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Tizanidine (Intranasal spray) for acute low back pain

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LAY SUMMARY

The lower back is the part of the back between the bottom of the ribs and the top of the legs. Low back pain is the most common of back pain. In most cases, it is not due to a serious disease or serious back problem, and the exact cause of the pain is not clear. This is called nonspecific lower back pain. When the pain lasts up to one month, this is known as acute low back pain. Sometimes the pain may develop immediately after lifting something heavy, or after an awkward twisting movement, or it can develop for no apparent reason. The severity of the pain can range from mild to severe. General symptoms of low back pain include: dull aching pain that travels to the buttocks, legs and feet, pain that is worse after prolonged sitting, pain that feels better when changing positions and pain that is worse after waking up and better after moving.

Tizanidine as an intranasal spray is being developed as a new treatment option for patients with acute low back pain. It works by blocking pain sensations that are sent to the brain, temporarily relaxing muscle tone. Tizanidine is already available in the tablet form as a short-acting muscle relaxer used to relieve the stiffness and restriction of muscles due to injuries or diseases of the spinal cord. If licensed, tizanidine prepared for intranasal administration will offer an alternative to the oral administration for patients with acute low back pain when short term dosing and a fast effect is desired.

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TARGET GROUP

Acute low back pain

TECHNOLOGY

DESCRIPTION

Tizanidine (Tizaspray) is a skeletal muscle relaxant, clinically used for the symptomatic treatment of stiffness and restriction of muscles resulting from multiple sclerosis, injury or disease of the spinal cord.[1] Tizanidine is a centrally acting skeletal muscle relaxant. Its principal site of action is the spinal cord, where the evidence suggests that, by stimulating presynaptic alpha2-receptors, it inhibits the release of excitatory amino acids that stimulate N-methyl-D-aspartate (NMDA) receptors. Polysynaptic signal transmission at spinal interneuron level, which is responsible for excessive muscle tone, is thus inhibited and muscle tone reduced. Tizanidine has no direct effect on skeletal muscle, the neuromuscular junction or on monosynaptic spinal reflexes. In addition to its muscle-relaxant properties, tizanidine also exerts a moderate central analgesic effect. In humans, tizanidine reduces pathologically increased muscle tone, including resistance to passive movements and alleviates painful spasms and clonus.[2]

In the completed phase III clinical trial in patients with acute low back pain, tizanidine was administered intranasally at 0.5mg. The treatment duration was not reported.[3]

Tizanidine does not currently have Marketing Authorisation in the UK in its intranasal formulation. As oral tablets (2mg and 4mg tablets), it is used for the symptomatic treatment of painful muscle spasm associated with musculoskeletal conditions. It is also used for spasticity associated with multiple sclerosis or spinal cord injury or disease.[4] Common (>10%) side effects include; drowsiness, tiredness, dizziness, reduction in blood pressure, increase in blood pressure when stopping the treatment suddenly, dry mouth, and a decrease or increase in heart rate[5]

INNOVATION and/or ADVANTAGES

In a study to evaluate the pharmacokinetic profile of tizanidine nasal spray compared to the oral formation, it was found that after intranasal administration, the absorption was consistently rapid (mean peak times < 1h) without unexpected adverse effects potentially increasing the bioavailability and the intranasal formulation achieved approximately 2.5-fold larger peak concentrations per milligram compared with the oral tablets.[6]

If licensed, tizanidine prepared for intranasal administration will offer an alternative to the oral administration for patients with acute low back pain when short term dosing and a fast effect is desired.

DEVELOPER

MDM S.p.A.

