ROUTES OF MEPTAZINOL CONJUGATION IN THE NEONATE

In a recent study in which meptazinol, a new analgesic, was administered to women in labour, the drug was found to be eliminated from the neonate at much the same rate as from the mother (Franklin *et al.*, 1981). In this respect, meptazinol offers an advantage over pethidine, at present the most widely used pre-partum analgesic in the U.K., which is disposed of much less readily in the neonate than in the mother, so exposing the infant to the respiratory depressant effects of the drug for a relatively long period (Cooper *et al.*, 1977).

Pethidine undergoes extensive oxidative metabolism in adults (Stillwell *et al.*, 1976). Reduction of the rate of the reactions in neonates accounts for the extended half-life of pethidine (Morselli *et al.*, 1980).

In the adult, meptazinol has been found to undergo extensive conjugation with glucuronic acid (Franklin *et al.*, 1976). Since there is evidence of low glucuronyl transferase activity in the neonate (e.g. salicylic acid conjugation, Garrettson *et al.* (1977); acetanilide conjugation, Vest & Strieff, (1959); chloramphenicol conjugation, Weiss *et al.* (1960); and oxazepam conjugation, Rane & Thomson, (1980)), it might have been expected that meptazinol elimination too would be impaired. The finding, on the contrary, of rapid clearance of this drug in the newborn suggested perhaps a compensatory metabolic pathway. Neonatal capacity for sulphate conjugation of phenols is similar to that in adults (Morselli *et al.*, 1980). Indeed it has been shown that phenolic sulphation is the predominant route of metabolism of paracetamol in the neonate and is only replaced by glucuronidation between 9 and 12 years of age (Miller *et al.*, 1976). Thus it was possible that meptazinol too underwent extensive sulphate conjugation in the neonate. The objective of the present study, therefore, was to compare the extent of sulphate and glucuronide conjugation of meptazinol in neonates and adults.

Urine samples were obtained from neonates and from four adult female volunteers. Meptazinol HCl (100 mg) had been administered i.m. to the mothers of these neonates at onset of labour and thereafter on demand. A single 50 mg dose was administered i.m. to the volunteers. Urine was collected from babies over the 0–8 h period after birth, and over the same period after administration to the volunteers.

Free meptazinol concentrations were determined using h.p.l.c. with fluorescence detection as described by Franklin *et al.* (1981).

Determination of meptazinol conjugates in urine was carried out by assay of liberated meptazinol after selective enzymic hydrolysis. Duplicate 10 μ l samples of urine were treated with bacterial β -glucuronidase (*E. coli* Type 1, obtained from Sigma Chemical Co.

Ltd., Poole, Dorset; 2500 units in 2 ml pH 7.4 phosphate buffer) or with molluscan β -glucuronidase/sulphatase (*Helix pomatia*, Type H-1, supplied by Sigma Chemical Co. Ltd; 10,000 units β -glucuronidase and 380–1000 units sulphatase in 2 ml of pH 5.0 acetate buffer) in the presence of 10 mM saccharo – 1,4-lactone, which maximally inhibited β -glucuronidase activity. In each case internal standard was added and samples were incubated at 37°C for 24 h. These conditions were found in preliminary experiments to effect complete hydrolysis of, respectively, meptazinol glucuronide and sulphate.

The samples were then centrifuged, the supernatant removed and adjusted to pH 9.7 with 1M bicarbonate buffer to give a final volume of 5 ml. Meptazinol concentrations in duplicate 500 μ l samples were assayed as described above.

There was no apparent difference in the ratio of sulphate/glucuronide conjugates in the adult and neonatal urine samples (Table 1). Thus there was no support for the view that a compensatory sulphation pathway accounted for the rapidity of meptazinol elimination in the neonate.

Neither could renal clearance represent a satisfactory explanation. It can be calculated that after i.v. dosage (Franklin, unpublished data), the plasma clearance of the drug is about 2 l min⁻¹, whereas the normal physiological process of glomerular filtration rate is only about 125 ml min⁻¹ (Beckett *et al.*, 1969). Indeed, renal excretion accounted for only 4.1 $\pm$ 1.0% (mean $\pm$ s.e. mean) of the total in the adults studied and thus the rate of renal excretion of unchanged drug must have been around 20 times slower than that of hepatic metabolism, i.e. the elimination half-life of meptazinol in the neonate would have been slower than that in the adult by a factor of this order if renal clearance of unchanged drug were to have become the major elimination route.

