Pharmacokinetics of tramadol and celecoxib in Japanese and Caucasian subjects following administration of Co-Crystal of Tramadol-Celecoxib (CTC): a randomised, open-label study

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Supplementary materials

Online Resource 1

Inclusion criteria

1. Provide written informed consent.
2. Healthy male or female subjects aged 20 to 45 inclusive.
3. Caucasian subjects or Japanese subjects.
4. Japanese subjects were defined as being born in Japan with both parents having Japanese descent. They must not have resided outside of Japan for more than 5 years.
5. Female subjects less than one year post-menopausal had to have a negative urine pregnancy test prior to the first dose of study medication, be non-lactating, and willing to use adequate and highly effective methods of contraception throughout the study. A highly effective method of birth control was defined as those which result in a low failure rate (i.e., less than 1% per year) when used consistently and correctly such as sterilisation, implants, injectables, combined oral

contraceptives, some hormonal intrauterine devices, true sexual abstinence, where this was in line with the preferred and usual lifestyle of the subject, or vasectomised partner.

6. Note: Periodic abstinence (calendar, ovulation, symptothermal, post-ovulation methods), declaration of abstinence for duration of study, and withdrawal were not acceptable methods of contraception).
7. Female subjects who were post-menopausal (defined as spontaneous amenorrhea for at least a year) or permanently sterilised (e.g. tubal occlusion, hysterectomy, bilateral salpingectomy) were not required to use any contraception.
8. Male subjects had to be willing to use contraception with their partners throughout the study and for 30 days after completion of the study and agree to inform the Investigator if their partner became pregnant during this time.
9. Body weight ranging from 50 to 90 kg and a BMI $\geq$ 18.0 and $\leq$ 25.0.
10. Healthy and free of significant abnormal findings as determined by medical history, physical examination, vital signs, laboratory tests and electrocardiogram.
11. Willing to eat all the food supplied throughout the study.
12. The subject's primary care physician had provided evidence to confirm that within the last 6 months of first dosing nothing in the subject's medical history precluded their enrolment into a clinical study. If the subject had no primary care physician in the United Kingdom the Investigator had to confirm that the subject was suitable to be enrolled into the study.

Exclusion criteria

1. Female subjects who were pregnant or lactating.

2. Any history of drug or alcohol abuse, misuse, physical or psychological dependence.
3. Any history of significant gastrointestinal, liver or kidney disease, or any other conditions that might have interfered with drug absorption, distribution, metabolism or excretion.
4. Use of opioid or opioid antagonist-containing medication in the past 30 days.
5. Any history of seizures, suicidal tendencies or symptomatic head trauma or history of clinically significant fainting.
6. History of respiratory depression, hypoxia or elevated carbon dioxide levels in the blood.
7. History of paralytic ileus, gastrointestinal disease or other clinically significant gastrointestinal problems.
8. History of significant cardiovascular, pulmonary, haematologic, neurological, psychiatric, endocrine, immunologic or dermatologic disease.
9. History of cerebrovascular bleeding.
10. Known hyperkalaemia.
11. Participation in a clinical drug study during the 90 days preceding the initial dose in this study.
12. Any significant illness during the 4 weeks preceding entry into this study.
13. Use of any medication including vitamins, herbal and/or mineral supplements during the 7 days preceding the initial dose or during the course of this study.
14. Refusal to abstain from food 10 hours preceding and 4 hours following CTC administration.

15. Refusal to abstain from caffeine or xanthine containing food or beverages, foods containing poppy seeds, and grapefruit juice within 48 hours before CTC administration and for the duration of study confinement.
16. Weekly alcohol intake exceeding the equivalent of 14 units/week for females and 21 units/week for males. (1 unit = ½ pint beer, 25 mL of 40% spirit or a 125 mL glass of wine).
17. Consumption of alcoholic beverages within 48 hours before CTC administration, and refusal to abstain from alcohol for the duration of the study confinement.
18. History of smoking or chewing tobacco within 90 days of CTC administration and use of tobacco products during the study.
19. Blood or blood products donated within 90 days prior to CTC administration or any time during the study, except as required by the protocol of this study.
20. Positive results of urine drug screen, alcohol test, pregnancy test, Hepatitis B surface antigen, Hepatitis C antibody, or human immunodeficiency virus (HIV) tests.
21. Known sensitivity and/or contraindication to tramadol, celecoxib, sulphonamides, opioids, COX-2 inhibitors, or related compounds or formulation excipients as well as severe hypersensitivity reactions (like angioedema) to any drugs.
22. Known presence of rare hereditary problems of galactose and/or lactose intolerance.
23. History of urticaria, allergic type reactions after taking acetylsalicylic acid (aspirin) or other nonsteroidal anti-inflammatory drugs.
24. History of inflammatory bowel disease, peptic, gastric or duodenal ulcer.
25. Use of monoamine oxidase inhibitors within 28 days before day 1 of this study.

26. Use of any enzyme modifying drugs, including strong inhibitors of cytochrome P450 (CYP) enzymes (such as cimetidine, fluoxetine, quinidine, erythromycin, ciprofloxacin, fluconazole, ketoconazole, diltiazem and HIV antivirals) and strong inducers of CYP enzymes (such as barbiturates, carbamazepine, glucocorticoids, phenytoin, rifampicin and St John's Wort), in the previous 28 days preceding the initial dose of this study.
27. Any history of tuberculosis and/or prophylaxis for tuberculosis.
28. Haemoglobin value below 130 g/L for male subjects and 115 g/L for female subjects at screening.
29. Refusal to allow their primary care physician (if they had one) to be informed of participation in the trial.
30. Failure to satisfy the Investigator of fitness to participate for any other reason.