Grünenthal Innovation, Global Preclinical R&D, Aachen, Germany

Introduction: Many opioid analgesics share common structural elements; however, minor differences in structure can result in major differences in pharmacological activity, pharmacokinetic profile, and clinical efficacy and tolerability.

Areas covered: This review compares and contrasts the chemistry, pharmacodynamics, pharmacokinetics, and CNS 'functional activity' of tapentadol and tramadol, responsible for their individual clinical utilities.

Expert opinion: The distinct properties of tapentadol and tramadol generate different CNS functional activities, making each drug the prototype of different classes of opioid/nonopioid analgesics. Tramadol's analgesia derives from relatively weak μ -opioid receptor (MOR) agonism, plus norepinephrine and serotonin reuptake inhibition, provided collectively by the enantiomers of the parent drug and a metabolite that is a stronger MOR agonist, but has lower CNS penetration. Tapentadol's MOR agonist activity is several-fold greater than tramadol's, with prominent norepinephrine reuptake inhibition and minimal serotonin effect. Accordingly, tramadol is well-suited for pain conditions for which a strong opioid component is not needed—and it has the benefit of a low abuse potential; whereas tapentadol, a schedule-II controlled substance, is well-suited for pain conditions requiring a strong opioid component—and it has the benefit of greater gastrointestinal tolerability compared to classical strong opioids. Both drugs offer distinct and complementary clinical options.

Keywords: analgesia, efficacy, MOR-NRI, synergy, tapentadol, tramadol, translational drug design

Expert Opin. Pharmacother. [Early Online]

1. Introduction

In the history of medicinal chemistry and pharmacology in drug discovery, chemists have created a variety of ways to describe a chemical structure and to characterize its relevant feature, and pharmacologists have created a variety of ways to describe differences in drug potency, affinity and intrinsic activity at receptor sites, and efficacy [1]. Both histories have converged on the recognition of the critical importance of discriminating drugs based on 'functional activity,' rather than on superficial similarities in chemical structure or *in vitro* assays.

The late writer and chemist Primo Levi complained in 1984 that there were only three acceptable ways to describe a molecule and that none of them were very good: i) the ambiguous molecular formula, ii) the nonlexical chemical graph, and iii) the (often obscure) chemical name [2]. Yet, because these were the only ways that chemists had at the time to describe a molecule's 'constitution,' they dominated the approaches to predicting what a molecule would do. These approaches were based on the 2D

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Article highlights.

- Tapentadol has an open-chain structure in the place of tramadol's cyclic structure, resulting in distinct chemical and biological properties.
- Both drugs combine, in different ways, opioid and nonopioid activities that act synergistically to produce analgesia. As they do so in mechanistically distinct ways, the resulting clinical attributes are different.
- Tapentadol, in a single molecule, combines relatively strong μ -opioid receptor agonism and norepinephrine reuptake inhibition, but has no relevant functional serotonin reuptake inhibition and no analgesically-active metabolite. The two enantiomers of tramadol contribute to different mechanisms (i.e., weak μ -opioid receptor agonism, as well as neuronal norepinephrine and serotonin reuptake inhibition); an analgesically active μ -opioid metabolite contributes to an extent dependent on dose and ADME factors.
- With much greater potency at the μ -opioid receptor compared to tramadol, tapentadol has a CNS functional opioid activity several-fold greater than tramadol's; its norepinephrine reuptake inhibition is the same or a little greater than tramadol's; and its serotonin activity is much reduced compared to that of tramadol.
- Tapentadol mainly undergoes Phase II metabolism (glucuronidation), whereas tramadol primarily undergoes Phase I (CYP2D6 and CYP3A4) metabolism.
- Tapentadol's opioid and norepinephrinergic activities are both present in the parent molecule; tramadol's opioid activity is mainly expressed in its primary metabolite, whereas its monoaminergic activity is primarily present in its parent molecule.
- Tapentadol's greater functional μ -opioid activity gives rise to potency and efficacy comparable to strong opioids; tramadol is widely used for multiple pain types where a strong opioid component is not needed or desired.
- Tapentadol is a controlled substance with reduced gastrointestinal adverse effects compared to classical strong opioids; tramadol has a history of long-term use and low abuse potential.
- Due to its unique features, it has been proposed that tapentadol belongs to a new pharmacological class, MOR-NRI.

This box summarizes key points contained in the article.

(two-dimensional) structural formula, only indicating stereochemistry with stereochemical descriptors. It is now known that this presentation of a chemical structure is an oversimplification that only focuses on the connectivity and binding mode of the atoms and, to some extent, their spatial arrangement. At the time, this was necessary for printed materials, but modern computers now allow greater flexibility to visualize 'lock-and-key fit' and the importance of 3D (three-dimensional) visualization of structure. To illustrate the limitations and potential pitfalls of the now archaic approach of comparing the 2D carbon skeleton (i.e., taking only the ring systems and the linkers connecting the ring systems into consideration [31]), tramadol would be erroneously compared to

the NSAID (non-steroidal anti-inflammatory drug) diflunisal, because both drugs have the same generalized carbon scaffold (wherein two ring systems are connected without a spacer group). Based on this type of chemotypic analysis, as described by Hu *et al.* [4], tramadol and diflunisal should act by common pharmacological mechanisms, which of course they do not.

Even SMILES (simplified molecular input line entry specification) [5], which was developed by David Weininger shortly after Levi's lament and intended to be a real lexicographic description, only facilitated methods that relied on the counting of elements of composition, chemical rules of thumb, classification algorithms, drug-like filters (e.g., the ubiquitous 'rule of five' [6]), 2D QSAR (quantitative structure-activity relationship) or molecular fingerprints. Whereas chemists may have elaborated beyond the elemental to include graph-related properties (such as aromaticity, hydrophobicity, hydrophilicity, hydrogen bond donors and acceptors, etc.), these are seldom fundamental and are often simply opinions on how molecules behave [1]. It is now universally recognized that the different types of interactions between molecules and a biological target strongly depend on the spatial arrangement of molecular fragments within the target macromolecule [7]. Thus 3D shape must be considered in order to predict essential aspects of the pharmacological activity of a molecule.

Therefore in the first section of this review, we describe how the 3D shape of tapentadol was rationally designed to produce a new compound having distinct pharmacodynamic and pharmacokinetic properties in order to achieve specific clinical goals.

Similar to the historical development of approaches to best (most fully) describe the chemical attributes of drugs, there has been equivalent development of approaches to best describe the pharmacological attributes of drugs. One of the earliest, because of its simplicity, was to use 'potency' (the amount of a drug required to produce a defined level of effect), typically reported as an ED_{ϵ} where ϵ is a specified level of effect. The limitations of such a measure are readily apparent, since such a measure is highly dependent on factors unrelated to the drug's mechanism of action. A clear example is looperamide, which is mechanistically a strong opioid, but is devoid of CNS (central nervous system) effects when administered orally, because it does not cross the blood-brain barrier. A more mechanistic measure of a drug's pharmacological attributes was devised and termed 'affinity' (the strength of attraction between a drug and its target) and is typically reported as a K_i value (for a review of the historical development of this concept [8]). Such a measure, however, does not account for the result of the binding, since antagonists have affinity for the drug's target site, but do not produce the effect. Therefore, in order to describe target activation, measures such as 'intrinsic activity' or 'intrinsic efficacy' at the target site (receptor) were introduced. The most comprehensive comparison of two drugs utilizes a composite of all of these measures as manifested in each drug's 'functional activity' (defined as the ratio of the estimated brain

concentration to the relevant functional EC_{50} or K_i value at a specified receptor or transporter site) in the desired therapeutic application—in this case, antinociception (in animals) or analgesia (in humans).

