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Method for increasing the bioavailability of metaxalone

Abstract

A method of increasing the bioavailability of metaxalone by administration of an oral dosage form with food is provided, as well as an article of manufacture comprising an oral dosage form of metaxalone in a suitable container and associated with printed labeling which describes the increased bioavailability of the medication in the container when taken with food.

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References Cited [Referenced By]

U.S. Patent Documents

3062827	Nov., 1962	Lunsford	260/307.	
3993767	Nov., 1976	Alphin et al.		
4036957	Jul., 1977	Alphin et al.		
4058621	Nov., 1977	Hill.		
4208405	Jun., 1980	Fouad.		
4784852	Nov., 1988	Johansson.		
4792449	Dec., 1988	Ausman et al.		
4820690	Apr., 1989	Gregory et al.		
5785976	Jul., 1998	Westesen et al.		
5840688	Nov., 1998	Tso.		
5977175	Nov., 1999	Lin.		
5989583	Nov., 1999	Amselem.		
6030988	Feb., 2000	Gilis et al.		
6099859	Aug., 2000	Cheng et al.		
6103269	Aug., 2000	Wunderlich et al.		
6114379	Sep., 2000	Wheelwright et al.		
6143325	Nov., 2000	Dennis et al.		
6197757	Mar., 2001	Perrier et al.		
6207178	Mar., 2001	Westesen et al.		
6265438	Jul., 2001	Steward.		
2001/0024659	Sep., 2001	Chen et al.		

Other References

Monograph No. 5838 of the Merck Index (11.sup.th ed., 1989) for metaxalone.
Lunsford et al., 82 J. Am. Chem. Soc. 1166 (1960).
Skelaxin.RTM. monograph, 2001 Physicians' Desk Reference.

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Claims

We claim:

1. A method of increasing the oral bioavailability of metaxalone to a patient receiving metaxalone therapy comprising administering to the patient a therapeutically effective amount of metaxalone in a pharmaceutical composition with food.

2. The method of claim 1 wherein the therapeutically effective amount is 200 mg to 900 mg.

3. The method of claim 1 wherein the therapeutically effective amount is 400 mg to 800 mg.

4. The method of claim 1 wherein the administration to the patient occurs between 30 minutes prior to 2 hours after consuming food.

5. The method of claim 1 wherein the administration to the patient is substantially at the same time as the consumption of the food.

6. The method of claim 1 wherein the administration to the patient is immediately after the consumption of food up to 1 hour after said consumption.

7. The method of claim 1 wherein the pharmaceutical composition comprises a tablet.

8. The method of claim 7 wherein the tablet is in unit dosage form.

9. A method of increasing the rate and extent of absorption of an oral dosage form of metaxalone as measured by the drug concentration attained in the blood stream over time in a patient in need of a therapeutic effect thereof comprising, administering to the patient a therapeutically effective amount of metaxalone in a pharmaceutical composition with food.

10. The method of claim 9 wherein the therapeutically effective amount is about 200 mg to about 900 mg.

11. The method of claim 9 wherein the therapeutically effective amount is from about 400 mg to about 800 mg.

12. The method of claim 9 wherein the administration to the patient occurs between about 30 minutes prior to about 2 hours after consuming food.

13. The method of claim 9 wherein the administration to the patient is substantially at the same time as the consumption of the food.

14. The method of claim 9 wherein the administration to the patient is immediately after the consumption of food up to about one hour after said consumption.

15. The method of claim 9 wherein the pharmaceutical composition comprises a tablet.

16. The method of claim 15 wherein the pharmaceutical composition comprises a unit dosage form.

17. A method of increasing the oral bioavailability of metaxalone to a patient receiving metaxalone therapy comprising administering to the patient a pharmaceutical tablet comprising 400 mg to 800 mg of metaxalone, with food, wherein the administration results in an increase in the maximal plasma concentration (Cmax) and extent of absorption (AUC(last)) of metaxalone compared to administration without food.

18. The method of claim 17 wherein the administration to the patient occurs between 30 minutes prior to 2 hours after consuming food.

19. The method of claim 17 wherein the administration to the patient is substantially at the same time as the consumption of the food.

