ion cluster technique was effective not only for the differentiation of the metabolites from other biological impurities but also for the structural elucidation. The metabolic transformation of the drug molecule was easily recognized by the shift of the fragment ions. Labeling the benzene ring of I with deuterium atoms readily clarified the metabolic transformations occurring in the benzene ring, since the elimination of each deuterium atom due to the biotransformation reduced the spacing of the ion clusters by 1 mass unit.

REFERENCES[8]

(1) T. Irikura, K. Nishino, N. Ito, M. Ito, and H. Ohkubo, *Jpn. J. Pharmacol.*, **20**, 287 (1970).

(2) H. Terayama, T. Narue, S. Kasai, M. Numata, H. Nakayama, T. Saito, and T. Irikura, *Chem. Pharm. Bull.*, **21**, 12 (1973).

(3) T. Irikura, Y. Nagatsu, S. Baba, and H. Sone, *Yakugaku Zasshi*, **94**, 802 (1974).

(4) S. Baba and S. Morishita, *Chem. Pharm. Bull.*, **23**, 1949 (1975).

(5) D. R. Knapp, T. E. Gaffney, and R. E. McMahon, *Biochem. Pharmacol.*, **21**, 425 (1972).

(6) R. E. McMahon, H. R. Sulivan, S. L. Due, and F. J. Marshall, *Life. Sci.*, **12**, 463 (1973).

(7) A. Zimmer, A. Prox, H. Pelzer, and R. Hankwitz, *Biochem. Pharmacol.*, **22**, 2213 (1973).

(8) W. E. Braselton, Jr., J. C. Orr, and L. L. Engel, *Anal. Biochem.*, **53**, 64 (1973).

(9) Y. Tanaka and M. Sano, *Chem. Pharm. Bull.*, **24**, 804 (1976).

(10) S. Baba, S. Morishita, and Y. Nagatsu, *Yakugaku Zasshi*, **96**, 1293 (1976).

(11) R. A. Hites and K. Biemann, *Anal. Chem.*, **42**, 855 (1970).

(12) H. Miyazaki, M. Ishibashi, M. Inoue, and M. Itoh, *J. Chromatogr.*, **99**, 553 (1974).

(13) T. Irikura, K. Musuzawa, K. Nishino, M. Kitagawa, H. Uchida, N. Ichinoseki, and M. Ito, *J. Med. Chem.*, **11**, 801 (1968).

(14) C. C. Sweeley, W. H. Elliott, I. Fries, and R. Ryhage, *Anal. Chem.*, **38**, 1549 (1966).

[8] For Part XIX, see M. Horie, S. Baba, Y. Kashida, and C. Hamada, *Yakugaku Zasshi*, **97**, 805 (1977).

Effect of Salicylamide and Acetaminophen on Dextromethorphan Hydrobromide Metabolism: Possible Pharmacological Implications

GOLLAMUDI RAMACHANDER *x, FLORENCE D. WILLIAMS, and JANE FRANCES EMELE

Received April 1, 1977, from the *Consumer Products Group, Warner Lambert Company, Morris Plains, NJ 07950.* Accepted for publication September 9, 1977.

*Present address: Department of Medicinal Chemistry, College of Pharmacy, University of Tennessee Center for the Health Sciences, Memphis, TN 38163.

Abstract □ The effect of salicylamide and acetaminophen on the metabolic fate of dextrorphan, the primary metabolite of dextromethorphan, was studied *in vivo* in the rat. Plasma dextrorphan levels were measured at 5-min intervals up to 20 min and at longer intervals up to 2 hr after dextromethorphan hydrobromide was administered orally either alone or in combination with salicylamide and acetaminophen. The combination gave rise to higher plasma dextrorphan levels than did dextromethorphan hydrobromide alone at most sampling times. Conjugation of dextrorphan was inhibited almost quantitatively by salicylamide and acetaminophen at the 5-min sampling time. Salicylamide alone increased the plasma dextrorphan levels when it was coadministered with dextromethorphan, but the differences were not statistically significant. The antitussive activity of dextromethorphan hydrobromide in the unanesthetized dog was faster in onset, greater in intensity, and longer in duration when it was coadministered with salicylamide and acetaminophen. It is suggested that salicylamide and acetaminophen may inhibit the metabolic inactivation of dextrorphan, thereby improving the cough-inhibiting potential of dextromethorphan hydrobromide.