Therefore in the second section of this review, we describe how the differences in the CNS functional activity of tapentadol and tramadol (based on the differences in their pharmacodynamic, pharmacokinetic, and functional activity characteristics) correlate with their clinical features and common uses. Escalating the dose of tramadol in an effort to match tapentadol's greater opioid activity is not a clinically feasible option because disproportionately more of the weaker opioid parent drug crosses the blood–brain barrier than does its stronger opioid metabolite (*O*-desmethyl tramadol). In fact, in the same models, the disparity gets progressively larger as the dose of tramadol is increased [9].

The significantly different pharmacodynamic, pharmacokinetic, and CNS functional activities of tapentadol and tramadol are consistent with, and provide the basis for understanding, the different clinical profiles of these two centrally acting analgesics.

2. Chemical differentiation of tapentadol from tramadol

Based on elucidation of the favorable aspects of the multimodal analgesic mechanism of action of racemic cyclohexyl analgesics (of which tramadol was one representative), a research program was initiated to design a new class of opioid/nonopioid analgesics that would combine MOR (μ -opioid receptor) agonism and norepinephrine reuptake inhibition, with minimal serotonergic activity. It was also desired that both activities would reside in a single parent molecule that does not require metabolic activation via the cytochrome P450 system.

2.1 The discovery of tapentadol

The 3D molecular shape of tapentadol is very different from that of tramadol, which manifests itself in the different pharmacological profiles of the two analgesics. In the following sections, these differences are described in more detail, including the chemical distinction between the cyclic structure of tramadol and the open-chain structure of tapentadol (Figure 1), resulting in reduced molecular complexity and a stronger CNS functional activity that is primarily derived from its two intrinsically synergistic mechanisms of analgesic action.

2.2 The dimethylaminomethyl fragment

The dimethylaminomethyl moiety is a significant part of the pharmacophore that is needed for interaction with MOR and interaction with the monoamine transporter system [10]. Demethylation is a metabolic pathway leading to CH_2-NH (CH_3) and CH_2NH_2 derivatives that lack significant analgesic activity [11,12]. Increasing the size of the nitrogen substituent or cyclic substitution also leads to inactive compounds. The dimethylaminomethyl fragment, therefore, appears to be essential for analgesic activity for both drugs.

2.3 The role of relative stereochemistry

Tramadol and tapentadol contain two chiral carbon atoms. Consequently, for both molecules, four stereoisomers exist as two diastereomeric pairs of enantiomers. However, tramadol is a racemate, whereas tapentadol is a pure enantiomer. The relative stereochemistry is critical for biological activity. In both cases, only the (*R,R*) and (*S,S*) isomers display analgesic activity, whereas the diastereoisomers are relatively inactive. The stereochemical requirements and dimethylaminomethyl fragment are the only common relationships between tapentadol [(–)-(1*R*,2*R*)-3-(3-dimethylamino-1-ethyl-2-methyl-propyl)-phenol hydrochloride] and tramadol [(1*RS*,2*RS*)-2-[(dimethylamino)methyl]-1-(3-methoxyphenyl)cyclohexanol] hydrochloride.

2.4 Cyclic core structure versus open-chain molecule

Several drugs possess cyclic aliphatic ring systems connected via linkers with other aromatic or hetero aromatic groups [13]. However, in the lead optimization phase, a cyclic ring system is typically modified by changing the ring size and introducing hetero atoms (such as nitrogen, oxygen, or sulfur) as well as introducing additional substituents in order to optimize desired hydrophobic or non-hydrophobic interactions with the biological target, thereby leading to an increase in the potency of a given lead structure. As a consequence, the cyclic structure is retained in many lead optimization programs due to the entropic and enthalpic balance of the thermodynamics of binding [14,15]. Cyclic structures generally have the advantage of decreasing the entropic proportion of the binding energy compared with open-chain molecules, leading to more flexible derivatives with greater ligand efficiency [16]. Additionally, many examples are known wherein an open-chain analog of a given drug loses biological activity completely; for instance, the open-chain analog of diazepam is completely inactive [17]. In the course of the development of tapentadol, it was found that opening the cyclohexane ring system led to active compounds while conserving the relative stereochemistry. However, the activity of the molecules was strongly dependent on the length of the side chain. It was found that a methyl group and an ethyl group at critical carbon atoms were optimal in the general formula. The preference of the pentyl chain in tapentadol compared with analogs containing the hexyl chain (comparable to the cyclohexane core ring of tramadol) was not predictable by any *in silico* tool available at the time and can still not be explained by usual structure–activity relationships.

2.5 A drug with an active metabolite versus a drug without one

The introduction of a phenolic hydroxy group instead of an aromatic methoxy group results in a dramatic change in pharmacological activity [10]. Whereas tramadol is a racemate with an active racemic metabolite (*O*-desmethyl tramadol, M1)

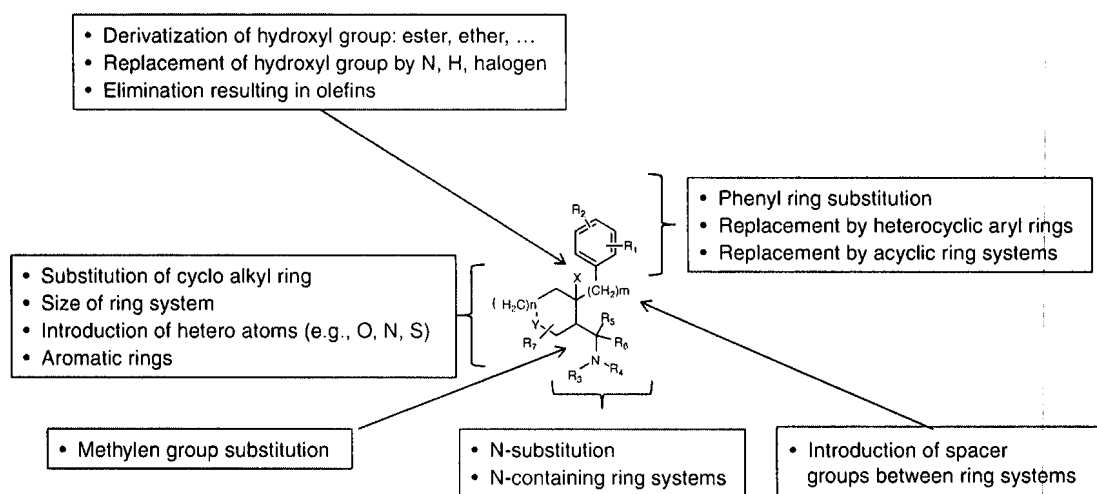


Figure 1. Summary of chemical modifications leading to the discovery of tapentadol. Shown is a generic structure of the class of cycloalkyl-based analgesic drugs. Tramadol is represented by $R_1 = 3\text{-OCH}_3$, $R_2 = \text{H}$, $R_3 = R_4 = \text{CH}_3$, $R_5 = R_6 = \text{H}$, $R_7 = \text{H}$, $n = 1$, $m = 0$, $Y = \text{CH}_2$, and $X = \text{OH}$.

that is generated following cytochrome P450 (CYP2D6)-mediated *O*-demethylation, tapentadol does not have analgesically active metabolites (i.e., both of its mechanisms of action reside within the parent molecule).

The enantiomers of open-chain phenolic structures showed increased analgesic activity compared to the cyclic tramadol-derived analogs. Consequently, the enantiomers were investigated separately in the optimization process described below.

2.6 Racemate versus pure enantiomer

In past decades, the pharmacopoeia was dominated by racemates [18]; however, since the emergence in the 1980s of new technologies that allowed the preparation of pure enantiomers in significant quantities, the awareness and interest in the stereochemistry of drug action has increased. The advances in stereoselective bioanalysis led to new awareness of the importance of stereoselective pharmacodynamics and pharmacokinetics, enabling the differentiation of the relative contributions of enantiomers to overall drug action. These factors have led to an increasing preference for selection of single enantiomers by both the pharmaceutical industry and regulatory authorities. Enantiomeric purity is now a primary objective in the design, discovery, development, launching, and marketing of new drugs [19].

