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DEFECTIVE HYDROXYLATION OF BUFURALOL ASSOCIATED WITH SIDE-EFFECTS OF THE DRUG IN POOR METABOLISERS

Bufuralol is a non-selective β-adrenoceptor blocking drug with some degree of intrinsic sympathomimetic activity (Angium , Ro 3–4787). First studies in man have shown that bufuralol has a longer duration of action and a greater potency than propranolol (Kilborn & Turner, 1974; Tschopp *et al.*, 1978). This lipophilic compound is metabolised by the liver and three metabolites of bufuralol have been identified in human plasma: an alcoholic or carbinol derivative (1'-hydroxybufuralol), a phenol derivative (4-hydroxybufuralol) and a ketone derivative (Francis *et al.*, 1976; Balant *et al.*, 1980). The carbinol and the ketone derivatives have been synthesised and shown to possess β-adrenoceptor blocking activity similar to parent drug (Francis *et al.*, 1976). The main constituent next to the parent compound in human plasma is the active carbinol derivative (Balant *et al.*, 1978a; Balant *et al.*, 1980).

During the course of kinetic studies with bufuralol in healthy volunteers we observed a subject who developed side-effects. A 21 year old Caucasian male took, when fasting, a 30 mg bufuralol tablet. Two hours after the bufuralol intake he became ill: he was pale, presented with profuse sweating, suffered pronounced nausea and vomited, the pulse was 64 beats/min and blood pressure fell to 95/65 mmHg. These unpleasant side-effects of the drug disappeared within the next 4 h. In this subject, plasma bufuralol concentrations were unusually high and carbinol concentrations low. This observation and a similar case previously reported (Balant *et al.*, 1976) suggest a pharmacogenetic anomaly for aliphatic hydroxylation of bufuralol (Balant *et al.*, 1978b), as recently described for alicyclic hydroxylation of debrisoquine (Mahgoub *et al.*, 1977; Price Evans *et al.*, 1980), N-oxidation of sparteine (Eichelbaum *et al.*, 1979); Bertilsson *et al.*, 1980), hydroxylation of phenytoin (Sloan *et al.*, 1981), or other oxidated drugs (Sloan *et al.*, 1978).

The family of this 'outlier' subject was then tested with bufuralol and with debrisoquine. The protocol was approved by the Institution Ethical Committee and informed consent was obtained from each subject. Bufuralol and 1'-hydroxybufuralol plasma concentrations were measured using a high-performance liquid chromatographic method (Haefelfinger, 1980). Figure 1 shows plasma concentrations of bufuralol and 1'-hydroxybufuralol in the family of our subject (F.K.) and Table 1, the pharmacokinetic parameters. With the exception of the father (Ar.K), bufuralol levels are high and 1'-hydroxybufuralol levels are extremely low, near the measurement limit of the assay (Table 1). The mother (E.K.) and the sister (A.K.), but not the father, presented the same pattern of vagal side-effects, including vomiting, as did our subject. These side-effects could be antagonised by an anticholinergic drug (hyoscine butylbromide, 20–40 mg i.m.) Members of this family have also been submitted to debrisoquine hydroxylation phenotyping (Price Evans *et al.*, 1980) and could be classified, excepting the father, as poor metabolisers for debrisoquine hydroxylation.

Polymorphic variation of drug hydroxylation is probably an enzymatic defect (Davies *et al.*, 1981) inherited as a single autosomal recessive trait (Price Evans *et al.*, 1980). Usually, subjects classified as poor metabolisers present merely an abnormal pharmacokinetics pattern of the drug and the direct clinical relevance of these blood concentration variations is often difficult to establish. With bufuralol a typical profile of side-effects emerges in poor metabolisers. We confirmed this finding in an additional study of 58 unselected caucasian volunteers. In this series 5 subjects ($= 8.6\%$) were poor metabolisers for bufuralol. The same 5 subjects, and they alone, were found to be poor metabolisers for debrisoquine, a percentage comparable to the
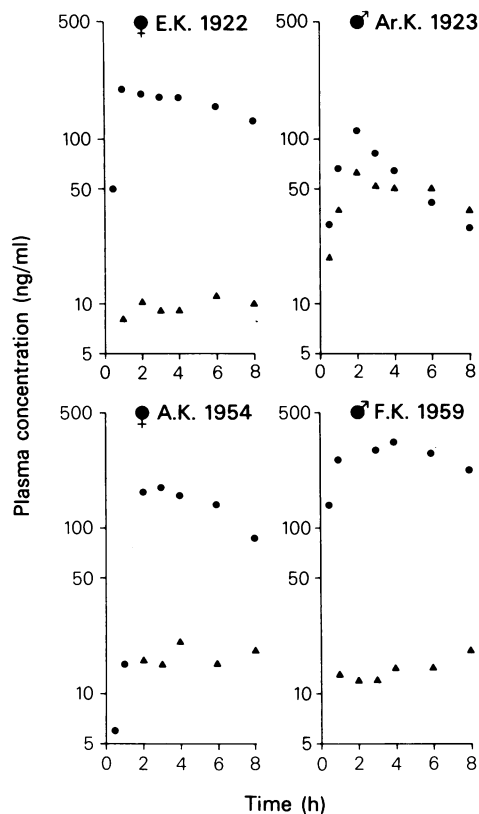
Figure 1   Plasma concentrations of bufuralol (●) and 1'-hydroxybufuralol (▲) after an oral dose of 30 mg bufuralol. The mother (E.K.), the daughter (A.K.) and the son (F.K.) are poor metabolisers and presented prominent side-effects not observed in the father (Ar.K) an extensive metaboliser.

