Chapter V

Rifampicin Content

Detailed reviews of the clinical pharmacokinetics of rifampicin are cited in Pharmacopoeia (1979; 1989). Most of these works are either on patients (Krishna *et al*, 1984) or in volunteers (Avachat *et al*, 1992). Most of the studies are on plasma, urine, saliva and other body fluids (Sunahara and Nakagawa, 1972). The absorption of the drug in the gastrointestinal tract when administered orally is of importance and also necessitates the studies in *in vivo* experimental animal models such efforts by Desaga Resomat model I and II have been tried by Patel *et al* (1981), but they have used mechanical models.

In rats the retention of rifampicin in organs was noted by Akimoto *et al* (1970); Rodriguez *et al* (1973); Zwolska-Kwiek *et al* (1980). Koroleva and Fomina (1976) noted high concentrations of rifampicin in liver and kidney of experimental rats. Use of parental route for rifampicin administration (zwolska-kwiek *et al* 1980) resulted in comparatively high levels

in different organs of rats. Zhang *et al* (1998), Bruzzese *et al* (2000) showed antibiotic accumulation in liver, lung, spleen, small intestine, kidney, skin, stomach *etc.* Liver showed maximum accumulation. But all the routes of administration allowed distribution and retention of rifampicin. 34-72 % binding of antibiotic was noted in organ homogenates. Twelve-day study in male albino rats showed many fold high concentrations of rifampicin in liver than blood and other organs; while in epididymal fats it was half than the blood concentrations (Zitkova *et al* 1982). In the rats where intrabronchial administration of rifampicin is compared with oral administration liver concentrations and blood concentrations of rifampicin did not differ (Shapovalov *et al*, 1982). But in tissue availability of the antibiotic on its intravenous administration was lower than that on its oral administration (Firsov *et al*, 1986). In in vitro studies Patel *et al* (1981) showed pH influence on uptake by the organs.

In the present attempt the efforts are made to study daily excretion of rifampicin through faecal matters and net absorbed rifampicin by some organs after the termination of the treatment on day 31st day of the treatment. The influence of

mandur bhasma on absorption in some soft organs and excretion through faeces was studied.

MATERIAL AND METHODS

Groups of male albino rats with five rats in each group were used for experimental work.

Group I- Normal rats were maintained for 30 days and were used as controls.

Group II- These rats were administered rifampicin (50 mg/kg body wt/day) for 30 days orally.

Group III- Rats from this group were given orally rifampicin 50 mg/kg body wt/day +10 mg mandur bhasma/kg body wt/day) for 30 days was given orally.

Group IV- To the rats of this group 10 mg mandur bhasma/kg body wt/day for 30 days.

RESULTS

Rifampicin contents in organs:

Accumulation of rifampicin was noted in different tissues of albino rats. The data on rifampicin in different tissues is given in Table 1 and Figure 1.