As a consequence of this changing climate toward drug chirality, pure enantiomers were used for further optimization. Subsequently, it was found that the MOR affinity of the enantiomer acting on the norepinephrine transporter was increased, and in the following steps, modifications were made to increase this MOR affinity.

2.7 Replacement of the aliphatic hydroxyl group

It is known for many drugs that their aliphatic hydroxyl group is essential for pharmacological activity [20].

Derivatization by introducing ester or ether groups in this position led to the loss of analgesic activity. However, replacement of the tertiary hydroxyl group by either fluorine or hydrogen resulted in a significant increase of MOR affinity for both enantiomers. The fluorine derivatives were not further developed due to physicochemical stability issues. Critically, the hydrogen derivative was found to have both activities in one molecule. While retaining the norepinephrine reuptake inhibition (NRI) component, the MOR agonism component was increased to achieve potent analgesic activity without the prominent serotonin reuptake inhibition (SRI) effect present in tramadol. Chemical innovations introduced in the development of tapentadol are summarized in Figure 2.

2.8 Tapentadol as a rationally designed polypharmacological ligand

Increasing evidence demonstrates that many pharmaceutically important compounds elicit their effects through binding to multiple targets. This so-called 'directed polypharmacology' is impacting conventional drug discovery and rational drug design strategies [21]. The single-target focus traditionally dominated compound optimization efforts, and a high degree of target specificity was typically considered a desirable goal of drug candidates. Systems biology, however, has revealed networked physiological systems with convergent, divergent, and integrated signaling pathways that involve extensive crosstalk among these pathways. The reduction of drug discovery to a single target is now seen to be a gross oversimplification that unduly minimizes the complexity of the pathophysiology [22]. Drug programs that assume a single-target mechanism, particularly for the CNS, can have extremely low success rates, with early hits often leading to costly failures at

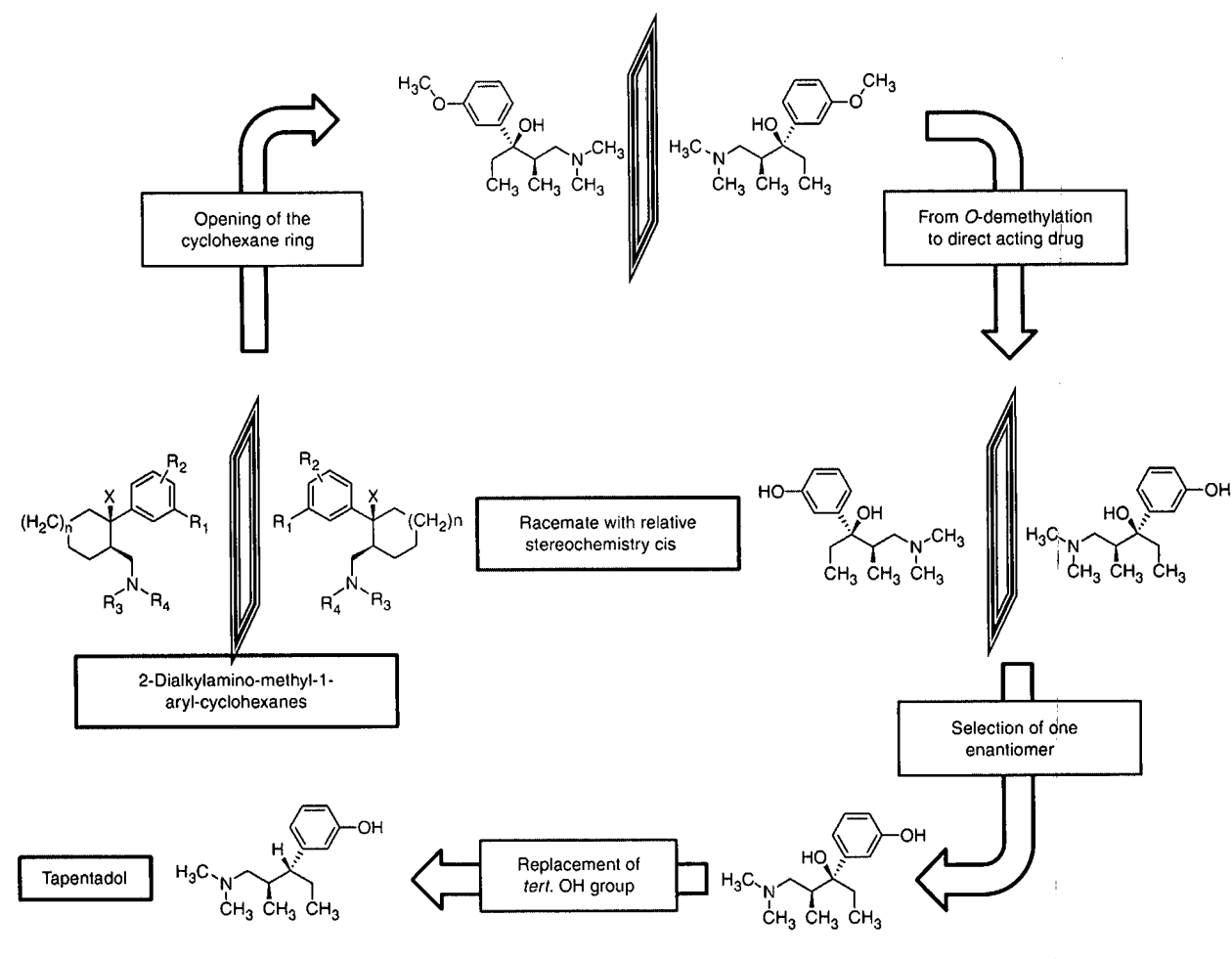


Figure 2. Chemical innovations introduced in the development of tapentadol.

the clinical stage. Furthermore, such drugs can produce excess adverse effects because of the high doses needed by single-mechanism agents. In many cases, the adverse effects contribute to a termination of drug intake, sometimes resulting in disease relapse, and major problems such as chronic pain remain unsolved [23]. In recent years, it has been increasingly appreciated that multi-pathophysiological medical conditions are most likely best treated by complementary multi-modal mechanisms of action. Hence, polypharmacology is beginning to be regarded as a general drug discovery principle—the so-called concept of Designed Multiple Ligands—that influences compound design, optimization, and evaluation [24,25].

3. Pharmacological differentiation of tapentadol from tramadol

The pronounced 3D differences in chemical structure of tramadol and tapentadol translate into a number of substantial functional differences.

3.1 Differences in opioid receptor binding affinity and functional activity

As shown in Table 1, tapentadol binds to recombinantly-expressed human MOR (hMOR) with an affinity (K_i value) of 0.16 μM [26]. For tramadol, its enantiomers, or its M1 (*O*-desmethyl) metabolite and enantiomers, a range of values has been reported [27,28]. From the most recent, the parent form of tramadol exhibits low hMOR affinity with a K_i value of 2.4 μM , whereas its (+)M1 metabolite exhibits much higher affinity with a K_i of 0.0034 μM [28]. Thus, the parent form of tramadol exhibits about 15-fold lower affinity for hMOR than does tapentadol and about 700-fold lower affinity than its (+) M1 metabolite. In comparison, tapentadol binds with nearly 50-fold lower affinity for hMOR than does the (+)M1 metabolite of tramadol. However, these binding numbers may underestimate the pharmacological strength of the interaction, as shown below when one measures functional activity.

In contrast to its lower binding affinity, the functional activity of tapentadol in the agonist-stimulated [^{35}S]GTP γS binding assay in cells recombinantly expressing hMOR is similar

Table 1. *In vitro* evaluation of the binding and functional activity of tapentadol, tramadol, and tramadol enantiomers and metabolites at rat and human MOR, NET, and SERT.

