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Letter to the Editors

Cimetidine does not appear to influence the distribution of metformin into human milk

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Three studies support the use of metformin in breastfeeding, with infant exposure that is <1% of the weight-adjusted maternal dose [1–3]. These studies further demonstrate that metformin has an unusually flat concentration–time profile in milk relative to plasma [1, 2]. This is in contrast to most drugs that display parallel milk and plasma profiles consistent with passive diffusion of unionized and unbound drug as the dominant mode of transfer [4]. Additionally, the observed milk to plasma (M : P) ratio based on the respective area under the concentration–time curves (AUCs) of 0.3–0.7 [1, 2] is lower than the ratios of 3.0 [5, 6] and 2.3 [7] predicted from two models that assume passive diffusion into milk [1]. Consequently, it seems likely that transport mechanisms other than passive diffusion may account for the distribution of metformin into milk.

The mRNA of many drug transporters including organic cation transporters (OCTs) has been identified in human lactating mammary epithelial cells [8]. Metformin is known to be a substrate for OCT1 and OCT2, which are involved in the hepatic and renal distribution of this compound, respectively [9, 10]. We undertook preliminary work to determine whether cimetidine, which has previously been shown to inhibit the renal tubular secretion of metformin via competitive inhibition of OCTs (presumably OCT2) [11] might influence the distribution of metformin into milk. Our aim was to study formally six mothers if an initial pilot of one individual suggested a signal was likely.

A healthy 35 year old Caucasian female (59 kg) who was on no other drug therapy and was ready to wean her 7 month old male infant (8.5 kg) from breast milk was studied. Cimetidine 400 mg twice daily (at 12 h intervals) was administered for seven doses, commencing at 20.00 h on the evening prior to administration of metformin. This is the dose that has been shown previously to inhibit the renal elimination of metformin [11]. A single dose of metformin 500 mg was given at 08.00 h the following day, and blood (5–10 ml) sampled at 0, 1, 2, 4, 8, 12, 24, 48 and 72 h, and the breasts emptied of milk via a breast pump approximately four times per day until 72 h post-dose. Metformin concentrations were analyzed using a previously published method with a limit of detection of 20 μg l^{-1} [12]. Pharmacokinetic analysis was undertaken using WinNonLin (Version 5.2) [Pharsight Corporation, Mountain View, CA, USA]. The AUCs from 0 to 72 h (AUC(0,72 h)) and 0 to infinity (AUC(0,∞)) were calculated using the log-linear trapezoidal rule. For extrapolation of the AUC from the last measurable point to infinity, the elimination rate constant was estimated using linear regression of the visually determined elimination phase. The relative infant dose in milk was calculated as previously published [1, 13]. For this calculation, it was assumed that the AUC(0,∞) after one dose of metformin 500 mg would be equivalent to the AUC(0,12 h) for a steady-state dosing regimen of 500 mg twice daily. Approval was obtained from the Canterbury Ethics Committee (New Zealand). Informed written consent was obtained from the participant.

Overall, the concentration–time profiles of metformin in plasma and milk were similar in appearance to those described in our previous study, where metformin 500 mg was administered to five women on no other interacting drugs (Figure 1) [1]. The plasma AUC(0,72 h) and AUC(0,∞) were comparable, at 2.98 and 3.03 mg l^{-1} h respectively, and were slightly below the range of 3.11–6.36 mg l^{-1} h seen in the earlier study [1]. For milk, the AUC(0,72 h) of 2.65 mg l^{-1} h was similar to what was observed in the two previous subjects who provided milk samples to 72 h (1.47 and 3.00 mg l^{-1} h). However, in the current case the AUC(0,72 h) accounted for less than 60% of the AUC(0,∞) (4.57 mg l^{-1} h) whereas in the two earlier cases it accounted for >94% [1]. The observed M : P_{AUC} based on a 72 h collection period was 0.9 whereas utilization of the AUC(0,∞) data suggested a higher M : P_{AUC} of approximately 1.5. These are both greater than the 0.3–0.7 observed in the previous study [1]. It is not clear whether this is the result of interindividual variability irrespective of

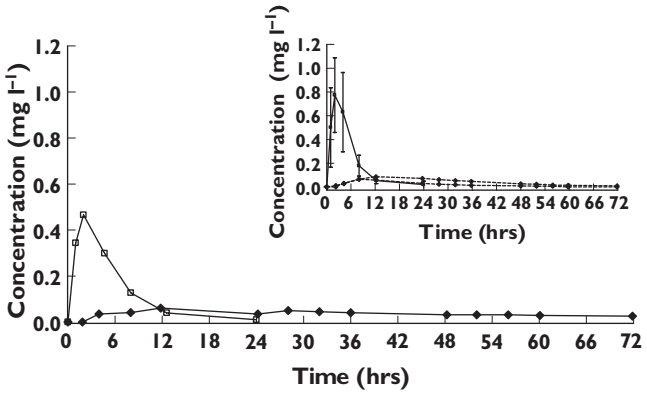

Figure 1

Concentration–time profile of metformin in plasma (□) and milk (◆) in a healthy volunteer after a single 500 mg dose during co-administration with cimetidine 400 mg twice daily. Insert: Plasma ($n = 5$) and milk ($n = 2$) concentrations after a single dose of metformin 500 mg in women not taking cimetidine [1]. Data presented as mean and 95% CI for the five subjects with plasma data, and as individual values for the two subjects who provided milk to 72 h post-dose

cimetidine administration or an influence of cimetidine over the distribution of metformin into milk.

Regardless of the observed variability in the AUC of metformin in milk, the calculated infant dose was approximately 0.3% of the weight-adjusted maternal dose. This is comparable with what has been observed previously [1–3] and is at least an order of magnitude less than the value of 10% which is often used to guide safety [13] indicating that cimetidine does not appreciably change the safety profile of metformin in breastfeeding.

The findings of this case do not necessarily refute the involvement of OCT in the disposition of metformin into milk, but suggest that the influence of cimetidine on the overall safety of metformin in breastfeeding is minimal.

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