Br. J. clin. Pharmac. (1991), **31**, 643–647 ADONIS 030652519100115K

A comparison of the pharmacokinetics of codeine and its metabolites in healthy Chinese and Caucasian extensive hydroxylators of debrisoquine

Q. Y. YUE, J. O. SVENSSON, F. SJÖQVIST & J. SÄWE
Department of Clinical Pharmacology, Huddinge University Hospital, Karolinska Institute, S-141 86 Huddinge, Sweden

1 The kinetics of codeine and metabolites were studied in eight unrelated healthy Chinese subjects following a single oral dose of 50 mg codeine phosphate. The data were compared with those from eight Caucasian subjects who were matched with the Chinese group according to their metabolic ratio (MR) of debrisoquine.

2 Mean values of C_{max} (445 nmol l^{-1}) and AUC (1660 nmol l^{-1} h) of codeine in the Chinese were significantly higher than those in the Caucasians (292 nmol l^{-1} and 1010 nmol l^{-1} h). Thus plasma clearance was significantly lower ($P < 0.02$) and the plasma half-life was longer ($P < 0.05$) in the Chinese.

3 Partial clearance by glucuronidation was significantly lower (0.79 ± 0.14 s.d. *vs* 1.42 ± 0.48 s.d. l h^{-1} kg^{-1}) in Chinese than in Caucasians.

4 The total urinary recovery of drug-related material in 48 h urine was similar in Chinese (82.2%) and Caucasians (84.4%). The recovery of unchanged codeine was significantly higher in Chinese (5.7%) than in Caucasians (3.3%).

5 The AUC ratios of codeine relative to its 6-glucuronide, morphine and norcodeine were 1:9, 35:1 and 4:1, respectively in Chinese. The corresponding ratios in Caucasians were 1:15, 50:1 and 6:1.

6 There was no significant difference between Chinese and Caucasians in the renal clearances of codeine and its primary metabolites.

7 Large interethnic differences in the kinetics of codeine have been shown. The Chinese are less able to metabolise codeine mainly because of a lower efficiency in glucuronidation.

Keywords codeine metabolism pharmacokinetics glucuronidation demethylation ethnic differences Caucasians Chinese

Introduction

Several studies have indicated important interethnic differences in drug metabolism and response. Recently, Zhou *et al.* (1989) reported a higher sensitivity to, but more efficient metabolism of, propranolol in Chinese compared with Caucasians. Another example is the finding of a larger volume of distribution and greater plasma clearance of diphenhydramine accompanied by less sedation and deterioration in psychomotor performance in Orientals relative to Caucasians (Spector *et al.*, 1980). A smaller apparent volume of distribution of diazepam has been reported in Chinese, probably reflecting their lower body mass (fat and stature), compared with that in Caucasians (Ghoneim *et al.*, 1981; Kumana *et al.*, 1987). Furthermore, a slower metabolism of diazepam has recently been shown in Chinese, and a difference in the substrate specificity of S-mephenytoin hydroxylase has been suggested (Zhang *et al.*, 1990). The clearance of paracetamol was found to be lower in Asians than in Europeans, probably the result of environmental differences (Mucklow *et al.*, 1980). In addition, differences exist between Oriental and Caucasian populations in the frequency of poor metabolisers of drugs that are metabolised by debrisoquine hydroxylase (Kalow *et al.*, 1980; Lou *et al.*, 1987; Yue *et al.*, 1988, 1989a,b) and by S-mephenytoin hydroxylase (Horai *et al.*, 1989; Nakamura *et al.*, 1985).

Correspondence: Dr J. Säwe, Department of Clinical Pharmacology, Huddinge University Hospital, Karolinska Institute, S-141 86 Huddinge, Sweden

Codeine is metabolised mainly by glucuronidation to codeine-6-glucuronide (C6G); minor routes of metabolism include *O*-demethylation to morphine (M) and *N*-demethylation to norcodeine (NC) (Adler *et al.*, 1955; Guay *et al.*, 1987, 1988; Rogers *et al.*, 1982; Yue *et al.*, 1989b,c). We have previously reported significant differences in the urinary excretion of codeine as well as of C6G in 133 healthy Chinese compared with 149 Swedish Caucasians (Yue *et al.*, 1989b). In order to understand this interethnic difference more clearly, we have studied the pharmacokinetics of codeine and its metabolites with a specific h.p.l.c. method in Chinese subjects and compared the data with those obtained in Caucasians (Yue *et al.*, 1991).

