THE INFLUENCE OF SMOKING ON THE INTER-SUBJECT VARIATION IN PENTAZOCINE ELIMINATION

D.P. VAUGHAN* & A.H. BECKETT

Department of Pharmacy, Chelsea College, University of London,
Manresa Road, London SW3

D.S. ROBBIE

Pain Clinic, Royal Marsden Hospital, Fulham Road, London SW3

- 1 The cumulative urinary excretion over 24 h of pentazocine, under conditions of acidic urinary pH, has been measured in smokers and non-smokers using both male and female subjects (seventy subjects in total).
- 2 A restricted urban population was studied.
- 3 An overall three-fold inter-subject variation in elimination was observed.
- 4 The cumulative urinary excretion of pentazocine was normally distributed in both smokers and non-smokers.
- 5 Smokers metabolize 40% more pentazocine than non-smokers.
- 6 It is concluded that induction is principally responsible for the observed subject variability.

Introduction

Even under conditions of acidic urinary pH, designed to minimize intra-subject variations, the blood levels and cumulative urinary excretion of pentazocine show considerable inter-subject variations (Beckett, Kourounakis, Vaughan & Mitchard, 1970; Vaughan & Beckett, 1974). Recently, the inter-subject variations in pentazocine elimination have been attributed to individual variations in metabolic oxidation rates (Vaughan & Beckett, 1974).

Clinically, the dose requirements for pentazocine as a supplement to nitrous oxide/oxygen anaesthesia are greater in smokers than non-smokers and are also higher in urban dwelling patients as compared with rural dwellers (Keer-Szanto & Pomeroy, 1971). These links between environment and pentazocine dosage requirements suggest that the oxidative enzymes responsible for pentazocine elimination are induced in smokers and urban subjects. In a previous study using only a small sample population, no distinct differences in the cumulative urinary excretion of orally administered pentazocine between smokers and non-smokers were observed (Vaughan & Beckett, 1974).

We have therefore investigated, in a larger urban

population, the elimination of pentazocine by smokers and non-smokers in order to establish the relative influence of environmental factors on pentazocine metabolism.

Methods

Subjects

Healthy Caucasian male and female volunteers whose ages ranged from 21-42 years were studied. None of the subjects had a previous history of jaundice or other major disease and none were receiving medication with the exception of oral contraceptive agents. Only subjects who worked in and had been resident in the Central London area for a minimum period of 2 years were investigated.

Experimental technique

The urine of each subject was maintained at an acidic pH (pH < 5.0), to minimize kidney tubular reabsorption of pentazocine, by oral administration of ammonium chloride (Beckett, 1966; Beckett & Tucker, 1966).

Urinary pH was checked prior to drug administration and subjects whose urinary pH was not sufficiently acidic (i.e. pH < 5.0) did not receive pentazocine.

* Present address: Department of Pharmacy, Sunderland Polytechnic, Sunderland SR1 3SD.

Figure 1 The 24 h cumulative urinary excretion of pentazocine (% dose), under conditions of an acidic urinary pH, in male smokers and non-smokers following an intramuscular dose (pentazocine base 30 mg).

Figure 2 The 24 h cumulative urinary excretion of pentazocine (% dose), under conditions of an acidic urinary pH, in female smokers and non-smokers following an intramuscular dose (pentazocine base 30 mg).

After pentazocine administration, the total (24 h) urine was collected as follows; at 2 h intervals for 14 h, on retiring, on rising and a final sample at 24 hours. Subjects whose urinary pH were not acidic ($\text{pH} < 5.0$) throughout the study were excluded from the trial. The protocol was approved by the Ethics Committee of the Royal Marsden Hospital.

Dosage and route

A single dose of pentazocine base (30 mg) as the lactate in aqueous solution (1 ml) was injected into the *gluteus maximus*, upper and outer quadrant.

Figure 3 Comparison of the 24 h cumulative urinary excretion of pentazocine (% dose), under conditions of an acidic urinary pH, in male and female non-smokers following an intramuscular dose (pentazocine base 30 mg).

Analytical method

Duplicate aliquots of the bulked urine samples were analyzed for pentazocine by the gas liquid chromatographic method of Vaughan & Beckett (1974).

Control urine samples, from each subject, were also analyzed by the same procedure to ensure the absence of interfering substances and other basic drugs.

