EUROPEAN JOURNAL OF DRUG METABOLISM AND PHARMACOKINETICS 2007, Vol. 32, No. 3, pp. 163-169

Absorption, metabolism, and excretion of ^{14}C-labeled Tapentadol HCl in healthy male subjects

ROLF TERLINDEN[1], JOACHIM OSSIG[1], FRANK FLIEGERT[2], CLAUDIA LANGE[3] and KARIN GÖHLER[2]

[1]Grünenthal GmbH, Preclinical Research and Development/Department of Pharmacokinetics; [2]Grünenthal GmbH, Department of Clinical Pharmacology; [3]Grünenthal GmbH, Analgesic Department, Aachen, Germany.

Received for publication: August 2, 2007

Key words: Tapentadol, analgesic, absorption, metabolism, excretion

SUMMARY

Tapentadol is a novel, centrally acting oral analgesic with a dual mode of action that has demonstrated efficacy in preclinical and clinical models of pain relief. The present study investigated and characterized the absorption, metabolism, and excretion of tapentadol in humans. Four healthy male subjects received a single 100-mg oral dose of 3-[^{14}C]-labeled tapentadol HCl for evaluation of the pharmacokinetics of the drug and the excretion balance of radiocarbon. The concentration-time profiles of radiocarbon in whole blood and serum and radiocarbon excretion in the urine and feces, and the expired CO_2 were determined. The serum pharmacokinetics and excretion kinetics of tapentadol and its conjugates were assessed, as was its tolerability. Absorption was rapid (with a mean maximum serum concentration [C_{max}], 2.45 µg-eq/ml; a time to C_{max}, 1.25-1.5 h), and the drug was present primarily in the form of conjugated metabolites (conjugated:unconjugated metabolites = 24:1). Excretion of radiocarbon was rapid and complete (>95% within 24 h; 99.9% within 5 days) and almost exclusively renal (99%: 69% conjugates; 27% other metabolites; 3% in unchanged form). No severe adverse events or clinically relevant changes in vital signs, laboratory measurements, electrocardiogram recording, or physical examination findings were reported. In our study group, it was found that a single oral dose of tapentadol was rapidly absorbed, then excreted into the urine, primarily in the form of conjugated metabolites, and was well tolerated.

INTRODUCTION

The search for an oral analgesic that effectively balances pain relief with an improved safety and tolerability profile compared with that of classic opioids has led to the development of compounds with multiple modes of action. One such compound, tapentadol, is a new and effective centrally acting analgesic with a dual mode of action. Its effects, due to both µ-receptor agonism and noradrenaline (NA) reuptake inhibition, are independent of metabolic activation, and it does not produce active metabolites. Besides being a strong centrally acting analgesic, tapentadol displays improved gastrointestinal tolerability compared to that of strong opioid analgesics (1,2).

Tapentadol is a pure enantiomer. In several animal species, investigation of its pharmacokinetic profile has shown extensive first-pass metabolism (3). The primary metabolic pathway is *via* direct glucuronidation, with sulfation of the phenolic hydroxyl group occurring to a minor extent. Minor phase-1 biotransformations include hydroxylation of the aromatic ring, as well as demethylation and subsequent conjugation. The results of *in vitro* studies have demonstrated that these metabolites are either unable to bind to, or have a low binding affinity for the µ-opioid re-

Please send reprint requests to: Dr Rolf Terlinden, Grünenthal GmbH, Preclinical Research and Development/Department of Pharmacokinetics, Zieglerstrasse 6, D52078 Aachen, Germany

ceptor, and are therefore not likely to contribute to the tapentadol's analgesic activity of (unpublished data).

To investigate and characterize the absorption, metabolism, and excretion of tapentadol in humans, a single oral 100-mg dose of 3-[^{14}C]-radiolabeled tapentadol HCl was administered to four healthy male subjects, and its pharmacokinetics, excretion rate and metabolites were subsequently determined.