Methods

Eight unrelated healthy Chinese (three women and five men) who have been staying in Sweden as visiting scientists for less than 5 years participated in the study. They were previously phenotyped with debrisoquine using the method of Lennard *et al.* (1977). Their individual characteristics and debrisoquine metabolic ratios are shown in Table 1. None was taking any medication. One volunteer smoked (10 cigarettes per day) and all were considered to be healthy on the basis of physical examination and blood tests. All subjects gave their written informed consent to participate in the study, which was approved by the Ethics Committee of the Huddinge Hospital.

The Caucasian control subjects are described in detail in a companion paper (Yue *et al.*, 1991). They were all extensive hydroxylators of debrisoquine.

Following an overnight fast, each subject received a single oral dose of 50 mg codeine phosphate (two 25 mg tablets, Kodein®, ACO). A standard lunch was provided 4 h after drug intake. Blood samples were collected in heparinized Vacutainer® tubes before and at 0.17, 0.33, 0.5, 0.67, 1, 1.5, 2, 3, 4, 5, 7, 9, 11 and 24 h after the dose. The blood samples were centrifuged and plasma was stored at −20° C until analysis. Serial urine samples were collected at 0–2, 2–4, 4–6, 6–8, 8–10, 10–12, 12–24, 24–36 and 36–48 h. Urine volumes and pH were measured and aliquots were stored at −20° C until analysed.

Table 1 Individual characteristics and debrisoquine metabolic ratios of eight Chinese healthy volunteers

Subject	*Age (years)*	*Sex*	*Body weight (kg)*	*Debrisoquine metabolic ratio*
1	45	M	63	0.41
2	27	M	59	0.24
3	38	M	60	0.51
4	34	M	81	1.40
5	33	F	44	3.86
6	30	F	57	0.20
7	36	F	59	0.88
8	32	M	61	4.14
Mean	34		61	1.46
s.d.	5		10	1.62

Codeine and its seven known metabolites morphine (M), M-3-glucuronide (M3G), M-6-glucuronide (M6G), normorphine (NM), codeine-6-glucuronide (C6G), norcodeine (NC), and NC-glucuronide (NCG) were measured in plasma and urine using ion-pair high performance liquid chromatography according to a modification of the method of Svensson (1986) (Yue *et al.*, 1989b,c).

Pharmacokinetic calculations were performed as described by Yue *et al.* (1991).

Metabolic ratios (MRs) were calculated from both plasma and urine data as follows:

$MR_{glucuronidation}$ = codeine/C6G;
$MR_{O\text{-demethylation}}$ = codeine/(M+M3G+M6G+NM);
$MR_{N\text{-demethylation}}$ = codeine/(NC+NCG+NM).

The unpaired Student's *t*-test and a U-test for *O*-demethylation data were used for comparisons between the two ethnic groups.

Results

Significantly higher C_{max} (445 ± 120 and 292 ± 95 nmol l^{-1}; $P < 0.02$) and higher AUC values (1660 ± 300 and 1010 ± 390 nmol l^{-1} h; $P < 0.005$) (Figure 1) and lower plasma clearances (1.26 ± 0.22 and 2.10 ± 0.84 l h^{-1} kg^{-1}; $P < 0.02$) were observed in the Chinese compared with the Caucasian subjects. The plasma half-life of codeine was longer in the Chinese than in the Caucasians (2.94 ± 0.49 and 2.34 ± 0.58 h; $P < 0.05$, Table 3). There was no difference between Chinese and Caucasians in the AUC of C6G (Figure 2). However, the half-life of this metabolite was longer in Chinese ($P < 0.05$, Table 3). The partial metabolic clearance by glucuronidation was significantly lower (0.79 ± 0.14 and 1.42 ± 0.48 l h^{-1} kg^{-1}; $P < 0.005$) (Table 2), while the MRs of glucuronidation calculated from both AUC and urine values were higher (0.11 ± 0.04 and 0.067 ± 0.024 for AUC; $P < 0.01$; 0.095 ± 0.04 and 0.049 ± 0.024 for urine; $P < 0.02$) in the Chinese. The correlation coefficients between MR_{AUC} and MR_{urine} for glucuronidation were 0.78 in Chinese and 0.93 in Caucasians.

