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Furaltadon in body fluid

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The fate and distribution of a drug in the tissues of the body indicate not only the site of its action but also its possible therateutic application. While absorption and excretion are of importance in the pharmacodynamics of the drug, its concentrations in blood, body fluids and tissue are key elements in selecting the suitable agent for a particular purpose and in deciding the best route of administration. It is well known that parenteral administration will provide higher blood levels more rapidly and hence, more significant tissue diffusion; however, many chemotherapeutic agents are more conveniently given per os and some of them are safe only by this route.

Following absorption, some chemotherapeutic agents, i.e., sulfonamides and antibiotics, are bound in part to plasma proteins. The bound portion loses its antibacterial action and, therefore, the antibacterial level of the drug is measured indirectly by th unbound portion.

The degree of plasma protein-binding of a drug influences not only its ease of diffusion but also its concentration in body fluids such as the cerebrospinal fluid. Although most drugs more easily pass the inflamed meninges than when the blood-brain barrier is normal, their diffusion is irregular and unreliable. Some

agents, however, for example, sulfonamides and chloramphenicol, provide adequate cerebrospinal fluid levels under normal conditions after peroral administration.

Maternofetal circulation has particular importance in the case of drugs to detect the concentration in blood, both in the mother and in the fetus. It has been found, for instance, that some agents, such as sulfonamides, penicillin, tetracyclines, chloramphenicol and streptomycin, pass the placental barrier and have been detected in the fetus at about one half the level found in the maternal circulation.

The concentration of a drug in human milk is studied not only to determine any activity in the mammary gland and adjacent tissues but also to find out the extent of possible transmission to nursing infants.

Furaltadone is a new systemic antibacterial agent for peroral administration. It has been used extensively with good results in miscellaneous infections of soft tissues, respiratory tract, and others, in infants, children and adults.[1-6]

Clinical studies have shown that after peroral administration this drug appears rapidly at demonstrable levels in blood. Such levels, although relatively low, have proved satisfactory for therapeutic efficacy.

It appears that maximal concentrations occur about 4 hours after administration and then decrease gradually. With a single dose of 100 mg., average blood levels 4 and 8 hours later were 1.54 and 0.64 mcg. per ml. respectively.[7]

The urinary excretion of furaltadone appears to be relatively slow. This would mean that the drug is retained longer in the body, thus producing a sustained blood level. Following a single dose of 400 mg., the average urinary excretion is 7.5 mg. per 24 hours, which represents an average of 2 per cent of the total daily dose, the greatest excretion apparently occurring during the first 4 to 8 hours after ingestion. After multiple doses, for example, every 6 hours, the 24-hour urinary excretion varies between 2 and 3.3 per cent of the total daily dose.[7]

FURALTADONE IN CEREBROSPINAL FLUID

Studies to determine furaltadone levels in the cerebrospinal fluid were conducted in 8 patients, 5 of whom had active or improving meningeal infections at the time of the study, while 3 had had lumbar punctures during the course of diagnostic studies for mental retardation. Age range was from 9 months to 6 years.

The drug was given perorally in a dosage of 10 mg. per lb. body weight every 6 hours (6 received a single dose and 2, two doses each) until the lumbar puncture was done. Simultaneously, plasma levels were determined in 2 of the patients, for comparison.

Table 1 and figure 1 show determinations in cerebrospinal fluid as compared to plasma levels (in 2 cases). Furaltadone appeared in the spinal fluid after a slight delay at levels somewhat lower than those found in plasma. The mean value of furaltadone in cerebrospinal fluid was 0.58 mcg. per ml. as opposed to 1.10 mcg. per ml. in plasma (about one half).

FURALTADONE IN UMBILICAL CORD BLOOD

One specimen of plasma from the umbilical cord was obtained from each of 13 infants, all of whom had been delivered spontaneously after varying lengths of labor. All mothers were reasonably healthy and came from charity institutions and having had various degrees of prenatal care.

These patients received furaltadone in doses of 250 mg. every 6 hours until delivery (9 received a single dose, 3, two doses and 1, three doses). The drug usually was given on an empty stomach without food be-

cause of the hazards involved with the imminent prospect of anesthesia. Even though 118 patients were used originally in this study, only 13 were considered because only in these was the drug successfully administered. Labor, evidently, increases markedly the incidence of vomiting.

After the cord was severed, blood from the placenta, prior to expulsion, was allowed to drip into sterile tubes. Maternal plasma was also collected simultaneously from 5 of the 13 patients, for comparison.