	MOR K_i Binding affinity (μM)	hMOR EC_{50} [^{35}S]GTP γS binding (μM)	hNET K_i Functional uptake (μM)	hNET K_i Binding affinity (μM)	hSERT K_i Binding affinity (μM)	rNET K_i Functional uptake (μM)	rSERT K_i Functional uptake (μM)
Tapentadol	0.16 [§]	0.67 [§]	0.75 [¶]	8.8 [§]	5.28 [§]	0.48 [§]	2.37 [§]
Racemic Tramadol	2.4 [†]	Inactive [#]	NA	14.6 [¶]	1.19 [‡]	0.78 [‡]	0.99 [‡]
(+) Tramadol	1.3 [‡]	NA	NA	NA	0.87 [¶]	2.51 [‡]	0.53 [‡]
(-) Tramadol	24.8 [‡]	NA	1.08 [¶]	NA	NA	0.43 [‡]	2.35 [‡]
Tramadol (+)M1	0.0034 [*]	0.86 [*]	NA	NA	NA	14.4 [#]	2.98 [#]
Tramadol (-)M1	0.24 [*]	> 50 [*]	NA	NA	NA	0.86 [#]	17.7 [#]

^{*}Affinity at human MOR measured by naloxone competitive inhibition [28].

[†]Affinity measured by competitive inhibition in rats [69].

[‡]Affinity at human MOR measured by naloxone competitive inhibition [26].

[¶]Hertrampf and Englberger (unpublished observations).

[#]Rat brain homogenates (Codd et al. (unpublished observations)).

h: Human; MOR: μ -opioid receptor; NA: Not available; NET: Norepinephrine (noradrenaline) transporter; r: Rat; SERT: Serotonin transporter.

to that of the higher-affinity (+)M1 metabolite of tramadol (tramadol parent displays no detectable functional activity) (Table 1) [26,28]. This highlights the importance of comparing drugs based on their functional activity rather than on an indirect measure such as binding affinity (which does not take into account intrinsic activity, target access, etc.). Just as a superficial similarity in 2D chemical structure is an unreliable indicator and underestimates the differences between the biological effects of tapentadol and tramadol, so too does a comparison based on *in vitro* binding affinity alone.

3.2 Differences in NET and SERT binding affinity and functional activity *in vitro*

Regarding interactions with the monoaminergic transporters NET and SERT, tapentadol binds to human NET (hNET) and SERT (hSERT) with K_i values of 8.8 [26] and 5.28 μM , respectively, whereas the tramadol parent binds to these targets with K_i values of 14.6 and 1.19 μM , respectively (Hertrampf & Englberger, unpublished observations) (Table 1).

In terms of the functional inhibition of these targets, tapentadol blocks norepinephrine uptake by hNET with a K_i value of 0.75 μM and serotonin uptake by rat SERT (data not available for the human ortholog) with a K_i value of 2.37 μM . In comparison, (-)-tramadol blocks the function of the hNET with a K_i value of 1.08 μM , and (+)-tramadol blocks rSERT with a K_i value of 0.53 μM , respectively (Table 1). Both tramadol M1 metabolite enantiomers are less potent at these transporters and achieve lower brain concentrations (see below) compared with their respective parents, thereby limiting their functional contributions to these mechanisms. Thus, tapentadol is slightly *more* potent than tramadol in blocking hNET and nearly fivefold *less* potent than tramadol in blocking rSERT.

Again, the above mechanistically insightful results highlight the importance of comparing drugs based on their functional activity rather than on binding affinity or other indirect measures. Only the former provides the added dimension

that elucidates the true nature and extent of the individual properties of two drugs, and hence of their differences.

In summary, the *in vitro* receptor binding and *in vitro* functional assays demonstrate that tapentadol and tramadol (including its M1 metabolite) are substantially different with respect to their MOR agonism, serotonin reuptake inhibition (tapentadol greater at the former and lesser at the latter compared with tramadol) and in the resulting *in vivo* effects. As discussed in the following sections, the differences are magnified *in vivo*, because of two factors: i) differences in functional activity *in vivo*, and ii) because of limited distribution of tramadol (+) M1 to the brain.

3.3 Differences in monoaminergic functional activity *in vivo*

The *in vivo* differences in NET and SERT profiles of tapentadol and tramadol become evident in microdialysis measurements in the ventral hippocampus in the rat. As shown in Figure 3, in this assay, tramadol produces large dose-dependent increases in both norepinephrine (about fivefold of baseline) and serotonin (about five- to sixfold of baseline) within its analgesic dose range [29]. In contrast, tapentadol produces a similarly large dose-dependent increase in extracellular norepinephrine levels (about five- to sixfold of baseline), but much lower increase in extracellular serotonin levels compared to tramadol (about twofold of baseline) within its analgesic dose range [26].

3.4 Differences in analgesic efficacy and the impact of metabolism

The substantial potency difference between tapentadol and tramadol was first established in animal models of pain. Across a variety of assays, tapentadol is consistently two to five times more potent than tramadol (e.g., ED_{50} value of 2.2 and 9.6 mg/kg i.v., respectively, in the rat tail flick test and ED_{50} values of 1.65 and 3.5 mg/kg i.v., respectively, in the rat spinal nerve ligation [SNL] model). This potency

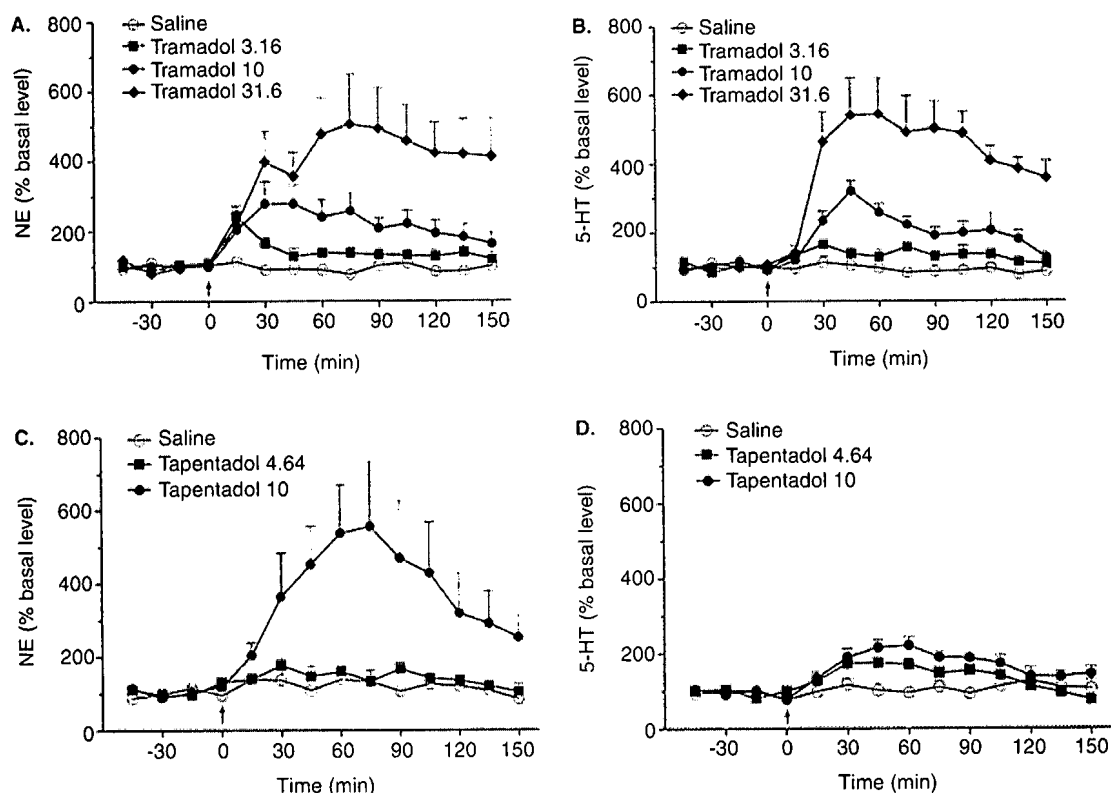


Figure 3. Microdialysis in the ventral hippocampus of freely moving rats after i.p. administration of tramadol (A, B) or tapentadol (C, D). Tramadol produced clear increases in extracellular levels of NE (A) and 5-HT (B). Tapentadol produced a clear increase in NE levels (C), but only a minor increase in 5-HT levels (D). Doses are indicated as mg/kg i.p.