MATERIALS, METHODS AND SUBJECTS STUDIED

Four healthy Caucasian male subjects between 18 and 45 years of age were enrolled in this phase I, open-label, single-dose, pharmacokinetic study conducted at one study center (SGS Biopharma) in B-2060 Antwerp, Belgium. They were selected according to protocol-specified inclusion criteria, which included being within 15% of ideal body weight for height and build, in good physical and mental health, having normal electrocardiogram (ECG) recordings, and with laboratory test results within a normal reference range. Exclusion criteria included the inability to comply with the constraints of full urine and stool collection, or having been exposed to ionizing radiation (except for routine or dental radiography) or to radioisotopes within 1 year prior to the study drug administration.

The study protocol and the informed consent form were approved by a registered Medical Ethics Committee, and the trial was performed in accordance with the Declaration of Helsinki and the Guidelines for Good Clinical Practice. All subjects gave their written informed consent prior to participating in the study.

A single capsule of 3-[^{14}C]-tapentadol HCl was administered orally to overnight-fasted subjects. Each capsule contained 100 mg tapentadol HCl (equivalent to 85.86 mg tapentadol) labeled with 1.867 MBq (50 μCi) ^{14}C, manufactured by Grünenthal GmbH (Germany). Figure 1 shows the location of the ^{14}C label within the tapentadol HCl structure.

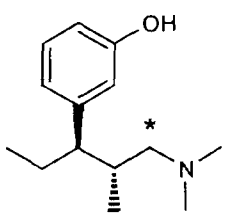

Figure 1. Location of the 3-[^{14}C] label within the tapentadol structure.

Food intake was restricted until 5 h post-drug administration, and subjects were not permitted to lie down for 2 h or to sleep for 6 h post-dose. Alcohol, grapefruit, and xanthine-containing beverages and foods were prohibited from 48 h pre-dose to 48 h post-dose. No drug treatment apart from paracetamol was allowed during the study period.

Samples of blood, urine, feces, and expired CO_2 were collected at regular intervals. Subjects remained in the clinical laboratory for the duration of the treatment period (at least 7 and up to 14 days post-dose, according to the proportion of radioactive label excreted as per protocol-specified discharge criteria). The blood samples (10 ml by venipuncture in the forearm) were collected pre-dose on Day 1 and then at 0.25, 0.5, 0.75, 1, 1.25, 1.5, 2, 3, 4, 5, 6, 8, and 12 h post-dose, after which they were taken once daily on Days 2–14. The collection of blood samples could be terminated prior to Day 14 if the concentrations of 3-[^{14}C] fell below 1 Bq/ml for two successive samples. The blood samples were collected using two 5-ml tubes for the determination of radioactivity and also for assays of the parent drug and its metabolites, respectively. All blood samples were evaluated for serum radioactivity, while whole blood radioactivity was measured only in samples obtained on Days 1–4. When whole blood radioactivity assays were required, approximately 1 ml was taken from one of the 5-ml blood samples, then pipetted into a small tube and stored at –70°C until transfer on dry ice to the analytical laboratory. For the determination of serum radioactivity, the remaining 4 ml was allowed to clot for 30–60 min at room temperature and then centrifuged (3500 rpm for 10 min at 10°C). The separated serum was transferred to a polypropylene tube, which was stored and transferred to the analytical laboratory, as previously described for whole blood. For assays of tapentadol and its metabolites, the second 5-ml sample was allowed to clot, then centrifuged (3000 rpm for 10 min), after which the separated serum was transferred to two polypropylene tubes, which were stored and transferred to the analytical laboratory in the same way as described above.

All voided urine were collected in plastic containers and refrigerated. The following fractions were collected: pre-dose, 0–4 h, 4–8 h, 8–12 h, and 12–24 h on Day 1, then one fraction per 24 h until Day 14 (336 h post-dose). Urine collection could be terminated before Day 14 if the combined cumulative excretion of the label (in the urine, feces, and expired CO_2) exceeded 95% of the actual dose, or if the amount of excreted radioactivity after the maximum in the urine was below 1.0% of the administered dose

in the two successive 24-h fractions. Each fraction was homogenized, and its weight was recorded together with the date and time at which the sample collection started and ended. One 10-ml sample for the determination of radioactivity and one 25-ml sample for further investigation were stored and transferred to the analytical laboratory, as noted above. The remainder was discarded.

