Dextromethorphan: polymorphic serum pattern of the *O*-demethylated and didemethylated metabolites in man

Ö. MORTIMER¹, B. LINDSTRÖM², H. LAURELL³, U. BERGMAN^{2,4} & A. RANE^{1,2}

¹Division of Clinical Pharmacology, The University Hospital, Uppsala, ²Department of Drugs, The National Board of Health and Welfare, Uppsala, ³The Swedish Road and Traffic Research Institute, Linköping and

⁴Division of Clinical Pharmacology, Huddinge Hospital, Stockholm, Sweden

1 The interindividual differences in serum concentrations of dextromethorphan (DM) and its metabolites were studied in 29 healthy subjects given 120 mg orally. They were also phenotyped according to the urinary ratio of debrisoquine and 4-hydroxy-debrisoquine.

2 Four (14%) subjects were found to be poor metabolizers (PM) with a dextromethorphan/dextrorphan metabolite ratio in plasma of 3.6 or more compared with extensive metabolizers (EM) with a ratio of 0.11 or less. Significant levels of 3-hydroxymorphinan were measurable in all individuals except two, both of whom were PMs. This subdivision corresponded to the phenotype determined by the metabolic ratio of debrisoquine ($r = 0.92$).

3 Twelve of the 29 subjects reported adverse drug reactions after dextromethorphan administration compared with none after placebo.

Keywords dextromethorphan dextrorphan debrisoquine phenotyping plasma concentrations side effects

Introduction

Dextromethorphan (DM) is an antitussive opioid congener without the analgesic and addictive properties of narcotics (Jaffe & Martin, 1985). It undergoes polymorphic oxidation (Pfaff *et al.*, 1983; Küpfer *et al.*, 1984; Schmid *et al.*, 1985, Larrey *et al.*, 1987) and 10% of human subjects are reported to be poor metabolizers on the basis of the formation rate of the *O*-demethylated metabolite dextrorphan (D). This pathway is concordant with debrisoquine 4-hydroxylation (Küpfer *et al.*, 1984; Schmid *et al.*, 1985). Other metabolic routes of DM include *N*-plus *O*-demethylation to 3-hydroxymorphinan (3-HM) and *N*-demethylation to 3-methoxymorphinan (3-MM) (Pfaff *et al.*, 1983). These metabolic pathways have not been investigated in detail, particularly not by studies of metabolite concentrations in blood.

The highest recommended daily dose of DM is

120 mg. Adverse drug reactions (ADRs) such as ataxia, sleep disturbances, euphoria and hallucinations after intake of high single doses have been described (Dodds & Revai, 1967; Jasinski, 1970; Shaul *et al.*, 1977).

DM has been sold 'over-the-counter' in Sweden and other countries for many years. However, recent outbreaks of abuse of DM in young people and addicts as well as several case reports on adverse drug reactions have forced the Swedish Drug Control Agency to reintroduce prescription.

We have investigated the pattern of metabolism of DM in healthy volunteers and monitored the side effects. Driving performance after DM, noscapine and placebo was also studied. We have also investigated the cosegregation of DM-demethylation with debrisoquine hydroxylation.

Correspondence: Dr Ö. Mortimer, Division of Clinical Pharmacology, The University Hospital, S-751 85 Uppsala, Sweden

Methods

Thirty healthy volunteers between 20 and 40 years of age took part in a randomized, double-blind, placebo controlled cross-over study comparing driving performance after intake of dextromethorphan and noscapine, (data from the noscapine study are not reported here). The study was carried out after approval of The Ethics Committee of the University Hospital and informed consent was obtained from the subjects before the start of the study. There was a wash out period of 1 week between the different drug administrations. Identical capsules were used containing dextromethorphan, noscapine or placebo. The subjects were not allowed to take any other drug 1 week before and during the study.

After a standard breakfast dextromethorphan hydrobromide was administered as capsules, together with 100 ml of water, in consecutive doses of 30, 30 and 60 mg at 2.5 h intervals.

The subjects participated in a driving performance test which started 2 h after each dose of the drug. A sophisticated driving simulator was used (Nordmark *et al.*, 1985; Laurell *et al.*, 1986) and the test lasted for approximately 20 min. Any spontaneously reported adverse drug reactions (ADRs) were registered after each session.

Venous blood samples (10 ml) were collected 2.5 h after each dose. Serum was separated by centrifugation and frozen at -20°C .

One subject was withdrawn from analyses of DM due to sampling errors.

On a later occasion twenty-one of the subjects took 10 mg of debrisoquine orally (Declinax, Roche) and urine was then collected for 6 h.

Serum concentrations reported here refer to samples collected 2.5 h after the third dose, unless stated otherwise. When concentrations were at or below the lower limit of sensitivity of the analytical method, the value of this lower limit was used for calculation of the metabolic ratio.