Tramadol data reprinted from [29] with permission from Elsevier.
Tapentadol data adapted from [26].

difference cannot be explained by the *in vitro* potency data alone (see above for details), because the EC_{50} of (+)M1 at MOR (0.86 μ M) is similar to that of tapentadol (0.67 μ M), and the K_i of tapentadol inhibition of hNET (0.75 μ M) is similar to that of tramadol (1.08 μ M).

To further analyze functional analgesic activity, we determined the 'CNS activity' (defined as the ratio of the estimated brain concentration in humans divided by the relevant functional EC_{50} or K_i value at the receptor or monoaminergic transporter) of tapentadol and tramadol plus its active metabolite M1. Specifically, we calculated the relative ratio of the human plasma steady-state C_{max} and C_{avg} (AUC/τ) values for tapentadol (100 mg every 4 h) and tramadol (200 mg b.i.d.) at steady state to the EC_{50} (MOR) or K_i (NET and SERT). For tapentadol, $C_{max} = 145$ ng/mL and $AUC = 3,071$ ng $\times$ h/mL (Terlinden *et al.*, unpublished observations). For (+)tramadol, $C_{max} = 323$ ng/mL (1.2 μ M) and $AUC = 2,784$ ng $\times$ h/mL ($C_{avg} = 0.4$ μ M), and for (-)tramadol, $C_{max} = 290$ ng/mL (1.1 μ M) and $AUC = 2,227$ ng $\times$ h/mL ($C_{avg} = 0.4$ μ M) [30]. For (+)M1, $C_{max} = 61$ ng/mL and $AUC = 697$ ng $\times$ h/mL, and for (-)M1, $C_{max} = 81$ ng/mL and $AUC = 761$ ng $\times$ h/mL [30]. For MOR, the EC_{50} values for tapentadol and tramadol (+)

M1 were based on agonist-stimulated [^{35} S]GTP γ S binding assay in cells recombinantly expressing human MOR. For NET, the K_i values were based on human functional transporter assays for tapentadol and (-)tramadol. For SERT, the K_i values were based on rat functional transporter assays for tapentadol and (+)tramadol. The potency of tapentadol measured in the rat functional NET assay (0.5 μ M) is about the same as that in the human (0.7 μ M); we assume that the same approximation is true for rat and human SERT. Notwithstanding differences in brain penetration as a function of dose, we also assumed that the plasma concentrations of (+) and (-)tramadol, tramadol (+) and (-) M1 and tapentadol represent a reasonable estimate of extracellular fluid or brain concentrations, based on microdialysis studies (Beier, Terlinden *et al.*, unpublished observations) [9]. Thus, the ratio of brain C_{max} of tapentadol to the EC_{50} at MOR (0.71 μ M/0.67 μ M = 1.06) is much larger than the ratio for tramadol (+)M1 (0.24 μ M/0.86 μ M = 0.28), thus leading to a much greater μ -opioid effect than tramadol (+)M1. Similar calculations of the ratio of brain C_{max} to the functional K_i for NET and SERT revealed approximately similar activity of tapentadol and the more NRI-selective (-)-enantiomer of tramadol at the NET and negligible activity of tapentadol at the SERT. This

fundamental distinction and differentiation between the two drugs is illustrated in Figure 4.

The 'CNS activity' ratios of tapentadol are about the same whether calculated using $C_{\max}$ or C_{avg} in contrast to tramadol (Figure 4A vs 4B). In either case, the CNS opioid activity of tapentadol is much greater than that of tramadol (3.73- to 6.91-fold). The contribution of NET inhibition is the same or even greater for tapentadol than for tramadol (0.94- to 2.60-fold). But tapentadol's SERT inhibition is only about 10–25% that of tramadol's, demonstrating the success of the medicinal chemistry effort to reduce this activity in creating a new drug.

3.5 Differences in the contribution of NRI and SRI activities to efficacy

The contribution of norepinephrinergic activity and the lack of relevant serotonergic activity of tapentadol were confirmed in a number of animal pain models. For example, Schröder *et al.* (2010) showed that the dose–response curve for the antinociceptive effect of tapentadol in a low-intensity tail flick model and for the antihypersensitive effect in a SNL model was shifted to the right by the α_2 -adrenoceptor antagonist yohimbine (increase of the ED_{50} value by 1.7-fold in the acute nociceptive pain model and by 4.7-fold in the chronic neuropathic pain model), but not by the 5-HT₂ receptor antagonist ritanserin [31]. An antagonism of the tapentadol effect by yohimbine and a lack of antagonism by ritanserin has also been observed in the CFA (complete Freund's adjuvant)-induced hyperalgesia model of chronic inflammatory pain [32]. In contrast, both the norepinephrinergic and serotonergic mechanisms have been demonstrated to contribute to the analgesic efficacy of tramadol. The antihypersensitive effect of tramadol in the SNL (spinal nerve ligation) model is reduced by both yohimbine and ritanserin (Christoph *et al.*, unpublished observations). Raffa *et al.* (1992) have also shown that the antinociceptive effect of intrathecal tramadol in a tail-flick model is blocked by both yohimbine and ritanserin [33].

3.6 Differences in source of synergy

A recent study has demonstrated that the two mechanisms of action of tapentadol show a very pronounced intrinsic synergy with respect to antinociceptive activity in a low-intensity tail-flick test in the rat [34]. In that study, indirect evidence was also obtained for an intrinsic antihypersensitive synergy in a SNL model. To our knowledge, this was the first demonstration of two mechanisms of action (MOR agonism and NRI) within one molecule interacting to produce a synergistic effect.

Synergistic interaction between the two enantiomers of tramadol has been reported in some pain models. Because the opioid, norepinephrinergic, and serotonergic activity of tramadol reside mainly in the (+)M1 metabolite, (–)tramadol enantiomer, and (+)tramadol enantiomer, respectively, tramadol can be interpreted as a combination of three molecules, each with different pharmacological and pharmacokinetic

properties. The fortuitous combination of these molecules leads to beneficial clinical attributes of the drug.

4. Metabolic differentiation of tapentadol from tramadol

With respect to its opioid component, tramadol must undergo hepatic metabolism to (+)M1 in order to achieve significant binding affinity at MOR. This metabolism is via the cytochrome P450 system, predominantly CYP2D6, but also CYP3A4 [35]. These enzymes show a pronounced genetic polymorphism. It is thus possible that standard doses of tramadol do not always yield satisfactory analgesia in CYP2D6 polymorphic patients [36]. Furthermore, many drugs are metabolized by this same enzyme system. Thus, drug–drug interactions might occur in cases of co-medication with other drugs that are metabolized by, or inhibit, this enzyme [37].

In the case of tapentadol, both mechanisms of action (MOR agonism and NRI) reside within the parent molecule. The metabolism of tapentadol is mainly via direct glucuronidation (Phase II metabolism) to the non-analgesic tapentadol-O-glucuronide. Glucuronidation is mediated via a number of different isoforms of UGT (uridine-diphosphate-glucuronyl-transferase), mainly UGT1A9, UGT2B7, and UGT1A6 (Terlinden *et al.*, unpublished observations). The expression of these enzymes shows only relatively little natural variation, and they have a high capacity and are not easily saturated [38]. Thus, the expected variability in effectiveness across a patient population is smaller, and CYP P450-based drug–drug interactions are less likely [39].