Thus the results of the present study imply that elimination of meptazinol by the neonate takes place essentially as in the adult by conjugation with glucuronic acid. Although some of the conjugates excreted by the infants could have been maternally derived, it was unlikely that the relative ratios of glucuronide, sulphate and unchanged drug would have been so similar in the neonate and the adult unless the neonate itself conjugated the drug extensively with glucuronic acid. Furthermore whereas basic, lipophilic drugs tend to cross the placenta quite readily, polar conjugates extensively ionized under physiological conditions, appear to do so less readily. Thus drug/conjugate ratio on the foetal side of the placenta has been shown to be substantially higher

Table 1 Concentrations of meptazinol and its glucuronide and sulphate conjugates in 0–8 h urine samples after i.m. administration

Subject	Unchanged meptazinol concentrations ($\mu\text{g ml}^{-1}$)	Glucuronide concentrations ($\mu\text{g ml}^{-1}$)	Sulphate concentrations ($\mu\text{g ml}^{-1}$)	Sulphate/glucuronide ratio	Mean $\pm$ s.e. mean
Neonates	1 0.86	21.8	4.0	0.18	0.37 $\pm$ 0.13
	2 1.80	20.1	6.2	0.31	
	3 5.48	42.2	26.1	0.62	
Adults	4 3.33	78.1	19.7	0.25	0.33 $\pm$ 0.12
	5 4.19	32.7	22.4	0.69	
	6 3.38	91.1	17.1	0.19	
	7 1.22	32.9	6.6	0.20	

Urine samples collected from adult women after i.m. administration of meptazinol and from neonates born to mothers administered the drug i.m. during labour.

than on the maternal side for a variety of compounds, e.g. oxazepam (Tomson *et al.*, 1979), lorazepam (Cummings & Whitelaw, 1981).

In conclusion, the results of the present study have demonstrated that sulphate conjugation is not a significant route of metabolism of meptazinol in neonates. Levels of glucuronyl transferase in the neonate are apparently sufficiently high to achieve rapid conjugation of meptazinol entering by transplacental passage from mothers administered doses of the drug adequate for relief of labour pain. The apparent discrepancy between this observation and the previous findings of impaired glucuronide conjugation of some other drugs in neonates may reflect the existence of several different, substrate-specific glucuronyl transferases.

There is evidence, at least in the rat, for more than

one such enzyme. For example, two forms which are differentially inducible by phenobarbitone and 3-methylcholanthrene have been separated by Bock *et al.* (1979).

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THE EFFECT OF AGE ON THE RESPONSES OF HUMAN ISOLATED ARTERIES AND VEINS TO NORADRENALINE

We were interested in the letter of Scott & Reid (1982), which reported that vascular α -adrenoceptor sensitivity was not altered with increasing age. We have recently reported studies on α -adrenoceptor mediated mechanisms in human isolated arteries and veins, obtained *post mortem* (Stevens & Moulds, 1980, 1981; Stevens *et al.*, 1981; Stevens & Moulds, 1982a, 1982b), and have also performed extensive studies investigating the antagonism of contractile effects of noradrenaline on arteries and veins by various vasodilating drugs (Lipe & Moulds, 1981, 1982). In these studies digital arteries and/or metacarpal veins were obtained from a total of 90 patients. Since the clinical details of the patients from whom the vessels were obtained were all recorded,

we are in a position to assess the effects of the age of the patients and the α -receptor mediated responses.

The arteries and veins were cut into spiral strips and studied as we have previously described (Jauernig & Moulds, 1978; Jauernig *et al.*, 1978). The maximal contractile response to 80 mM KCl, and then at least two cumulative concentration-effect curves to noradrenaline were obtained on each arterial or venous strip. If more than one strip was cut from the same vessel, the mean of the values for that vessel was used. The following values were calculated from the second noradrenaline concentration-effect curve: $E_{\max}$ (g)-maximum response to noradrenaline expressed in grams; $E_{\max}$ (% KCl)-the maximum response to noradrenaline expressed as a percentage

Table 1 Statistical analysis (using Spearman's rank correlation test and linear regression) of the relationship between age of patient, and the $E_{\max}$ for noradrenaline, the pD_2 for noradrenaline and the contractile response to KCl (80 mmol/l) in human arteries and veins.

Correlation	Tissue	Sex	r_s	r	n
Noradrenaline $E_{\max}$ (% KCl)	Artery	Male	0.372*	0.366*	35
		Female	0.260	0.218	25
	Vein	Male	0.157	0.170	36
		Female	0.093	0.103	16
Noradrenaline pD_2	Artery	Male	0.129	0.069	35
		Female	0.069	0.110	25
	Vein	Male	0.245	0.287	36
		Female	0.121	0.199	16
KCl $E_{\max}$ (g)	Artery	Male	-0.296	-0.385*	35
		Female	-0.084	-0.007	25
	Vein	Male	-0.337*	-0.282	36
		Female	-0.251	-0.197	16
Noradrenaline $E_{\max}$ (g)	Artery	Male	-0.083	-0.278	35
		Female	-0.098	-0.022	25
	Vein	Male	-0.246	-0.189	36
		Female	-0.135	-0.070	16

n = number of patients

* = $P < 0.05$ (Student's *t*-test)

r_s = Spearman correlation coefficient

r = correlation coefficient (linear regression)