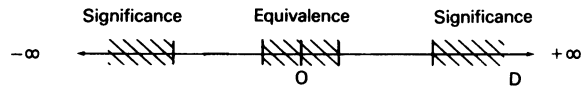

Figure 1 Conclusions for increasing values of the observed difference (sample size and variance being equal). For given sample size and variance, large differences can reach significance; small differences can (eventually) allow rejection of the hypothesis that treatments differ by the smallest relevant difference. In-between (eventually) may be a region of indifference (no conclusion possible).

This process, mentioned by Feinstein (1975) as calculation of 'P_B' can be applied to comparisons of two proportions with a method described by Dunnet & Gent (1977) or to a comparison of two means, as in a trial comparing two antidepressants by Coudray, Dufour, Garello, Mollo, Pascal, Poisson, Scotto, Simart, Sormani & Tourane (1978) with a test using non-central t-distribution. If, for a positive observed difference, a positive Δ is not rejected, it may be possible to reject the opposite hypothesis $\delta = -\Delta$.

In that case, one of the treatments can be told to be 'at least equivalent' to another.

It is interesting to notice that this problem is symmetrical to the question recently discussed in this Journal (Chaput de Saintonge, Vere & Sharman, 1977; Wade & Waterhouse, 1977), namely: if treatments are significantly different, is a clinically relevant difference proven?

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References

BARR, D.R. (1969). Using confidence intervals to test hypotheses. *J. quality Technology*, **1**, 256–258.

CALIMLIM, J.F., WARDELL, W.M., LASAGNA, L., GILLIES, A.J. & DAVIS, H.T. (1974) Effect of naloxone on the analgesic activity of methadone in a 1:10 oral combination. Time and cost of flirting with the null hypothesis in tests of equivalence. *Clin. Pharmac. Ther.*, **15**, 556–564.

CHAPUT DE SAINTONGE, D.M. VERE, D.W. & SHARMAN, V.L. (1977). Diazepam or nitrazepam? a question of cost. *Br. J. clin. Pharmac.*, **4**, 492–494.

CHAPUT DE SAINTONGE, D.M. & MENDELL, N.R. (1977). Power curves in clinical trial reports. *Br. J. clin. Pharmac.*, **4**, 656 P.

CORONARY DRUG PROJECT GROUP (1973). The Coronary Drug Project. Design, methods and baseline results. *Circulation*, **47**, 1–50.

COUDRAY, J.P., DURFOUR, H., GARELLO, J.L. MOLLO, Y., PASCAL, F., POISSON, D., SCOTTO, J.C., SIMART, G., SORMANI, J. & TOURANE, G. (1978). Un essai Nomifensine–Nortriptyline mené en double-aveugle et en ambulatoire par des psychiatres praticiens. Résultats et commentaires. *Nouv. Presse Med.*, **7**, 2333–2338.

DEROGATIS, L.R., BONATO, R.R. & YANG, K.C. (1968). The power of IMPS in psychiatric drug research as a function of sample size, number of raters, and choice of treatment comparison. *Arch. Gen. Psychiat.*, **19**, 689–699.

DUNNETT, C.W. & GENT, M. (1977). Significance testing to establish equivalence between treatments with special reference to data in the form of 2 × 2 tables. *Biometrics*, **33**, 593–602.

FEINSTEIN, A.R. (1975). Clinical biostatistics XXXIV the other side of 'statistical significance' alpha, beta, delta, and the calculation of sample size. *Clin. Pharmac. Ther.*, **18**, 491–505.

MATTHYSSE, S. (1978). Concept of 'significance' misunderstood. *Arch. Gen. Psychiat.*, **35**, 904.

OVERALL, J.E., HOLLISTER, L.E. & DALAL, S.N. (1967). Psychiatric drug research. Sample size requirement for one vs. two raters. *Arch. Gen. Psychiat.*, **16**, 152–161.

SACKETT, D.L., SPITZER, W.O., GENT, M. & ROBERTS, R.S. (1974). The Burlington randomized trial of the nurse practitioner: Health outcomes of patients. *Ann. intern. Med.*, **80**, 137–142.