Overall, tapentadol thus has a simpler pharmacokinetic-pharmacodynamic profile than does tramadol. Moreover, tapentadol does not have any active metabolites relevant for its analgesic activity [38], avoiding variable response due to genetic variability and in metabolism [40–42].

5. Clinical efficacy

In the clinical setting, an equianalgesic ratio of approximately 5:1 for long-acting formulations of tapentadol and oxycodone has been estimated (based on individually adjusted dose) [43]. This translates to an approximate ratio of 1:1.5 to 1:4 for tapentadol to tramadol, depending on conversion rates between morphine and oxycodone, and between morphine and tramadol, in the published literature [44–46]. This roughly corresponds to the potency difference between tapentadol and tramadol seen in a range of animal pain models (see above). Hence, even assuming a conservative conversion rate of 1:2 between tapentadol and tramadol, based on the recommended maximum daily dose of 400 mg for long-acting tramadol [47], this would be expected to achieve only 40% of the analgesic effect of a maximum daily dose of long-acting tapentadol (500 mg) [48]. An intermediate daily dose of 250 mg tapentadol would correspond to 500 mg tramadol, which already exceeds the recommended tramadol daily dose. The efficacy of tramadol is often optimized by a 'start

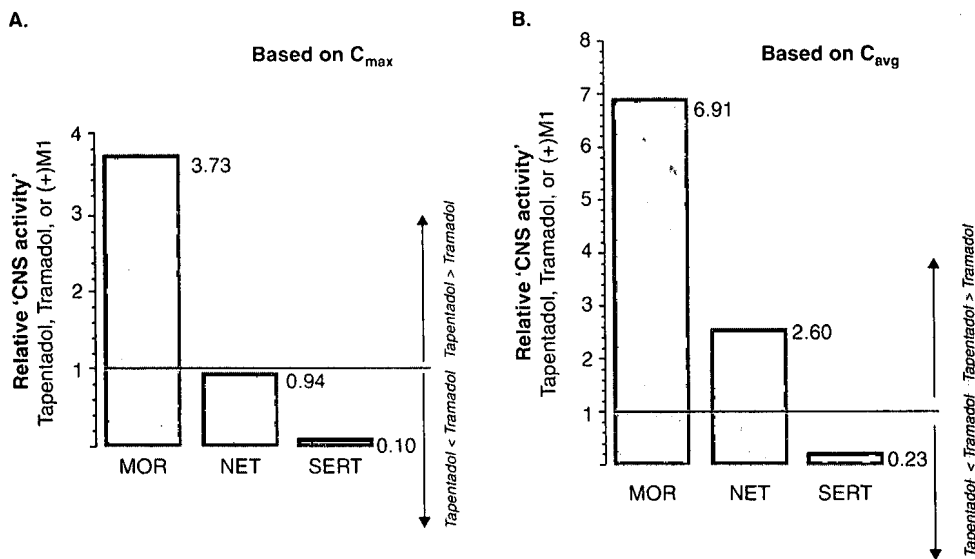


Figure 4. Comparison of the relative 'CNS Activity' (defined as the ratio of the estimated brain concentration in humans divided by the relevant functional EC₅₀ or K_i value at the receptor or monoaminergic transporter) of tapentadol and tramadol [(–) for NET and (+) for SERT] or tramadol (+)M1 metabolite (for MOR) in humans. A. C_{max}. B. C_{avg}.

Table 2. Summary of the functional differentiation of tapentadol and tramadol.

- Tapentadol is a single molecule; tramadol is a racemate
- Tapentadol has no analgesically active metabolites; tramadol has an active metabolite
- The main pathway of tapentadol metabolism is glucuronidation; tramadol is metabolized mainly via the CYP450 enzyme complex
- Tapentadol has substantially more CNS functional activity at MOR than does tramadol, about the same or more functional activity at NET, and substantially less functional activity at SERT
- The mechanisms of action of tapentadol reside in a single molecule; the mechanisms of action of tramadol reside in different molecules (enantiomers of the parent and M1 metabolite)
- Tapentadol is two to five times more potent than tramadol across a range of animal pain models. Likewise, clinically, tramadol is most effective for treating pains not requiring a strong opioid, whereas tapentadol is effective in treating pain requiring the efficacy level of strong opioids (e.g., oxycodone)
- In clinical trials, tapentadol has been shown to have comparable efficacy to oxycodone with more favorable tolerability; in usual practice, tramadol is not used for this level of pain
- Tapentadol is a schedule II drug in the United States and scheduling is in place or anticipated for all major countries where it is marketed, whereas tramadol is not scheduled in all major countries

CNS: Central nervous system; MOR: μ -opioid receptor; NET: Norepinephrine (noradrenaline) transporter.

low, go slow' approach and titration to the desired dose. However, escalating the tramadol dose in an effort to achieve the same opioid-effect as tapentadol is not a clinically viable option because: i) the dose needed would likely exceed the recommended maximum, and ii) the ratio of the brain concentration of M1 (which provides the major contribution to the opioid activity of tramadol) to the brain concentration of parent drug decreases as the oral tramadol dose is increased [9]. Further experience with a broader patient population is necessary to come to a more definite conversion rate.

A more in-depth comparison of the clinical efficacy, safety, and tolerability of tapentadol and tramadol is beyond the scope of this

paper (which explicitly focuses on the chemical and pharmacological features of the two drugs). The clinical features of tramadol have been comprehensively covered in many reviews [49-51], and there are also already some overviews of the features of tapentadol [52-54]. A direct comparison of both drugs may also be inappropriate in the present context. As outlined above, due to the different potency and efficacy, both drugs target largely different pain intensities and thus different patient populations, making a direct comparison of both drugs not feasible. In fact, the expected higher efficacy of tapentadol has led to the decision in early clinical development to use oxycodone (rather than tramadol) as the reference comparator in clinical studies. Thus, the

efficacy and tolerability profile of tapentadol has largely been established based on the comparison with oxycodone, not with tramadol [55].

6. Conclusion

Tramadol and tapentadol are mechanistically and therapeutically distinct drugs although they share certain superficial chemical structural similarities (for summary, see Table 2). The pharmacological and functional differences that are observed *in vitro* and *in vivo* translate into significant clinical differences. Tramadol's somewhat complex, but fortuitous, combination of enantiomers and activemetabolite, plus pharmacokinetic profile, provides effective analgesia where a strong opioid component is not needed [56], with a low frequency of abuse [57-59]. Tapentadol's combined synergistic MOR agonism and NRI within a single molecule yields high and reliable analgesic efficacy for the treatment of pains comparable to oxycodone with more favorable gastrointestinal tolerability [60-62]. The novel features of its mechanism of action has led several authors to suggest that tapentadol should be considered in a new pharmacological class of drugs, the MOR-NRI [63-66].

7. Expert opinion

The centrally acting analgesics tapentadol and tramadol are chemically, pharmacologically, and metabolically distinct drugs. These differences in pharmacodynamic and pharmacokinetic properties—and most importantly their CNS functional activity—place them in separate classes of the category of multi-mechanistic opioid/nonopioid analgesic drugs, and result in unique and complementary options for use in different clinical situations. Tapentadol has been suggested to be a representative of a new class termed MOR-NRI. Clinical experience will determine whether this is a useful categorization for physicians trying to select the best analgesic match for a particular type of pain or for certain populations of pain patients.

Recent publications lament the lack of success of the translational research approach to drug discovery. This has been particularly true in the area of analgesic drug discovery, in which an NCE (new chemical entity) strong analgesic had not been approved in the preceding 25 years. Tapentadol demonstrates how such a targeted strategy can lead to an innovative and effective new drug. Tapentadol was built upon advances in the understanding of the basic science of pain and mechanisms of analgesia—coupled with directed medicinal chemistry modifications—to yield a new drug whose designed properties offer a differentiated clinical ('bench-to-bedside') profile.