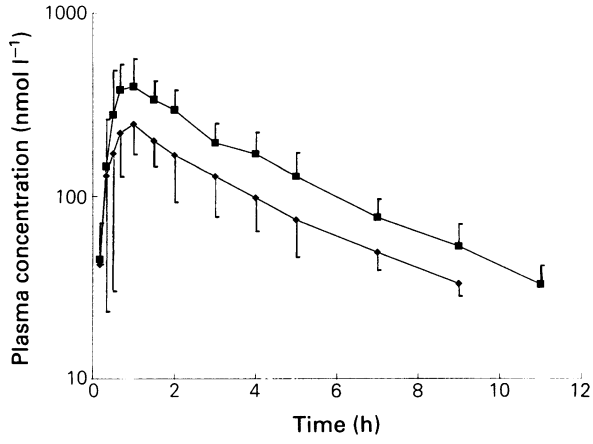

Figure 1 Plasma concentration-time curves of codeine in eight Chinese (■) and eight Caucasian (◆) subjects after a single oral 50 mg dose of codeine phosphate (mean ± s.d.).

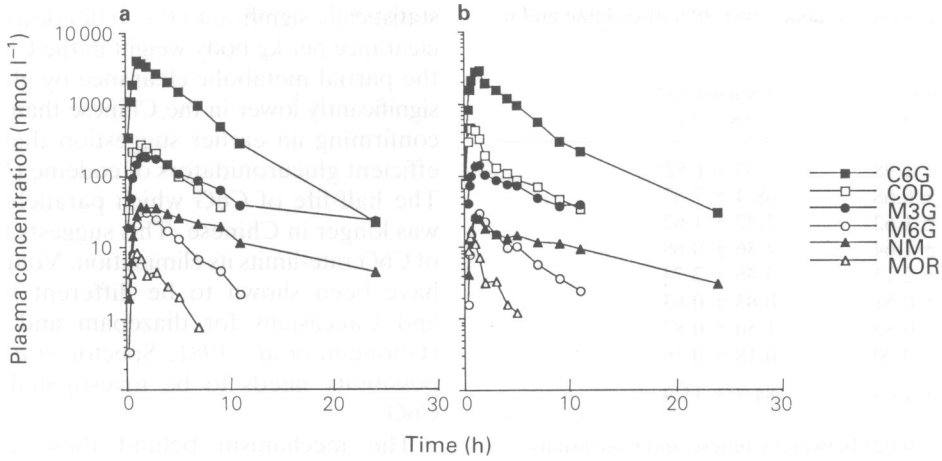

Figure 2 Plasma concentration-time curves of codeine and its metabolites in a representative Caucasian extensive metaboliser (EM) of debrisoquine (a) and a Chinese subject (b) after a single oral 50 mg dose of codeine phosphate. Data for NC and NCG were omitted for the sake of clarity.

Table 2 Age, bodyweight, some kinetic parameters and MRs of codeine in Chinese and Caucasian EM (mean ± s.d.)

	Chinese	*Caucasians*[a]	P
Age (years)	34.4 ± 5.5	33.4 ± 3.9	NS
DB MR[b]	1.46 ± 1.62	1.60 ± 1.72	NS
Body weight (kg)	61 ± 10	66 ± 10	NS
Plasma clearance ($l\ h^{-1}\ kg^{-1}$)	1.26 ± 0.22	2.10 ± 0.84	< 0.02
Partial metabolic clearance ($l\ h^{-1}\ kg^{-1}$)			
Glucuronidation	0.79 ± 0.14	1.42 ± 0.48	< 0.005
O-demethylation	0.091 ± 0.035	0.124 ± 0.098	NS
N-demethylation	0.113 ± 0.039	0.174 ± 0.079	NS

[a] Data of Caucasian extensive metabolisers (EM) of debrisoquine are from Yue *et al.* (1991).
[b] DB MR: debrisoquine metabolic ratio.

Table 3 Kinetic parameters of codeine and its three major metabolites after single oral 50 mg dose of codeine phosphate in Chinese and Caucasian EM[a] (mean ± s.d.)

