Comparison of the Analgesic Efficacy and Tolerability of Tramadol 100mg Sustained-Release Tablets and Tramadol 50mg Capsules for the Treatment of Chronic Low Back Pain

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Summary

This multicentre, randomised, double-blind, parallel-group study was designed to examine the analgesic efficacy and tolerability of a newly developed tramadol slow-release (SR) tablet in comparison with immediate-release tramadol capsules in patients with chronic low back pain which had persisted despite intervention with other pharmacological and/or nonpharmacological measures. 103 patients were treated with tramadol SR tablets twice daily (2 × 100 mg/day) and 102 patients with capsules 4 times daily (4 × 50 mg/day) over a period of 3 weeks. The medication in both groups (verum/placebo) was administered 4 times daily to ensure the double-blind character of the study ('double-dummy technique'). In case of insufficient pain relief the patients received 2 × 200mg SR/day as an escape medication (open design). Daily pain intensity was assessed by patients on a 4-step verbal rating scale. At the end of the study retrograde assessment of analgesia was done by the patient using a 5-step classification. Sufficient pain relief could be achieved in approximately 60% of the patients (116 patients) who completed the 3-week treatment period. There was no difference in pain relief (SR 59% and capsules 59%) and in course of pain intensity between both groups. Furthermore, 30 patients (15.3%) were satisfactorily treated with the escape medication. Adverse events were reported at a similar rate in both groups (54.4% with the SR tablet formulation and 52.9% with the capsules). The main adverse events were nausea (16.6%), dizziness (14.1%), vomiting (9.8%), tiredness (7.8%), diaphoresis (6.3%), headache (6.3%), constipation (6.3%) and dry mouth (6.3%). With the exception of diaphoresis, constipation and dry mouth, adverse events decreased in incidence during the study. The results confirmed the equivalence with regard to efficacy and tolerability of twice-daily administration of tramadol SR tablets compared with 4-times-daily administration of tramadol capsules.
Tramadol, a cyclohexanol derivative, is a synthetic centrally acting analgesic agent with both opioid[1,2] and non-opioid activities.[3] It acts as a weak agonist at opioid receptors, binding to µ, κ and δ receptors,[1] but with preferential affinity for the µ receptor.[2] Additionally, it has been shown to inhibit neuronal reuptake of both noradrenaline and 5-hydroxytryptamine (5-HT) and to stimulate the release of 5-HT.[2,4] Tramadol is a racemic mixture and its mechanism of action via opioid and noradrenergic/serotonergic mechanisms is related to the independent effects of its two enantiomers.[5] Interestingly, the enantiomers act synergistically to achieve an enhanced antinociceptive effect without any detrimental effects on tolerability.[3]

Tramadol was introduced in Germany in 1977 and has since been used by over 39 million patients in more than 70 countries.[6] It has recently been launched in the UK[7] and in the USA.[6] Unlike conventional opioids, tramadol has not been associated with clinically significant respiratory depression, and is further differentiated by its low potential for the development of tolerance, dependence and abuse.[8,9] Tramadol is therefore a suitable analgesic for the management of various acute and chronic pain conditions.[5,10-12] In particular, it has been shown to be of use in chronic pain such as that associated with tumour burden[13] and nonmalignant conditions[12-15] including chronic low back pain.[6]

Until recently, tramadol was available in immediate-release formulations (drops, capsule, suppository, solution for injection) only, which normally necessitated a 4-times-daily administration. A slow-release (SR) film-coated tablet has now been formulated that has been designed to reduce the administration frequency and provide the opportunity for only twice-daily administration.

The present study was conducted to compare the efficacy and tolerability of tramadol when administered as SR tablets (twice daily) or capsules (4 times daily) in patients with chronic low back pain.

A fixed dose of 200 mg/day tramadol was chosen within the double-blind phase as a result of the finding that the majority of patients with chronic low back pain have sufficient pain relief at this dosage.[16]

Patients and Methods

Patients

Patients aged > 18 years with chronic and persistent moderate to severe low back pain (≥ 3 months) justifying treatment with opioids were eligible for inclusion. These included hospitalised patients or outpatients with low back pain due to degenerative changes (spondylarthrosis, osteochondrosis), postdiscectomical syndrome, postoperative complaints (e.g. spondylodesis), discogenic lumbar pain syndrome or osteoporotic processes.

Patients receiving nonpharmacological treatment of their condition (e.g. physiotherapy, chiropractic, kinetotherapy, acupuncture) that commenced more than 3 weeks before the start of the study were eligible for inclusion provided such therapy remained unchanged during the study.

All patients were required to provide written informed consent to participate.

Exclusion criteria for entering the study were chronic low back pain with primary inflammatory aetiology, tumour or metastases, presence of psychiatric disease, current pension proceeding or claims for insurance, and concomitant treatment with other analgesics or psychotropic agents.

Further principal exclusion criteria for safety reasons were a history of cerebral convulsions, treatment with or discontinuation of monoamine oxidase inhibitors within 2 weeks of study entry, known hypersensitivity to opioids, and a history or evidence of substance abuse. Lactating or pregnant women were also ineligible for participation.

Methods

The study was conducted using a multicentre, randomised, double-blind, parallel-group design. Patients were randomised to treatment with tramadol hydrochloride 200 mg/day either as SR tablets (twice daily) or capsules (4 times daily). All patients received verum/placebo tablets twice daily and placebo/verum capsules 4 times daily, to ensure blinding ('double-dummy' technique). The duration of the study was fixed at 3 weeks.

At study entry, each patient received a thorough