PATIENT GROUP

BACKGROUND

Low back pain is the most common back problem.[7] It refers to pain in the lumbosacral area of the back, between the bottom of the ribs and the top of the legs.[8] The lumbar area serves a number of functions for the human body including structural support, movement, and protection of certain body tissues. Therefore, injury to the structures important for weight bearing, such as the bony spine, muscles, tendons, and ligaments, often can be detected when the body is standing erect or used in various movements.[9] Traditionally, low back pain is divided into three categories: acute, sub-acute and chronic. Acute pain lasts up to one month, sub-acute pain lasts 1 to 3 months while chronic pain is defined as when symptoms have been present for more than three months.[10]

Specific causes of low back pain include sciatica, vertebral fracture, intra-abdominal pathologies, and more rarely, ankylosing spondylitis, cancer, and infection. Non-specific low back pain is diagnosed when the pain cannot be attributed to a specific cause, although in many cases, may be related to trauma, or musculoligamentous strain.[11] Depending on the cause of low back pain, the onset of symptoms can vary widely, they may develop slowly over time or come and go but worsen over time. Common symptoms of low back pain include dull aching pain that travels to the buttocks, legs and feet, pain that is worse after prolonged sitting, pain that feels better when changing positions and pain that is worse after waking up and better after moving.[12]

CLINICAL NEED and BURDEN OF DISEASE

Up to 60% of the adult population can expect to have low back pain at some time in their life. A UK population-based cross-sectional study of 15,272 people aged 25 years and older found the 1-month period prevalence of low back pain to be 28.5%, peaking at age 41–50 years. Low back pain was reported by one in four people aged over 80 years.[13]

Around 9.11 million (approximately 17%) of the English population suffer from back pain, of which 5.5 million have severe back pain. About 20% of all musculoskeletal consultations in the UK are related to the back and 14% are related specifically to the lower back.[14]

In England in 2010, lower back pain was extremely common and was the largest single cause of loss of disability adjusted life years (DALYs), and the largest single cause of years lived with disability (YLDs).[15]

In England in 2016/2017 there were 87,666 hospital admissions with a primary diagnosis of low back pain (ICD-10 code M54.5) resulting in 56,579 bed days and 61,362 day cases.[16]

PATIENT PATHWAY

RELEVANT GUIDANCE

NICE GUIDANCE

- NICE guidelines. Low back pain and sciatica in over 16s: assessment and management (NG59). November 2016.
- NICE quality standard. Low back pain and sciatica in over 16s (QS155). July 2017.

- NICE interventional procedure guidance. Percutaneous electrothermal treatment of the intervertebral disc annulus for low back pain and sciatica (GID-IP2803). Expected publication date: TBC
- NICE interventional procedure guidance. Lateral interbody fusion in the lumbar spine for low back pain (IPG574). February 2017.
- NICE interventional procedure guidance. Percutaneous coblation of the intervertebral disc for low back pain and sciatica (IPG543). November 2016.
- NICE interventional procedure guidance. Percutaneous intradiscal radiofrequency treatment of the intervertebral disc nucleus for low back pain (IPG545). January 2016.
- NICE interventional procedure guidance. Percutaneous electrothermal treatment of the intervertebral disc annulus for low back pain and sciatica (IPG544). January 2016.
- NICE interventional procedure guidance. Peripheral nerve-field stimulation for chronic low back pain (IPG451). March 2013.
- NICE interventional procedure guidance. Non-rigid stabilisation techniques for the treatment of low back pain (IPG366). November 2010.
- NICE interventional procedure guidance. Endoscopic laser foraminoplasty (IPG31). December 2003.

NHS ENGLAND and POLICY GUIDANCE

- NHS England. 2013/14 NHS Standard Contract for Specialised Pain (Adult). D08/S/a

OTHER GUIDANCE

- Noninvasive Treatments for Acute, Subacute, and Chronic Low Back Pain: A Clinical Practice Guideline from the American College of Physicians. April 2017.[17]
- European guidelines for the management of acute nonspecific low back pain in primary care. 2006.[18]

CURRENT TREATMENT OPTIONS

Treatment options for back pain will vary depending on the severity of the condition. A general practitioner may offer advice on self-help measures, prescribe medication or refer a patient to specialist such as a physiotherapist.[19]

Self-help treatments include:[20]

- Staying active
- Carrying out back exercises and stretches
- Using hot and cold packs e.g. ice packs and a hot water bottle
- Relaxing and staying positive

Guidelines recommend the use of medicinal products such as:

- Oral non-steroid anti-inflammatory drug (NSAID) for managing acute low back pain[21]
- A weak opioid, either alone or with paracetamol, can be used to manage acute low back pain only if an NSAID is contra-indicated, not tolerated or ineffective[21]
- Benzodiazepines are sometimes used to manage acute low back pain (particularly in loss of lordosis); however evidence to support their use is very weak[22]

