indicated by authors), because in our study, blood samples were drawn as soon as 2 min after bolus end.

The total body clearance ($Cl_t = 615$ ml/min) showed that elimination occurred by the extra-renal as well as renal routes. Renal clearance ($Cl_u = 190$ ml/min) represents one-third of total clearance. This value is in good agreement with urine elimination of unchanged drug measured as % of drug injected ($30.3 \pm 4.4\%$ during the first 24 h and $30.8 \pm 4.5\%$ in 72 h). The urine elimination of acetylmetabolite is $14.9 \pm 3.3\%$ in 24 h and $17.9 \pm 4.0\%$ in 72 h (% of drug injected, corrected for molecular weight).

The volume of tissue distribution ($V_3 = 1.0$ l/kg) of acebutolol is the lowest of β-adrenoceptor-blockers; it is comparable with atenolol (1.3 l/kg, Mason, Winer, Kochat, Cohen & Bell, 1979), oxprenolol (1.3 l/kg, Mason & Winer, 1976) and practolol (1.6 l/kg, Bodem & Chidsey, 1973); metoprolol has the highest V_3 (5.6 l/kg, Regardh, Borg, Johansson, Johnsson & Palmer, 1974).

In conclusion, acebutolol pharmacokinetic analysis, after a bolus infusion, can be described as a three open compartment model.

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CONTROLLED TRIAL OF METOCLOPRAMIDE IN THE INITIATION OF BREAST FEEDING

The superiority of breast milk for the health of the human neonate is unchallenged. However, many women do not succeed in breast feeding and abandon it early because of anxiety that the child is not being adequately fed. It is not clear how many of these women have a genuinely inadequate supply of milk but it would be an advantage if some means existed of increasing milk production temporarily. Increasing prolactin secretion might be a possible approach.

Synthetic thyrotropin releasing hormone (TRH, Roche) stimulates prolactin release (Jeppsson, Nilsson, Rannevik & Wide, 1976) and increases milk production in lactating women (Tyson, Khojandi, Huth & Andreasson, 1975; Zarate, Villalobos,

Canales, Soria, Arcovedo & MacGregor, 1976). Metoclopramide (Maxolon, Beecham) is a more effective releasing agent for prolactin than TRH. There is some indication that it increases milk production in women with lactation failure (Sousa, 1975). One placebo controlled trial showed that metoclopramide was more effective than placebo at maintaining failing lactation (Guzman, Toscano, Canales & Zarate, 1979).

In the present study, the extent to which metoclopramide passed into breast milk was first investigated. Ten patients who were breast feeding their infants 7–10 days after delivery were given a single oral dose of 10 mg metoclopramide. Two hours later, samples of blood and of expressed breast milk were obtained. Metoclopramide concentrations were measured in these samples by gas liquid chromatography (Bateman, Kahn, Mashiter & Davies, 1978).

The mean ($\pm$s.e. mean) concentration of metoclopramide base in plasma 2 h after dosing was 68.5 ± 29.6 ng/ml. The mean concentration in breast milk at the same time was 125.7 ± 41.7 ng/ml. These figures are consistent with the known tendency (Rasmussen, 1966) for basic drugs to be more highly concentrated in milk which is acidic, pH 7.0, compared with plasma. Even assuming a total milk intake of 1 l/day, the average intake of metoclopramide by the infant would not exceed 130 μg or 45 μg/kg, a subtherapeutic dose.

Following this initial study a randomized controlled trial of metoclopramide treatment was carried out. Patients undergoing elective or emergency Caesarean section were asked how they intended to feed their babies. Those intending to breast feed for a minimum of 3 months were recruited into the study and allocated at random and double-blind to active or placebo treatment. Active treatment consisted of metoclopramide 10 mg orally 3 times daily from the first postoperative day for 7 days. Placebo treatment was identical except that the capsules used were filled with lactose. Patients were visited daily by one of the investigators and at each visit their problems with breast feeding were discussed and advice and encouragement was given. Outcome was assessed by the mode of feeding of the baby at 10 days, 6 weeks and 3 months after delivery. All clinical studies were approved by the Ethics Committee of Queen Charlotte's Hospital.

Twenty women were recruited into the study and all completed the protocol. No subjective or objective side effects which could be related to drug treatment were noted. The ten women randomly allocated to metoclopramide were in most respects similar to those assigned to receive placebo (see Table 1). About half the women were sectioned electively and three of those in each group were significantly premature. However, while three infants in the metoclopramide group had to be nursed in the paediatric intensive care ward, none of the placebo group babies were separated from their mothers.

All twenty mothers succeeded in establishing breast feeding and all were breast feeding when they were discharged from hospital. However, at 6 weeks two mothers in the placebo group and one in the metoclopramide group had stopped breast feeding while at 3 months the fallout was considerably greater (6 in each group).

Two interesting conclusions can be drawn from this study. The first is that metoclopramide treatment has not been demonstrated superior to placebo treatment in establishing breast feeding in women after Caesarean section. The second conclusion is that both treatments were remarkably successful. Women who had had a Caesarean section were chosen because they find it particularly difficult to breast feed and the 100% success rate in establishing breast feeding seen here is remarkable; our previous experience had suggested that fewer than half of these women would succeed. Unfortunately, actual figures on the rate of success in breast feeding after Caesarean section are difficult to find; none seem to have been published. Why did the women in this trial succeed so remarkably even when given lactose placebo? The most obvious explanation is that these women were involved in a trial and were thus motivated strongly to succeed in their intention and the advice and encouragement they received was sufficient to enable them to overcome their various difficulties. It is particularly noteworthy that even those three women whose babies remained in the intensive care ward for 4, 6 and 17 days respectively, established breast feeding, commencing by expressing their milk to enable it to be tube-fed to their infants.

Our most important conclusion is, therefore, that

Table 1 Comparison of mothers in the two treatment groups and their success in breast feeding

	Placebo group	*Metoclopramide group*
Number	10	10
Maternal age $\pm$s.e. mean	32 ± 3	30 ± 6
Primip/Multip	9/1	8/2
Elective/Emergency	4/6	5/5
Premature delivery <37 weeks	3	3
Infants in special care	0	3
Breast feeding at		
10 days	10	10
6 weeks	8	9
3 months	4	4

interest, advice and encouragement are of paramount importance in enabling a woman to establish successful breast feeding. The study also demonstrates the absolute necessity of studying a placebo control group in evaluating any treatment thought to be of benefit in establishing breast feeding.

However, this negative result does not allow us to dismiss metoclopramide entirely as being of no potential value to women attempting to breast feed. The treatment appears to be well tolerated and it is a subjective impression that the three women who expressed breast milk may have succeeded particularly well as a result of the treatment. In less favourable circumstances, such as secondary lactation failure or where practical support for breast feeding women is less good, then the treatment might still be worthy of trial, particularly if it were given for a longer period. Since completing the trial, a similar investigation comparing placebo with metoclopramide 20 mg daily has been published in twenty-one puerperal women with a post-history of defective lactation. Those patients treated with active drug had a persistent elevation of prolactin levels and maintained good lactation. The placebo treated women showed an abrupt fall in prolactin and failure of lactation (Guzman, Toscano, Canales & Zarate, 1979). Our results indicate that the small net excretion of the drug is unlikely to be a hazard for the infant.

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