8.9% observed among white British subjects (Price Evans *et al.*, 1980). In our series 4 out of the 5 poor metabolisers presented the same side-effects as the family we described and only 3 out of the 53 extensive metabolisers did ($P<0.001$). In extensive metabolisers, the possible compensatory β-adrenoceptor blocking effect of the active metabolite does not seem to play an important role on the occurrence of side-effects. They are not related to β-adrenoceptor blockade but probably to vagal stimulation. This report confirms that hydroxylation of β-adrenoceptor blocking drugs can be added to the list of polymorphic metabolism pathways and this fact may have clinical relevance.

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Table 1   Pharmacokinetic parameters of bufuralol and its carbinol derivative (1'-hydroxybufuralol) after a 30 mg oral dose in a family of poor metabolisers* and after a 60 mg oral dose in a control group of healthy subjects ($n = 8$).

Bufuralol dose	Subjects	Bufuralol		
		$AUC_{o \to \infty}$ $(ng\,ml^{-1}\,h)$	$T_{1/2}$ (h)	C_{max} $(ng\,ml^{-1})$
30 mg	E.K.*	2760	8.6	186
	Ar.K.	606	3.3	112
	A.K.*	1602	5.4	176
	F.K.*	4437	7.5	433
60 mg	Controls (mean±s.d)	896±481	2.7±0.9	164±69
		Carbinol		
30 mg	E.K.*	†	†	11
	Ar.K.	363	9.8	62
	A.K.*	†	†	20
	F.K.*	†	†	18
60 mg	Controls (mean±s.d.)	1004±322	6.1±1.5	104±39

* Poor metaboliser for bufuralol and debrisoquine (debrisoquine/4-hydroxydebrisoquine urinary ratio >12.6 [Price Evans *et al.*, 1980]).
† Not measurable (measurable limit = 10 ng/ml plasma).

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THE SECOND PEAK IN THE SERUM LEVELS CURVE AFTER ORAL ADMINISTRATION OF A SLOW-RELEASE QUINIDINE DOSAGE FORM: EFFECT OF FOOD

Oral administration of a slow-release dosage form of quinidine gluconate has been reported to lead to two peaks in the serum level curve (Greenblatt *et al.*, 1977; Covinsky *et al.*, 1979). It has been postulated, as suggested for acetaminophen by Clements *et al.* (1978), that this phenomenon could be attributed to a biphasic gastric emptying pattern (Covinsky *et al.*, 1979). We now report that the second maximum could be related to the standard lunch which is provided to subjects in bioavailability studies after a standard fasting period following drug administration.

To investigate the effect of food on the serum level curve of this drug, a clinical study of a fast- and slow-release dosage form of quinidine gluconate (tablets A: Quinate ® from Rougier, Chambly, Québec, lot no. 02XD, and B: Quinaglute ® from Cooper Laboratories, Cedar Knoll, N.J., lot no. E, 9160, respectively) has been undertaken (Spénard *et al.*, 1982). Two groups of nine healthy volunteers participated in the study after giving informed consent. In two crossover studies (one latin square for each dosage form) single doses of quinidine gluconate equivalent to 405 mg quinidine base were administered on three separate occasions, 1 week apart. After fasting for 10 h, each subject received in random sequence this single dose according to three modes T of administration: without (T_1), before (T_2) and after (T_3) a standard breakfast. A standard lunch was given after a 4 h fasting period, following the administration of the drug. Venous blood samples were drawn from a heparin lock where the first 1 ml of blood was rejected or by venipuncture. Blood specimens were collected prior to dosing and at 0.5, 1.0, 1.25, 1.5, 1.75, 2.0, 2.25, 2.5, 2.75, 3.0, 3.5, 4.0, 4.5, 5.0, 6.0, 8.0, 10.0, 12.5, 15.0, 24.0, 32.0, 48.0 and 72.0 h after drug administration. The serum concentration of quinidine was determined by a modification of the h.p.l.c. method of Drayer *et al.* (1977). Quinine was used as the internal standard. The residue of the extract, obtained from 100 μl of serum, was reconstituted in 100 μl of methanol and 10 μl were injected into the liquid chromatograph (Spénard *et al.*, 1982).