Table 2 and figure 2 show determinations in umbilical cord blood, as compared with plasma levels (in 5 cases). From these studies, it appears that furaltadone crosses the placenta after a slight delay, but does not reach the levels found in maternal plasma. The mean value of the cord plasma level was 0.5 mcg. per ml., about three fourths that of maternal plasma (0.74 mcg. per ml).

FURALTADONE IN HUMAN MILK

Twenty-three samples of breast milk were obtained from 12 patients (2 to 5 days postpartum) following peroral administration of furaltadone (1 sample from each of 6 patients, 4 from 1 patient, 3 from each of 3 patients and 2 from each of 2 patients).

The drug was given in a dose of 250 mg. with milk, every 6 hours. No complaints were made by 11 of the 12 patients, and only 1 complained of heartburn shortly after taking the drug; there was no vomiting or nausea in this group of patients.

Shortly before obtaining the specimen of milk, 8 of these patients were subjected to venipuncture to determine simultaneous plasma concentrations. An ordinary breast pump was used to obtain the first 5 to 10 cc of milk.

Table 3 and figure 3 show determinations in breast milk as compared to plasma levels (in 8 cases). Figure 4 shows serial determinations of the drug excretion in human milk. In general, this study indicates that furaltadone concentrations in human milk are considerably higher than those found in plasma, suggesting that the human mammary gland excretes this drug. Although there was considerable variation in these levels, they were usually twice those of plasma. The mean concentration of furaltadone in these 23 milk-specimens was 1.71 mcg. per ml. whereas the mean plasma level was 0.9. One patient showed a fourfold higher level of the drug in milk than in the plasma.

CONCLUSIONS

Clinical studies were conducted to determine concentrations of furaltadone, a new systemic antibacterial agent, after its peroral administration, in cerebrospinal fluid (8 patients), in umbilical cord blood (13 infants), and in human milk (12 puerperal patients).

In spinal fluid, the drug appeared at demonstrable concentrations, after a slight delay, somewhat lower (about one half) than in plasma.

Umbilical cord studies showed that furaltadone crosses the placental barrier, also after a slight delay, and appears in the fetal circulation at levels about three fourths those of maternal plasma.

In human milk, the drug was found at concentrations considerably higher, usually twice that of plasma, suggesting excretion of this drug by the mammary gland.

Colorimetric determinations were made to determine concentration of furaltadone in human blood, spinal fluid and breast milk. Standard solutions were prepared using a pure crystalline compound of furaltadone, utilizing a toluene extraction procedure with an absorption spectrum in the range of 400-460 mu.

REFERENCES

1. Glas, W. W., and Britt, E. M.: The Management of Hospital Infections, Symposium on Antibacterial Therapy, The Michigan and Wayne County Acadamies of General Practice, Detroit (Sept. 12) 1959.

2. Prigot, A.; Felin, A. J., and Mullins, S.: Persistent Resistant Infections, Symposium on Antibacterial Therapy, The Michigan and Wayne County Academies of General Practice, Detroit (Sept. 12) 1959

3. Leming, B. H.: Selection of Antibacterial Agents, Symposium on Antibacterial Therapy, The Michigan and Wayne County Academies of General Practice, Detroit Sept. 12) 1959.

4. Lysaught, J. N., and Cleaver, W.: Childhood Bacterial Infections, Symposium on Antibacterial Therapy, The Michigan and Wayne County Academies of General Practice, Detroit (Sept. 12) 1959.

5. Christenson, P. J., and Tracy, C. H.: Furaltadone-A New Systemic Antibacterial Agent, Curr. Ther. Res. 2:22-29 (Jan.) 1960.

6. Weiner, A. L.: Newer Systemic Chemotherapy of Bacterial Dermatoses, unpublished.

7. Eaton Laboratories, Personal Communication

TABLE 1

FURALTADONE IN CEREBROSPINAL FLUID AND PLASMA

Patients	Time (1) Hr.	Min	Cerebrospinal Fluid Level (mcg./ml.)	Plasma Level (mcg./ml.)
*1	0	30	0	---
*2	2	30	0.06	---
3	5	--	0.86	---
4	3	--	0.93	1.20
*5	9	--	0.43	---
*6	8	--	0.74	1.00
*7	2	--	0.47	---
8	0	45	-0	---
Mean Values			0.58	1.10

*infected meninges

(1) The time given represents hours and minutes after the initial dose and corresponds to the time at which the specimen was obtained.

Dose: 10 mg. per lb. body weight. every 6 hr.