Fecal collection started on Day 1 and continued until the time point specified for the termination of urine collection was reached. All stools were collected in plastic bags, which were then placed in appropriately labeled plastic boxes. Samples were stored and transferred in the same manner as for urine. Prior to radiocarbon assay, each stool was thawed and homogenized with water. A 10-ml sample of each stool was kept frozen for further investigation by the laboratory in question, and the remainder was discarded.

CO_2 samples were collected pre-dose after blood sampling on Day 1 and at 0.5, 1, 2, 3, 4, 6, 8, 12, and 24 h post-dose. Subjects blew gently through a glass straw into a vial containing a base suitable to trap 1 mM CO_2. The end-point was reached when the phenolphthalein indicator remained consistently bleached. Samples were then immediately capped, and refrigerated at 2–8°C until transfer to the analytical laboratory.

For serum and whole blood samples, the following parameters were calculated from the radiocarbon concentrations in each sample and its tapentadol (unconjugated and conjugated drug) equivalent: the maximum serum concentration (C_{max}) of tapentadol, the time to reach the C_{max} (T_{max}), the area under the concentration-time curve from 0 to 120 min (AUC_{0-120}), the apparent terminal half-life of radiocarbon ($t_{1/2}$), and the radiocarbon concentrations in blood cells, assessed from the concentrations in the serum, in whole blood and from the hematocrit. For urine, the radiocarbon concentrations in each sample were used to calculate the daily radiocarbon excretion rate (dU/dt) and, if possible, the excretion half-time and the cumulative renal excretion of radiocarbon up to the last measurable sample. The concentrations of unconjugated and conjugated tapentadol were also determined in urine. For the feces, the radiocarbon concentrations in each sample were used to calculate the daily radiocarbon rate of excretion and the cumulative fecal excretion determined for radiocarbon up to the last measurable sample. For expired CO_2, the specific radioactivity determined for each sample was used to calculate the cumulative excretion of radiocarbon over 24 h, assuming standardized daily CO_2 production. The excretion balance of radiocarbon was calculated from the above determinations.

Liquid scintillation spectrometry was the method used for the determination of radiocarbon in the above-mentioned expired CO_2 traps (single determinations), serum and urine samples (triplicate determinations), whole blood samples were combusted to CO_2 which was trapped (duplicate determinations), and stool sample aliquots were homogenized with water and also combusted to CO_2 which was trapped (quadruplicate determinations). Assays were performed by SGS-Biopharma (B-2060 Antwerp Belgium) according to standard procedures. Lower limits of quantification (LLOQ) amounted to 0.17 Bq/ml for the urine, 0.34 Bq/ml for the serum, 1.22 Bq/ml for whole blood, 0.43 Bq/g for fecal homogenates and 0.48 Bq/mmol for expired CO_2.

The concentrations of tapentadol and its conjugates were also determined in the serum and urine. The concentration in the serum was determined after liquid/liquid extraction by a validated ion-pair reversed-phase high performance liquid chromatography (HPLC) method using fluorometric detection. The concentrations of conjugates were determined in the previously extracted samples after a second extraction performed after cleavage of the conjugates with β-D-glucuronidase glucuronosohydrolase/Aryl-sulfate sulfohydrolase (Helix Pomatia; aqueous solution stabilized with thimerosal). The standard curves were linear in the measured range, i.e., from 0.5–200 ng/ml of serum and 2.5–1000 ng/ml of urine. The LLOQ amounted to 0.5 ng/ml and 2.5 ng/mL for tapentadol in the serum and urine, respectively. The overall inaccuracy (expressed as percent deviation from the nominal value) and precision (expressed in terms of the coefficient of variation) for quality controls assayed during the analysis of the study samples were well below 15% at all concentrations examined.