	Codeine			*C6G*			*M*			*NC*		
	Chinese	*Caucasian*	P	*Chinese*	*Caucasian*	P	*Chinese*	*Caucasian*	P	*Chinese*	*Caucasian*	P
C_{max} ($nmol\ l^{-1}$)	445 ±120	292 ±95	< 0.02	3090 ±512	3610 ±640	NS	16.6 ±11.9	8.4 ±8.2	NS	65 ±32	41 ±18	NS
t_{max} (h)	1.06 ±0.42	1.0 ±0.38	NS	1.54 ±0.39	1.21 ±0.33	NS	0.81 ±0.34	0.83 ±0.25	NS	1.11 ±0.52	0.88 ±0.32	NS
AUC ($nmol\ l^{-1}\ h$)	1660 ±303	1010 ±391	< 0.005	15200 ±2780	15200 ±2690	NS	48 ±39	20 ±20	NS	410 ±329	163 ±87	NS
$t_{½}$ (h)	2.94 ±0.49	2.34 ±0.58	< 0.05	3.44 ±0.50	2.79 ±0.50	< 0.05	2.72 1.49	2.10 1.61	NS	3.75 1.83	2.62 1.32	NS
CL_R ($l\ h^{-1}\ kg^{-1}$)	0.047 0.023	0.051 0.023	NS	0.095 0.016	0.089 0.020	NS	0.13 0.042	0.16 0.099	NS	0.18 0.093	0.20 0.092	NS

[a] Data of Caucasian extensive metabolisers (EM) of debrisoquine are from Yue *et al.* (1991).

The urinary MR of *N*-demethylation was higher in Chinese (0.67 ± 0.20) than in Caucasians (0.43 ± 0.25) ($P < 0.05$). However, there was no difference between the two ethnic groups in partial metabolic clearance by *N*-demethylation (Table 2).

No significant difference was observed with regard to the *O*-demethylation reaction between the two ethnic groups. Both groups showed large interindividual variation in *O*-demethylation (Tables 3 and 4).

The urinary recovery of drug-related material in 48 h urine was similar in Chinese (82.2 ± 15.6% of dose) and Caucasians (84.4 ± 15.9%; $P > 0.05$, Table 4). The recovery of unchanged codeine, however, was significantly higher in Chinese than in Caucasians (5.71 ± 1.98 and 3.33 ± 1.52% of dose; $P < 0.02$). There was no significant difference in the urinary recovery of the metabolites (Table 4) nor in renal clearances of codeine and its metabolites (Table 3).

Table 4 Urinary recovery (% dose) over 48 h of codeine and its metabolites

	Chinese (n = 8)	*Caucasians*[a] (n = 8)
Cod	5.71 ± 1.98	3.33 ± 1.52*
C6G	62.0 ± 6.68	68.4 ± 7.67
NC	3.26 ± 1.62	2.32 ± 1.62
NCG	3.70 ± 1.64	4.36 ± 0.68
M3G	4.20 ± 2.13	3.46 ± 2.74
M6G	0.98 ± 0.51	0.83 ± 0.63
NM	2.02 ± 0.83	1.50 ± 0.87
Mor	0.32 ± 0.20	0.18 ± 0.16
Total	82.2 ± 15.6	84.4 ± 15.9

*Student's *t*-test ($P < 0.02$) between Chinese and Caucasians.
[a] Data for Caucasian extensive metabolisers (EM) of debrisoquine are from Yue *et al.* (1991).

In Chinese, the AUC ratios of codeine relative to C6G, M and NC were 1 : 9, 35 : 1 and 4 : 1, respectively. The corresponding values in Caucasians were 1 : 15, 50 : 1 and 6 : 1 (Table 3).

Four of the eight Chinese volunteers experienced slight tiredness or dizziness and one of the Caucasians reported tiredness.