Data are given as mean $\pm$ s.d. The statistical evaluation of the average speed of the driving test was by means of analysis of variance.

Analyses

Dextromethorphan, D and 3-HM were measured by two separate procedures. The chromatographic system used consisted of an M45 pump and a U6K injector from Millipore Waters (Milford, MA, USA). The detector was an FS970 spectrophotofluorometer (Spectra-Physics, Santa Clara, CA, USA) operated at an excitation wave-

length of 200 nm with no emission cut-off filter. The column (stainless steel 150×4.6 mm i.d.) was slurry packed with nucleosil-C 5 μ (Macherey-Nägel, Duren, GFR). The eluent consisted of an aqueous solution of laurylsulphate (2 mM) and sodium phosphate buffer (10 mM, pH 2.1) mixed with acetonitrile. For dextromethorphan analysis the percentage acetonitrile was 42% whereas for the metabolites it was 41%.

The plasma samples were extracted according to the method of East & Dye (1985). For the measurement of dextromethorphan the volume of hexane in the washing step was reduced to 7 ml, using hexane containing 0.1% of diethylamine instead of triethylamine.

The lower limits of determination were 1, 5 and 10 ng ml $^{-1}$ for DM, D and 3-HM, respectively.

The measurement of debrisoquine and its metabolite 4-hydroxy-debrisoquine was performed with a liquid chromatographic assay (Westwood *et al.*, 1986).

Results

There were large interindividual differences in serum concentrations of dextromethorphan, dextrorphan and 3-hydroxymorphinan (Table 1). When comparing data after each of the three doses the intra-individual variation in the metabolic ratio DM/D was moderate (up to three-fold) compared with the interindividual differences. The results after the third dose were chosen for phenotyping the subjects. This classification of phenotype was not affected by the sample time selected.

Four of 29 subjects (14%) had very low serum concentrations (range = 5–27 ng ml $^{-1}$) of D (the *O*-demethylated metabolite). The serum concentrations of DM were highest in these subjects (range = 64–98 $\mu\text{g ml}^{-1}$). In contrast, other subjects had high concentrations of D (range = 37–990 ng ml $^{-1}$) and low concentrations of DM (range = 1–41 $\mu\text{g ml}^{-1}$).

These two groups were characterized by a large difference in the DM/D ratio and were easily identified after the first dose of DM. The bimodal distribution pattern as observed after the third dose, displayed a more than 1000-fold difference in the metabolic DM/D ratio (Figure 1).

The four subjects with the highest DM concentrations and the lowest concentrations of D had ratios of DM/D in the range 3.6–15 and were designated as poor metabolizers (PM). The other subjects had ratios in the range 0.002–0.1 and were designated as extensive metabolizers (EM).

Table 1 Plasma concentrations of dextromethorphan (DM), dextrorphan (D) and 3-hydroxymorphinan (3-HM) after three consecutive doses of 30, 30 and 60 mg of DM. There were 29 healthy participants (characterized as extensive (EM) and poor (PM) metabolizers of DM), who took the doses at 2.5 h intervals. Values are mean and range of plasma drug concentrations (ng ml^{-1})

Dose	<i>DM</i> (ng ml^{-1})		<i>D</i> (ng ml^{-1})		<i>3-HM</i> (ng ml^{-1})	
	<i>EM</i> n = 25	<i>PM</i> n = 4	<i>EM</i> n = 25	<i>PM</i> n = 4	<i>EM</i> n = 25	<i>PM</i> n = 4
1	3.5 (1–12)	15 (11–20)	283 (5–422)	17 (5–37)	111 (20–176)	14 (10–27)
2	4.0 (1–14)	41 (25–48)	384 (15–678)	14 (5–19)	165 (20–326)	14 (10–28)
3	7.5 (1–41)	83 (64–98)	619 (37–990)	18 (5–27)	254 (20–414)	17 (10–37)

Table 2 Metabolic ratios of DM and its metabolites among 25 extensive and four poor metabolizers. Values are calculated from plasma concentration data

	<i>Dextrorphan</i> <i>Dextromethorphan</i>	<i>3-hydroxymorphinan</i> <i>Dextromethorphan</i>
Extensive metabolizers	9–430	6–101
Poor metabolizers	0.1–0.4	0.1–0.4
	<i>3-hydroxymorphinan</i> <i>Dextrorphan</i>	
Extensive metabolizers	0.3–1.3	
Poor metabolizers	0.6–1.4

Figure 1 Semilogarithmic frequency distribution histogram of dextromethorphan/dextrorphan metabolic ratios calculated from plasma concentration data of 29 healthy subjects.

Figure 2 Dextromethorphan *O*-demethylation vs the debrisoquine hydroxylation polymorphism in 21 subjects. Dextromethorphan metabolic ratios are plotted against the debrisoquine metabolic ratio ($r = 0.92$).