Keyphrases □ Dextromethorphan hydrobromide—metabolism, effect of salicylamide and acetaminophen, rats □ Metabolism—dextromethorphan hydrobromide, effect of salicylamide and acetaminophen, rats □ Salicylamide—effect on metabolism of dextromethorphan hydrobromide in rats □ Acetaminophen—effect on metabolism of dextromethorphan hydrobromide in rats □ Antitussives—dextromethorphan hydrobromide, metabolism, effect of salicylamide and acetaminophen, rats □ Analgesics—acetaminophen and salicylamide, effect on metabolism of dextromethorphan hydrobromide in rats

Many drugs are eliminated from the body by biotransformation to glucuronide and sulfate conjugates that are pharmacologically inactive. The enzyme systems responsible for the formation of such metabolites are saturable at relatively low drug concentrations (1, 2). Concomitant administration of drugs that undergo conjugation *in vivo* was reported to result in a competitive inhibition of the respective enzymatic processes (3–5).

The main routes of metabolism of dextromethorphan, a widely used nonnarcotic antitussive agent, are *O*- and *N*-demethylation followed by subsequent conjugation of the desmethyl metabolites to glucuronides and sulfates, with *O*-demethylation being the predominant pathway (6–10). The *O*-demethylation product, dextrorphan (*d*-3-hydroxy-*N*-methylmorphinan), was reported to possess antitussive activity in the dog (11). Salicylamide, a weak analgesic and antipyretic agent, is metabolized primarily to the ether glucuronide and ester sulfate (2). The main metabolites of the analgesic drug acetaminophen are the glucuronide and sulfate conjugates (12, 13).

Self-administration of analgesic preparations along with antitussives is common. This investigation determined, in experimental animals, if the biotransformation of dextromethorphan is affected by concurrent administration of salicylamide or a combination of salicylamide and acetaminophen and if the antitussive activity of dextromethorphan is altered by such multidrug therapy.

EXPERIMENTAL

Materials—The drugs and chemicals used were: dextromethorphan

Table I—Effect of Coadministering Dextromethorphan Hydrobromide with Salicylamide on the Plasma Dextrorphan Levels in Rats

Minutes Postdrug	Plasma Dextrorphan Levels, ng/ml[a]: Dextromethorphan Hydrobromide, 10 mg/kg	Plasma Dextrorphan Levels, ng/ml[a]: Dextromethorphan Hydrobromide, 10 mg/kg, plus Salicylamide, 15 mg/kg
5	7 ± 2 (10)	44 ± 17 (9)
10	127 ± 17 (10)	170 ± 15 (10)
15	185 ± 22 (12)	214 ± 23 (12)
20	245 ± 23 (10)	239 ± 21 (11)
30	209 ± 15 (10)	218 ± 18 (10)
45	120 ± 16 (8)	133 ± 22 (8)
60	153 ± 21 (9)	110 ± 16 (10)

[a] Mean ± *SE*. Numbers in parentheses refer to number of animals. One determination was made on each rat.

hydrobromide[1]; dextrorphan[1]; ethyl acetate[2], spectroquality; and *n*-hexane[3], analytical reagent grade.

Methods—*Determination of Dextrorphan in Plasma*—Unconjugated dextrophan was determined by the procedure of Ramachander *et al.* (14). Plasma (3.0 ml) was adjusted to pH 9.5 by the addition of about 0.6 ml of a saturated solution of sodium carbonate and extracted with 15 ml of ethyl acetate. The mixture was centrifuged, and a 12-ml aliquot of the organic layer was shaken with 3.0 ml of 1.0 *N* HCl.

The acid layer was separated, and its fluorescence was measured[4]. The fluorescence and excitation wavelengths were 310 and 280 nm, respectively, and the slit dials were set to give a bandpass of 8 nm for excitation and 5 nm for fluorescence. The concentrations of dextrorphan in the samples were read from a calibration curve whose validity was determined by including three or four known concentrations of the drug added to rat plasma with each series of unknowns.