During the study period, all adverse events (AEs) either reported spontaneously by the subjects and/or in response to an open question from the investigator were recorded and classified according to MedDRA version 7.1. Clinical and laboratory measurements (hematology, serum laboratory values, quantitative and qualitative urinalysis), vital sign assessments, physical examinations, and ECG assessments were carried out at selection of subjects prior to the trial and discharge. Vital sign assessments and physical examinations were also carried out immediately before and 24 h after drug dosage.

Statistical calculations were performed using SAS for Windows, version 6.12. Demographic (age, height, weight), pharmacokinetic data and vital sign,

laboratory, and ECG assessments were recorded by standard statistics (mean, standard deviation, minimum, median, maximum) for all subjects. No calculations regarding statistical power could be performed due to the limited number of subjects. The sample size, however, was considered to be sufficient to provide adequate excretion and metabolism information on 3-[^{14}C]-labeled tapentadol HCl.

RESULTS

Four male subjects were enrolled in the study, received medication, completed the trial period, and were available for pharmacokinetic evaluation. They had a mean age of 38 years (range: 28–45 yr), a mean height of 184 cm (range: 176–193 cm), and a mean weight of 80 kg (range: 75–84 kg). All were in good physical and mental health, with normal vital signs and with positive ECG and clinical laboratory results.

Each subject received 100 mg of 3-[^{14}C]tapentadol HCl, which corresponded to 85.86 mg of tapentadol. The actual radiocarbon dose of received was 1.867 MBq, or a specific activity 21.74 kBq/mg tapentadol HCl.

Tapentadol was rapidly absorbed, achieving a C_{max} in the serum (mean, 2.45 µg-eq base/ml) between 1.25 and 1.5 h (Table I). In the serum, it was primarily present in the form of conjugated metabolite (Fig. 2); the ratio of conjugates to unconjugated tapentadol was 24:1. The C_{max} of conjugated tapentadol, i.e. 1.69 µg-eq base/ml (range, 1.30–2.07 µg-eq base/ml), occurred between 1.25 and 2.0 h. The serum concentrations of unconjugated tapentadol were very low in all subjects (Table II). The mean total AUC_{0-120} (unconjugated + conjugated) in the serum amounted to 7.45 µg-eq base.h/ml (range, 6.56–8.90 µg-eq base.h/ml) and accounted for approximately 64% of the total radiocarbon AUC_{0-120} (mean, 11.6 µg-eq.h/ml; range, 10.7–13.3 µg-eq.h/ml).

Table I. Individual and mean pharmacokinetic parameters for radiocarbon in the serum

	Subject					
Parameter	1	2	3	4	Mean	SD[e]
C_{max}[a] (µg-eq base/ml)	2.63	2.30	1.85	3.01	2.45	0.49
T_{max}[b] (h)	1.25	1.50	1.50	1.25	1.38	0.14
AUC_{0-120}[c] (µg-eq base•h/ml)	11.4	10.7	11.1	13.3	11.6	1.2
$t_{1/2}$[d] (h)	3.89	3.66	4.10	4.05	3.93	0.20

[a]C_{max}: Maximum serum concentration; [b]T_{max}: Time to C_{max}: [c]AUC_{0-120}: Area under the serum concentration-time curve from time 0 to 120 min; [d]$t_{1/2}$: Apparent terminal half-life; [e]SD: Standard deviation

Table II. Individual and mean pharmacokinetic parameters for unconjugated, conjugated, and total tapentadol in the serum

	Subject					
Parameter	1	2	3	4	Mean	SD[e]
Unconjugated						
C_{max}[a] (µg-eq base/ml)	0.05	0.03	0.08	0.10	0.07	0.03
T_{max}[b] (h)	1.25	2.00	0.75	1.50	1.38	0.52
AUC_{0-120}[c] (µg-eq base•h/ml)	0.22	0.25	0.37	0.35	0.30	0.08
$t_{1/2}$[d] (h)	3.20	4.38	5.35	5.07	4.50	0.96
Conjugated						
C_{max} (µg-eq base/ml)	1.82	1.55	1.30	2.07	1.69	0.33
T_{max} (h)	1.25	1.50	2.00	1.25	1.38	0.52
AUC_{0-120} (µg-eq base•h/ml)	6.52	6.31	7.17	8.53	7.13	1.00
$t_{1/2}$ (h)	3.55	3.10	6.25	4.98	4.47	1.43
Total						
C_{max} (µg-eq base/ml)	1.88	1.58	1.36	2.16	1.74	0.35
T_{max} (h)	1.25	1.50	2.00	1.25	1.50	0.35
AUC_{0-120} (µg-eq base•h/ml)	6.77	6.56	7.56	8.90	7.45	1.06
$t_{1/2}$ (h)	3.50	3.17	6.16	4.95	4.44	1.38