TABLE 2

FURALTADONE IN UMBILICAL CORD AND MATERNAL PLASMA

Patients	Time (1) Hr.	Time (1) Min.	Cord Plasma Level (mcg./ml.)	Maternal Plasma Level (mcg./ml.)
1	5	36	0.38	---
2	12	10	1.00	---
3	7	6	0.60	0.93
4	4	35	0.46	---
5	2	15	0.30	---
6	5	20	0.73	---
7	0	45	0	0.20
8	1	20	0	---
9	3	15	0.26	---
10	6	40	1.10	1.07
11	8	10	0.82	0.99
12	1	30	0.15	0.62
13	2	10	0.58	---
Mean Values			0.50	0.74

(1) The time given represents hours and minutes after the initial dose and corresponds to the time at which the specimen was obtained.

Dose: 250 mg. every 6 hr.

TABLE 3

FURALTADONE IN HUMAN MILK

Patient	Specimen	Time (1) Hr.	Time (1) Min	Breast Milk Level mcg/ml.	Plasma Level mcg./ml.
1-------		25	15	1.22	---
2-------		21	15	1.25	---
3-------		25	0	1.62	---
4-------(a		22	0	0.38	---
(b		25	0	2.38	---
5-------(a		10	0	0.33	0.58
(b		14	0	2.23	---
(c		17	15	***	---
(d		33	15	0.55	---
6-------		10	0	1.73	0.85
7-------(a		14	0	4.80	1.00
(b		17	15	2.70	---
(c		33	15	4.50	---
8-------(a		10	0	0.75	1.00
(b		17	15	1.25	---
(c		33	15	1.40	---
9-------		10	0	2.04	1.55
10------(a		13	0	1.70	0.85
(b		17	45	2.38	---
11------(a		13	15	1.40	0.95
(b		17	15	1.45	---
(c		33	0	2.00	---
12------		10	0	1.25	0.43
				---	---
Mean Values				1.71	0.90

***-negligible

1) The time given represents hours and minutes after the initial dose at which the specimen was obtained.

Dose: 250 Mg. every 6 hr.

