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SALICYLATE EXCRETION IN BREAST MILK

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SUMMARY

Excretion of salicylate in human breast milk was studied using a sensitive high-pressure liquid chromatographic method. Following oral administration of 500, 1000 and 1500 mg acetylsalicylic acid to 6 healthy nursing mothers, salicylate appeared in milk not later than one hour and reached its maximum levels (0.58, 1.60 and 3.87 mg%, respectively) in 2–6 h. The non-linear relationship between the dose and milk peak level is attributed to the well established saturable metabolism of salicylates.

INTRODUCTION

Many drugs are contraindicated in breast-feeding mothers since they may cross the blood–milk barrier and cause potential risk to the suckling infant (Anderson, 1977). Information regarding the kinetics of these transports are, however, limited. This is mainly due to the difficulties in finding volunteer mothers and/or to the lack of available sensitive methods for microdetermination of drugs in breast milk.

Acetylsalicylic acid (ASA) is administered to nursing mothers with precautions because it has been reported to appear in their milk (Kwit and Hatcher, 1935; Putter et al., 1974; Erickson and Oppenheim, 1979; Berlin et al., 1980). There is, however, controversy over the extent of its presence in breast milk. The purpose of this study was to determine the rate and extent of salicylate appearance into breast milk following administration of different oral doses of ASA to lactating mothers.

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MATERIALS AND METHODS

Volunteers

Six healthy nursing mothers who were fully informed about the objective of the experiment volunteered for the project. They ranged in age from 24 to 32 years with a mean of 29 years, weighed from 46 to 65 kg with a mean of 58 kg and were between 2 and 8 months post-partum with a mean of 5 months. The volunteers were not allowed any other medication a week prior to and during the experiment.

Methods

In a cross-over fashion, one, two and three 500 mg tablets of ASA[1] were orally administered to mothers one hour after a regular breakfast. Babies went to the breast prior to or immediately after the mother's breakfast and were not nursed during the experiment. The breasts were totally emptied after the last sample collections. Approximately 5 ml samples were collected at various time intervals (Table 1). Further milk samples were obtained from two mothers (S.J., 1500 mg of ASA and G.R., 1500 mg of ASA) 1.5 h after emptying the breasts. To avoid salicylate condensation in the fatty layer of milk separated upon storage, that would have resulted in non-homogeneous distribution of drug in milk, 1 ml of fresh samples were transferred to 25 ml Teflon insert screw cap glass centrifuge tubes and kept frozen until the day of analysis. Salicylate was extracted from the 1 ml thawed milk by adding a 1 ml solution of 10 μg/ml phenytoin in methanol as internal standard, a 0.5 ml solution of 20% potassium bisulfate as acidifier, sufficient distilled water to make up 5 ml and 10 ml ether. The tubes were shaken vigorously for 20 min. The ether layer was then removed, evaporated under vacuum and the residue was dissolved in 0.25 ml methanol. Aliquots of 25 μl were injected into a high-pressure liquid chromatograph[2] equipped with a dual-channel fixed wavelength (254 and 280 nm) ultraviolet detector and a 30 cm RP-ODS column with an inside diameter of 3.9 mm and a 10 μm (spherical) particle size [3]. The mobile phase was methanol–water–acetic acid (30 : 65 : 5) which was pumped with a flow-rate of 2 ml/min under 2100 psi pressure.

Salicylate was quantified against salicylic acid standards, prepared in presence of drug-free human milk, under the same conditions described above. The peak height ratio method was employed and a linear relationship (correlation coefficient of 0.99) was found between the height ratio and amount in the examined range (0.20–15 μg).

Retention times for salicylic acid and phenytoin were 5.7 and 11.5 min, respectively. No interfering peaks resulted from blank milk or samples taken prior to the drug administration. Under these conditons, ASA appeared 4.4 min after the injection. The observed 280/254 ultraviolet absorption for salicylic acid was 2.51 and phenytoin had negligible absorption at 280 nm.

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[1] Aspirin, Bayer, Iran.

[2] Model 224U, Waters Associates.

[3] μ-Bondapac C-18, Waters Associates.

