AstraZeneca

SH-TPO-0002

SUMMARY

ASTRAZENECA PHARMACEUTICALS

FINISHED PRODUCT: Exanta™

ACTIVE INGREDIENT: Melagatran /H 376/95(ximelagatran)

Trial title (number): Efficacy and safety of oral treatment twice daily with H 376/95 (ximelagatran), preceded by subcutaneous injections with melagatran, compared with dalteparin subcutaneous once daily, as prophylaxis against thromboembolic complications after total hip or knee replacement (METHRO II)

Developmental phase: IIb
First subject recruited:14 September 1998
Last subject completed:06 June 1999
Approval date:28 February 2001

OBJECTIVES

Primary objective.

To establish a statistically significant relationship between dose of melagatran/ H 376/95 (ximelagatran) and the frequency of thromboembolic events. To find the optimal dose of melagatran/ H 376/95 in terms of balancing efficacy (the frequency of thromboembolic events) and safety (special regards to bleeding complications).

Efficacy was assessed as the total combined frequency of thromboembolic events:
- Confirmed overall deep vein thrombosis (DVT)
- Confirmed pulmonary embolism (PE)

Safety was assessed with special reference to bleeding complications:
- Frequency of severe bleeding
- Volume of blood loss
- Volume of transfusion
- Changes in hemoglobin

The recording of thromboembolic events and bleeding complications covered the time interval from the start of study drug administration to the day of phlebography (in total 8-11 days of active treatment).

Secondary Objective.

To determine the efficacy (the frequency of thromboembolic events) and safety (bleeding complications and adverse events) of the melagatran/ H 376/95 groups relative to dalteparin.

The proportion of patients with confirmed proximal DVT was assessed between the treatment groups.

To assess the incidence of verified symptomatic venous thromboembolic complications occurring between phlebography and the follow-up visit (4-6 weeks).

To make a preliminary estimate of the cost-effectiveness of oral H 376/95 initiated by s.c. melagatran compared to dalteparin.

METHODS

STUDY DESIGN

This was a multicentre, international, randomised, double-blind, double-dummy, parallel group dose-finding study comparing the efficacy and safety of four different doses (1, 1.5, 2.25 and 3 mg) of s.c. melagatran b.i.d. for 1-3 days followed by oral doses (8, 12, 18 and 24 mg) of H 376/95 b.i.d. versus one dose level of dalteparin (5000 IU s.c., q.d.).

DIAGNOSIS AND MAIN CRITERIA FOR INCLUSION/EXCLUSION

Patients were included in the study if the following criteria were met:

1. Patient scheduled for primary elective total hip or total knee replacement
2. 18 to 85 years of age
3. Weight 50 kg to 110 kg
4. Signed informed consent to participate in the study

Patients were excluded from the study if any of the following criteria were met:

1. History of deep vein thrombosis or pulmonary embolism
2. Suspicion of post-thrombotic state
3. Trauma with immobilisation, within 12 weeks prior to the surgery
4. Leg amputation
5. Treatment with anticoagulant or antiplatelet drugs within 7 days prior to surgery. (N.B.500 mg or less daily of Acetylsalicylic acid (ASA) and short-acting NSAID with T½ <20 h were allowed.)
6. Known allergy to contrast media or iodine
7. Known disorder associated with increased risk of bleeding
8. History of intracranial bleeding
9. Ischaemic stroke during the last year
10. Known intraocular bleeding during the last year
11. History of gastrointestinal bleeding disorder and/or endoscopically verified ulcer disease within the last year prior to surgery
12. Major surgical procedure within 12 weeks prior to surgery
13. Ongoing malignancy
14. Cytostatic treatment within the past 6 months
15. Uncontrolled hypertension (SBP > 200 mmHg or DBP > 110 mmHg)
16. Renal impairment (serum creatinine above the upper limit of laboratory references) or nephrectomy or kidney transplantation patients. Amendment no 2, dated 21 December 1998, defined renal impairment as serum creatinine above 150 μ mol/L.
17. Known liver disorder or ASAT (GOT) and/or ALAT (GPT) > 2 times the upper limit of the laboratory references
18. Anaemia (Hb < 100 g/L)
19. Platelet count < 100 x 10^9/L
20 Current or previous heparin-induced thrombocytopenia
21. Childbearing potential (only females who have had a hysterectomy, are ≥ 1 year postmenopausal or have had a tubal ligation ≥ 1 year ago are acceptable).
22. Known drug addiction and/or alcohol abuse
23. Previously randomised in this study
24. Participation in any other clinical trial within one month prior to surgery (including devices)
25. Mental condition preventing understanding of the aims, investigational procedures or possible consequences of the study