20. The method of claim 17 wherein the administration to the patient is immediately after the consumption of food up to 1 hour after said consumption.

21. The method of claim 1, further comprising informing the patient that the administration of a therapeutically effective amount of metaxalone in a pharmaceutical composition with food results in an increase in the maximal plasma concentration (Cmax) and extent of absorption (AUC(last)) of metaxalone compared to administration without food.

22. The method of claim 1, wherein the metaxalone is from a container with printed labeling advising that administration with food results in an increase in the maximal plasma concentration (Cmax) and extent of absorption (AUC(last)) of metaxalone compared to administration without food.

Description

FIELD OF THE INVENTION

The invention relates to methods for increasing the bioavailability of a medicinal agent, namely metaxalone (5-[(3,5-dimethylphenoxy)methyl]-2 oxazolidinone).

BACKGROUND OF THE INVENTION

Metaxalone (Skelaxin.RTM.) has the following chemical structure and name: ##STR1##

5-[(3,5 -dimethylphenoxy)methyl]-2 oxazolidinone

Skelaxin is indicated as an adjunct to rest, physical therapy, and other measures for the relief of discomforts associated with acute, painful musculoskeletal conditions. The mode of action of this drug has not been clearly identified, but may be related to its sedative properties. Metaxalone does not directly relax tense skeletal muscles in man. The commercially available tablet contains: metaxalone, 400 mg along with inert compression tableting excipients.

Metaxalone is further described at Monograph no. 5838 of the Merck Index (Eleventh Addition, Merck & Co., 1989) and is also identified by CAS Registry Number: 1665-48-1. It is also known by the drug code, AHR-438; and the drug product containing it is marketed as Skelaxin.RTM. (a trademark of Elan Pharmaceuticals, Inc.).

Preparation of metaxalone is described in Lunsford et al., J. Am. Chem. Soc. 82, 1166 (1960) and U.S. Pat. No. 3,062,827 to Lunsford Nov. 6, 1962 Assignee A. H. Robins), which is incorporated herein in its entirety by reference. The '827 patent discloses the compound and related species as anticonvulsants and antispasmodics, however, these activities have not been borne out by clinical experience.

Metaxalone is a central nervous system depressant that has sedative and skeletal muscle relaxant effects. Metaxalone is indicated as an adjunct to rest, physical therapy and other measures for the relief of discomforts associated with acute, painful muscoloskeletal conditions. See Skelaxin.RTM. monograph, 2001 Physicians' Desk Reference.RTM., Medical Economics Company, Inc. (publisher) Montvale, N.J.

The most frequent reactions to metaxalone include nausea, vomiting, gastrointestinal upset, drowsiness, dizziness, headache, and nervousness or "irritability." Other adverse reactions are: hypersensitivity reaction, characterized by a light rash with or without pruritus; leukopenia; hemolytic anemia; jaundice.

Pharmacokinetic studies have not previously been conducted to date to evaluate the effect of food on the pharmacokinetics of metaxalone. The hydrophobicity of the metaxalone molecule and the dosage amount required for a therapeutic effect both point to probably limited absorption from the gut when administered orally. More oral bioavailability of the drug substance has been sought to increase both speed of onset and amount of therapeutic effect.

BRIEF DESCRIPTION OF THE DRAWINGS

FIG. 1 is a plot of the mean plasma concentration of metaxalone in nanograms per milliliter versus the time elapsed from administration of the dosage form. Two (2) plots are shown for the 400 mg dosage form administered with and without food.

SUMMARY OF THE INVENTION

The subject of this invention is the unexpected finding that administration of metaxalone with food increases both the rate and extent of absorption via the oral dosage form in human subjects.

One aspect of this invention is a method of increasing the bioavailability of metaxalone in a human patient receiving metaxalone therapy wherein the metaxalone is contained in a pharmaceutical composition, which method comprises administering a therapeutically effective amount of metaxalone to the patient with food.

Another aspect of the invention is providing a method of increasing rate and extent of metaxalone absorption as measured by the drug concentration attained in the blood stream over time of a patient receiving, the drug in an oral dosage form which method comprises administering a therapeutically effective amount of metaxalone to the patient with food.