Varying concentrations of dextrorphan (5–500 ng/ml) were added to normal rat plasma in the presence of 20 μg of salicylamide or 20 μg of salicylamide plus 20 μg of acetaminophen. The plasma was then assayed for free and total dextrorphan. Salicylamide and acetaminophen did not interfere with the measurement of dextrorphan. Salicylamide, 15 mg/kg, or salicylamide, 15 mg/kg, plus acetaminophen, 10 mg/kg, was administered orally to rats, and blood was obtained at 15 and 30 min. Known amounts of dextrorphan were added to the separated plasma, which was analyzed according to the described procedure. The measurement and recoveries of dextrorphan were unaffected.

Determination of Total Dextrorphan (Free and Conjugated) in Plasma—Plasma samples obtained at 0 and 5 min after dextromethorphan hydrobromide (10 mg/kg) administration were analyzed for total dextrorphan by the method of Ramachander *et al.* (14). Plasma (3.0 ml) was adjusted to pH 5.5 with 3.0 *N* acetic acid and incubated at 37° for 2 hr with 0.16 ml of an enzyme solution[5] containing 100,000 units of β-glucuronidase and 50,000 units of sulfatase/ml. The conjugates of dextrorphan appeared to undergo quantitative hydrolysis by 2 hr because longer periods of incubation did not improve the recoveries of the free drug. The pH was then adjusted to 9.5 with a saturated solution of sodium carbonate, and the mixture was analyzed for dextrorphan.

A calibration curve was constructed by plotting fluorescence intensity against concentration of dextrorphan added to drug-free plasma. Regression analysis of the least-squares line fitting the data points provided an equation for the curve as $y = 0.2658x + 3.728$ with $r = 0.9956$, where y represents fluorescence units and x is nanograms of dextrorphan per milliliter of plasma. Recovery of added amounts of dextrorphan to plasma was 70%. To determine method precision, eight samples to which dextrorphan was added to plasma to yield a concentration of 400 ng/ml and four samples containing 600 ng/ml were analyzed in duplicate over 6 months. The coefficients of variation at these two concentrations were 8 and 4%, respectively.

The fluorescence spectrum of dextrorphan extracted from plasma was identical with that of dextrorphan in 1.0 *N* HCl but not with that of the unmetabolized drug. Extracts from plasma of rats administered dextromethorphan hydrobromide exhibited fluorescence spectra characteristic of dextrorphan but not of dextromethorphan.

[1] Hoffmann-La Roche Inc., Nutley, N.J.
[2] Matheson, Coleman and Bell, Norwood, Ohio.
[3] Mallinckrodt Chemical Works, St. Louis, Mo.
[4] Perkin-Elmer model MPF-3 fluorescence spectrophotometer.
[5] Glusulase, Endo Laboratories, Garden City, N.Y.

Table II—Effect of Coadministering Dextromethorphan Hydrobromide with Salicylamide and Acetaminophen on the Plasma Dextrorphan Levels in Rats

Minutes Postdrug	Plasma Dextrorphan Levels, ng/ml[a]: Dextromethorphan Hydrobromide, 10 mg/kg	Plasma Dextrorphan Levels, ng/ml[a]: Dextromethorphan Hydrobromide, 10 mg/kg, plus Salicylamide, 15 mg/kg, plus Acetaminophen, 10 mg/kg
0	0	0
5	7 ± 3[b]	60 ± 10[b]
10	127 ± 26	227 ± 59
15	180 ± 22[c]	314 ± 39[c]
20	243 ± 20	240 ± 35
30	230 ± 38	245 ± 63
45	135 ± 16	174 ± 23
60	145 ± 34	159 ± 23
90	69 ± 14	93 ± 28
120	48 ± 11	74 ± 16

[a] Mean of 10 rats ± *SE*. [b] Significance of the difference between the two treatment groups was <0.05 as determined by the two-tailed *t* test. [c] Significance of the difference between the two treatment groups was <0.01.

Treatment of Animals—Groups of 10 female Sprague–Dawley rats, 160–200 g, were fasted for 18 hr. They then received by stomach tube aqueous solutions of: (*a*) dextromethorphan hydrobromide, 10 mg/kg; (*b*) a combination of dextromethorphan hydrobromide, 10 mg/kg, and salicylamide, 15 mg/kg; or (*c*) a mixture of dextromethorphan hydrobromide, 10 mg/kg, salicylamide, 15 mg/kg, and acetaminophen, 10 mg/kg. Blood samples were withdrawn into heparinized tubes by cardiac puncture immediately prior to and at 5, 10, 15, 20, 30, 45, 60, 90, and 120 min after drug administration.