Discussion

A main aim of this study was to compare the capacity to glucuronidate codeine in Chinese and Caucasian subjects. It is known that *O*-demethylation of codeine co-segregates with the hydroxylation of debrisoquine both *in vivo* (Chen *et al.*, 1988; Yue *et al.*, 1988, 1989a,c) and *in vitro* (Dayer *et al.*, 1988; Mortimer *et al.*, 1990). It is also known that the frequency of poor metabolisers of these drugs is different in Chinese and Caucasian populaions with regard to both phenotyping and genotyping determinations (Lou *et al.*, 1987; Yue *et al.*, 1989a,b). In an earlier study including Caucasians, we have demonstrated that poor hydroxylators of debrisoquine excreted more C6G and NC than extensive metabolisers in urine collected 8 h after oral codeine, and that this phenomenon might be a consequence of a low expression of the *O*-demethylation pathway (Yue *et al.*, 1989c). To avoid this genetic influence on the pharmacokinetics of codeine, we matched our two ethnic groups according to their debrisoquine MRs (Table 3).

Possible genetic differences in the renal tubular secretion of debrisoquine have been suggested since the mean amount of drug that is excreted unchanged shows wide population differences (Kalow, 1984). In the present study, however, we did not observe any significant difference between the two ethnic groups in the renal clearance of codeine nor any of its metabolites (Table 3). In addition, there were higher C_{max} and AUC values and lower plasma clearances in the Chinese subjects, indicating that they were less able to metabolise codeine. The nonsignificant 8% difference in mean body weights does not influence the interpretation as there was a statistically significant ($P < 0.02$) decrease also in plasma clearance per kg body weight in the Chinese. In addition, the partial metabolic clearance by glucuronidation was significantly lower in the Chinese than in the Caucasians, confirming an earlier suggestion that Chinese are less efficient glucuronidators of codeine (Yue *et al.*, 1989b). The half-life of C6G which paralleled that of codeine was longer in Chinese. This suggests that the formation of C6G rate-limits its elimination. Volumes of distribution have been shown to be different between Orientals and Caucasians for diazepam and diphenhydramine (Ghoneim *et al.*, 1981; Spector *et al.*, 1980), and this possibility needs to be investigated for codeine and C6G.

The mechanism behind these ethnic differences remains to be studied. Glucuronidation reactions are catalysed by a group of isoenzymes which have different but overlapping specificities. Glucuronidation of codeine has been shown to be induced by smoking and by oral contraceptive use (Yue *et al.*, 1989b), and to be inhibited *in vitro* by commonly used drugs such as M, chloramphenicol, diazepam and amitriptyline (Yue *et al.*, 1990a). This *in vitro* study has also demonstrated a correlation between the glucuronidation of codeine and that of M. Hence the findings of the present study with codeine might be predictive for the glucuronidation of M.

Urine pH has been found to correlate directly with the urinary excretion of C6G and NCG and inversely with that of codeine. However, there was no significant difference in urine pH between 149 Caucasians and 133 Chinese healthy volunteers (Yue *et al.*, 1989b). The Chinese volunteers in this study ate more Chinese food than Western food and kept the Chinese habits of drinking more tea than coffee. Thus, environmental factors could contribute to the observed interethnic difference in glucuronidation. The higher urinary MR for *N*-demethylation in Chinese observed in this study was consistent with the finding of a previous population study (Yue *et al.*, 1989b). The failure to show any difference between Chinese and Caucasians in plasma MR or partial clearance by *N*-demethylation may reflect the relatively small sample size of the present study.

Several metabolites of codeine, including M, M6G, NM and NC, have been shown to have analgesic effects (Lasagna & De Kornfeld, 1958; Miller & Anderson, 1954; Osborne *et al.*, 1988; Sanfilippo, 1948). On the other hand, codeine itself could account for most of its analgesic or side effects in view of its relatively high plasma concentration (Quiding *et al.*, 1986). We have observed a 50% increase in C_{max} and AUC in the Chinese subjects, which might be of some clinical importance. It may be significant that lower doses of codeine have been recommended for Chinese subjects (Jiang, 1984) compared with Caucasians. The analgesic potency of C6G in unknown.

In conclusion, we have shown a large interethnic difference in the pharmacokinetics of codeine. Chinese subjects are less able to metabolise this drug, due to a lower efficiency in glucuronidation.

The work was supported by the Swedish Research Council (3902) and the Swedish Cancer Society (1910-B88-01V). Samples of codeine metabolites were kindly provided by the National Institute of Drug Abuse, USA.

References

Adler, T. K., Fujimoto, J. M., Way, E. L. & Baker, E. M. (1955). The metabolic fate of codeine in man. *J. Pharmac. exp. Ther.*, **114**, 251–262.