Preferably the therapeutic amount is between about 200 mg to about 900 mg, and more preferably between about 400 mg to about 800 mg. Unit dosage forms are preferred.

Preferably the food is a solid food with sufficient bulk and fat content that it is not rapidly dissolved and absorbed in the stomach. More preferably the food is a meal, such as breakfast, lunch or dinner. Advantageously the dosage is administered to the patient between about 30 minutes prior to about 2 hours after eating a meal, most advantageously the dosage is administered within 15 minutes of eating a meal. The terms "without food", "fasted" and "an empty stomach" are defined to mean the condition of not having consumed solid food for about 1 hour prior to until about 2 hours after such consumption.

Yet another aspect of this invention is providing information to prescribing physicians and patients receiving metaxalone therapy useful in maximizing the therapeutic effect of the oral dosage form, by recommending that metaxalone be taken within about half an hour of consuming food.

Another aspect of this invention is an article of manufacture that comprises a container containing a pharmaceutical composition comprising metaxalone wherein the container holds preferably the metaxalone composition in unit dosage form and is associated with printed labeling instructions advising of the differing absorption when the pharmaceutical composition is taken with and without food.

The effect of food on metaxalone absortpion was identified in a study designed to compare the bioavailability of 400 mg of metaxalone in the formulation the drug product Skelaxin.RTM. administered to healthy volunteers with and without food.

An objective was to evaluate the bioavailability of metaxalone when administered to subjects with and

without food. A single center, single dose, open-label, two-period, randomized, crossover trial in healthy subjects was conducted over a period of approximately 32 days.

The two study drug treatments were as follows:

Treatment A: metaxalone tablet (400 mg) administered with food

Treatment B: metaxalone tablet (400 mg) administered without food

In fed treatment condition A, study drug was taken 15 minutes after th e test meal. The test meal was consumed over a 15 minute time period. There was a 6-day washout period between study drug administrations. Seventeen blood samples were collected, starting with baseline (0 hour) and at the following time points: 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 4.5, 5, 6, 8, 12, 16, 24, and 36 hours.

A total of 44 subjects (31 males/13 females) were enrolled and dosed. Only the plasma of subjects who completed the study were assayed and used for the pharmacokinetic analysis.

A single center, single dose, open label, two-period crossover trial was devised for study in healthy subjects. Each administration was a single oral dose of one Skelaxin.RTM. 400 mg tablet with or without food. The study drug was administered as follows:

Treatment A: One (1) 400 mg tablet of metaxalone with 240 mL of room temperature water with food: Breakfast was given to the subjects 30 minutes prior to dosing and eaten within a 15 minute period. The dose of study drug was administered to the subjects 15 minutes after the breakfast was finished.

The breakfast consisted of the following:

2 eggs (fried in butter);

2 strips of bacon;

2 slices of toast with butter;

4 ounces of hash brown potatoes;

1 glass whole milk (8 ounces).

Treatment B: 1 tablet of metaxalone) with 240 mL of room temperature water without food. The study drug was administered with 240 mL room temperature water. A mouth check was performed to verify that the subjects swallowed the dose. Subjects were sequentially dosed at 1 minute intervals. The actual time of dosing was recorded on the Master Flow Sheet (refer to the Appendix 16.3.2 Clinical Study Data). Drug administration (1.times.400 mg capsule) was assisted with 240 mL of room temperature water consumed under direct observation. Immediately after administration of product, the subject's oral cavity was checked to confirm complete medication and fluid consumption. Dosing was completed as scheduled in 42 of 44 subjects.

The drug substance, metaxalone; was dosed in tablet form. Content: 400 mg; Route: Oral, Batch/Lot No.: SKLWW263F; Expiration Date: FEB03; Manufacturer: West-Ward Pharmaceutical Corp

All pharmacokinetic parameters were analyzed by noncompartmental methods. The following PK parameters were calculated for the two PK profiles and are defined as follows:

Tmax: Time to maximum concentration;

Cmax: Observed maximum concentration;

kel: Slope of terminal linear portion of concentration/time curve;

T1/2: Half-life of metaxalone calculated as: 0.693/Kel;

AUC(last): Area under the curve to last quantifiable concentration as measured by the trapezoidal rule;

AUC(inf): The AUC value extrapolated to infinity calculated as: AUC(inf)=AUC(last)+C(t)last/Kel where C(t)last is the last measurable concentration.