Plasma was separated by centrifugation and analyzed for free or total dextrorphan according to one of the described procedures. For the determination of total dextrorphan, only the samples obtained at 0 and 5 min were used. Ten rats were used per time period for the determination of either free or total dextrorphan. Plasma from one rat was employed to obtain one experimental value of either free or total dextrorphan.

Evaluation of Antitussive Activity in Unanesthetized Dogs—The antitussive activity was determined according to the method of Tedeschi *et al.* (15), which involves counting the number of coughs produced by an electrically induced vibration of a tracheal magnet. Three preparations were administered to four dogs in a crossover design. The dogs were fasted for 18 hr and were given by a stomach tube: (*a*) dextromethorphan hydrobromide, 5.0 mg/kg, as a 25-ml aqueous solution followed by two successive washes with 25 ml of water each; (*b*) dextromethorphan hydrobromide–salicylamide–acetaminophen (5:7.5:5), 17.5 mg/kg, as a 35-ml aqueous solution followed by two successive washings with 20 ml of water each; (*c*) dextromethorphan hydrobromide–salicylamide–acetaminophen (5:3.25:2.5), 10.75 mg/kg, as a 35-ml aqueous solution followed by two washings with 20 ml of water each; or (*d*) salicylamide–acetaminophen (7.5:5) 12.5 mg/kg, as a 35-ml aqueous solution followed by two washings with 20 ml of water each. All drugs were originally brought into solution by gentle warming in a water bath at 40° and then cooled to room temperature as clear solutions.

Control readings were taken for 3 hr before medication and at 5, 10, 15, and 20 min and 1, 2, 3, and 4 hr thereafter. Drug effects were calculated in terms of percent inhibition of the number of coughs.

RESULTS

Effect of Coadministering Dextromethorphan Hydrobromide with Salicylamide on Plasma Dextrorphan Levels—Upon oral administration of dextromethorphan hydrobromide, 10 mg/kg, to female rats, dextrorphan appeared in plasma at very low levels (7 ng/ml) by 5 min, reached peak levels (245 ng/ml) at 20 min, and declined thereafter. Coadministration of the same dose of dextromethorphan with salicylamide, 15 mg/kg, resulted in higher average concentrations of dextrorphan at 5, 10, 15, 30, and 45 min. The differences, however, were not statistically significant ($p > 0.05$). The results are summarized in Table I.

Effect of Coadministering Dextromethorphan Hydrobromide with Salicylamide and Acetaminophen on Plasma Dextrorphan Levels—The effects of coadministering dextromethorphan hydrobromide (10 mg/kg) with salicylamide (15 mg/kg) and acetaminophen (10 mg/kg) on the average plasma levels are shown in Table II. When the drug

Table III—Effect of Enzyme Hydrolysis on Plasma Dextrorphan Levels in Rats 5 min after the Oral Administration of Dextromethorphan Hydrobromide, Either Alone or in Combination with Salicylamide

Treatment	Plasma Dextrorphan Levels, ng/ml (Mean ± *SE*)[a]	
	Free	Total[b]
Dextromethorphan hydrobromide, 10 mg/kg	7 ± 3[c]	71 ± 10[c,d]
Dextromethorphan hydrobromide, 10 mg/kg, plus salicylamide, 15 mg/kg, and acetaminophen, 10 mg/kg	60 ± 10[d]	74 ± 14[d]

[a] Ten rats were used in each treatment group. [b] Free plus conjugated. Determined after hydrolysis with glucuronidase and arylsulfatase. [c] Significance of the difference between the two treatment groups was <0.01 as determined by the two-tailed *t* test. [d] The three treatment groups were not significantly different from each other.

was administered alone, dextrorphan appeared at very low levels in plasma by 5 min, reached peak levels (243 ng/ml) at 20 min, and declined thereafter. In the postabsorption phase of the curve, a plateau was noticed between 45 and 60 min. With the drug combination, a significantly higher average dextrorphan concentration (60 ng/ml) was noted at 5 min ($p < 0.05$). A mean peak concentration of 314 ng/ml was attained earlier and was significantly higher than the 15-min average concentration of 180 ng/ml obtained after administration of dextromethorphan alone.

