Mianserin in breast milk

Post partum depression may occur in up to 20% of new mothers [1]. Some cases are of a severity requiring antidepressant treatment. Concern is often expressed about the passage of antidepressant drugs into the breast milk and the effects the drugs might have on the infant if breast feeding is continued. We report two cases of depression associated with childbearing treated with mianserin and the passage of this drug into breast milk.

Case 1: a 32 year old nurse (70 kg) presented with major depressive illness which had commenced in the mid trimester of her pregnancy and continued following the birth of her first child. Initial treatment was with dothiepin to a maximum dose of 275 mg day^{-1}. After 4 weeks at this dose, she had made minimal progress and there was a concern about the poor bonding with the child. There was a family history of depression responsive to mianserin. Dothiepin was discontinued and mianserin commenced. After 9 days at 60 mg mianserin per day administered as a single dose at night, maternal plasma and breast milk samples were collected 15 h after the last dose. At this time the infant was 3 months of age and weighed 5.3 kg.

Case 2 was 30 years old (72 kg) with a personal history of mild depression (not requiring treatment) following the birth of her first three children. Following the birth of her fourth child she developed severe depression requiring admission and treatment with ECT and antidepressants. She failed to respond to dothiepin and developed extensive rash and oedema with clomipramine treatment. Mianserin was commenced and increased to 40 mg day^{-1} as a single nocturnal dose. After 14 days of a constant dose regimen, maternal plasma and breast milk samples were collected 15 h after the last dose. A urine specimen was obtained from the infant at the same time. The infant was 5 months of age and weighed 6.5 kg.

Mianserin and its major metabolite, desmethylmianserin, were assayed in plasma, milk or urine by h.p.l.c. Separation of drugs and internal standard (6-azamianserin) was affected at ambient temperature with a reversed-phase column (μ-Bondapak, C_{18}, 30 cm × 3.9 mm). The mobile phase was acetonitrile-0.05 M potassium dihydrogen phosphate (50:50, v/v pH 6.5) at a flow rate of 2.5 ml min^{-1}. Eluants were detected at 214 nm. Drugs were extracted from plasma, breast milk or urine into hexane-isoamyl alcohol (98:2 v/v after the pH was adjusted to > 10 with sodium hydroxide, back extracted into hydrochloric acid and then extracted into hexane. Recovery was 65–85% for all three fluids with breast milk having the lowest average recovery (~65%) based on the ratio of the slopes of the extracted and methanol standard curves. The limit of determination of the method was 10 μg l^{-1} from 2 ml of fluid. Precision of the assay at 25 μg l^{-1} was ~ 8% for mianserin and ~18% for desmethylmianserin in all three fluids.

Concentrations of parent drug and metabolite in plasma and breast milk are shown in Table 1. While it is possible to calculate a milk to plasma (M/P) ratio from these data, it is important to note that the ratio is best calculated from serial samples as the pharmacokinetics of the drug in milk are unlikely to parallel those in plasma [2]. Nevertheless, the M/P ratio may be used as an approximation for calculating infant dose according to the fomula [2].

$$D\text{inf} = C_{ss}\ (\text{mother}) \times \text{M/P ratio} \times \text{V milk}$$

where
Dinf = dose to the infant (mg kg^{-1} day^{-1})
C_{ss} (mother) = maternal steady state plasma concentration
V milk = daily volume of milk ingested (1 kg^{-1}) assumed to be 0.15 l kg^{-1}.

The M/P ratio for case 1 was 3.6 for mianserin which gives Dinf of 0.012 mg kg^{-1} day^{-1}, while in case 2, the M/P ratio was 0.8 and the Dinf was 0.003 mg kg^{-1} day^{-1}. The intake of the infants was 1.4% and 0.5%, respectively, of the maternal mianserin intake. For desmethylmianserin, the intake calculated as a fraction of the maternal mianserin dose was 0.2% and 0.5%, respectively. The infants suffered no untoward effects as a result of this intake and only relatively small amounts (close to the limit of detection of the assay) were found in the urine of one infant (Table 1).

