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Efficacy and safety of 4-aminopyridine in patients with chronic spinal cord injury (Eficacia y seguridad de la 4-aminopiridina en pacientes con lesión crónica de médula espinal)

Submission date
21/02/2009

Recruitment status
No longer recruiting

Registration date
30/03/2009

Overall study status
Completed

Last Edited
30/03/2009

Condition category
Injury, Occupational Diseases, Poisoning

[ ] Prospectively registered
[ ] Protocol
[ ] Statistical analysis plan
[ ] Results
[ ] Individual participant data
[ ] Record updated in last year

Plain English summary of protocol
Not provided at time of registration

Contact information

Type(s)
Scientific

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Additional identifiers

Protocol serial number
99-716-0126

Study information

Scientific Title
Efficacy and safety of 4-aminopyridine in patients with chronic spinal cord injury: a randomised double-blind placebo-controlled parallel-group trial

Study objectives
4-Aminopyridine (4-AP) is an effective and safe drug in the treatment of spinal cord injury (SCI) patients.

Ethics approval required
Old ethics approval format

Ethics approval(s)
National Institutional Review Board (IRB) (Mexico), approved in September 1999

Primary study design
Interventional

Study design
Randomised double-blind placebo-controlled parallel-group study (first phase), followed by an open-label study (second phase)

Study type(s)
Treatment

Health condition(s) or problem(s) studied
Spinal cord injury

Interventions
First phase: Randomised double-blind placebo-controlled trial. Identical capsules containing 4-AP (oral) 5 mg or placebo were prepared. The 4-AP as given as gelatin capsules containing 4-AP 5 mg and microcrystalline cellulose as the excipient. Placebo capsules contained only the excipient. Each patient was administered two capsules every 8 hours, for a total of 6 capsules /day. Initially, all patients completed a run-in period of two weeks with placebo.

Patients randomised to the 4-AP-placebo sequence then received one 4-AP capsule and five placebo capsules/day for 1 week (i.e., 4-AP dosage was 5 mg/day). The 4-AP dosage was increased by 5 mg/week by substitution of placebo by 4-AP capsules, such that patients received 6 capsules/day throughout the study. At 6 weeks, patients in the 4-AP group were receiving 4-AP 30 mg/day. The 30 mg/day dosage was maintained for 7 weeks. These patients then switched to the opposite treatment and received placebo (6 capsules/day) for 12 weeks.

Patients in the placebo-4-AP sequence received placebo for 12 weeks after the run-in period. Then they received 4-AP starting with 5 mg/day increasing by 5 mg/week to a maximum of 30 mg /day, and maintaining the 30 mg/day dosage for 7 weeks, as described above. There was no washout period.

Second phase, an open-label trial. All patients received 10 mg of 4-AP the first, 20 mg the second and 30 mg the third week, and continued their medical surveillance every 4 weeks. An additional

increase of 10 mg each of 4-AP was done every 2 or 3 months to those patients with: a) absence of adverse reactions (AR) or minor AR, b) hepatic enzymes or bilirubin levels below two times the upper limit of normal, and c) an electroencephalogram (EEG) with no epileptic activity. The treatment was stopped when the patient did not feel positive clinical changes with the last highest doses during at least two months of continued treatment.

Intervention Type
Drug

Phase
Not Applicable

Drug/device/biological/vaccine name(s)
4-Aminopyridine

Primary outcome(s)
1. Motor and sensation measurements: Sensory function was tested and scored for 2 modalities: pin prick and light touch in all dermatomes. Muscle strength was tested in each of the 20 key muscles. Evaluation of both sides was expressed in a single score. The American Spinal Cord Injury Association (ASIA) Impaired Scale (AIS) was used to classify the cases as complete or incomplete.
2. Independence measurements: The Spinal Cord Injury Independence Measure has 16 questions on self-care, respiratory and sphincter management and mobility in and out of home which ranges from 0 (total dependence) to 100 points (total independence).