[a]C_{max}: Maximum serum concentration; [b]T_{max}: Time to C_{max}: [c]AUC_{0-120}: Area under the serum concentration-time curve from time 0 to 120 min; [d]$t_{1/2}$: Apparent terminal half-life; [e]SD: Standard deviation

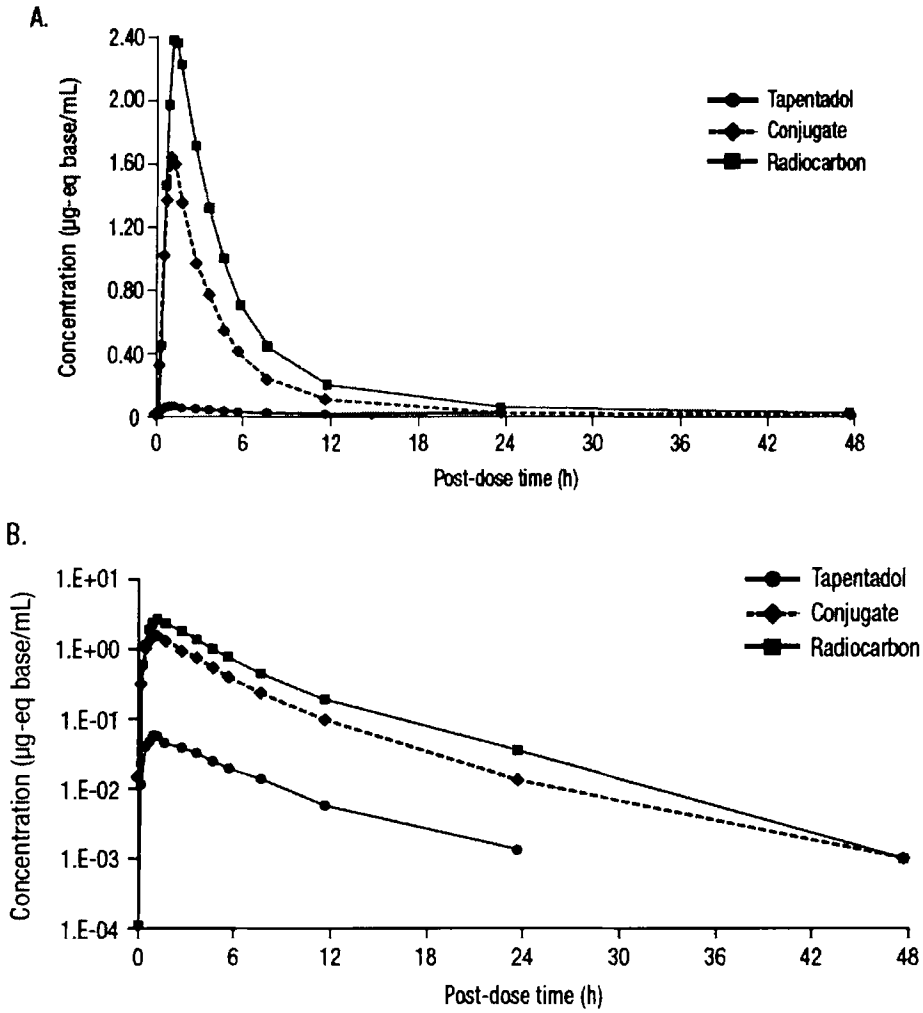

Figure 2. Average concentration-time profiles of tapentadol conjugates (closed diamonds), tapentadol (closed circles), and radiocarbon (closed squares) after oral administration of 100 mg 3-[^{14}C]-labeled tapentadol HCl (1.867 MBq radiocarbon) to 4 healthy male subjects. Values are arithmetic means, and shown as linear coordinates (a) and semi-log coordinates (b).

