150 mg daily of this compound would be an average therapeutic dose. In the case of bupropion the therapeutic dose is usually 100–150 mg three times daily.

Imipramine, like desipramine, quite clearly decreases the sensitivity to intravenous tyramine. Bupropion, by contrast, produced no significant change. These effects were clearly apparent using the parametric analysis of variance, but a similar trend appeared using non-parametric statistics even in this small group of subjects. In view of this it seems un-

likely that the antidepressant effect of bupropion results from blockade of noradrenaline uptake.

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PRELIMINARY STUDIES ON THE DISPOSITION OF MEPTAZINOL IN THE NEONATE

At present the most widely used pre-partum analgesic in the United Kingdom is pethidine even though it is appreciated that this may cause significant respiratory depression. Furthermore pethidine readily crosses the placenta and yet the neonate is less well able to dispose of the drug than is the mother (Cooper, Stephen & Aggett, 1977). The average neonatal elimination half-life has been estimated to be 22 h which is approximately 7 times longer than that of healthy adults (Caldwell *et al.*, 1978). This delayed excretion is likely to exacerbate any respiratory complications seen in the infant.

Meptazinol is a new major analgesic which has recently been shown to be useful in alleviating labour pain (Jackson & Robson, 1980). In contrast to pethidine it has been shown to produce minimal effects on respiration (Jordan *et al.*, 1978). Furthermore the drug has a relatively short half-life, 2.2 ± 0.05 h (mean $\pm$ s.e. mean) (Rosseel *et al.*, 1975), which could be advantageous to its use as a pre-partum analgesic. While previous studies have shown meptazinol to cross the placenta freely (Jackson & Robson, 1980) no investigations have been reported on the disposition in the neonate. This communication describes preliminary results from such a study.

Thirteen women participated in this trial. Their weights ranged from 55–91 kg (72 ± 3.4 kg, mean $\pm$

s.e. mean). They were given meptazinol 100–150 mg i.m. Ten received a single injection approximately 3 h prior to delivery, while the remaining three patients had one or two earlier doses separated by 3 h intervals. Heparinized blood samples were taken at birth from both mother and infant from a cephalic or femoral vein. Subsequently samples were taken from the infant at various times selected from 4, 8, 12, 18 and 24 h after birth.

Plasma concentrations of meptazinol were determined using an HPLC method with fluorescence detection. Briefly, 0.5 ml plasma was extracted with 3 ml ethyl acetate after the addition of 0.1 ml pH 9.5 1 M bicarbonate buffer and 100 ng of internal standard, Wy 23128 (the *N*-cyclopropyl analogue of meptazinol). After vortex mixing for 2 min followed by centrifugation, the ethyl acetate layer was removed and reduced to dryness under a stream of nitrogen at 50°C. The residue was reconstituted in 150 μ l 66% aqueous methanol and 100 μ l injected onto a Spherisorb CN column (Phase Separations Ltd, Queensferry, Clwyd, U.K.). The column was eluted with 45% methanol in 0.5% aqueous ammonium acetate at a flow rate of 2 ml min⁻¹. Meptazinol was detected by means of its natural fluorescence (282 nm excitation, and 300 nm emission). The approximate retention times of the drug and internal standard were 4.3 and 5.5 min

Table 1 Concentrations of meptazinol in maternal and neonatal plasma following intramuscular administration of the drug to women in labour

Patient	Dose (mg)	Time between dose and delivery (h. min)	Initial maternal concentration (ng ml ⁻¹)	Initial neonatal concentration (ng ml ⁻¹)	Neonate concentration (ng ml ⁻¹)					Neonate/maternal ratio
					4 h	8 h	12 h	18 h	24 h	
1	150	2 h 55 min	265	119	34	—	—	<3	—	0.45
2	100	3 h 25 min	41	21	13	—	3	—	<3	0.51
3	100	3 h	99	49	—	—	—	3	—	0.49
4	{ 150	0 h 30 min	—	126	—	—	<3	—	<3	
	{ 150	(last dose)								
5	150	2 h 45 min	105	71	32	—	—	<3	—	0.68
6	{ 150	3 h	148	79	24	—	—	<3	—	0.53
	{ 125	(last dose)								
	{ 150									
7	150	2 h 30 min	166	68	16	—	<3	—	—	0.41
8	125	2 h	343	124	39	—	<3	—	—	0.36
9	100	2 h 15 min	117	69	47	—	<3	—	—	0.59
10	150	4 h 30 min	59	58	—	7	—	—	<3	0.98
11	150	1 h 30 min	166	73	—	—	4	—	<3	0.44
12	125	3 h 20 min	82	54	—	3	—	—	<3	0.66
13	{ 150	5 h 45 min	22	16	—	—	—	<3	<3	0.73
	{ 150	(last dose)								

— = No result.

respectively. The lower limit of sensitivity of the method was ~ 3.0 ng ml⁻¹.