These two cases show that mianserin and its major metabolite, like the majority of drugs, pass into breast milk [2]. The infant is likely to be exposed to only a small percentage of the maternal dose without significant untoward effects, although hypersensitivity reactions unrelated to dose may occur. Clearly further

Table 1 Maternal and infant mianserin and desmethylmianserin concentrations in body fluids during breast feeding

	Maternal plasma		*Breast milk*		*Infant plasma*		*Infant urine*	
Case	*MIANS*	*DM*	*MIANS*	*DM*	*MIANS*	*DM*	*MIANS*	*DM*
1	22	20	80	10	ND	ND	ND	ND
2	25	<10	20	20	NS	NS	12	14

MIANS: Mianserin concentration (μg l^{-1})
DM: Desmethylmianserin concentration (μg l^{-1})
ND: not detected
NS: no sample

studies are necessary to establish the safety of mianserin in breast feeding. The M/P ratios determined here are based on only a single time point at steady-state and therefore are subject to reservations about their accuracy. However, a consideration of the kinetics of mianserin suggests that these values might represent an 'at worst' situation. A more detailed study with serial sampling would be required to answer this question. Furthermore, samples obtained from fore- and hind-milk are a potential source of variation in the M/P ratio. In this study hind-milk samples were obtained where lipid content is higher [3] and the M/P ratio is likely to be higher for a lipid soluble drug such as mianserin. Further detailed studies of psychotropic agents used in the treatment of post-partum disorders is required both to reassure nursing mothers and to establish risks for the infant.

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Adenosine agonists and global cerebral ischaemia

In his article on therapeutic interventions in acute stroke Dr Lees [1] mentioned that NMDA receptor antagonists may offer improved cytoprotection and thus exciting prospects for acute stroke treatment. In his paper he does not mention adenosine which is supposed to enhance cerebral ischaemic tolerance. What may be the effects of an increased adenosine concentration during ischaemia? Adenosine inhibits presynaptically the release of excitatory neurotransmitters such as glutamate and aspartate. Adenosine in concentrations found during brain ischaemia effectively blocks voltage dependent Ca channels and hyperpolarizes the presynaptic membrane by opening K channels [2]. Postsynaptically in addition to its Ca channel blockade, adenosine stabilizes the membrane potential by opening the K channels and in that way additionally prevents neuronal Ca accumulation [3].

Regarding the therapeutic use of adenosine or its metabolically stable analogues it is difficult to administer them because they produce severe side effects such as hypotension and cardiodepression. In order to study the neuroprotective action of increased intracerebral adenosine concentration we used a xanthine derivative propentofylline (1-(5′-oxohexyl)-3-methyl-7-propyl-xanthine) that decreased adenosine inactivation by inhibiting its cellular uptake. In our experiments male Wistar rats (mean weight: 292 g) were subjected to global forebrain ischaemia by 4-vessel occlusion [4]. In a two stage procedure the vertebral arteries were first cauterized at the level of the ala foramina. In a modification of the technique originally described by Pulsinelli crossclamping of the common carotid arteries was performed 7 days after the first procedure and for 10 min only. This way maximum survival could be achieved without inadequate brain stem perfusion causing respiratory failure. Global ischaemia was severe enough to cause irreversible and reproducible neurological damage to cortical and hippocampal structures. All rats were fasted overnight and had a mean body temperature of 36.9° C. Only animals having a flat line EEG record were included in the study. Postoperative convulsions or persistent EEG activity were exclusion criteria. In all cases anaesthesia was induced with pentobarbitone (32 mg kg^{-1} body weight i.m.). On the third postoperative day the brains were perfusion fixed with formaldehyde, removed, stored in formaldehyde and embedded in paraffin. Coronal sections were cut and stained with haematoxyllin- eosin. Only hyperchromatic cellular lesions were considered to be truly caused by global ischaemia rather than artefacts. Examination was performed in a blinded fashion by a neuropathologist. Propentofylline (0.75 mg kg^{-1}, intraperitoneally) was administered in the treatment group ($n = 15$) immediately after declamping with the onset of reperfusion. The reference group ($n = 15$) did not receive any cerebroprotective drugs and additionally three animals were sham operated with induction of anaesthesia only without causing cerebral ischaemia. Differences in neuronal damage between control animals and treated rats were statistically analyzed by multi-variant analysis (Student-Newman-Keul Test).

Looking at the rat brain as a whole there were more than 4% cellular lesions in the control group in contrast to 0.8% in the treatment group ($P < 0.01$). In our experimental model cortical and neocortical regions proved to be most vulnerable when exposed to global

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