SPRIET, A. & BEILER, D. (1978). Table to facilitate determination of symmetrical confidence intervals in bioavailability trials using Westlake's method. *Eur. J. Drug Metab. Pharmacokin.*, **2**, 129–132.

STRICKLAND, I.D., CHAPUT DE SAINTONGE, D.M., BOULTON, F.E., FRANCIS, B., ROUBIKOVA, J. & WATERS, J.I. (1977). The therapeutic equivalence of oral and intravenous iron in renal dialysis patients. *Clin. Nephrol.*, **7**, 55–57.

WADE, O.L. & WATERHOUSE, J.A.H. (1977). Significant or important? *Br. J. clin. Pharmac.*, **4**, 411–412.

WESTLAKE, W.J. (1976). Symmetrical confidence intervals for bioequivalence trials. *Biometrics*, **32**, 741–744.

WULFF, H.R. (1973). Confidence limits in evaluating controlled therapeutic trials. *Lancet* **i**, 969–970.

THE LEVELS OF ANTICONVULSANTS IN BREAST MILK

It has been suggested that when epileptic women being treated with anticonvulsant drugs become pregnant, the drug might be transferred through the placenta (Mirkin, 1971; Rane, Garle, Borgå & Sjöqvist, 1974; Rane, Bertilsson & Palmer, 1975; Hosokawa, Yamamoto, Kugo, Hirata, Otsuki,

Suzuki & Chiba, 1978) and therefore might affect the foetus. Furthermore, if an infant is suckled by a mother taking anticonvulsants, the drug might be administered to the infant indirectly through the maternal milk.

There have been few reports (Mirkin, 1971; Pynnönen & Sillanpää, 1975; Pynnönen, Kanto, Sillanpää & Erkkola, 1977; Svensmark & Schiller, 1960) about the concentration of anticonvulsants in maternal milk and to help elucidate this problem, we report here the relative concentrations of diphenylhydantoin (DPH), phenobarbital (PB), primidone (PMD), carbamazepine (CBZ) and ethosuximide (ETS) in maternal serum and milk.

Our subjects were nine female patients with epilepsy being treated at Hirosaki University Hospital and its related hospitals. Their ages ranged from 22 to 30 years (mean age, 26.4 ± 3.2 years).

Milk and serum were collected simultaneously during the period from the third to 32nd day after delivery (mean period, 10.4 ± 1.5 days). All subjects had received several anticonvulsants. Women who took their drugs irregularly before and after the delivery, or those who were given prolactin intramuscularly were also included in this trial. The samples were stored in a refrigerator immediately after collection. Serum and milk levels of the drugs were measured using gas liquid chromatography (GLC) and enzyme immunoassay (EMIT, Anti-epileptic Drugs Assay, 1975). Measurement by GLC was performed using a slight modification (Kaneko, 1978) of Miyamoto's method (Miyamoto, Seino, Ikeda & Yamagami, 1973).

Chronological observations were not made in the present investigation except for a few cases where the drug levels in the serum and maternal milk were measured several times after the delivery. The concentration of the drugs in maternal serum lay in the following ranges: from 2.1 to 5.7 μg/ml for DPH, 2.5 to 42 μg/ml for PB, 0.8 to 15.7 μg/ml for PMD, 3.2 to 6.2 μg/ml for CBZ and 18 to 39 μg/ml for ETS. In the same patients the following amounts of anticonvulsants were excreted into the milk: 0.5 to 1.4 μg/ml of DPH, 0.5 to 33.0 μg/ml of PB, 0.5 to 6.7 μg/ml of PMD, 0.8 to 3.8 μg/ml of CBZ and 18 to 24 μg/ml of ETS. The relationship of the anticonvulsant level in milk to that in serum (milk/serum ratio, (M/S) expressed as a %) is shown in Table 1. The ratios for the various anticonvulsants were as follows: about 18% for DPH, about 45% for PB, about 80% for PMD, about 39% for CBZ and about 78% for ETS. The values for PB showed wide variation. The M/S ratio of PMD and ETS was high and these drugs seemed to be highly excreted in milk.