Results

Urinary pH

Six subjects were excluded from the trial because of a failure to achieve or maintain an acidic urinary pH throughout the 24 h collection period. During the trial period, urinary pH remained within the range pH 4.5-5.0.

Chromatographic analysis

No control urine samples when assayed for pentazocine gave chromatographic peak at or close to the retention times of pentazocine or its internal standard (dipipanone).

Cumulative urinary excretion

The cumulative urinary excretion of pentazocine, expressed as a percentage of the administered dose, for each subject are presented in Figures 1 and 2: Figure 1 gives the results for male smokers ($n = 21$) and non-smokers ($n = 21$); Figure 2 gives the results for female smokers ($n = 13$) and non-smokers ($n = 15$). In Figure 3 the results for male and female non-smokers are compared.

Table 1 The mean values of pentazocine excreted in urine, % dose in 24 h, and the statistical parameters used for comparing the inter-subject variations in the drug's elimination

<i>Male subjects</i>	
<i>Smokers</i>	<i>Non-smokers</i>
$n = 21$	$n = 21$
$D = 0.134$	$D = 0.138$
mean = 10.32%	mean = 14.2%
$S^2 = 7.96$	$S^2 = 5.736$
<i>Female subjects</i>	
<i>Smokers</i>	<i>Non-smokers</i>
$n = 13$	$n = 15$
$D = 0.179$	$D = 0.157$
mean = 11.78%	mean = 16.4%
$S^2 = 12.62$	$S^2 = 16.69$
F-test	
Male smokers v male non-smokers	$F_{20}^{20} = 1.39$
Female smokers v female non-smokers	$F_{12}^{14} = 1.32$
Male non-smokers v female non-smokers	$F_{14}^{20} = 2.91$
t test	
Male smokers v male non-smokers	$t = 4.8$ ($P < 0.001$)
Female smokers v female non-smokers	$t = 3.16$ ($0.001 < P < 0.005$)
Behrens-Fisher test	
Male non-smokers v female non-smokers: $\theta = 2.02$, $63^\circ < \theta < 64^\circ$ is not significant at a 5% level ($\theta \approx 2.06$ for significance).	

D Kolmogorov-Smirnov one sample test for significant deviation from normal distribution

S^2 Sum of the squares of the deviation

Statistical analysis

For the purpose of statistical analysis, the results of pentazocine excretion from the test population are divided into four groups (i.e. male smokers, male non-smokers, female smokers and female non-smokers). The statistical parameters obtained for each group are given in Table 1.

There is no evidence (Kolmogorov-Smirnov one sample test for significant deviation from normal distribution, see D in Table 1; in each case the value of D could have occurred by chance by a probability > 0.2) to suggest that the four groups of subjects are not drawn from normally distributed populations. Consequently, an *F*-test is appropriate to establish if the variances between pairs of groups differ significantly from each other. The *F* values demonstrate that the total variance in the male and female population are sufficiently similar to permit the use of a *t*-test for comparing the mean sample differences between smokers and non-smokers. The value of *F* for the

population of male and female non-smokers indicates that a *t*-test is inappropriate to compare the mean pentazocine excretion values in these two groups; an appropriate test is a Behrens-Fisher test.

The data from male smokers were not compared with the data from female smokers since other variables (i.e. the number of cigarettes smoked) could yield an erroneous statistical parameter.

Discussion

Pentazocine is not excreted in significant amounts ($< 1\%$ of the administered dose) in the faeces (Beckett *et al.*, 1970). Consequently, the 24 h cumulative urinary excretion of pentazocine obtained when the urinary pH is acidic is used to compare the relative metabolic elimination of the drug in smokers and non-smokers. This is done for the following reasons:

(a) Considerable intra-subject variation in the

cumulative urinary excretion of pentazocine is observed under conditions of uncontrolled urinary pH. However, when the kidney tubular reabsorption of this weakly basic drug is minimized by maintenance of an acid pH, intra-subject variations in urinary elimination are negligible and the excretion of pentazocine is independent of urinary volume (Vaughan & Beckett, 1974, Vaughan, 1972).

(b) Under controlled acidic conditions, the excretion of pentazocine is complete in 24 h and the urinary excretion rate is directly related to the blood levels (Beckett *et al.*, 1970).

