digoxin exposure, using the previously described technique.

The results of this study are shown in Table 1. No statistical significant differences were demonstrated in the studied parameters in normal spermatozoa between the different digoxin concentrations in this *in vitro* study (non-parametric Wilcoxon Rank Sum Test).

The results showed a lack of effect of digoxin *in vitro* on various parameters of normal human spermatozoa functions.

Although the exact mode of action of the cardiac glycosides is not fully understood, their principal action involves the inhibition of a Na-K ATPase (Smith, 1988). The interaction between digoxin and the sodium pump shows all the characteristics of a drug-receptor relationship, including specificity, affinity and reversibility (Howarth *et al.*, 1990).

The present results are in contradiction to the ouabain effect on spermatozoa motility shown in different animal species. Two explanations for these variations are suggested, 1) a wide variation in cardiac glycoside binding affinity of the constitutive form of the alpha-subunit between some mammalian species (Herrera *et al.*, 1987) or/and 2) methodological differences.

Further studies using the other Na-K ATPase inhibitors are needed to elucidate the role of this enzyme in human spermatozoa motility in normal and abnormal conditions.

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Excretion of temazepam in breast milk

Temazepam is a short-acting benzodiazepine hypnotic which is commonly prescribed for breast feeding mothers during the first 1–2 weeks following delivery. To our knowledge, there is only one report of temazepam in breast milk in a woman who was taking high-dose diazepam and oxazepam (Dusci *et al.*, 1990). Since there is widespread patient and physician concern over drug transfer into breast milk, we undertook a study to assess the excretion of temazepam into milk during the routine use of temazepam as a hypnotic in the early post partum period.

The study was approved by the Ethics Committee of the King Edward Memorial Hospital for Women and 10 breast feeding women gave written informed consent to their participation. The women ranged in age from 24–34 years, weighed between 59 and 74 kg and were less than 15 days post partum. Temazepam (10–20 mg) was given as a bedtime hypno-sedative and all participants had received the drug for at least 2 days prior to study. Milk samples were collected immediately before and after a feed and venous blood samples were taken 0.4–1.6 h after the mid-point of the feed. In two studies, blood samples were obtained from the nursing infants at the same time as the maternal sample. The concentrations of temazepam and oxazepam in plasma and milk were measured by high performance liquid chromatography as described previously (Dusci *et al.*, 1990) with the minor modification that a detection wavelength of 240 nm was used. The limit of detection for both drugs was 5 $\mu g\ l^{-1}$. Several of the women were taking other concurrent medications, but none of these interfered in the assay procedure.

Data for the mothers are summarised in Table 1. The temazepam dose rate varied from 0.16–0.32 mg kg^{-1} day^{-1}. Temazepam (53 ± 16 $\mu g\ l^{-1}$; mean ± s.e.mean) was present in plasma from all participants while oxazepam (7 and 9 $\mu g\ l^{-1}$) could be detected only in patients 4 and 10 respectively. In milk, temazepam was detected at concentrations of 28 and 26 $\mu g\ l^{-1}$ in the pre and post feed samples respectively for patient number 10 only, while oxazepam was below the limit of detec-

Table 1 Temazepam dose rate, and concentrations of temazepam and oxazepam in maternal plasma

Patient[a] *number*	*Dose* (*mg kg*$^{-1}$ *day*$^{-1}$)	*Blood sample time* (*h after dose*)	*Plasma concentration* (*μg l*$^{-1}$) *Temazepam*	*Oxazepam*
1	0.16	13.3	58	<5
2	0.17	14.8	36	<5
3	0.18	21.3	8	<5
4	0.20	13.9	55	7
5	0.27	10.3	43	<5
	0.27	12.8	46	<5
6	0.29	12.5	32	<5
7	0.31	14.6	42	<5
	0.15	16.5	19	<5
8	0.31	13.5	18	<5
9	0.31	17.6	48	<5
	0.31	14.4	53	<5
10	0.32	14.1	234	9

[a]Patients 5, 7 and 9 were studied on each of two consecutive days.

tion for all patients. The milk:plasma ratio for temazepam was 0.12 in patient 10 and ranged from <0.09–<0.63 (mean <0.18) in the other nine patients where its milk concentration was below the limit of detection.

The mean plasma concentrations of temazepam (measured 14.6 ± 0.7 h after dose) were similar to 24 h steady-state trough concentrations reported following single or multiple 20 mg oral doses of the drug in healthy volunteers (Fuccella *et al.*, 1977; Ochs *et al.*, 1984). The milk:plasma ratios are in agreement with those previously reported for temazepam, as a metabolite of diazepam (Dusci *et al.*, 1990).