There have been several previous reports which show that anticonvulsants are excreted into milk. In 1960, Svensmark & Schiller reported the concentration of DPH in milk. In their study, when the serum level of DPH was 28 μg/ml, 6 μg/ml of the drug was excreted into the milk; the M/S value, therefore, being about 21%. There is a close agreement between Svensmark & Schiller's (1960) value and the value obtained in the present study (18%). Mirkin (1971) reported the concentration of DPH in milk in two patients. In these patients about 19–47% and 43–69% of the serum level of DPH were excreted into the milk respectively. These values are higher than those presented here. Pynnönen and his co-workers reported (1975, 1977) that about 60% of the serum level of CBZ was excreted into milk. Although one case in our study showed an M/S ratio of about 61% the mean ratio (about 39%) was lower than that given by Pynnönen's group.

Though the mean M/S ratio for PB was 45%, it was noted that individual values deviated widely and the reason for such variations is unknown. However, since its ionization constant (pK_a) is 7.2 (Vajda, Williams, Davidson, Falconer & Breckenridge, 1974) it might be suggested that PB is excreted into milk by the same mechanism as its excretion into saliva (McAuliffe, Sherwin, Leppik & Pippenger, 1977; Kaneko, 1978; Honda, Nishihara, Koda, Saito,

Table 1 Anticonvulsant serum and milk concentrations

Drug	*Serum concentration (μg/ml)*	*Milk concentration (μg/ml)*	*Milk concentration/ serum concentration (%)*	n
DPH	4.5 ± 1.4	0.8 ± 0.3	18.1 ± 5.9	9
PB	19.3 ± 14.5	10.4 ± 10.8	45.9 ± 24.9	8
PMD	2.8 ± 2.5	2.3 ± 2.2	80.9 ± 17.6	12
CBZ	4.3 ± 1.7	1.9 ± 1.6	39.4 ± 19.3	3
ETS	29.3 ± 8.0	21.3 ± 2.8	78.8 ± 32.8	4

Each value is the mean ± s.d.
DPH = diphenylhydantoin PB = phenobarbitone PMD = primidone
CBZ = carbamazepine ETS = ethosuximide

Nakagawa & Tamura, 1978). Ionized PB molecules do not pass easily through the lipoid membrane of the mammary gland cells and as the pH of the milk affects the ionization of PB, the change of pH may greatly affect the M/S ratio of the drug. The ratio of the salivary level of PB to the serum level (sa/se ratio) was $31.7 \pm 9.5\%$ (Kaneko, 1978). The reason for the M/S ratio being higher than the sa/se ratio might be due to the pH of milk being more neutral than that of saliva.

PMD and ETS showed high levels in milk (high M/S ratio) and both anticonvulsants were also excreted readily into saliva (Kaneko, 1978; Honma, Kaneko & Suzuki, in preparation). In the case of DPH and CBZ there was no significant difference between the M/S ratio (18.1 ± 5.9, 39.6 ± 19.3 respectively) and the sa/se ratios (13.4 ± 4.6, 31.8 ± 8.3 respectively) (Kaneko, 1978) and there is a possibility that the M/S ratio could be estimated from the sa/se ratio for these drugs.

In our study, the serum levels of various anticonvulsants were somewhat lower than reported therapeutic levels (EMIT, 1975; Kaneko, Suzuki, Fukushima & Sato, 1978). An investigation is now in progress to determine whether this was due to the pregnancy or to irregular medication during the pregnancy.

In order to decide whether epileptic mothers should be allowed to give their milk to their infants many factors should be considered, including the maternal doses of anticonvulsants, the suckling volume of milk and the metabolic capacity of the infants. Firstly, the amount of anticonvulsants transferred to the infant through the milk can be calculated from the product of the suckled volume of the milk and the concentration of anticonvulsants in the milk. Since Japanese mothers have a tendency to refuse to have their milk taken, we have to measure anticonvulsants level in saliva or serum. If the M/S ratio or the sa/se ratio is determined accurately, the concentration of anticonvulsants in milk can be estimated by calculating the M/S ratio or the sa/se ratio $\times$ serum level of anticonvulsants. If anticonvulsants have been transferred through the placenta to the foetus, the drug may have already caused some enzyme induction at that stage and the capacity for metabolizing anticonvulsants may be expected to be elevated in the newborn (Pynnönen & Sillanpää, 1975). Further investigations would be necessary to confirm this possibility.