Statistical Analysis

All statistical analyses were performed using SAS.RTM. software version 6.08 or higher. The PK parameters between the two treatments were compared using an appropriate ANOVA model (analysis of variance) that includes term for treatment, sequence, and period effect. Ninety percent confidence interval was computed for the Cmax and AUC values of the fed treatment with fasting as the reference treatment. During the study there were no protocol deviations to confound the pharmacokinetic and bioavailability analyses. Study results were not corrected for drug potency. The individual test results are summarized in table I

TABLE I

Summary of AUC.sub.inf and Ln-Transformed AUC.sub.inf for Skelaxin .RTM. Administered With Food (A) vs. Skelaxin .RTM. Administered Without Food (B)
Log.sub.e

Subj	Ln Seq.	A: With Food (ng/mL)	B: Without Food (ng/mL)	Ratio (A - B)	% Ratio (A/B)	% Ratio (A/B) *100	Log.sub.e A Ln(A)	Log.sub.e B Ln(B)	Ln (Ratio)
2	1	9031	9855	824	0.916	91.64	9.108	9.196	0.087
3	2	9609	13103	3494	0.733	73.33	9.170	9.481	0.310
4	2	5011	3867	1144	1.296	129.58	8.519	8.260	0.259
5	1	3389	2530	859	1.340	133.95	8.128	7.836	0.292
6	2	10456	7302	3154	1.432	143.19	9.255	8.896	0.359
7	2	11217	11103	114	1.010	101.03	9.325	9.315	0.010
8	2	4025	3857	168	1.044	104.36	8.300	8.258	0.043
9	2	13708	8876	4832	1.544	154.44	9.526	9.091	0.435
11	2	8122	6570	1552	1.236	123.62	9.002	8.790	0.212
12	1	6739	5470	1269	1.232	123.20	8.816	8.607	0.209
13	2	4614	4360	254	1.058	105.83	8.437	8.380	0.057
14	1	17347	13467	3880	1.288	128.81	9.761	9.508	0.253

15	2	5488	3535	1953	1.552	155.25	8.610	8.170
0.440								
16	1	12327	12025	302	1.025	102.51	9.420	9.395
0.025								
17	1	4070	3320	750	1.226	122.59	8.311	8.108
0.204								
18	1	5296	4365	931	1.213	121.33	8.575	8.381
0.193								
19	2	8022	8271	249	0.970	96.99	8.990	9.021
0.031								
20	2	2962	2874	88	1.031	103.06	7.994	7.963
0.030								
21	1	9143	7173	1970	1.275	127.46	9.121	8.878
0.243								
22	2	11873	7742	4131	1.534	153.36	9.382	8.954
0.428								
23	1	10456	9983	473	1.047	104.74	9.255	9.209
0.046								
24	1	6507	5529	978	1.177	117.69	8.781	8.618
0.163								
25	2	12143	10272	1871	1.182	118.21	9.405	9.237
0.167								
26	1	4519	5391	872	0.838	83.82	8.416	8.592
0.176								
27	1	5208	5061	147	1.029	102.90	8.558	8.529
0.029								
28	2	5197	5012	185	1.037	103.69	8.556	8.520
0.036								
29	1	10355	11601	1246	0.893	89.26	9.245	9.359
0.114								
30	1	7350	6452	898	1.139	113.92	8.902	8.772
0.130								
31	1	7899	7677	222	1.029	102.89	8.974	8.946
0.029								
32	2	6719	4440	2279	1.513	151.33	8.813	8.398
0.414								
33	2	11295	11316	21	0.998	99.81	9.332	9.334
0.002								
34	2	13357	13580	223	0.984	98.36	9.500	9.516
0.017								
35	2	10710	10138	572	1.056	105.64	9.279	9.224
0.055								
36	1	19077	19329	252	0.987	98.70	9.856	9.869
0.013								
37	1	6727	4454	2273	1.510	151.03	8.814	8.402
0.412								
38	2	19024	9934	9090	1.915	191.50	9.853	9.204
0.650								
39	1	3060	3284	224	0.932	93.18	8.026	8.097
0.071								
40	1	5188	4203	985	1.234	123.44	8.554	8.344
0.211								
41	1	7273	6574	699	1.106	110.63	8.892	8.791
0.101								
42	2	3958	3642	316	1.087	108.68	8.283	8.200
0.083								
43	1	8837	4642	4195	1.904	190.37	9.087	8.443
0.644								
44	2	11427	11935	508	0.957	95.74	9.344	9.387
0.043								