Effect of Coadministration of Dextromethorphan Hydrobromide with Salicylamide and Acetaminophen on Relative Amounts of Free and Total Dextrorphan in Rat Plasma—Five minutes after the oral administration of dextromethorphan hydrobromide (10 mg/kg), the mean plasma dextrorphan level in a group of 10 rats was 7 ng/ml (Table III). Enzyme hydrolysis of the 5-min plasma samples from 10 similarly treated rats resulted in an average concentration of 71 ng/ml, which was significantly higher than the value of 7 ng/ml from the former group ($p < 0.01$). Five minutes after the oral administration of dextromethorphan hydrobromide (10 mg/kg) with salicylamide (15 mg/kg) and acetaminophen (10 mg/kg), the mean plasma dextrorphan concentration in a group of 10 rats was 60 ng/ml. Upon enzyme hydrolysis of the plasma samples from 10 similarly treated rats, the average concentration of the metabolite was 74 ng/ml. The latter three groups were not significantly different from each other.

Effect of Salicylamide and Acetaminophen on Antitussive Activity of Dextromethorphan Hydrobromide in Unanesthetized Dogs—The cough inhibition elicited by a 5.0-mg/kg dose of dextromethorphan hydrobromide administered alone or in combination with salicylamide and acetaminophen in unanesthetized dogs is illustrated in Fig. 1. When coadministered with salicylamide (3.25 mg/kg) and acetaminophen (2.50 mg/kg), the antitussive activity of dextromethorphan hydrobromide (5.00 mg/kg) at 20 min was significantly higher than when given alone ($p < 0.05$). The combination of the same dose of the latter with salicylamide (7.5 mg/kg) and acetaminophen (5.0 mg/kg) was even more potent with respect to:

1. Onset of activity. The combination was significantly more active than dextromethorphan hydrobromide at 5 min ($p < 0.02$).
2. Intensity of effect. The percent cough inhibition with the combination at 20 and 60 min was 48.3 and 38.0, respectively; that with the drug alone was 14.5 and 14.3, respectively. The levels of significance of these differences were $p < 0.05$ at 20 min and $p < 0.01$ at 60 min.
3. Duration of activity. Whereas dextromethorphan hydrobromide had marginal activity at 4 hr (percent cough inhibition, 1.5), the combination was significantly more active (percent cough inhibition, 12.5, $p < 0.02$).

Salicylamide and acetaminophen (7.5:5), 12.5 mg/kg, had a negligible antitussive effect. The cough inhibition at any time interval was less than 2%.

DISCUSSION

Kamm *et al.* (6) observed that the primary metabolic pathway of dextromethorphan in the rat is *O*-demethylation, leading to the formation of dextrorphan. Although 3-hydroxymorphinan was present in the urine and bile of rats treated with dextromethorphan, there was no evidence for the presence of 3-methoxymorphinan in these fluids. It was proposed that the formation of 3-hydroxymorphinan may be explained by very rapid *O*-dealkylation of 3-methoxymorphinan to the completely dealkylated 3-hydroxymorphinan.

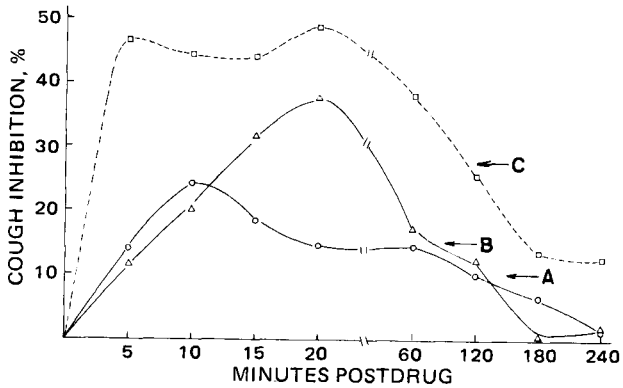

Figure 1—*Effect of salicylamide and acetaminophen on the antitussive activity of dextromethorphan hydrobromide in the unanesthetized dog. Key: A, dextromethorphan hydrobromide, 5 mg/kg; B, dextromethorphan hydrobromide, 5 mg/kg, plus salicylamide, 3.25 mg/kg, plus acetaminophen, 2.5 mg/kg; and C, dextromethorphan hydrobromide, 5 mg/kg, plus salicylamide, 7.5 mg/kg, plus acetaminophen, 5 mg/kg. Each point represents an average of values from four dogs.*

