Pharmaceutical Research, Vol. 5, No. 7, 1988

Report

Dextromethorphan Pretreatment Induces Antipyrine Clearance in the Rat

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Received November 23, 1987; accepted February 4, 1988

Numerous agents that undergo extensive first-pass metabolism have been shown to inhibit oxidative drug metabolism. To examine whether this effect is related to the chemical structure or pharmacokinetic characteristics of the inhibiting agent, we determined the effect of dextromethorphan (a compound which exhibits pharmacokinetic similarities to, but is chemically dissimilar from, previously studied agents) on the disposition of antipyrine. A single oral dose of dextromethorphan hydrobromide, 100 mg/kg, 1 hr prior to antipyrine administration had no significant effect on the pharmacokinetics of this model substrate. The administration of dextromethorphan at the same dose twice daily for 3 days and an additional dose 1 hr prior to antipyrine administration resulted in a 33% increase in the clearance of antipyrine. These data indicate that dextromethorphan is capable of inducing hepatic microsomal enzymes. Studies are needed to determine if this effect also occurs upon chronic administration in humans. These data suggest that the pharmacokinetic characteristic of extensive first-pass metabolism is not necessarily associated with inhibition of drug metabolism.

KEY WORDS: antipyrine; dextromethorphan; drug metabolism; enzyme induction; pharmacokinetics.

INTRODUCTION

Dextromethorphan is a widely used antitussive agent that is found in numerous nonprescription cough and cold products. While studies have demonstrated that its antitussive properties are equal to that of codeine (1,2), the compound is essentially devoid of the respiratory depressant effects and addiction liability of codeine. Recent studies have demonstrated that the O-demethylation of dextromethorphan exhibits a polymorphic pattern in humans which cosegregates with polymorphic debrisoquine hydroxylation (3–6). This observation has led to the suggestion that dextromethorphan, due to its innocuousness and ubiquitous availability, be used as a probe for debrisoquine hydroxylation polymorphism (5). Thus, in addition to its widespread use as a nonprescription antitussive agent, the use of this compound is likely to increase in pharmacogenetic studies.

After oral administration, dextromethorphan is subjected to extensive first-pass metabolism (7–9). A number of other important therapeutic agents which undergo extensive first-pass metabolism have been found to inhibit oxidative drug metabolism. For example, encainide (10), metoprolol (11), propafenone (12), propranolol (11), and verapamil (13) are all subject to extensive first-pass metabolism and have been shown to inhibit cytochrome P-450-dependent metabolism. Since dextromethorphan is also subject to extensive first-pass metabolism, we postulated that it may also inhibit drug metabolism. Stitzel *et al.* (14) found that dextromethorphan inhibited the elimination of hexobarbital in the isolated perfused rat liver. These same investigators, however, were unable to detect a significant effect of dextromethorphan on hexobarbital elimination *in vivo* (15). To study this phenomenon further, we examined the effect of dextromethorphan on the elimination of antipyrine, a model substrate for oxidative metabolism *in vivo*.

MATERIALS AND METHODS

Chemicals. Antipyrine was purchased from Aldrich Chemical Company (Milwaukee, Wis.). Dextromethorphan hydrobromide (Lot No. 825-405FB-00) was a gift from Pennwalt Corporation (Rochester, N.Y.). Propylene glycol and ethyl ether were obtained from VWR Scientific (Chicago, Ill.). All chemicals were used as received.

Animals and Treatment. Male Sprague Dawley rats weighing 194 to 235 g had an indwelling cannula implanted in the right jugular vein under light ether anesthesia 1 day prior to antipyrine administration (16). On the day of the study, animals were individually housed in plastic metabolism cages and antipyrine (20 mg/kg) dissolved in physiologic saline (10 mg/ml) was infused through the cannula at a rate of 0.34 ml/min. Serial blood samples (0.25 ml) were obtained through the cannula over a 5-hr period. Plasma was separated by centrifugation and stored at −20°C until analyzed by a high-performance liquid chromatographic (HPLC) method described previously (17). Preliminary experiments in which animals received dextromethorphan without anti-

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0724-8741/88/0700-0437$06.00/0

pyrine revealed that dextromethorphan administration did not result in any interfering peaks.