Chen, Z. R., Somogyi, A. A. & Bochner, F. (1988). Polymorphic *O*-demethylation of codeine. *Lancet*, **ii**, 914–915.

Dayer, P., Desmeules, J., Leemann, T. & Striberni, R. (1988). Bioactivation of the narcotic drug codeine in human liver is mediated by the polymorphic monooxygenase catalyzing debrisoquine 4-hydroxylation (cytochrome P-450 db1/bufl). *Biochem. Biophys. Res. Commun.*, **152**, 411–416.

Ghoneim, M. M., Korttila, K., Chiang, C. K. (1981). Diazepam effects and kinetics in Caucasians and Orientals. *Clin. Pharmac. Ther.*, **29**, 749–756.

Guay, D. R. P., Awni, W. M., Halstenson, C. E., Findlay, J. W. A., Opsahl, J. A., Abraham, P. A., Jones, E. C. & Matzke, G. R. (1987). Pharmacokinetics of codeine after single- and multiple-oral-dose administration to normal volunteers. *J. clin. Pharmac.*, **27**, 983–987.

Guay, D. R. P., Awni, W. M., Findlay, J. W. A., Halstenson, C. E., Abraham, P. A., Opsahl, J. A., Jones, E. C. & Matzke, G. R. (1988). Pharmacokinetics and pharmacodynamics of codeine in end-stage renal disease. *Clin. Pharmac. Ther.*, **43**, 63–71.

Horai, Y., Nakano, M., Ishizaki, T., Ishikawa, K., Zhou, H. H., Zhou, B. J., Liao, C. L. & Zhang, L. M. (1989). Metoprolol and mephenytoin oxidation polymorphisms in Far Eastern Oriental subjects: Japanese versus mainland Chinese. *Clin. Pharmac. Ther.*, **46**, 198–207.

Jiang, M. X. (1984). In *Pharmacology*, pp. 143. Ren Min Wei Sheng Chu Ban She, 1984.

Kalow, W., Otton, S. V., Kadar, D., Endrenyi, L. & Inaba, T. (1980). Ethnic difference in drug metabolism: debrisoquine 4-hydroxylation in Caucasians and Orientals. *Can. J. Physiol. Pharmac.*, **58**, 1142–1144.

Kalow, W. (1984). Pharmacoanthropology: Drug metabolism. *Fed. Proc.*, **43**, 2326–2331.

Kumana, C. R., Lauder, I. J., Chan, M., Ko, W. & Lin, H. J. (1987). Differences in diazepam pharmacokinetics in Chinese and white Caucasians—relation to body lipid stores. *Eur. J. clin. Pharmac.*, **32**, 211–215.

Lasagna, L. & De Kornfeld, T. J. (1958). Analgesic potency of normorphine in patients with postoperative pain. *J. Pharmac.*, **124**, 260–263.

Lennard, M. S., Silas, J. H., Smith, A. J. & Tucker, G. T. (1977). Determination of debrisoquine and its 4-hydroxy-metabolite in biological fluids by gas chromatography with flame-ionization and nitrogen-selective detection. *J. Chromatogr.*, **133**, 161–166.

Lou, Y. C., Liu, Y., Bertilsson, L. & Sjöqvist, F. (1987). Low frequency of slow debrisoquine hydroxylation in a native Chinese population. *Lancet*, **ii**, 852–853.

Miller, J. W. & Anderson, H. H. (1954). The effect of *N*-demethylation on certain pharmacologic actions of morphine, codeine and meperidine in the mouse. *J. Pharmac.*, **112**, 191–196.

Mortimer, Ö., Persson, K., Ladona, M. G., Spalding, D., Zanger, U. M., Meyer, U. A. & Rane, A. (1990). Polymorphic formation of morphine from codeine in poor and extensive metabolizers of dextromethorphan: Relationship to the presence of immunoidentified cytochrome P-450IId1. *Clin. Pharmac. Ther.*, **47**, 27–35.

Mucklow, J. C., Fraser, H. S., Bulpitt, C. J., Kahn, C., Mould, G. & Dollery, C. T. (1980). Environmental factors affecting paracetamol metabolism in London factory and office workers. *Br. J. clin. Pharmac.*, **10**, 67–74.