Fig. 1 Furaltadone in Cerebrospinal Fluid

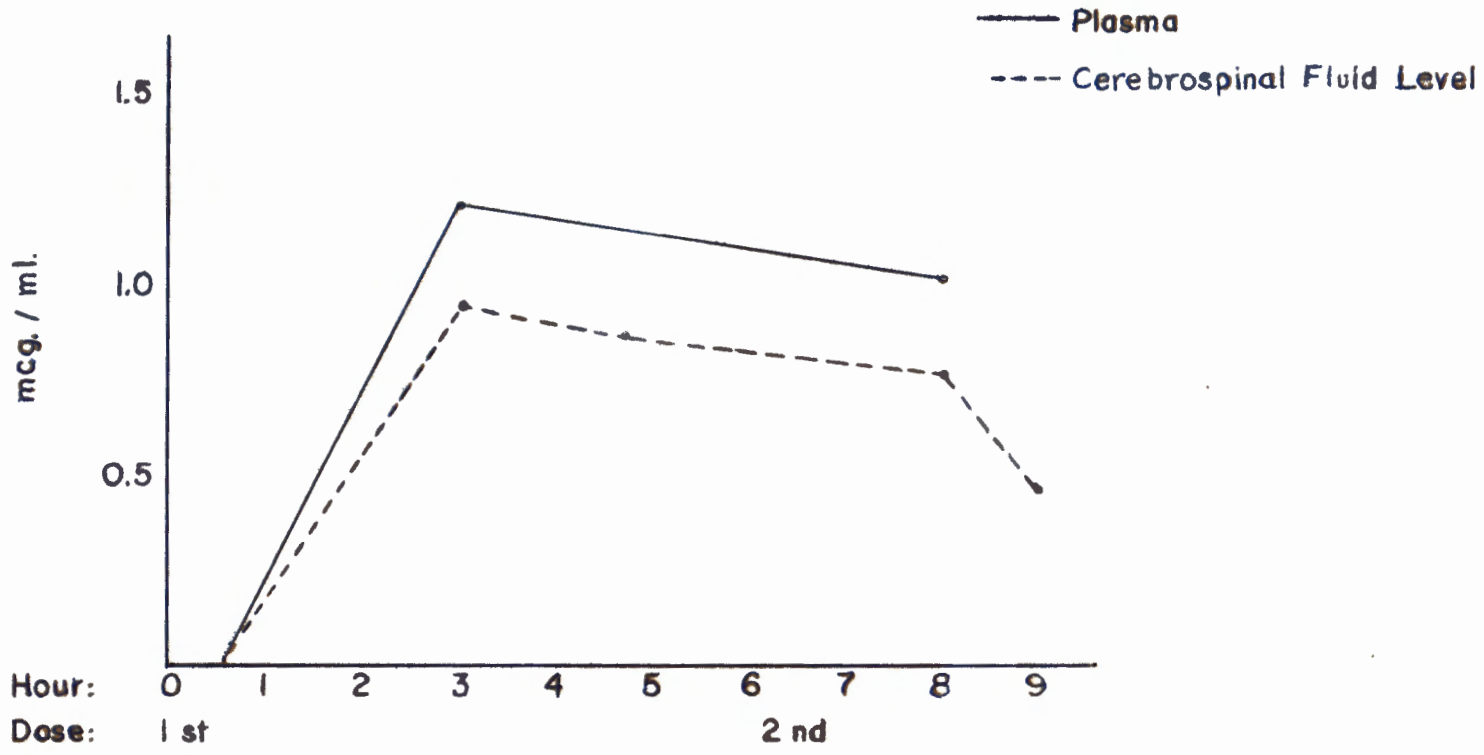

Fig.2 Furaltadone in Umbilical Cord and Maternal Plasma

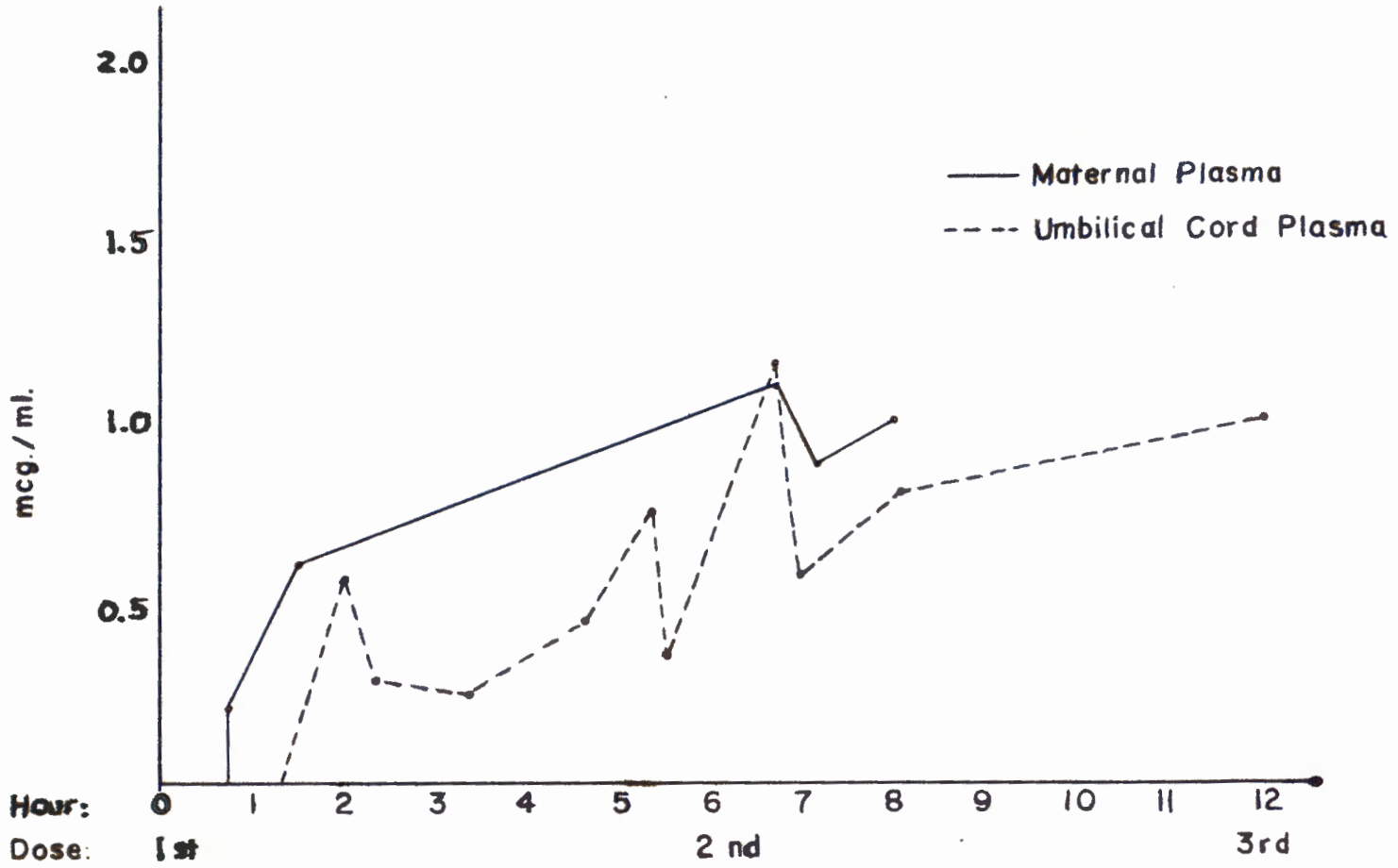