In our present study, one case showed the high value of 33 μg/ml of PB in the milk. If the suckled volume of the milk is estimated as 500 ml/day in the newborn, it means that in this case the neonate would take about 16.5 mg of PB a day. As this estimated amount is fairly high for an infant, bottle feeding should be given also to reduce intake of maternal milk.

Some of our patients experienced epileptic attacks during pregnancy or after the delivery. In these cases, higher doses of anticonvulsants were required to control the attacks. Such incidents may possibly cause an increase in the amount of anticonvulsants excreted in the milk. On the other hand, the maternal milk should be fed as much as possible, because the maternal milk provides the immunological protection to the infant. It is therefore necessary to investigate more completely how much anticonvulsant the infant can tolerate. The milk concentration should also be measured more accurately at fixed intervals after the delivery and without the complication of irregular medication and treatment with prolactin. With this provision, the effective criteria for suckling during anticonvulsant medication might be accurately established.

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References

EMIT (1975). *Antiepileptic Drug Assays,* Package Insert, Syva, Corp. Palo Alto, Calif. 94364.

HONDA, Y., NISHIHARA, K., KODA, Y., SAITO, Y., NAKAGAWA, F. & TAMURA, Z. (1978). Reliability and usefulness of salivary phenytoin and phenobarbital concentrations. *Jap. J. clin. Psychiat.*, **7**, 309–319 (in Japanese).

HONMA, H., KANEKO, S. & SUZUKI, K. (1979). Salivary ethosuximide level in chronically treated patients. In preparation.

HOSOKAWA, K., YAMAMOTO, H., KUGO, T., HIRATA, J., OTSUKI, S., SUZUKI, T. & CHIBA, T. (1978). Serum anticonvulsant level of mother—neonate during pregnancy and delivery. *Bull. J. Neurol. Soc.*, **19**, 171 (in Japanese).

KANEKO, S. (1978). A study on anticonvulsant level in body fluids. IInd report: Dialyzed serum (free form), CSF and saliva level. *Psychiat. Neurol. Jap.*, **80**, 29–42 (in Japanese).

KANEKO, S., SUZUKI, K., FUKUSHIMA, Y. & SATO, T. (1978). Study on carbamazepine serum level in epileptic patients treated only with carbamazepine: with special reference to its efficacy and side effects. *Psychiat. Neurol. Jap.* **80**, 537–560 (in Japanese).

McAULIFFE, J.J., SHERWIN, A.L., LEPPIK, I.E. & PIPPENGER, C.E. (1977). Salivary levels of anticonvulsants: a practical approach to drug monitoring. *Neurology*, **27**, 409–413.

MIRKIN, B.L. (1971). Diphenylhydantoin: placental transport, foetal localization, neonatal metabolism and possible teratogenic effects. *J. Pediatr.*, **78**, 329–337.

MIYAMOTO, K., SEINO, M., IKEDA, Y. & YAMAGAMI, H. (1973). Gas chromatographic determination of phenytoin, phenobarbitone, primidone, carbamazepine and pheneturide (or acetylpheneturide) from the same serum specimen. In *Methods of Analysis of Anti-Epileptic Drugs*, ed. Meijer, J.W.A., Meinardi, H., Gardner-Thorpe, C. & van der Kleijn, E., pp. 106–110. Amsterdam: Excerpta Medica.

PYNNÖNEN, S. & SILLANPÄÄ, M. (1975). Carbamazepine in mother's milk. *Lancet*, **ii**, 563.

PYNNÖNEN, S., KANTO, J., SILLANPÄÄ, M. & ERKKOLA, R. (1977). Carbamazepine: placental transport, tissue concentrations in foetus and newborn, and level in milk. *Acta pharmac. tox.*, **41**, 244–253.