Tramadol, a centrally acting analgesic with an established record of efficacy and safety, grew out of a discovery program designed to identify novel opioid analgesics. However, the complete picture of its mechanism of action was elucidated to a great extent after-the-fact. Its analgesic mechanisms do not reside in a single molecule, but instead in a fortuitously balanced combination of parent and metabolite molecules and each of their

enantiomers. In contrast to this serendipitous combination of mechanisms, tapentadol was custom-designed to rationally combine two analgesic mechanisms (MOR agonism and NRI) that individually and synergistically produce analgesia in models of various types of pain—within a single molecule. As part of this development, tapentadol was designed to have less serotonergic activity. The result is an innovative drug that retains the advantages of combining synergistic mechanisms of action, but with a significantly greater 'functional' opioid component and a relatively greater inhibition of the NET than of the SERT, all in a single molecule with no analgesically active metabolites. The focus on norepinephrinergic activity and the lack of relevant serotonergic activity takes into account the recent recognition that the role of serotonin in the context of pain therapy is ambivalent. While, on the one hand, serotonin functions, besides NE, as a transmitter in the descending pain inhibitory system, in contrast to NE, serotonin is also a transmitter in descending excitatory projections. Thus, in contrast to NE, serotonin not only has an anti-nociceptive effect, but can also have a pro-nociceptive effect [67,68], questioning the value of this mechanism for profound analgesic effects.

The discovery of tapentadol involved multiple steps of chemical innovations to become a unique drug. Compared to tramadol, it has a greater CNS functional activity at MOR, about the same or slightly more at NET, and substantially less at SERT. This translates into a higher potency and clinical efficacy of tapentadol compared to tramadol, despite the fact that tapentadol has a lower MOR activity than M1-tramadol, because M1-tramadol does not cross the blood-brain barrier in the same ratio as the tramadol dose is increased [9].

The two drugs thus have unique preclinical and clinical profiles appropriate for specific populations of pain patients. Tramadol offers an effective, non-scheduled (in all major countries) analgesic option that can provide pain relief for long-term use where strong opioids are not needed or desired, with low abuse potential [57-59]. Its use is optimized by titration to a dose that is compatible with use in patient populations and conditions in which the long-term use of NSAIDs, acetaminophen, or strong opioids is not desirable. The new tapentadol offers analgesia comparable to oxycodone with more favorable gastrointestinal tolerability [60-62]. The synergistic contribution of its multi-modal mechanism (MOR plus NRI) results in greater analgesic potency in a variety of preclinical models of pain, including neuropathic pain. This is also evident from the clinical dose conversion factors, for which a ratio in the range of 1:1.5 to 1:4 for tapentadol to tramadol can be estimated. Thus, with a recommended maximum daily dose of 400 mg of long-acting tramadol only 40% of the analgesic effect of a maximum daily dose (500 mg) of long-acting tapentadol can be expected (assuming a conservative conversion factor of 1:2). Already intermediate doses of tapentadol would correspond to tramadol doses exceeding the recommended daily dose, and escalation of the tramadol dose to match tapentadol's analgesic efficacy is not a viable option. Thus, the two drugs provide complementary options for a broad spectrum of types and

magnitudes of pain, giving patients more treatment options and potentially leading to better pain management.

More generally, tapentadol might serve as a template for rational drug discovery efforts in other therapeutic areas. Once the mechanistic targets that account for an existing drug's clinical utility (or disadvantages) are identified, target-directed (or off-target-avoiding) compounds can be designed and tested. By such an iterative process, the biological targets can be refined and improvements can be made, resulting in new drugs that have differentiating clinical attributes that benefit patients in different yet complementary ways. Tapentadol serves as an example both of the approach itself and of the benefits that can result from such an approach.

Declaration of interest

RB Raffa previously worked for Johnson & Johnson and is a speaker, advisory-panel member, consultant, and/or basic science funded researcher for Johnson & Johnson, Grünenthal GmbH and/or several other pharmaceutical companies involved in analgesics research, but receives no royalty (cash or otherwise) from the sale of any product. T Christoph, W Englberger, T Hertrampf, B Kögel, K Schiene, R Terlinden, and T Tzschenke are employees of Grünenthal GmbH. H Buschmann and W Strassburger are former employees of Grünenthal GmbH. G Eichenbaum and CM Flores are employees of Janssen Research & Development, LLC.

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Tapentadol Hydrochloride

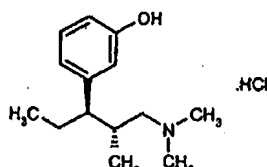
Prop INNM: USAN

*Analgesic
Mu-Opioid Receptor Agonist
Noradrenaline Reuptake Inhibitor*

CG5503

BN200

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



$C_{14}H_{23}NO \cdot HCl$

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

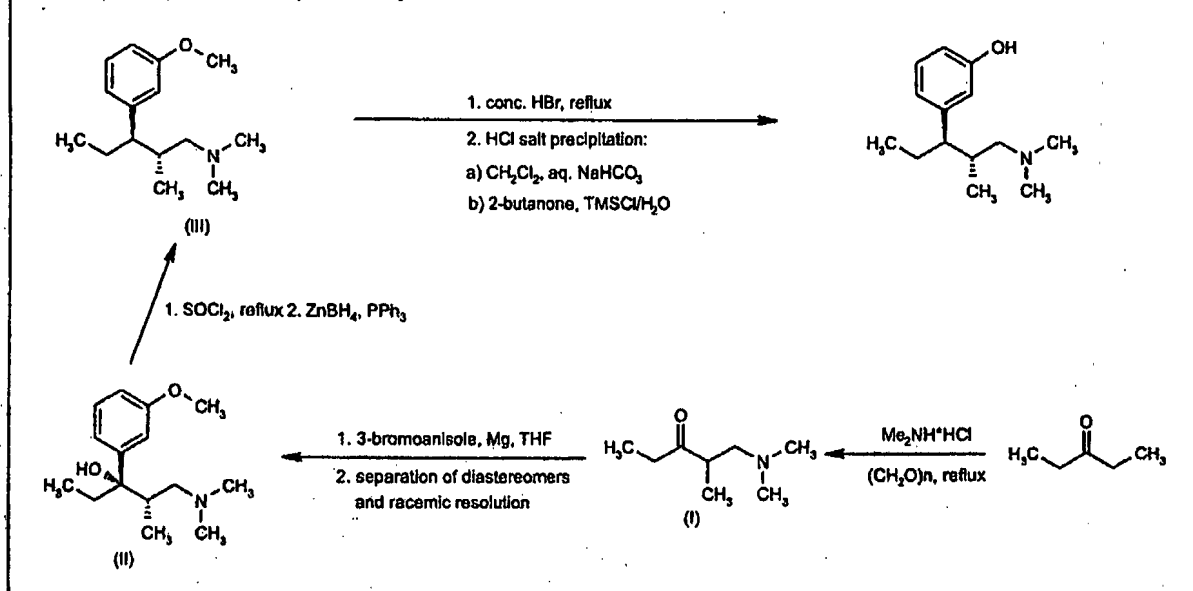
methods, e.g., starting from diethyl ketone, which is transformed under standard Mannich conditions to racemic (I). The Grignard reaction with 3-bromoanisole and subsequent separation of diastereomers (crystallization as HCl salt from 2-butanone with $TMSCl/H_2O$) and enantiomers (HPLC, CS phase) gives (-)-(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 $0.023 \mu\text{M}$, respectively).

Tapentadol was characterized in a GTP γ S assay with human recombinant MOR as a MOR agonist ($\text{EC}_{50} = 0.67 \mu\text{M}$). 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 $1.49 \mu\text{M}$, 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 $0.5 \mu\text{M}$. In contrast to its NA reuptake-inhibitory properties, the reuptake of 5-HT was only weakly inhibited ($K_i = 2.4 \mu\text{M}$) 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 ($K_i = 0.47$ - $1.19 \mu\text{M}$). 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 $1 \mu\text{M}$); 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 potentially 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 tapentadol¹ and morphine¹ 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. ¹All drug doses for preclinical and clinical testing are for the hydrochloride salt.