EFFICACY and SAFETY

Trial	EduraCT number: 2014-003040-12, NCT02934061, TZSA2; tizaspray vs sirdalud; phase III
Sponsor	MDM S.p.A.
Status	Completed
Source of Information	EU Clinical Trials Register[3], ClinicalTrials.gov[23]
Location	Romania and Italy
Design	Randomised – controlled
Participants	n= 234 aged 18-64 years; n= 2 aged 65-84 years; average low back pain intensity moderate to severe
Schedule	Randomised to either 8.169 mg/ml of tizanidine hydrochloride corresponding to 0.5 mg of tizanidine base/70 µL puff. 3 x 1 puff daily, intranasal administration; or 2,29 mg/tablet of tizanidine hydrochloride corresponding to 2.0 mg of tizanidine base. 3 x 1 tablet daily, oral route.
Follow-up	Not reported
Primary Outcomes	[Time Frame: days: 1] • "Hand-to-floor" distance • Low back pain intensity scale (0 to 100 mm VAS) • Schober test (positive/negative)
Secondary Outcomes	[Time frame: days: 3] • "Hand-to-floor" distance • Low back pain intensity scale (0 to 100mm VAS) • Schober test (positive/negative) • Roland disability questionnaire (RDQ) • Number of patients taking paracetamol tablets [Time frame: days: 8] • "Hand-to-floor" distance • Low back pain intensity scale (0 to 100mm VAS) • Schober test (positive/negative) • Roland disability questionnaire (RDQ) • Number of patients taking paracetamol tablets
Key Results	Primary endpoints • Hand-to-floor distance: In the intention-to-treat (ITT) population, the decrease in hand-to-floor distance observed in the Tizaspray® group was higher than that observed in the Sirdalud® group at Visit 2 (-7.20 vs. -4.27, $p<0.01$) and the difference increased at Visit 3 (-15.51 vs. -11.51, $p<0.05$). The

	difference between the two groups was statistically significant at both visits (p<0.001), when adjusted for baseline values and clinical sites. • Low back pain during visits: In the ITT population, the decrease in average low back pain was more evident in the Tizaspray® group than in the Sirdalud® group already at Visit 2 (-18.48 vs. -14.27, respectively; treatment difference -4.21, p<0.05) and the difference between the two groups increased up to Visit 3 (treatment difference -9.26). The difference between the two groups was statistically significant at both visits when adjusted for baseline values and clinical site (p<0.01667 at Visit 2 and p<0.001 at Visit 3). The analysis of the three different low back pain measures (on movement, at rest and when sleeping) at Visit 2 and Visit 3 confirmed the higher improvement obtained with Tizaspray®. The decrease observed at Visit 3 was statistically significant for each measure, both with adjusted and unadjusted analysis. • Daily low back pain on movement, at rest and when sleeping: The difference in the decrease in low back pain on movement between treatment groups was constantly increasing after Day 1 and it was statistically significant at Day 6 (p<0.01) and Day 7 (p<0.01667); when adjusted for baseline values and clinical sites, the significance level was p<0.001 on both these days. The difference in the decrease in low back pain at rest between treatment groups was also constantly increasing after Day 1 and statistically significant since Day 4 (p<0.05) and it climbed up to -9.11 (p<0.01) at Day 7, results confirmed by the adjusted analysis (p<0.001 at Day 7). The difference in the decrease in low back pain when sleeping was increasing after Day 2 and statistically significant since Day 6 (p<0.1667). The adjusted estimates gave statistically significant results since Day 4 (p<0.1667) • Schober's test: In the ITT population, the proportion of patients negative to the Schober's test was slightly higher in the Tizaspray® group already at Visit 2 (day3): 33% vs. 27.8%, but the difference was not statistically significant. At Visit 3 (Day 8) the proportion of patients negative to Schober's test in the Tizaspray® group was 73.7% and 59.6% in the Sirdalud® group, and chi-square test was statistically significant (p<0.05) . When adjusted for clinical sites, the logistic regression highlighted the outstanding significant protective effect of Tizaspray® against the Schober's test positivity (OR 0.35, 95% CI 0.17-0.73; p<0.01) The PP analysis confirmed the results of the ITT analysis. Secondary endpoints • Pain relief: In the ITT population, the pain relief is constantly better in the Tizaspray® group. In fact, at Visit 2, 53.1% of the patients in this group had a moderate to total pain relief against 42.6% in the Sirdalud® group. The proportions of patients with no pain relief were 18.3% and 2.6% in the Sirdalud® and Tizaspray® group, respectively, and the difference was statistically significant (p<0.05). At Visit 3, the proportions of patients with considerable to total pain relief were 74.6% and 49.1% in the Tizaspray® and Sirdalud® group, respectively, and the difference was statistically significant (p<0.001)