Animals received dextromethorphan hydrobromide, 100 mg/kg, or vehicle (propylene glycol) orally 1 hr prior to antipyrine administration. In a second experiment, another group of animals received the same dose of dextromethorphan or vehicle twice daily (between 7 and 8 AM and again between 4 and 5 PM) for 3 days preceding the experiment. Animals were administered an additional dose 1 hr prior to antipyrine administration on the study day. Preliminary studies in our laboratory indicated that this vehicle had no significant effect on the pharmacokinetics of antipyrine (data not shown), a result recently confirmed in humans (24).

Data Analysis. The initial antipyrine plasma concentration was calculated from the zero intercept of the plasma concentration versus time curve using unweighted nonlinear least-square regression. Statistical moment analysis was used to obtain the model-independent pharmacokinetic parameters (18). Pharmacokinetic parameters between control and treatment groups were compared using Student's two-tailed unpaired t test. A value of $P < 0.05$ was considered statistically significant. Data are presented as mean ± standard deviation.

RESULTS

Figure 1 illustrates the mean antipyrine plasma concentration versus time profile in control animals and those pretreated with a single oral dose of dextromethorphan hydrobromide, 100 mg/kg. The data in Table I indicate that there was no significant difference in any of the pharmacokinetic parameters between the two groups. The plasma concentration versus time profile in animals receiving multiple doses of dextromethorphan is illustrated in Fig. 2. As shown in Table I, rats pretreated with dextromethorphan hydrobromide, 100 mg/kg, twice daily exhibited a significantly higher clearance of antipyrine than did control animals. Antipyrine clearance was increased by 33% in the treated group com-

Table I. Effect of Oral Dextromethorphan Hydrobromide on the Pharmacokinetics of Antipyrine in the Rat[a]

Treatment	N	Pharmacokinetic parameter[b] CL (ml/min/kg)	$t_{1/2}$ (min)	V_{ss} (ml/kg)
Control	6	9.97 (1.50)	66.6	996 (245)
DM × 1[c]	5	9.37 (0.85)	70.7	993 (181)
Control	7	8.33 (0.80)	68.6	828 (69)
DM × 7[d]	6	11.04 (2.62)*	56.3	843 (79)

[a] CL, clearance; $t_{1/2}$, harmonic mean half-life; V_{ss}, steady-state volume of distribution; DM, dextromethorphan hydrobromide.
[b] Data are presented as mean (± SD).
[c] Animals received a single dose of vehicle (propylene glycol) or dextromethorphan hydrobromide, 100 mg/kg, 1 hr prior to antipyrine administration.
[d] Animals received vehicle or dextromethorphan hydrobromide, 100 mg/kg, twice daily for 3 days prior to antipyrine administration and again 1 hr prior to antipyrine administration.
* $P < 0.05$.

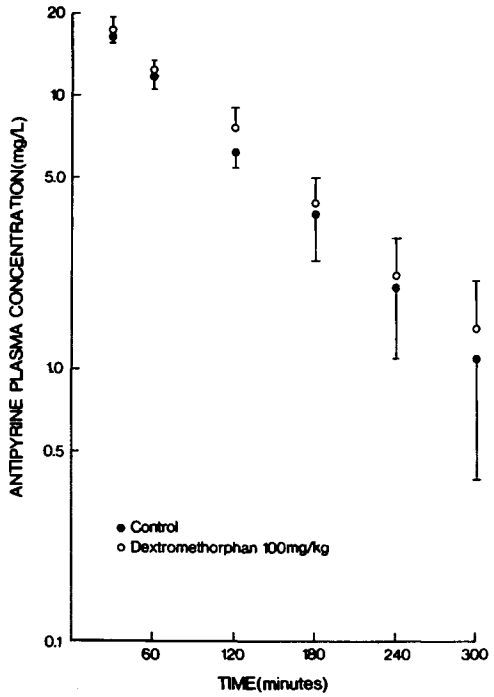

Fig. 1. Mean antipyrine plasma concentration versus time profile in animals which received a single dose of vehicle or dextromethorphan hydrobromide, 100 mg/kg, orally 1 hr prior to antipyrine administration. Bars represent 1 SD.