Table III. Excretion balance for radiocarbon (% of dose)

	Subject					
Route	1	2	3	4	Mean	SD[b]
Urine	98.7	98.5	99.0	98.3	98.6	0.3
Feces	1.59	0.664	0.870	1.84	1.24	0.57
Expired CO_2	0.039	0.048	< LLOQ[a]	0.020	0.035	0.015
Total	100	99.1	99.8	100	99.9	0.52

[a] LLOQ, Lower limit of quantification; [b] SD, Standard deviation

The mean radiocarbon C_{max} in whole blood was 1.40 µg-eq base/ml (range, 1.05–1.60 µg-eq base/ml), with T_{max} occurring at 1.25–1.5 h. Mean (standard deviation) $AUC_{0\text{-}120}$ in whole blood amounted to 5.85 (0.40) µg-eq base.h/ml.

Excretion was rapid, with more than 50% of the dose excreted after 4 h and over 95% being excreted within 24 h of dosing. The apparent half-life ($t_{1/2}$) was 3.93 h. Excretion was almost exclusively renal, with 99% being excreted in the urine. Sixty-nine percent of identified radioactivity excreted in the urine in the form of conjugates (glucuronide and sulfate), approximately 27% as other metabolites, and 3% as unchanged tapentadol.

Fecal (1%) and expired CO_2 (negligible) were found to be non-insignificant routes of excretion (Table III). The excretion balance was complete (mean, 99.9% recovery) after approximately 5 days.

Three subjects reported AEs that were classified as possibly or probably related to the study medication, all of which were mild in severity and resolved spontaneously without medical treatment (vertigo: three subjects; eye irritation: two subjects). There were no clinically relevant changes in vital signs, laboratory measurements, ECG recording, or physical examination findings.

DISCUSSION AND CONCLUSIONS

In healthy subjects given a single oral 100-mg dose of 3-[^{14}C]-tapentadol HCl, the absorption and elimination rates were rapid, with no quantifiable radioactivity detected at 48 h post-dose. Excretion was almost exclusively by renal elimination (99%), with only 1% being excreted in the feces. Expired CO_2 was a non-significant route of elimination, which demonstrates that the drug was labeled in a metabolically stable position. Only 3% of the dose was eliminated in the form of unchanged tapentadol, with almost the entire dose being metabolized to inactive conjugates (96%). The conjugates exceeded the unconjugated tapentadol by a factor of 24 to 1.

It was concluded that tapentadol was well tolerated in these four healthy subjects.

Orally administered tapentadol is cleared by hepatic glucuronidation via the UDP-glucuronosyltransferase (UGT) pathways by the UGT1A9 and UGT2B7 enzymes (data on file, Grünenthal). It is well known that the induction or inhibition of drug-metabolizing enzymes can lead to increased clearance or toxic accumulation of co-administered drugs (4-9), and the issue of drug-drug interactions mediated by drug-metabolizing enzymes is of considerable clinical interest as a significant proportion of prescribed drugs undergo metabolic changes. For example, the results of an analysis of the 200 most-prescribed drugs in the United States in 2002 showed that more than 75% became metabolized. The majority of these utilized cytochrome P450 (CYP450) enzyme pathways; less than 1 in 10 were glucuronidated (10). At present, few agents are known to be potent inhibitors of UGTs *in vitro*, and clinically relevant drug-drug interactions have rarely been reported (10). Pharmacokinetic interaction studies conducted on drugs metabolized by glucuronidation have typically reported changes on the order of 2- to 4-fold when activators or inhibitors of UGTs were co-administered (11-13). Addition of the UGT activator alamethacin to human liver microsomes has been found to increase the rate of glucuronidation of the extensively glucuronidated drug zidovudine by approximately 3.5-fold, while the addition of the UGT inhibitor D-saccharic acid 1,4-lactone had no effect on zidovudine glucuronidation (11). An increase of approximately 2-fold in the AUC of morphine was obtained when morphine was co-administered to patients with clomipramine and of approximately 1.3-fold when it was obtained when it was co-administered with amitriptyline (13). This minor difference in results is most likely because multiple UGT enzymes metabolize these drugs and the metabolic pathways in question are of high capacity. Based on our current knowlrdge of these pathways, it is assumed that the potential for drug-drug interactions with tapentadol is low.