	• Short-term time course of low back pain intensity: In the ITT population, the difference between the two treatment groups was already evident 30 minutes after treatment administration and grew up to 90 minutes. The differences were increasing day by day. The difference between treatment groups was statistically significant at 30 and 60 minutes after the study treatment administration on each day. At 90 minutes, at Day 1 only the unadjusted analysis was statistically significant ($p<0.05$), at Day 2 both analyses gave statistically significant results and at Day 3 only the adjusted analysis gave statistically significant results. The difference in low back pain registered 180 minutes after the study treatment administration was still slightly higher in the Tizaspray® group on Day 2 and Day 3. • Roland Disability Questionnaire (RDQ): In the ITT population, the differences between treatment groups are in favor of the Tizaspray® at both visits and the differences are statistically significant ($p<0.05$ at Visit 2 and $p < 0.001$ at Visit 3) for both adjusted and unadjusted analysis • Schober's test (as a continuous variable): In the ITT population, the difference between treatment groups was in favor of Tizaspray® and statistically significant at both visits ($p<0.001$), using both unadjusted and adjusted analysis. • Use of rescue medicine: In the ITT population, the difference in the use of rescue medicine between treatment groups was in favor of the Tizaspray® group, in terms of mean number of tablets taken (1.68 less tablets taken). The difference was statistically significant when adjusted for clinical site ($p<0.05$). The proportion of patients that took the rescue medicine was lower in the Tizaspray® group (59.8% vs, 69.9% - OR = 0.58; p=0.0678).
Adverse effects (AEs)	Only 18 patients out of 234 (7.69%) experienced at least an adverse event during the study. Six patients in the Sirdalud® group experienced globally ten AEs and twelve patients in the Tizaspray® group experienced globally twentyone AEs. The proportion of AEs was similar between the two treatment groups for headache and somnolence. The patients treated with Tizaspray® experienced aphtous ulcer, nausea, hyperkalemia, burning sensation (1 event each) and nasal discomfort or pruritus (9events in 3 patients), events that did not occur in the Sirdalud® group. At the contrary, patients treated with Sirdalud® experienced fatigue, asthenia and disturbance in attention (1 event each), events that did not occur in the Tizaspray® group. Other differences were less relevant.
Expected reporting date	September 2017

ESTIMATED COST and IMPACT

COST

The cost of tizanidine in its intranasal formulation is not yet known.

Tizanidine (oral) is already marketed in the UK to relieve the stiffness and restriction of muscles resulting from multiple sclerosis, injury or diseases of the spinal cord;[5] a pack of 120 x 2mg tablets costs £3, a pack of 120 × 4mg tablets costs £39.[24]

IMPACT – SPECULATIVE

IMPACT ON PATIENTS AND CARERS

☐ Reduced mortality/increased length of survival	☒ Reduced symptoms or disability
☐ Other	☐ No impact identified

IMPACT ON HEALTH and SOCIAL CARE SERVICES

☐ Increased use of existing services	☒ Decreased use of existing services
☐ Re-organisation of existing services	☐ Need for new services
☐ Other	☐ None identified

IMPACT ON COSTS and OTHER RESOURCE USE

☐ Increased drug treatment costs	☐ Reduced drug treatment costs
☐ Other increase in costs	☐ Other reduction in costs
☐ Other	☒ None identified

OTHER ISSUES

☐ Clinical uncertainty or other research question identified	☒ None identified

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