Competitive inhibition of glucuronide and sulfate formation by salicylamide and acetaminophen was reported in humans (16). The observed elevation in the plasma dextrorphan levels in the presence of salicylamide and acetaminophen may be due to similar phenomena, with the three drugs acting as competing substrates. This possibility finds rationale in the observation that all plasma dextrorphan was present in the free form 5 min after the administration of the combination to the rat whereas only 10% was unconjugated after treatment of the animals with dextromethorphan alone. Salicylamide alone had some effect in increasing the plasma dextrorphan levels when coadministered with dextromethorphan hydrobromide, but the observed differences were not statistically significant. The effect was more pronounced when salicylamide and acetaminophen were coadministered with dextromethorphan hydrobromide.

Upon oral administration to dogs, dextromethorphan was metabolized to dextrorphan, 3-methoxymorphinan, and 3-hydroxymorphinan (9). Of these metabolites, only dextrorphan was reported to possess antitussive activity in the dog (11). The present investigation demonstrates that salicylamide and acetaminophen potentiate the antitussive activity of dextromethorphan hydrobromide in the dog. On the basis of findings in the rat, this potentiation may be a result of an inhibition of the conjugation of dextrorphan, the *O*-demethylated metabolite of dextromethorphan, to pharmacologically inactive metabolites. It is possible that processes other than metabolic intervention are operative in the dog inasmuch as the combination had a more prolonged effect in this species than in the rat. More comprehensive studies appear necessary to delineate precisely the site of inhibition by salicylamide and acetaminophen in the metabolic pathway of dextromethorphan.

These findings are of importance in multiple drug therapy and its clinical implications.

REFERENCES

(1) W. Barr, *Drug Inf. Bull.*, **3**, 27 (1969).
(2) G. Levy and T. Matsuzawa, *J. Pharmacol. Exp. Ther.*, **156**, 285 (1967).
(3) G. Levy and J. H. Procknal, *J. Pharm. Sci.*, **57**, 1330 (1968).
(4) G. Ramachander, F. D. Williams, and J. F. Emele, *ibid.*, **62**, 1498 (1973).
(5) E. Dybing, *Biochem. Pharmacol.*, **25**, 1421 (1976).
(6) J. J. Kamm, A. B. Taddeo, and E. J. Van Loon, *J. Pharmacol. Exp. Ther.*, **158**, 437 (1967).
(7) K. Willner, *Arzneim.-Forsch.*, **12**, 26 (1963).
(8) C. Elison and H. Elliott, *J. Pharmacol. Exp. Ther.*, **144**, 265 (1964).
(9) A. Brossi, O. Hafliger, and O. Schneider, *Arzneim.-Forsch.*, **5**, 62 (1955).
(10) R. Versie, A. Noirsfalise, M. Neven, and R. Malchair, *Ann. Med. Leg.*, **42**, 561 (1962).
(11) W. M. Benson, P. F. Stefko, and L. O. Randall, *J. Pharmacol. Exp. Ther.*, **109**, 189 (1953).
(12) A. J. Cummings, M. L. King, and B. K. Martin, *Br. J. Pharmacol. Chemother.*, **29**, 150 (1967).

(13) G. L. Mattock, I. J. McGilveray, and D. Cook, *Can. J. Pharm. Sci.*, **6**, 35 (1971).
(14) G. Ramachander, F. D. Williams, and J. F. Emele, *J. Pharm. Sci.*, **66**, 1047 (1977).
(15) R. E. Tedeschi, D. H. Tedeschi, J. T. Hitchens, L. Cook, P. A. Mattis, and E. J. Fellows, *J. Pharmacol. Exp. Ther.*, **126**, 338 (1959).
(16) G. Levy and H. Yamada, *J. Pharm. Sci.*, **60**, 215 (1971).

ACKNOWLEDGMENTS

Part of the antitussive studies were conducted at Pharmakon Laboratories, Scranton, Pa., by Dr. Richard Matthews, to whom the authors express their appreciation. The authors also acknowledge the interest of Dr. Herbert A. Lieberman.

Bioavailability of Erythromycin Stearate: Influence of Food and Fluid Volume

P. G. WELLING *x, H. HUANG, P. F. HEWITT, and L. L. LYONS

Received June 20, 1977, from the *Center for Health Sciences, School of Pharmacy, University of Wisconsin, Madison, WI 53706.* Accepted for publication September 9, 1977. *Present address: School of Medicine, Department of Therapeutics and Clinical Pharmacology, Queen Elizabeth Hospital, Edgbaston, Birmingham B15 2TH, England.