In contrast to drugs that are primarily metabolized by UGT enzymes, changes as high as 37-fold have been reported for CYP450 enzymes when an inhibitor is co-administered, thereby suggesting that drug-drug interactions resulting from the inhibition of these enzymes could have significant clinical effects (14). Among the classic opioids, oxycodone, codeine, dihydrocodeine, and hydrocodone are metabolized by the CYP2D6 and CYP3A4 enzymes. Numerous inhibitors of CYP2D6 have been identified, including several cardiovascular drugs and antidepressants. In the case of oxycodone, the drug-drug interactions can result in a significant increase in noroxycodone plasma concentrations and a decrease in oxymorphone plasma concentrations (15).

Potential drug-drug interactions have also been associated with the degree of drug bounding to serum proteins. *In vitro* analyses using human serum have revealed that only 20% of tapentadol is bound to serum proteins, primarily to albumin (3). This finding is somewhat lower than that regarding the protein binding characteristics of classical opioids, such as morphine (20%–35%) and oxycodone (45%) (16,17). These preclinical data thus further support the low risk for potential drug-drug interactions with tapentadol.

Tapentadol is a pure enantiomer and has no active metabolites that contribute to its analgesic activity; the benefits of these characteristics therefore are twofold. Firstly, the full analgesic activity of tapentadol is contained within a single molecule. In contrast, if an agent has enantiomers with different activities, their combination may influence its analgesic and tolerability profiles (18,19). Secondly, although active metabolites of some agents may contribute to

their overall analgesic effect (4,20), the absence of active metabolites as regards to tapentadol should be advantageous, because consistent analgesic activity can thus be expected in the majority of patients. Decreased efficacy has been reported with the centrally acting agent, codeine, associated with decreased formation of active metabolites in individuals who are poor CYP2D6 metabolizers, and therefore variability in analgesic effect among patients can occur (21).

In conclusion, tapentadol is a novel, centrally acting analgesic with a dual mode of action based on both μ-receptor agonism and NA reuptake inhibition. It is rapidly absorbed and excreted after oral administration to healthy subjects, and as a result, it is not expected to accumulate systemically. Its activity is independent of metabolic activation and this drug has no active metabolites. Further, because glucuronidation, the major metabolic pathway for tapentadol, is of high capacity, metabolic saturation is not likely to occur. Drug-drug interactions are unlikely, in particular because no potent inhibitors of UDP-glucuronosyltransferases are known thus far. The unique mechanism of action of this analgesic agent has the potential to improve the treatment of moderate to severe pain, and ongoing clinical studies are investigating the effects of tapentadol in pain-relief models. Recent studies have demonstrated the efficacy of this drug as a strong centrally active analgesic with improved gastrointestinal tolerability compared to that of strong opioid analgesics (1,2).

Acknowledgments

This study was sponsored by Grünenthal GmbH, Aachen, Germany.