The four PMs and 17 of the EMs exhibited the same metabolic phenotypes with DM as with debrisoquine (Figure 2). This is in good agreement with the results of Schmid *et al.* (1985).

The ratio between 3-HM and DM also varied about 1000-fold. There was less variation (four-fold) in the ratio between the two metabolites (3-HM/D) as shown in Table 2.

No ADRs were reported during placebo treatment. Twelve of 29 subjects reported adverse drug reactions during DM administration. Usually the subjects complained of dizziness, vertigo, ataxia, nervousness, nausea and vomiting. These subjects included three of the four poor metabolizers and nine of the 25 extensive metabolizers.

The results of the driving tests did not reveal any statistically significant differences in driving performance between subjects treated with DM and subjects treated with placebo. Subjects reporting side-effects were also analyzed separately according to the results of the driving tests but no statistically significant differences were found.

Discussion

Our results confirm those of Pfaff *et al.* (1983) that DM is subject to polymorphic *O*-demethylation

to dextromethorphan, and also confirms that this drug oxidation polymorphism presumably is under similar genetic control to debrisoquine 4-hydroxylation. We also found that in addition to D the 3-HM metabolite was measurable at similar concentrations in the serum of 23 individuals. In two of four individuals who were classified as poor metabolizers, there were no measurable levels of 3-HM in the plasma. The relatively limited variation in the 3-HM/D ratio indicates that the further biotransformation of D by an *N*-demethylation to 3-HM is not rate limiting. If these reactions are catalyzed by different enzymes, our findings may be explained by differences in the kinetics of the two enzymes.

The peak serum concentrations of D and DM appear within 1–2 and 2–4 h, respectively (Pfaff *et al.*, 1983). Nevertheless the classification of PM and EM in our material was the same when other sampling times were applied. The present data are based on only one blood sample 2.5 h after the last dose.

Among the EM two subjects had nearly as high serum concentrations of DM as the PM and as high serum concentration of D as the EM. The DM/D ratios in these subjects were 0.11 and 0.08, respectively. Another subject had a low serum concentration of DM (2 ng ml⁻¹) but the serum concentration of D (5–15 ng ml⁻¹) was as low as in the poor metabolizers. He had a DM/D ratio of 0.1. This ratio is very approximate because the concentrations of DM and D are close to the limits of detection of the assays. It is possible that these individuals represent an intermediate group of subjects. Because of the large variation in metabolism it seems difficult to identify a third group by using single blood samples. Similarly, collection of urine up to 8 h after the dose did not contribute to the identification of this possible intermediate group (Schmid *et al.*, 1985).

Pfaff *et al.* (1983) found six of 46 (13%) healthy volunteers to be PM based on plasma concentrations and urinary excretion of DM. Schmid *et al.* (1985) found 9% to be PM in a group of 268 healthy volunteers as assessed on the basis of DM in urine during 8 h after dose. They found an antimode in the DM/D metabolic ratio of 0.3 separating the two phenotypes from each other. These values are nearly identical to our results obtained from serum concentration data. Pfaff *et al.* (1983) found a third group of subjects (6%) that had longer D elimination half-life (6.2 h compared with 1.2–2 h) in plasma and larger amounts of DM excreted in the urine as compared with the EM.

Similar to Schmid *et al.* (1985) we found a complete concordance between the results of the

debrisoquine and the dextromethorphan phenotyping test. Thus based on our limited material the frequency of PMs of debrisoquine in our study is similar to what has previously been published in a Swedish population (Steiner *et al.*, 1985).

The plasma concentrations of 3-HM varied to about the same extent as D. Thus, the 3-HM/D ratio varied between 0.3 and 1.40 and there was no difference in this ratio between the PM and EM groups. This is in good agreement with results of the metabolite ratio in urine reported by Pfaff *et al.* (1983). This ratio did not reflect the metabolic phenotype.

If 3-HM is formed via 3-MM then it must be presumed that the formation of 3-HM is rapid enough not to leave any measurable levels of 3-MM in plasma. Unpublished results from our laboratory have shown that 3-MM and D formation rates are of the same order of magnitude in human liver preparations incubated with DM (Mortimer *et al.*, in preparation).

ADRs were reported in three of four PMs.

The limited number of volunteers precludes any possibility of relating the metabolic phenotype to the liability to develop ADRs.

The total dose of 120 mg DM equals the highest recommended daily dose (Swedish PDR). This amount was administered in 5 h to our subjects and therefore, a relative high frequency of ADRs was observed.

In conclusion, this study has shown that patients may be classified into PM and EM on the basis of plasma metabolite analyses. An additional didemethylated metabolite was also found to be present and to co-vary with the D concentrations. Further studies are needed to show if particular side-effects may be linked to phenotype.

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