TEST PRODUCT, BATCH NUMBER, DOSAGE AND MODE OF ADMINISTRATION

· 1 mg melagatran b.i.d., s.c. for 1-3 days followed by 8 mg H 376/95 b.i.d. orally. Batch no H 1371-01-01-02 and H 1392-01-01-01.

- 1.5 mg melagatran b.i.d., s.c. for 1-3 days followed by 12 mg H 376/95 b.i.d. orally. Batch no H 1347-02-01-01 and H 1359-02-01-01.
- 2.25 mg melagatran b.i.d., s.c. for 1-3 days followed by 18 mg H 376/95 b.i.d. orally. Batch no H 1390-01-01-01 and H 1393-01-01-01.
- 3 mg melagatran b.i.d., s.c. for 1-3 days followed by 24 mg H 376/95 b.i.d. orally. Batch no H 1391-01-01-01 and H 1360-02-01-01.
- Placebo syringes contained sodium chloride 9 mg/ml. Batch no H 1363-01-01-02.

COMPARATOR PRODUCT, BATCH NUMBER, DOSAGE AND MODE OF ADMINISTRATION

- Dalteparin 5000 IU, s.c., b.i.d. for 8-11days. Batch no H 1369-01-01-02 and placebo tablets b.i.d. orally batch no. H 1383-01-01-01.
- Placebo syringes contained sodium chloride 9 mg/ml. Batch no H 1363-01-01-02.

DURATION OF TREATMENT

The patients were treated with melagatran s.c. for 1-3 days and with oral H 376/95 for a total of 8-11 days. The comparator drug dalteparin was also given for a total of 8-11 days.

MAIN VARIABLE(S):

- EFFICACY

- Distal and/or proximal DVT verified by phlebography on the final day of the study drug treatment and the day after the final day of treatment with the comparator drug dalteparin.
- Clinical symptomatic PE verified by pulmonary angiography or spiral CT, evaluated by the Independent Adjudication Committee.

- SAFETY

- Severe bleedings
- Volume of blood loss
- Transfusion volume
- Changes in hemoglobin

STATISTICAL METHODS

To investigate a dose-response relationship between dose of melagatran or H 376/95, a logistic regression model was used, relating the risk of VTE to the log-transformed dose of melagatran or H 376/95, adjusting the risk for the following factors: Type of surgery, Gender, Anaesthesia, Age and known risk factors for DVT. The same analysis was also made for the event of proximal DVT and/or PE.

Between group comparisons of the risk of VTE were made using the odds ratio with a 95% CI as a measurement of relative effect.

RESULTS

PATIENTS

	melagatran /	**dalteparin**	**Total**
	H 376/95		
No. planned	380x4 groups	380	1900
No. randomised patients where	1495	381	1876

surgery was performed			
Males/Females	585/910	151/230	1876
Mean age (range)	66.4 years	66.5 years	
No. analysed for efficacy	1169	308	1477
No. analysed for safety	1515	385	1900
No. completed	1086	291	1377

SUMMARY

- EFFICACY RESULTS

The primary objective, to show a significant dose-response relationship between risk of VTE and the amount of melagatran/H 376/95 given, was met, with a very low and significant p-value for the combined population of THR and TKR patients with consistent results in the THR and TKR subpopulations ($p<0.001$ and $p=0.0014$, respectively).

The number of patients with confirmed DVT and/or PE was 111 (37.8%), 70 (24.1%), 71 (23.7%) and 43 (15.1%) in the melagatran / H 376/95 dose groups, starting with the lowest dose. In the dalteparin group, the corresponding number was 87 (28.2%).