RANE, A., GARLE, M., BORGÅ, O. & SJÖQVIST, F. (1974) Plasma disappearance of transplacentally transferred diphenylhydantoin in the newborn studied by mass fragmentography. *Clin. Pharmac. Ther.*, **15**, 39–45.

RANE, A., BERTILSSON, L. & PALMER, L. (1975). Disposition of placentally transferred carbamazepine (Tegretol®) in the newborn. *Eur. J. clin. Pharmac.*, **8**, 283–284.

SVENSMARK, O. & SCHILLER, P.J. (1960). 5,5-Diphenylhydantoin (Dilantin) blood level after oral or intravenous dosage in man. *Acta pharmac. tox.*, **16**, 331–346.

VAJDA, F., WILLIAMS, F.M., DAVIDSON, S., FALCONER, M.A. & BRECKENRIDGE, A. (1974). Human brain, cerebrospinal fluid and plasma concentrations of dephenylhydantoin and phenobarbital. *Clin. Pharmac. Ther.*, **15**, 597–603.

CIMETIDINE EXCRETION INTO BREAST MILK

Most drug substances are excreted into human breast milk, but early reports of finding no drug in milk have probably been limited by analytical deficiencies. The transfer of drug from plasma to milk is mainly brought about by passive diffusion of the unionized non-protein bound drug, though an active transport mechanism has been postulated to occur for some drugs (Rasmussen, 1971). Catz & Giacoia (1972) have discussed in detail the various physicochemical factors involved in drug excretion into milk.

The clinical significance of reports on drug concentration in human milk together with maternal serum concentrations (O'Brien, 1974; Anderson, 1977) has been hampered by methodological deficiencies. Firstly, the use of single dose administration does not truly reflect the clinical situation in which drugs are given chronically and thus may accumulate in the body depending on the half-life of the drug and the dosing interval. Secondly, the timing and frequency of blood and milk sampling may significantly influence the results obtained, since milk levels may not equilibrate as rapidly as plasma levels. For example, theophylline distribution into milk reaches a peak level 1–3 h after dosing compared with 30 min in plasma (Yurchak & Jusko, 1976). Finally, the extent of breast milk emptying may influence the milk to plasma ratio. It is the purpose of this communication to present the results of a study of cimetidine excretion into the milk of a nursing mother following (a) single dose administration in which the breast is frequently expressed of milk and (b) chronic dosing in which the drug is allowed to accumulate in plasma and milk.

The subject was a 25 year old (53 kg) nursing mother who had been breast feeding for 6 months. She received cimetidine for a radiologically proven duodenal ulcer and consented to participate in the study. On the first day of the study, as much milk as possible was expressed and the subject then received 400 mg cimetidine (Smith, Kline; Dauelsberg) (equivalent of two Tagamet tablets). During the next 10 h, five milk and blood samples were collected, milk was expressed as thoroughly as possible, and an aliquot was taken for subsequent analysis. During the following 3 days, the subject took 200 mg three times daily plus 400 mg at night, a dosing schedule recommended for duodenal ulcer treatment (Brogden, Heel, Speight & Avery, 1978). During this time, the subject expressed milk only when necessary to relieve discomfort, for her baby was now being bottle fed. On day 4 of the study, before the morning, midday and late afternoon dose, blood and milk samples were collected.

Cimetidine in plasma and milk was analysed by the HPLC method of Randolph, Osborne, Walkenstein & Intoccia (1977). A standard curve was prepared from drug free milk and plasma covering the concentrations between 0.05 and 4.5 μg/ml from milk and 0.5 to 2.0 μg/ml from plasma. When concentrations of cimetidine exceeded these limits, the samples were diluted with drug free plasma or milk as required. The coefficient of variation of cimetidine in milk was 3.1% ($n=5$) and in plasma 5.6% ($n=7$).

In all milk samples assayed, cimetidine was found in concentrations higher than those in the corresponding plasma sample. The results of the single dose study are