Abstract □ The influence of various test meals and coadministered water volumes on erythromycin stearate bioavailability from orally dosed film-coated tablets was studied in healthy human subjects. Serum erythromycin levels were uniformly reduced by all test meals, with the reduction in mean peak serum levels varying from 47 to 60%. Serum erythromycin levels also were reduced significantly in fasted individuals when the accompanying water volume was reduced from 250 to 20 ml. The apparent drug absorption rate constant was not influenced by treatments. This result is probably due to rapid degradation of solubilized, unabsorbed drug in the GI tract. Higher and more uniform serum erythromycin levels are obtained when erythromycin stearate tablets are given on an empty stomach together with an adequate water volume.

Keyphrases □ Erythromycin stearate—bioavailability, effect of food and fluid volume, humans □ Bioavailability—erythromycin stearate, effect of food and fluid volume, humans □ Absorption, GI—erythromycin stearate, effect of food and fluid volume, humans □ Antibacterials—erythromycin stearate, bioavailability, effect of food and fluid volume, humans

Since the introduction of erythromycin in 1952 (1) and subsequent observations that the drug may be irregularly absorbed from the GI tract (2), a large number of derivatives and formulations have been prepared to optimize its stability and absorption.

The bioavailability of one such derivative, erythromycin stearate, has been examined from an oral suspension (3, 4) and film-coated tablets (4–6). One study (4) suggested that erythromycin stearate in film-coated tablets may be absorbed into the circulation at a faster rate than erythromycin base from coated tablets. However, the overall absorption efficiency of antibiotic from the two dosage forms was similar.

Reports on the influence of food on erythromycin stearate absorption are conflicting. Absorption from the suspension appears not to be influenced by food (3), while absorption from film-coated tablets is reduced (5, 6). However, the reported studies have several shortcomings in that the types and sizes of meals and the time intervals between eating and dosing were generally not specified. Furthermore, the volumes of fluid ingested with the drug were not described. The only mention of fluid volume occurred in one study (6) where subjects took the drug with as much fluid as desired.

In view of the marked influence that different meals, varying time intervals between food and drug ingestion, and volumes of fluid taken with a drug may have on drug absorption (7), this study examined erythromycin stearate bioavailability in human volunteers with these factors carefully controlled.

EXPERIMENTAL

The overall design was similar to that described previously (8). Subjects were two female and four male healthy volunteers. The females were 22 and 24 years old and weighed 64 and 50 kg. The males were 22–33 years old (mean 27) and weighed 66–82 kg (mean 73). All subjects were shown to be in good physical condition by medical examination.

Protocol—Verbal assurance was obtained from all subjects that they had taken no known enzyme-inducing agents for 1 month, and no other drugs for 1 week, preceding the study. Subjects were instructed to take no drugs other than the required doses of erythromycin stearate during the study.

Subjects were fasted overnight before each treatment and were permitted to eat no food, apart from test meals, until 4 hr after dosing. On the morning of a treatment, each subject drank 250 ml of water on arising, at least 1 hr before dosing. Medication was administered at 8:00 am; blood samples (~5 ml) were collected from a forearm vein for serum in vacuum tubes[1] immediately before and at 0.5, 1, 2, 4, 6, 8, and 12 hr after dosing. Serum was deep frozen (−18°) until assayed. Assays were routinely carried out within 1 week of sampling.

Treatments—Erythromycin stearate was administered as single 500-mg doses consisting of two 250-mg film-coated tablets[2]. High carbohydrate, high protein, and high fat meals were prepared and standardized as described previously (9). The following treatments were administered:

Treatment 1—Two tablets with 250 ml of water immediately following a standard high carbohydrate meal.

Treatment 2—Two tablets with 250 ml of water immediately following a standard high fat meal.

Treatment 3—Two tablets with 250 ml of water immediately following a standard high protein meal.

Treatment 4—Two tablets with 20 ml of water on a fasted stomach.

Treatment 5—Two tablets with 250 ml of water on a fasted stomach.

[1] Vacutainers.
[2] Bristamycin, Bristol Laboratories.