TABLE 1

BREAST MILK SALICYLATE CONCENTRATIONS (mg%) FOLLOWING ADMINISTRATION OF 500, 1000 AND 1500 mg ACETYLSALICYLIC ACID TO HEALTHY NURSING MOTHERS

Subject	Dose (mg)	Hours after administration						
		1	2	3	4	5	6	8
S.A.	500	0.33	0.50	0.50	0.50	0.33	0.22	–
	1000	0.83	1.29	1.46	1.51	–	1.40	–
	1500	2.29	3.41	4.81	4.20	4.78	4.10	–
S.S.	500	–	0.67	–	0.67	–	0.60	–
	1000	–	1.24	–	1.05	–	0.99	–
	1500	0.81	2.11	2.81	–	2.75	–	1.73
Z.A.	500	0.31	0.48	–	0.40	–	0.38	–
	1000	0.80	1.80	–	1.63	–	1.57	–
B.N.	500	0.35	0.62	–	0.78	–	0.41	–
	1000	1.11	2.00	–	1.80	–	2.11	–
	1500 *	1.35	2.81	–	3.39	–	2.70	–
S.J.	500	0.42	0.57	–	0.60	–	0.28	–
	1000	1.30	1.76	–	1.63	–	1.49	–
	1500	–	4.35	–	4.44	–	4.41	–
G.R.	500	0.42	0.42	–	0.40	–	0.21	–
	1000	1.18	1.17	–	1.20	–	0.98	–
	1500 *	1.87	3.33	–	3.96	–	3.71	–

* 1.5 h following termination of the test and emptying the breasts, the examined samples showed no detectable salicylate.

RESULTS AND DISCUSSION

Table 1 depicts salicylate concentrations in breast milk of nursing mothers taking single oral doses of 500, 1000 and 1500 mg ASA. Salicylate appeared in all the examined samples not later than 1 h (first samples) post-dosing indicating a rapid passage into breast milk. In all cases, salicylate concentration increased to certain maximum levels (C_{max}) and then declined steadily but so slowly that C_{max}s did not appear as sharp peaks. The time of C_{max} attainment (T_{max}) varied between 2 and 4 h post-dosing except for one case (B.N., 1000 mg) which occurred after 6 h.

Previously reported T_{max} values are 5–8 h (Berlin et al., 1980) and 9 h (Putter et al., 1974). Considering the slow decline of salicylate in breast milk, the differences in the observed T_{max}s do not present a significant discrepancy. The lack of sharp peak salicylate concentrations in breast milk may make the exact measurement of T_{max} difficult.

The mean observed salicylate C_{max}s following administration of 500, 1000 and 1500 mg ASA were 0.58, 1.60 and 3.87 mg%, respectively (Table 1) indicating a non-linear relationship between C_{max} and dose (Fig. 1). This is not unexpected since salicylate metabolism is a dose-dependent phenomenon (Levy,1965). When the amount of salicylate in the body exceeds certain levels, its biotransformation process becomes half-saturated

and results in non-linear elimination kinetics. A non-linear pharmacokinetic may be more drastically demonstrable in milk. This is because the unbound salicylate is dependent upon the total salicylate concentration in plasma (Furst et al., 1979) and, due perhaps to the same phenomenon, the ratio of saliva to plasma concentration increases upon elevation of salicylate plasma levels (Rumble et al., 1980). Thus, the greater the unbound fraction of the drug, the higher may its transferable portion to saliva be. The same mechanism may very likely hold true for the passage of salicylate into breast milk. Therefore, parallel to the saturable metabolism, increased unbound/total plasma salicylate levels following administration of larger doses, may further potentiate the non-linearity. However, since in this work plasma salicylate concentrations are not measured this suggestion remains speculative.

In our laboratory, in a routine bioavailability test, following administration of 500 mg tablets of regular ASA to 8 healthy subjects, a mean plasma salicylate C_{max} of 5.45 mg% with coefficient of variation of 26% was obtained (unpublished work). This suggests a more than 9-fold larger value for plasma concentration as compared to the breast milk level which is in agreement with that reported by Putter et al. (1974). These authors observed average plasma salicylate C_{max} of 8.2 mg% and simultaneous milk salicylic acid and total metabolites C_{max} of 1.1 mg% following administration of 1000 mg ASA to nursing mothers. Levy (1975) recovered 0.18–0.36% of single doses of 20 mg/kg sodium salicylate given to 4 mothers from their breast-fed infants urine. Correcting for the molecular weight of ASA and considering the average body weight of our subjects, a 1307 mg ASA dose corresponds to that of 20 mg/kg sodium salicylate given by Levy. At this dose level, the estimated mean salicylate concentration in milk is 2.8 mg% (Fig. 1). After attainment of C_{max}, the drug input into breast milk, due to the declined plasma salicylate level, may reach a negligible quantity. Therefore, assuming ingestion of 100 ml milk, the estimated 2.8 mg (0.21% of the dose) may be a reasonable approximation of the total salicylate fed to an infant. Samples taken from subjects B.N. and G.R., 1.5 h after