Differences were declared to be significant at the 5% level. The ratio of the geometric means for the

in-transformed data and the corresponding 90% confidence intervals were calculated for AUC(last), AUC(inf), and Cmax. The calculations for the confidence intervals used the least squares means (LSMEANS) and the standard error of the estimate, both generated by the SAS.RTM. software.

The lower limit of quantitation for metaxalone was 10 ng/mL. For statistical analysis, subject sample values below the lower limit of quantitation were reported as zero.

Tables IIa and IIb summarize the results of the analyses performed on the pharmacokinetic parameters obtained from the fed and fasted states.

TABLE IIa

Metaxalone	Ln-Transformed AUC(last)	Ln-Transformed AUCinf	Ln-Transformed Cmax
Treatment A Geometric Mean	7525.00	7630.53	1536.23
Treatment B Geometric Mean	6094.12	6615.24	865.34
% Ratio	123.48	115.35	177.53
90% Confidence Interval	(116.40, 130.99)	(109.24, 121.80)	(156.62, 201.23)

TABLE IIb

Metaxalone		AUC(last)	AUCinf	Cmax	Tmax	T1/2	
Treatment A Mean	Least Squares	8439.62	8541.31	1773.61	4.29	2.37	
Treatment B Mean	Least Squares	6961.81	7478.90	983.37	3.32	9.04	

With a 5% significance level, the ANOVA detected statistically significant differences between treatments for in-transformed AUC(last), AUCinf, and Cmax, as well as for untransformed AUC(last), AUC(inf), Cmax, Tmax, T1/2, and Kel. The ANOVA detected no statistically significant differences between periods or between sequences.

The mean T.sub.1/2 (half-life) of metaxalone with food and without food were 2.37 and 9.04 hours respectively. The exact reason for this discrepancy is unclear. However, the AUC last is outside the confidence interval, indicating a significant food effect.

Ratio (A/B) of least-squares means for AUC(last), AUC(inf) and Cmax were 123.48%, 115.35% and 177.53%, respectively demonstrating that metaxalone administered with food increased both its rate and extent of absorption.

ANOVA detected statistically significant differences between treatments for In-transformed AUC(last), AUC(inf), and Cmax, as well as for untransformed AUC(last), AUC(inf),Cmax, T1/2, and Kel. ANOVA did not detect any statistically significant differences between treatments for untransformed Tmax.

Conclusion: Administration with food increases both the rate and extent of absorption of metaxalone 400 mg tablets when administered as a single dose. The bioavailability of metaxalone 400 mg tablets increased when administrated with food.

Article of Manufacture

The article of manufacture comprises a container holding an immediate release pharmaceutical composition

suitable for oral administration of metaxalone in combination with printed labeling instructions providing a discussion of when a particular dosage form should be administered with food and when it should be taken on an empty stomach. The composition will be contained in any suitable container capable of holding and dispensing the dosage form and which will not significantly interact with the composition and will further be in physical relation with the appropriate labeling advising that an immediate release tablet dosage form has less somnolence associated with its use if taken on an empty stomach and an immediate release multiparticulate dosage form has less somnolence associated with its use if taken with food. The labeling instructions will be consistent with the methods of treatment as described hereinbefore. The labeling may be associated with the container by any means that maintain a physical proximity of the two, by way of non-limiting example, they may both be contained in a packaging material such as a box or plastic shrink wrap or may be associated with the instructions being bonded to the container such as with glue that does not obscure the labeling instructions or other bonding or holding means.

While the invention has been described by discussion of embodiments of the invention and non-limiting examples thereof, one of ordinary skill in the art may, upon reading the specification and claims, envision other embodiments and variations which are also within the intended scope of the invention and therefore the scope of the invention shall only be construed and defined by the scope of the appended claims.

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