(c) Similar inter-subject variation in the cumulative urinary excretion of pentazocine are observed both after oral and parenteral drug administration (Beckett *et al.*, 1970), indicative of differences in the metabolism of the drug rather than differences in the absorption of the drug.

(d) The blood level time curve of pentazocine is described by a multiple exponential function consistent with a three-compartment model and the terminal drug half-life ($T_{1/2}$) is insensitive to variations in the elimination rate. In contrast, the area below the blood-level time curve and cumulative urinary excretion are sensitive indices of changes in metabolic elimination (Vaughan & Beckett, 1974).

(e) The analgesic effect is directly related to the blood levels of pentazocine (Berkowitz, Asling, Shnider & Way, 1969).

(f) The relative urinary excretion of pentazocine following oral and parenteral administration accurately predicts the clinical efficacy of the drug after oral administration (Beckett *et al.*, 1970).

In the urban population sampled, there was a significant difference in the urinary elimination of pentazocine between smokers and non-smokers. Smokers eliminate 40% less pentazocine than non-smokers (Table 1). Nicotine releases anti-diuretic hormone and thus smokers may have a reduced urine flow rate. Such a reduction in urine volume could diminish renal drug clearances. However, under conditions of an acidic urinary pH, the excretion of pentazocine is independent of urinary volume (Vaughan & Beckett, 1974). Also there is no significant difference (5% level) between the mean urinary volumes of smokers and non-smokers. Consequently, in subjects who excrete different amounts of pentazocine the relative urinary elimination (% dose in 24 h) reflects their relative metabolic rates.

Assuming that the difference in the mean cumulative urinary excretion of unchanged pentazocine is related to plasma drug concentrations, the differences in the mean cumulative urinary excretion of unchanged drug (Table 1)

indicates that both male and female smokers would require 40% more pentazocine than non-smokers to achieve a given analgesic effect. The latter estimate of possible dosage requirement is in agreement with a clinical estimate of a 50% higher dosage requirement in smokers (Keeri-Szanto & Pomeroy, 1971).

Pentazocine is extensively metabolized by oxidation (Pittman, Rosi, Cherniak, Merola & Conway, 1969) and only a small percentage is excreted as its glucuronide (Vaughan & Beckett, 1974). The observed differences in elimination (Figure 1) suggest that tobacco smoking induces the liver enzymes responsible for drug oxidation. Enhanced drug metabolism resulting from enzyme induction, caused by smoking, has previously been reported in man, e.g. nicotine (Beckett & Triggs, 1967) and phenacetin metabolism (Pantuck, Hsiao, Maggio, Nakamura, Kuntzman & Conney, 1974). A decreased clinical efficacy of the analgesic propoxyphene has also been observed in cigarette smokers (Boston Collaborative Drug Surveillance Program, 1973). These observations indicate that enhanced drug metabolism and reduced clinical response in smokers may be a frequent phenomena for drugs metabolized by oxidative routes.

Female non-smokers excreted 1.5% more pentazocine than male non-smokers (Figure 3). However, the difference is not statistically significant (see Table 1, at a 5% level $\theta \approx 2.06$ for significance) and a sex linked variation is therefore not established.

An overall three-fold inter-subject variation in pentazocine elimination was observed for both male and female subjects regardless of their smoking habits, i.e. a much greater variation than that observed between smokers and non-smokers. A higher incidence of side effects has been associated with subjects who excrete the most pentazocine (Berkowitz *et al.*, 1969; Burt & Beckett, 1971; Vaughan & Beckett, 1974), but in all the latter studies no controlled assessment of side effects was attempted. However, adjustment of a patient's dosage could lead to a better therapeutic use of pentazocine and a lower incidence of side effects in clinical practice.

The variation in the elimination of pentazocine in the general population may be larger than that observed in the restricted urban population reported herein.

From limited observations, a bimodal distribution in pentazocine elimination has been suggested (Mitchard, 1971). However, in the present study the cumulative excretion of pentazocine was normally distributed and no evidence for a poly-modal distribution was observed (see Table 1). This normal distribution in

the four groups of subjects indicates that a direct genetical influence is not responsible for the observed variability in elimination or that such a factor, if present, is concealed by other factors, e.g. environmental induction.

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