The milk:plasma ratio for temazepam was similar to those for lormetazepam and oxazepam (Humpel *et al.*, 1982; Wretlind, 1987), but was approximately one half of those for diazepam, *N*-desmethyldiazepam or lorazepam (Brandt, 1976; Summerfield & Neilsen, 1985), one third of that for clonazepam (Soderman & Matheson, 1988), one fifth of those for nitrazepam and flunitrazepam (Kanto *et al.*, 1979; Reider & Wendt, 1973) and one fortieth of that for quazepam (Hilbert *et al.*, 1984). This order of milk:plasma ratios for the benzodiazepines is in general agreement with the order of the log P octanol/buffer coefficients for these drugs (Greenblatt *et al.*, 1983a; Hilbert *et al.*, 1984). Predictably, the relatively water soluble temazepam partitions poorly while the highly lipid soluble quazepam partitions extensively into milk. Neither temazepam nor its metabolite oxazepam could be detected in the plasma taken from the infants of patients 1 and 2. No adverse effects related to temazepam were observed in any of the ten infants.

The significance of neonatal temazepam intake via breast milk will be determined by the concentration in milk, the amount absorbed and its clearance in the infant. In adults, the major pathway for metabolism of temazepam is by conjugation with glucuronic acid and there is also a minor *N*-demethylation pathway to oxazepam (Greenblatt *et al.*, 1983b). While the disposition of temazepam in neonates has not been documented, several isoenzymes of UDP-glucuronosyltransferase have been identified in the neonatal liver. Glucuronidation of bilirubin, testosterone and 1-naphthol at birth was only 10–20% of adult levels increasing to 20–130% of adult levels at twelve months of age (Coughtrie *et al.*, 1988). Thus neonates are likely to have limited ability to eliminate temazepam by glucuronidation. In addition, the half-life of oxazepam which is cleared largely by glucuronidation is known to be three to four fold longer in neonates than adults (Tomson *et al.*, 1979).

Limitations of the present study include the fact that milk and plasma drug concentrations were measured some 15 h after a hypnotic dose of temazepam and that our patients were studied in the first 2 weeks post partum, at a time when milk lipid and protein composition may be variable. Nevertheless, only very small amounts of temazepam were found in breast milk and even if bioavailability was high, the neonate would receive negligible amounts of temazepam. Although our study shows low neonatal exposure to temazepam via breast milk, infants so exposed should be monitored carefully for drug effects such as somnolence and poor feeding.

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Itraconazole concentrations in airway fluid and tissue

The treatment of allergic bronchopulmonary aspergillosis (ABPA) is predominantly symptomatic, with oral corticosteroids being used to limit the host's immune response to *Aspergillus*. Despite demonstrable *in vitro* activity, oral and inhaled antifungal agents have been reported to be of little value in treating ABPA (Crompton & Milne, 1973; Thompson, 1988). Presumably this is related to poor penetration into lung tissue although no data are available regarding antimycotic drug concentrations in such tissues.

The antifungal agent, itraconazole, is an orally effective imidazole compound which is particularly active against *Aspergillus* species and, therefore, has been used in patients with invasive aspergillosis and aspergilloma (Denning *et al.*, 1989; Impens *et al.*, 1990). However the potential for this agent to be used in ABPA will depend on its ability to achieve effective concentrations in both mucosal secretions and airway tissues. It seems likely that sufficient lumenal and mucosal concentrations will be required to reduce the fungal population in the airway lumen and thereby reduce the potential for enhancing the immunological response.

Recently we treated a patient with severe ABPA with itraconazole and obtained samples for drug assay.

A 40 year old man with seemingly corticosteroid resistant ABPA was successfully treated with itraconazole for several months. He underwent routine fibreoptic bronchoscopy 28 h after the last dose of a course of treatment with 100 mg itraconazole given on alternate days. During the procedure bronchial washings,

Table 1 Itraconazole concentrations in bronchoalveolar lavage fluid, airway tissue, plasma and nails

Sample	*Itraconazole concentrations*	
Bronchial washings	5–14 nmol l^{-1}	(n = 2)
Bronchoalveolar lavage	13–25 nmol l^{-1}	(n = 3)
Bronchial biopsy	1.7 pmol mg^{-1} dry weight	(n = 5, pooled)
Plasma*	0.85 μmol l^{-1}	
Nails*	0.31 pmol mg^{-1} dry weight	

*Sample taken several months earlier while dosage was 200 mg day^{-1}.

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