REFERENCES

1. Weber H., Hallman C., Steup A. et al. (2006): Efficacy and safety of tapentadol HCl in patients with pain after bunionectomy. J. Pain, 7(suppl 1), S3. Abstract 312.
2. Kleinert R., Hallmann C., Steup A., Black P., Goldberg J., Desjardins P. (2006): Efficacy of a single dose of tapentadol HCl for analgesia after third molar surgery. J. Pain, 7(suppl 1), S44. Abstract 773.
3. Terlinden R., Ossig J., Fliegert F., Gohler K. (2006): Pharmacokinetics, excretion, and metabolism of tapentadol HCl, a novel centrally acting analgesic, in healthy subjects. J. Pain, 7(suppl 1), S26. Abstract 689.
4. Armstrong S.C., Cozza K.L. (2003): Pharmacokinetic drug interactions of morphine, codeine, and their derivatives: theory and clinical reality, Part II. Psychosomatics, 44, 515–520.
5. Lugo R.A., Satterfield K.L., Kern S.E. (2005): Pharmacokinetics of methadone. J. Pain Palliat. Care Pharmacother., 19, 13–24.
6. Bruce R.D., Altice F.L., Gourevitch M.N., Friedland G.H. (2006): Pharmacokinetic drug interactions between opioid agonist therapy and antiretroviral medications: implications and management for clinical practice. J. Acquir. Immune. Defic. Syndr., 41, 563–572.
7. Hollenberg P.F. (2002): Characteristics and common properties of inhibitors, inducers, and activators of CYP enzymes. Drug Metab. Rev., 34, 17–35.
8. Ito K., Iwatsubo T., Kanamitsu S., Ueda K., Suzuki H., Sugiyama Y. (1998): Prediction of pharmacokinetic alterations caused by drug-drug interactions: metabolic interaction in the liver. Pharmacol. Rev., 50, 387–412.
9. Bjornsson T.D., Callaghan J.T., Einolf H.J. et al. (2003): The conduct of in vitro and in vivo drug-drug interaction studies: a Pharmaceutical Research and Manufacturers of America (PhRMA) perspective. Drug Metab. Dispos., 31, 815–832.
10. Williams J.A., Hyland R., Jones B.C. et al. (2004): Drug-drug interactions for UDP-glucuronosyltransferase substrates: a pharmacokinetic explanation for typically observed low exposure (AUCi/AUC) ratios. Drug Metab. Dispos., 32, 1201–1208.
11. Boase S., Miners J.O. (2002): In vitro-in vivo correlations for drugs eliminated by glucuronidation: investigations with the model substrate zidovudine. Br. J. Clin. Pharmacol., 54, 493–503.
12. Lin J.H., Wong B.K. (2002): Complexities of glucuronidation affecting in vitro in vivo extrapolation. Curr. Drug Metab., 3, 623–646.
13. Ventafridda V., Bianchi M., Ripamonti C. et al. (1990): Studies on the effects of antidepressant drugs on the antinociceptive action of morphine and on plasma morphine in rat and man. Pain, 43, 155–162.
14. Boxenbaum H. (1999): Cytochrome P450 3A4 in vivo ketoconazole competitive inhibition: determination of Ki and dangers associated with high clearance drugs in general. J. Pharm. Pharm. Sci., 2, 47–52.
15. Heiskanen T., Olkkola K.T., Kalso E. (1998): Effects of blocking CYP2D6 on the pharmacokinetics and pharmacodynamics of oxycodone. Clin. Pharmacol. Ther., 64, 603–611.
16. Lugo R.A., Kern S.E. (2004): The pharmacokinetics of oxycodone. J. Pain Palliat. Care Pharmacother., 18, 17–30.
17. Lugo RA, Kern SE (2002): Clinical pharmacokinetics of morphine. J. Pain Palliat. Care Pharmacother, 16, 5–18.
18. Friderichs E., Becker R. (1991): Correlation of tramadol and M_1 serum levels with antinociceptive activity in mice. Naunyn Schmiedebergs Arch. Pharmacol., 343 (Suppl.), R9. Abstr. 36.
19. Raffa R.B., Friderichs E., Reimann W. et al. (1993): Complementary and synergistic antinociceptive interaction between the enantiomers of tramadol. J. Pharmacol. Exp. Ther., 267, 331–340.
20. Poulsen L., Arendt-Nielsen L., Brosen K., Sindrup S.H. (1996): The hypoalgesic effect of tramadol in relation to CYP2D6. Clin. Pharmacol Ther., 60, 636–644.
21. Desmeules J., Gascon M.P., Dayer P., Magistris M. (1991): Impact of environmental and genetic factors on codeine analgesia. Eur. J. Clin. Pharmacol., 41, 23–26.