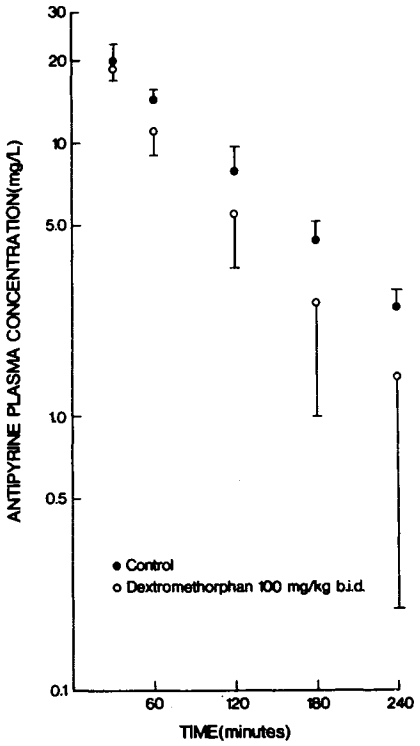

Fig. 2. Mean antipyrine plasma concentration versus time profile in animals which received vehicle or dextromethorphan hydrobromide, 100 mg/kg, twice daily for 3 days and 1 hr prior to antipyrine administration. Bars represent 1 SD.

pared to the control group (11.04 ± 2.62 vs 8.33 ± 0.80, respectively).

DISCUSSION

Previous studies have demonstrated that numerous drugs subject to extensive first-pass metabolism are capable of inhibiting cytochrome P-450-dependent hepatic metabolism. The relationship between first-pass metabolism and inhibition of drug metabolism is unclear. Most of the agents studied to date, however, exhibit some structural similarities (10–12). In an effort to determine whether this phenomenon was related to the chemical structure of these agents or the pharmacokinetic characteristic of extensive first-pass metabolism, we examined an agent which was structurally very different yet displayed similar pharmacokinetic characteristics. In addition to being subject to extensive first-pass metabolism, several of these agents have also been demonstrated to exhibit a polymorphic metabolic profile which cosegregates with debrisoquine hydroxylation (19–21). Thus, dextromethorphan was chosen as a model substrate since it undergoes extensive first-pass metabolism, exhibits a metabolic profile which cosegregates with debrisoquine hydroxylation, and is structurally dissimilar to previously studied agents.

Unlike other agents subject to extensive first-pass metabolism, we found that single-dose administration of dextromethorphan had no effect on the elimination of antipyrine. Since some agents may exhibit inhibition only after multiple-dose administration, we examined the effect of multiple doses of dextromethorphan. Interestingly, we found that dextromethorphan administration resulted in an induction of antipyrine clearance. The magnitude of induction observed (33%) was considerably less than that seen with other inducers. For example, 2 days of pretreatment with phenobarbital, 50 mg/kg/day, results in an approximately 200% increase in antipyrine clearance (22), while 3-methylcholanthrene, 18 mg/kg/day, for 3 days increases antipyrine clearance by about 140% (23). Thus, compared to these "classic" inducers, dextromethorphan would be characterized as a weak inducer in the rat.

Obviously, these results are difficult to extrapolate to the human situation. The dose of dextromethorphan, when used as an antitussive agent, ranges from 90 to 120 mg/day. Animals in the present study received 200 mg/kg/day. Our data suggest, however, that the phenomenon of inhibition of drug metabolism by agents subject to extensive first-pass metabolism may be dependent upon the chemical structure of the agents rather than their pharmacokinetic characteristics. Further studies with other agents which exhibit an extensive first-pass metabolism but are chemically dissimilar are needed to test this hypothesis.

ACKNOWLEDGMENTS

This work was supported in part by the Roland T. Lakey Education, Research and Development Fund. The technical assistance of Philip W. Knowlton and Mok-Thoong Chong is gratefully acknowledged. Dextromethorphan hydrobromide was generously supplied by Dr. Lewis P. Amsel, Division of Analytical and Pharmaceutical Services, Pennwalt Corporation.

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