The results of these investigations are presented in Table 1 and show a neonatal/maternal plasma concentration ratio of 0.57 ± 0.05 (mean $\pm$ s.e. mean) which is of a similar order to that reported previously by Jackson & Robson (1980) who found a value of 0.96 ± 0.31 (mean $\pm$ s.e. mean). Furthermore meptazinol was rapidly eliminated from the neonate. In six neonates for whom plasma concentration data 12 h after birth is available it can be seen that the average concentration had fallen to $<5\%$ of the initial value. (In adults, assuming a 2.2 h half-life, plasma concentrations would also be expected to be $<5\%$ of initial values at this time.) In a further five infants, where plasma concentrations were measured 18 h after birth, levels were below the detectable limit of 3 ng/ml. By contrast a similar study with pethidine has shown that at 24 h after birth neonatal plasma levels were still $\sim 36\%$ of initial values ($n = 36$) (Caldwell, personal communication).

This difference may be a reflection of the different metabolic routes taken by the two compounds. In adults pethidine is the subject of extensive phase I oxidative metabolism involving ester hydrolysis, *N*-demethylation and *N*-oxidation (Stillwell, Myram & Stewart, 1976), reactions which are known to be much reduced in the neonate (Morselli, Franco-Morselli & Bossi, 1980). Meptazinol on the other hand undergoes exclusively phase II conjugation with

glucuronic acid (Franklin, Aldridge & de B. White, 1976), a metabolic route of considerable capacity. However, there have been a number of reports which show that glucuronide conjugation too may be impaired in the neonate, e.g. salicylic acid conjugation (Garrettson, Procknal & Levy, 1977), acetanilide conjugation (Vest & Strieff 1959), chloramphenicol conjugation (Weis, Glazko & Weston, 1960) and oxazepam conjugation (Rane & Thomson, 1980). One possible explanation for the essentially unaltered disposition of meptazinol in the neonate may lie in the now appreciated existence of several different, substrate specific, glucuronyl transferases (Sanchez & Tephly, 1974). It is possible that the particular enzyme concerned with meptazinol conjugation has a high affinity for the drug and is present in adequate amounts even at birth. Certainly in adults the drug undergoes a major first pass effect indicating a substantial capacity for conjugation. Alternatively, while glucuronyl transferase activity might in fact be deficient in the infant a compensatory sulphate conjugation mechanism may come into play. It has been reported that neonatal capacity for sulphate conjugation is similar to that of adults (Morselli *et al.*, 1980). A compensatory sulphate conjugation pathway has been shown to operate in the disposition of paracetamol in the neonate (Miller, Roberts & Fischer, 1976).

While the scientific basis for this lack of impairment of meptazinol metabolism in the neonate must

await resolution, the fact remains that the drug is rapidly eliminated and the duration of any side effects such as vomiting and dizziness is likely to be limited in the newborn infant. This has recently been confirmed in a more extensive study on the utility of meptazinol in labour pain (Nicholas & Robson, to be published).

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FAVOURABLE EFFECTS OF YOHIMBINE ON CLOMIPRAMINE-INDUCED ORTHOSTATIC HYPOTENSION: A DOUBLE-BLIND STUDY

Tricyclic induced orthostatic hypotension is a frequent side effect often more severe than many clinicians seem to believe (Glassman *et al.*, 1979).

In a preliminary open study of 11 patients (Des Lauriers *et al.*, 1979) we showed that yohimbine, a presynaptic α -noradrenergic receptor blocking agent, had favourable effects on orthostatic hypotension induced by clomipramine, a tricyclic antidepressant. We believe the hypotension seen with clomipramine is probably the result of the blockade of α -adrenergic post-synaptic receptors. Our initial findings suggested a favourable effect:

- on blood pressure figures upon standing: the decrease in systolic blood pressure was 32 mmHg before treatment and 11 mmHg after 1 week treatment.
- on clinical symptoms (mainly dizziness) which disappeared in 10 out of 11 subjects.

A double-blind controlled trial was undertaken in order to confirm these findings.

All subjects were hospitalized, depressed patients presenting with clomipramine-induced orthostatic hypotension after at least 5 days of treatment. Patients were included in the trial if the decrease in