The percentage of patients (ITT pop) with proximal DVT and/or PE were 9.2%, 6.6%, 4.7% and 2.5% for the melagatran / H 376/95 dose-groups, and 6.5% for dalteparin. Statistically significant odds ratios between combined frequency of proximal DVT and/or PE were found for the 3 mg/24 mg group compared with the 1 mg/8 mg group (95% CI 0.11-0.58), the 1.5 mg/12 mg group and also compared with the dalteparin group.

In total, 37 symptomatic DVTs and 13 verified PEs occurred during the study. Eleven events (9 DVT, 2 PE) occurred in the 1 mg/8 mg dose group, 7 events (5 DVT, 2 PE) in the 1.5 mg/12 mg group, 15 events (10 DVT, 5 PE) in the 2.25 mg/18 mg group and 4 events (3 DVT, 1 PE) in the 3 mg/24 mg group. Thirteen events (10 DVT, 3 PE) occurred in the dalteparin group.

During the treatment period there were six events of PE confirmed by the adjudication committee and five symptomatic PEs where the diagnosis could not be excluded.

- SAFETY RESULTS

Mortality was low (0.3%) and did not differ from other large orthopaedic studies of similar design.

There was a tendency to a dose-related increase of severe bleedings in THR patients in the melagatran + H 376/95 dose groups. There was no such tendency in TKR patients. The risk of severe bleeding in the dalteparin group was approximately equal to the two middle-dose groups of melagatran + H 376/95. Mean and median total bleeding volumes were numerically higher in all melagatran + H 376/95 dose groups compared to the dalteparin group. There was also a tendency to a dose-related increase in total bleeding volumes in THR patients on melagatran + H 376/95. There was no such tendency in TKR patients. Other factors related to increases in bleeding volumes were increased duration of surgery, male sex, uncemented prosthesis, and general anaesthesia. Targeted questions about specific postoperative complications (haematoma, wound infections) also showed a tendency to dose-related increase. The immediate preoperative start of melagatran s.c. may be the probable cause of the increase in bleedings and bleeding-related events since most of these problems occurred between the administration of the first and second dose.

Maximum plasma levels of melagatran were achieved 0.5-1.0 hours after the injection, i.e. in most cases during ongoing operation. This may also explain the increased bleeding risk.

The frequency of adverse events (collected by open questioning and/or spontaneous reporting) and serious adverse events were also dose-related in the melagatran + H 376/95 groups. These findings probably reflect the dose-related increase of severe bleedings and bleeding volumes. There was a correlation between the occurrence of confusion and the melagatran + H 376/95 groups. Confusion was also related to high age and large bleeding volumes. Most cases of confusion recovered during continuous treatment with melagatran + H 376/95. Thus, it is less likely that confusion is a true adverse drug reaction on melagatran and/or H 376/95. It is doubtful whether allergic reactions and skin reactions are related to melagatran and/or H 376/95 but further analyses will be done in future studies.

As expected after major surgery, there were numerous changes of laboratory parameters. These were most probably related to surgery as such, e.g. a decrease in blood hemoglobin and s-albumin as well as increases in B-platelets and B-leukocytes. The increase in liver enzymes (S-ALAT and S-ASAT) was most pronounced in the dalteparin group. Microscopic haematuria was more common in the melagatran + H 376/95 groups compared to the dalteparin group. The reason for this may be that melagatran is concentrated and excreted in the urine.

Reference:

1. Eriksson BI, Bergqvist D, Kalebo P, Dahl OE, Lindbratt S, Bylock A, Frison L, Eriksson UG, Welin L, Gustafsson D. Ximelagatran and melagatran compared with dalteparin for prevention of venous thromboembolism after total hip or knee replacement: the METHRO II randomised trial. Lancet 2002;360(9344):1441-1447.

As with any comprehensive clinical trial programme, individual studies may include both approved and non-approved treatment regimens, including doses higher than those approved for clinical use. Before prescribing Exanta™ (ximelagatran) or melagatran, Healthcare Professionals should view their specific country information