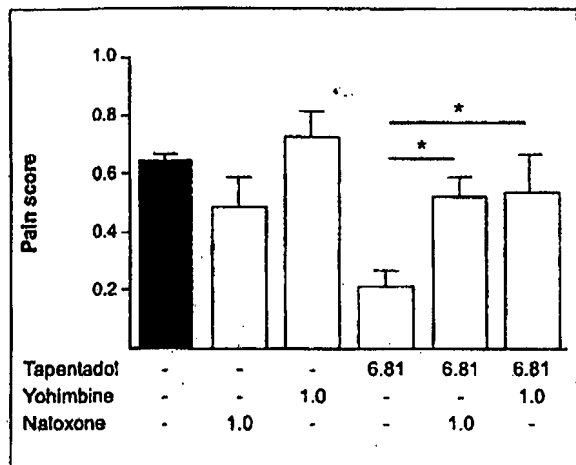


Fig. 1. Antagonism of tapentadol-induced analgesia by the MOR antagonist naloxone and the α_2 -adrenoceptor antagonist yohimbine in the formalin test. The figure shows the pain score (according to a rating scale) during phase II of the test. $n=10$ rats per group. * $p < 0.05$ versus tapentadol treatment. "-" 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%).

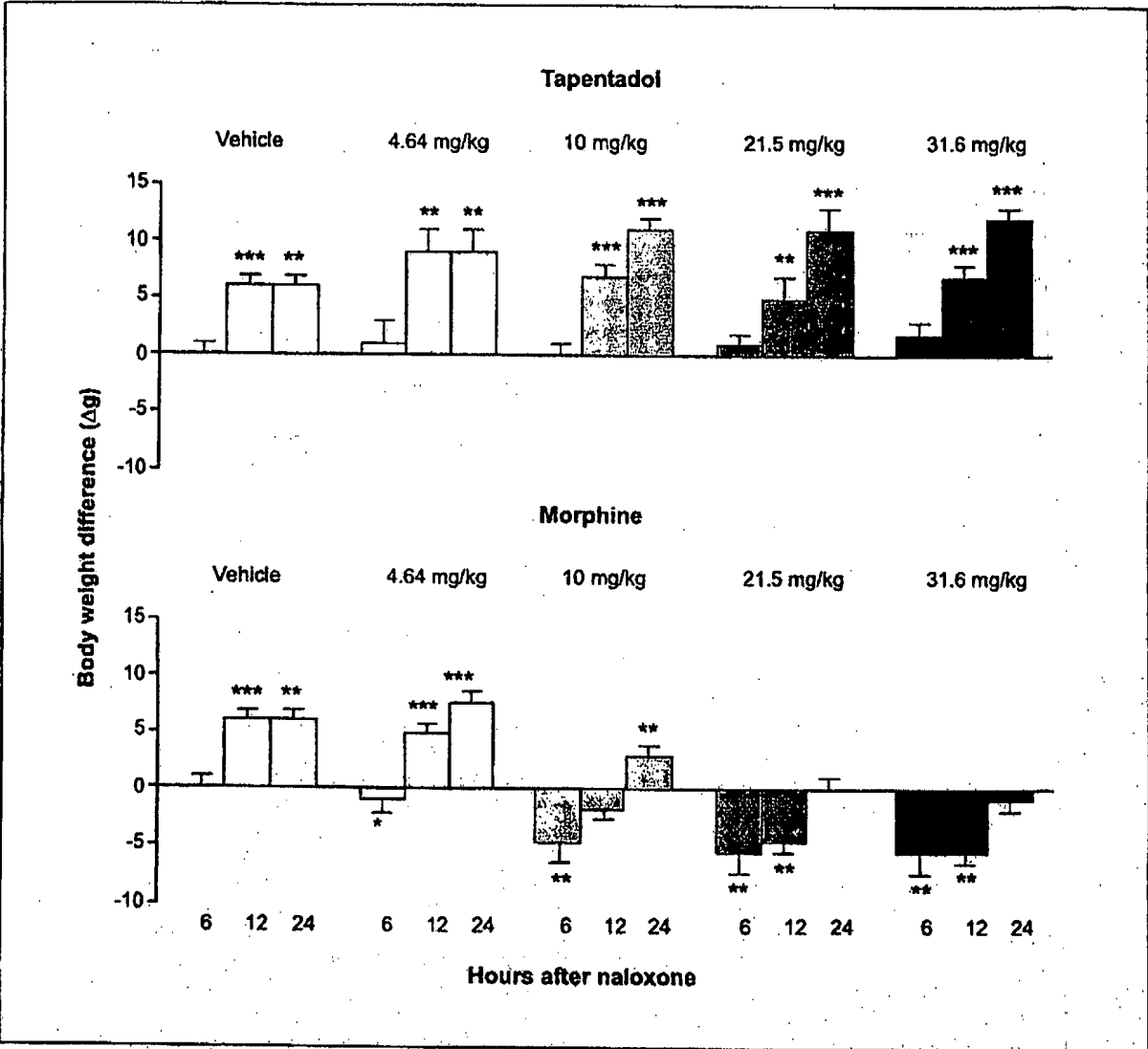


Fig. 2. Comparison of the physical dependence liability of tapentadol and morphine in rats. Data show the effects of naloxone-precipitated withdrawal on body weight measured 6, 12 and 24 h after i.d. treatment with tapentadol or morphine during 3 weeks. n=12 rats per group. *p < 0.05, **p < 0.01, ***p < 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 _{1/2} (h)	4.1	4.9
CL (CL _T) (ml/min)	1531	5007
V _z (V _{zT}) (l)	540	2127
F (%)	—	32

IR: immediate release; C_{max}: peak plasma concentration; t_{max}: time to C_{max}; t_{1/2}: 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_{50} 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

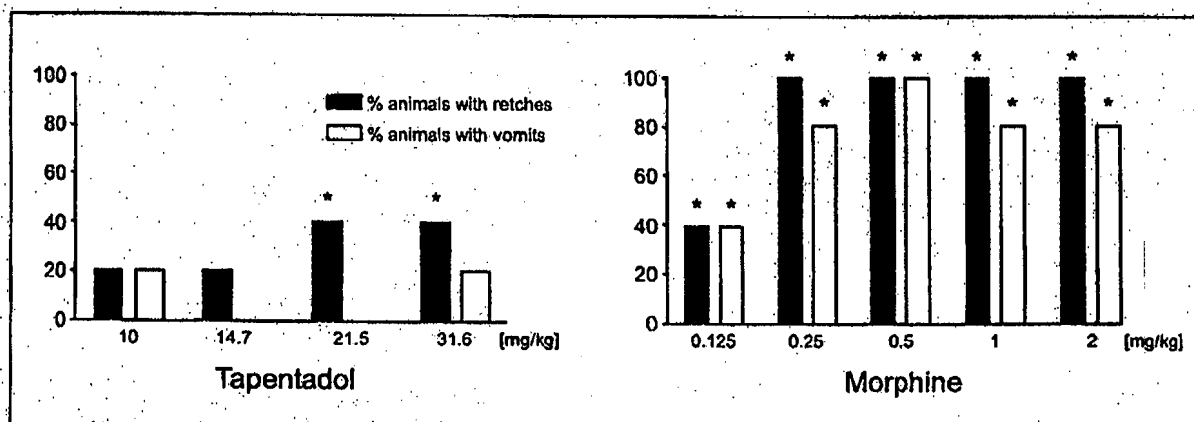


Fig. 3. Comparison of the liability of tapentadol (i.p.) and morphine (s.c.) to induce emesis in ferrets. Data represent the percentage of animals showing retches and/or vomits. $n=10$ ferrets per group. * $p < 0.05$ versus vehicle control.

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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