Fig.3 Furaltadone in Breast Milk and Plasma

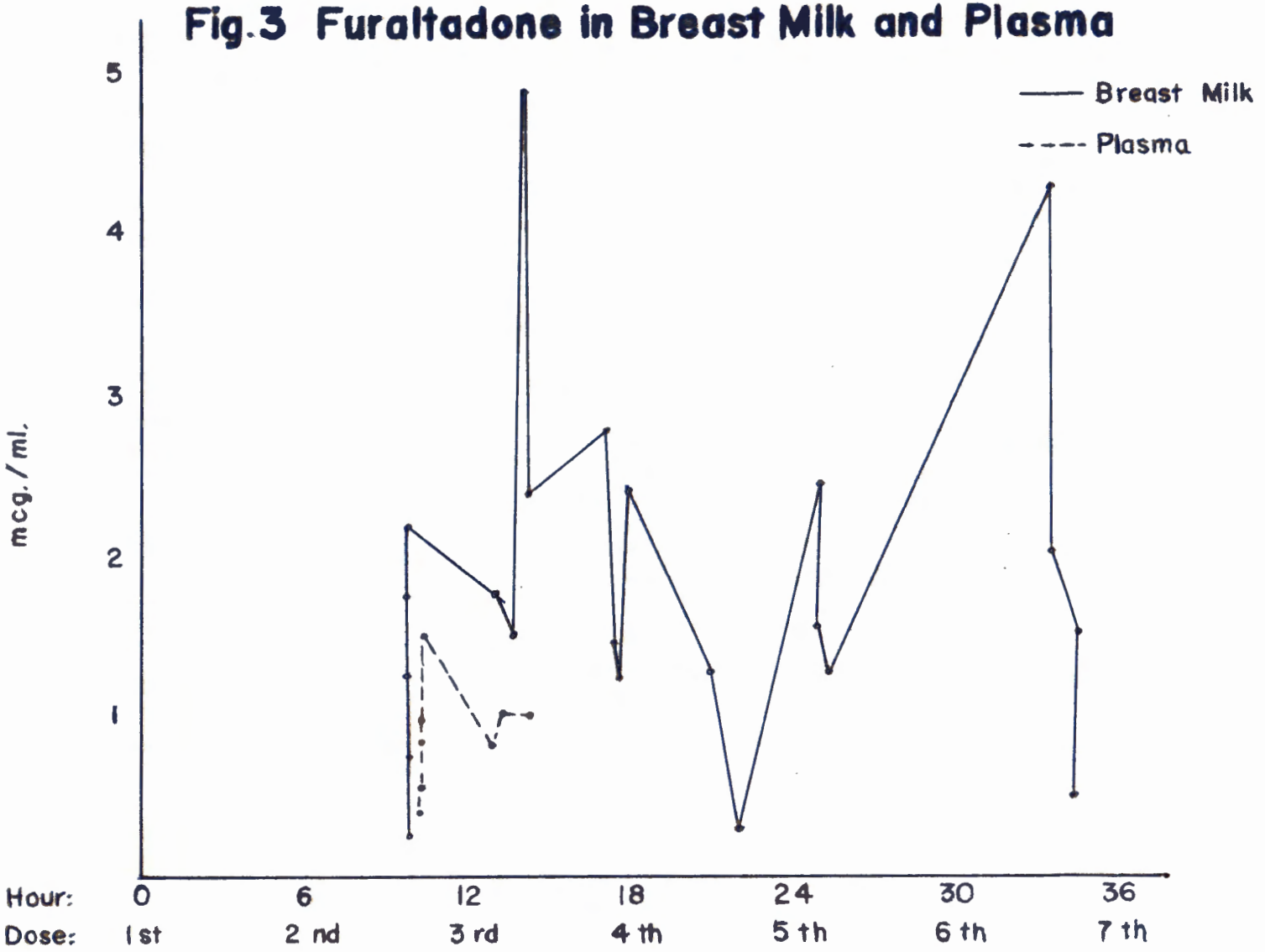

Fig. 4 Serial Determination of Furaltadone Excretion in Human Milk