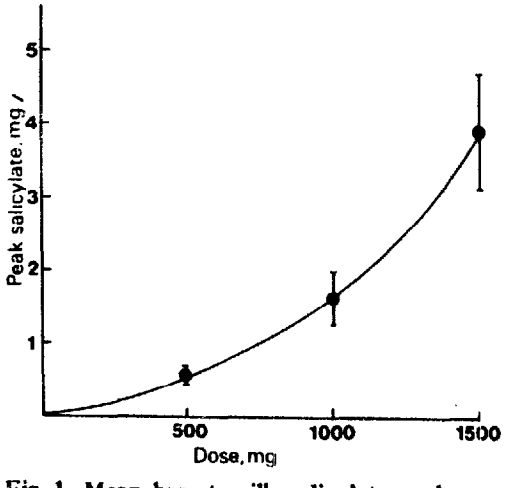

Fig. 1. Mean breast milk salicylate peak concentrations following administration of 500, 1000 and 1500 mg acetylsalicylic acid to healthy nursing mothers. Bars indicate standard deviations of the means.

termination of the tests and emptying the breasts contained no detectable salicylate which might support the above suggestion. Thus, our observation also agrees closely with that of Levy (1975).

Kwit and Hatcher (1935) detected salicylate in human breast milk when sodium salicylate doses larger than 600 mg were administered. Their reported milk salicylate concentrations varied between trace amounts and 4 mg%. Recently, Erickson and Oppenheimer (1979) published a case study in which they reported a breast milk salicylate concentration less than detectable level (5 mg%) with a corresponding plasma concentration of 18 mg% following ingestion of 4 mg/day ASA.

More recently, however, Berlin et al. (1980) contradicted all the previously published data. Following administration of single oral doses of 650 mg ASA to 10 nursing mothers, they observed milk salicylate peak concentrations of 17.3–48.3 mg%. These authors also measured saliva drug levels simultaneously and found peak concentrations of 1.0–4.5 mg% which were approximately 8–38 times greater than those reported by Graham and Rowland (1972).

Considering the acidic nature of salicylic acid and its protein binding characteristics (Ekstrand et al., 1979), one will not expect the milk/plasma concentration ratio to exceed unity even if all the unionized non-protein-bound fraction of the drug diffuses into breast milk. Other acidic drugs such as mefenamic acid (Buchanan et al., 1968) and flufenamic acid (Buchanan et al., 1969) have also been reported to appear in milk concentrations below those in plasma. Therefore, the observation of Berlin et al. (1980) seems to require clarification.

The results of this study indicate that ingestion of single doses of ASA even as high as 1.5 g do not seem to produce milk salicylate levels of clinical (Done et al., 1979) or toxicological (Levy, 1968) significance. Administration of repetitive salicylate doses to nursing mothers, however, may have serious consequences. Though Erickson and Oppenheim (1979) detected less than 5 mg% salicylate in breast milk of a mother taking 4 g/day ASA for 4 days, more detailed studies seem necessary to provide information regarding this aspect. Nevertheless, as stated by Erickson and Oppenheim (1979), in view of the antiplatelet action of salicylates (O'Brien, 1970), these drugs may be contraindicated in mothers of suckling infants with hematological or clotting disorders. This consideration is of greater significance for newborn infants because they eliminate salicylates very slowly and have an extremely limited capacity for its elimination (Levy and Garrettson, 1974). The elimination of salicylate by newborn infants becomes apparent first-order only when the amount of salicylic acid in body is below 2 mg. In the adult human this value is approximately 200 mg (Levy, 1965). Therefore, the safety of feeding newborn infants with salicylate-containing mother's breast milk remains questionable.

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