Timepoints of assessment for all primary and secondary outcome measures: Patients in the double-blind controlled trial were subjected to pretreatment assessment and at 12 and 24 weeks after starting the 4-AP. Patients in the open-label trial were evaluated at month 6 and 12 of continued treatment or at time when the highest doses of 4-AP were reached before the end of the study.

Key secondary outcome(s)
Somatosensory evoked potentials (SSEPs), sphincter bladder/anal sensation/control in both genders, psychogenic erection in males:
2. Sphincter function: The anal function was graded as sensation when the patient was able to differentiate when the rectum was full and ready to empty, and control when the patient was able to stop the faecal evacuation with enough time to get the bathroom and eliminate the faecal material. Bladder function was graded as was done for anal function. Positive or negative was the final result of both sensation and control.
3. Psychogenic erection was evaluated in male patients. Presence or absence was the final result.
4. Electrophysiological evaluation: The SSEPs were elicited by electrical stimulation
5. Safety evaluation: Safety surveillance was done every 4 weeks from the beginning of the study, intentionally searching for AR, measuring vital signs, doing physical examinations and performing EEG and laboratory tests (blood and urine samples: creatinine, blood urea nitrogen, total cholesterol, tryglycerides, total direct, and indirect bilirubin, alanine aminotransferase, aspartate aminotrasferase, alkaline phosphatase, creatinine kinase, lactic acid dehydrogenase, sodium, potassium, chloride, calcium and phosphorus. A complete blood cell count with differentials and a routine urialysis and urine culture also obtained at each visit)

Timepoints of assessment for all primary and secondary outcome measures: Patients in the double-blind controlled trial were subjected to pretreatment assessment and at 12 and 24

weeks after starting the 4-AP. Patients in the open-label trial were evaluated at month 6 and 12 of continued treatment or at time when the highest doses of 4-AP were reached before the end of the study.

Completion date
28/02/2008

Eligibility

Key inclusion criteria
Patients with SCI were eligible for the study if they met the following criteria:
1. Tetraplegia or paraplegia for more than 1.5 years before the study began,
2. Both males and females, aged 18-60 years
3. Neurologic injury level of C4-L1
4. Medically stable and able to breathe independently
5. Stable neurologic deficits for more than 90 days before the study
6. Absence of antiepileptic antecedent and electroencephalogram without epileptic activity, and paralysed extremities without passive limitations (healthy joints)
7. For females: postmenopausal or surgically sterile, or using an acceptable method of birth control

Participant type(s)
Patient

Healthy volunteers allowed
No

Age group
Adult

Lower age limit
18 Years

Upper age limit
60 Years

Sex
All

Key exclusion criteria
1. Pressure ulcers, skin infections, or phlebitis
2. History of cardiovascular disease (syncope, arrhythmia, or myocardial infarction within the last two years), systolic blood pressure greater than 150 or less than 70 mm Hg, diastolic blood pressure greater than 110 or less than 50 mm Hg, or heart rate greater than 110 or less than 50 beats/minute;
impaired hepatic function (total hepatic enzyme or bilirubin levels greater than 2 times the upper limits of normal) or impaired renal function (creatinine level greater than 2 times the upper limits of normal) less than 6 months before the study
3. Known allergy to pyridine-containing drugs
4. Neurologic, degenerative, or psychiatric disorders that would impair the patient's ability to

complete the protocol
5. Any illness or abnormality that would jeopardize patients safety or interfere with the conduct of the study
6. History of substance abuse
7. Inability to discontinue excluded concomitant drug therapy

Date of first enrolment
01/01/2000

Date of final enrolment
28/02/2008

Locations

Countries of recruitment
Mexico

Study participating centre
Instituto Mexicano del Seguro Social
Mexico City
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CP 06725

Sponsor information

Organisation
Mexican Social Security Institute (Instituto Mexicano del Seguro Social) (Mexico)

ROR
https://ror.org/03xddgg98

Funder(s)

Funder type
Government

Funder Name
Mexican Social Security Institute (Instituto Mexicano del Seguro Social) (Mexico)

Results and Publications

Individual participant data (IPD) sharing plan

IPD sharing plan summary
Not provided at time of registration