Nakamura, K., Goto, F., Ray, W. A., McAllister, C. B., Jacquz, E., Wilkinson, G. R. & Branch, R. A. (1985). Interethnic differences in genetic polymorphism of debrisoquin and mephenytoin hydroxylation between Japanese and Caucasian populations. *Clin. Pharmac. Ther.*, **38**, 402–408.

Osborne, R., Joel, S., Trew, D. & Slevin, M. (1988). Analgesic activity of morphine-6-glucuronide. *Lancet*, **i**, 828.

Quiding, H., Anderson, P., Bondesson, U., Boréus, L. O. & Hynning, P. Å. (1986). Plasma concentrations of codeine and its metabolite, morphine, after single and repeated oral administration. *Eur. J. clin. Pharmac.*, **30**, 673–677.

Rogers, J. F., Findlay, J. W. A., Hull, J. H., Butz, R. F., Jones, E. C., Bustrack, J. A. & Welch, R. M. (1982). Codeine disposition in smokers and nonsmokers. *Clin. Pharmac. Ther.*, **32**, 218–227.

Sanfilippo, G. (1948). Contributo sperimenteale all'ipotesi della smetilazione della codeina nelläorganismo. I. Influence della dose sull'assuefazione alla codeina. II. Assuefazione alla codeina attenuta con somministrazione prolungata di morfina. *Boll. Soc. Ital. Biol. Sper.*, **24**, 723–726.

Spector, R., Choudhury, A. K., Chiang, C. K., Goldberg, M. J. & Ghoneim, M. M. (1980). Diphenhydramine in Orientals and Caucasians. *Clin. Pharmac. Ther.*, **28**, 229–234.

Svensson, J. O. (1986). Determination of morphine, morphine-6-glucuronide and normorphine in plasma and urine with high-performance liquid chromatography and electrochemical detection. *J. Chromatogr.*, **375**, 174–178.

Yue, Q. Y., Bertilsson, L., Dahl-Puustinen, M. L., Säwe, J., Sjöqvist, F., Johansson, I. & Ingelman-Sundberg, M. (1989a). Disassociation between debrisoquine hydroxylation phenotype and genotype among Chinese. *Lancet*, **ii**, 870.

Yue, Q. Y., Hasselström, J., Svensson, J. O. & Säwe, J. (1991). Pharmacokinetics of codeine and its metabolites in Caucasian healthy volunteers: comparisons between extensive and poor metabolizers of debrisoquine. *Br. J. clin. Pharmac.*, **31**, 635–641.

Yue, Q. Y., Svensson, J. O., Alm, C., Sjöqvist, F. & Säwe, J. (1989b). Interindividual and interethnic differences in the demethylation and glucuronidation of codeine. *Br. J. clin. Pharmac.*, **28**, 629–637.

Yue, Q. Y., Svensson, J. O., Alm, C., Sjöqvist, F. & Säwe, J. (1989c). Codeine *O*-demethylation co-segregates with polymorphic debrisoquine hydroxylation. *Br. J. clin. Pharmac.*, **28**, 639–645.

Yue, Q. Y., Säwe, J., Svensson, J. O. & Sjöqvist, F. (1988). Interindividual and interethnic differences in the *O*-demethylation and glucuronidation of codeine—Observations in Chinese and Swedish volunteers. *5th Southeast Asian and Western Pacific Regional Meeting of Pharmacologists*. Beijing, China, July 1988.

Yue, Q., von Bahr, C., Odar-Cederlöf, I. & Säwe, J. (1990). Glucuronidation of codeine and morphine in human liver and kidney microsomes: effect of inhibitors. *Pharmac. Tox.*, **66**, 221–226.

Zhang, Y., Reviriego, J., Lou, Y., Sjöqvist, F. & Bertilsson, L. (1990). Diazepam metabolism in native Chinese poor and extensive hydroxylators of S-mephenytoin: Interethnic differences in comparison with Caucasian subjects. *Clin. Pharmac. Ther.*, **48**, 496–502.

Zhou, H. H., Koshakji, R. P., Silberstein, D. J., Wilkinson, G. R. & Wood, A. J. J. (1989). Racial differences in drug response. Altered sensitivity to and clearance of propranolol in men of Chinese descent as compared with American whites. *New Engl. J. Med.*, **320**, 565–570.

(Received 24 July 1990, accepted 6 December 1990)