Table 1 - Concentration of Rifampicin in tissues of Rats

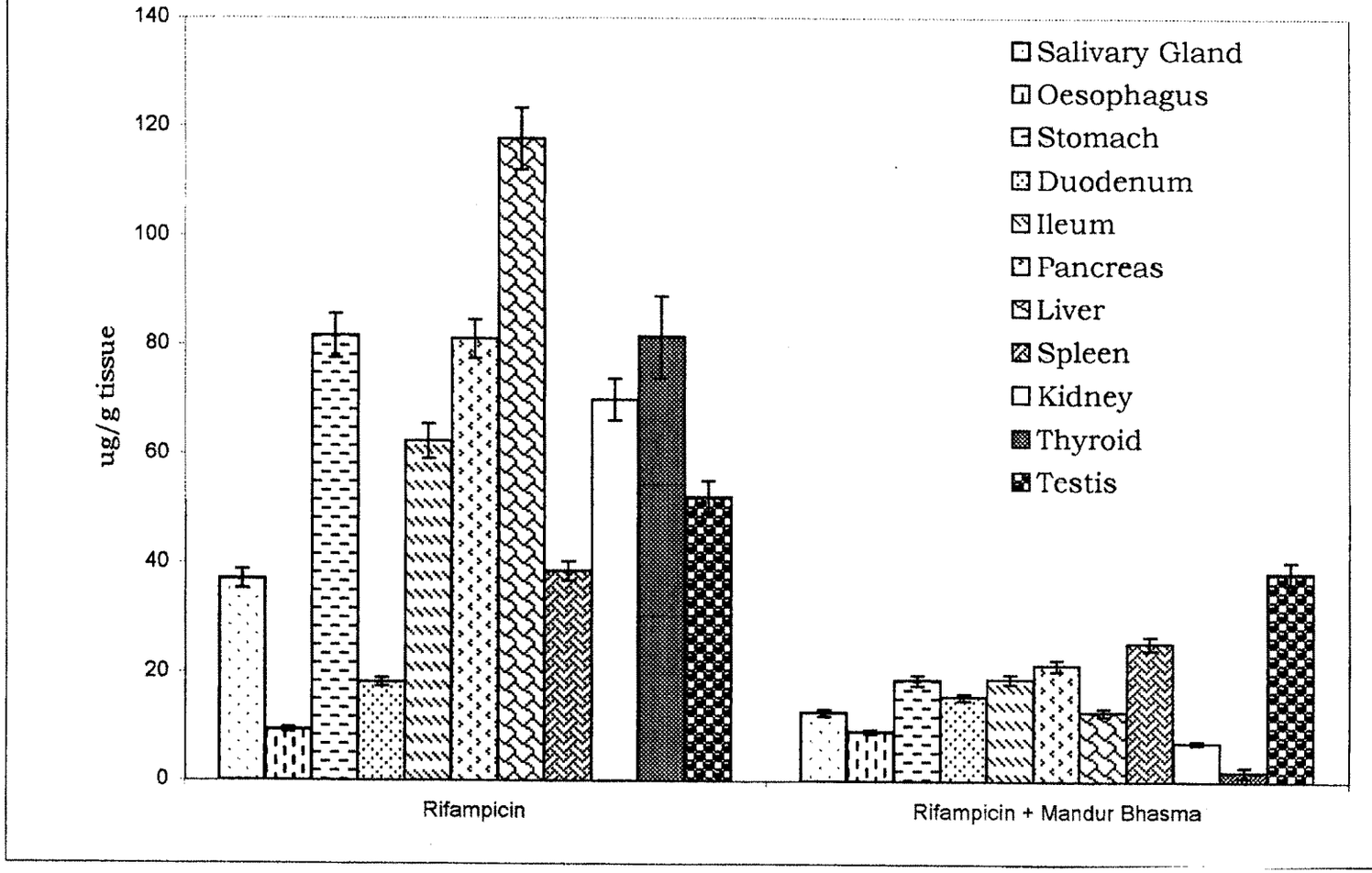
(Values are expressed as µg/g tissue)

No	Organ	Rifampicin	Rifampicin + Mandur Bhasma
1	Salivary Gland	37.15 ± 1.68	12.78 ± 0.63[c]
2	Oesophagus	9.48 ± 0.43	9.20 ± 0.42[d]
3	Stomach	81.62 ± 4.03	18.74 ± 0.98[c]
4	Duodenum	18.27 ± 0.76	15.62 ± 0.69[d]
5	Ileum	62.39 ± 3.21	18.89 ± 0.87[c]
6	Pancreas	81.08 ± 3.52	21.46 ± 1.06[c]
7	Liver	117.75 ± 5.65	12.85 ± 0.68[c]
8	Spleen	38.54 ± 1.79	25.53 ± 1.24[c]
9	Kidney	70.00 ± 3.74	7.29 ± 0.36[d]
10	Thyroid	81.40 ± 7.50	1.85 ± 0.99[c]
11	Testis	52.15 ± 2.97	38.36 ± 2.05[b]

Values are mean ± SE of 6 animals

P Values - a< 0.05, b< 0.01, c< 0.001 & d> 0.05

Table 1 - Concentration of Rifampicin in tissues of Rats



The rats of group I and III did not show presence of rifampicin in any of the organs studied, as it is not the present naturally in animal bodies. Rifampicin administered rats (Group II) showed presence of rifampicin in different organs studied. Liver showed highest accumulation of rifampicin 117.75 μg/gm wet weight of tissue and the lowest content was found in oesophagus. The amount of rifampicin in descending order was noticed in the different tissues as liver; stomach; thyroid; pancreas; kidney; ileum; testis; spleen; salivary gland; duodenum; oesophagus. In oesophagus, stomach, duodenum, Ileum, salivary glands, pancreas, kidney, testes, thyroid gland and spleen the rifampicin content was 9.48, 81.27, 18.27, 62.39, 37.15, 81.08, 70.00, 52.15, 81.40 and 38.54 μg/g tissue respectively.

Mandur bhasma did not lower rifampicin contents from oesophagus (2.95 %), while the rifampicin accumulation was reduced in salivary glands (65.60 %), stomach (18.74 %), duodenum (14.50 %), ileum (69.80 %), pancreas (73.53 %), liver (89.09 %) spleen (33.76), Kidney (89.59) thyroid (77.11 %), and testis (25.68).

Table 2 - Effects of Rifampicin and rifampicin + mandur bhasma on rifampicin in faecal matter of albino rats

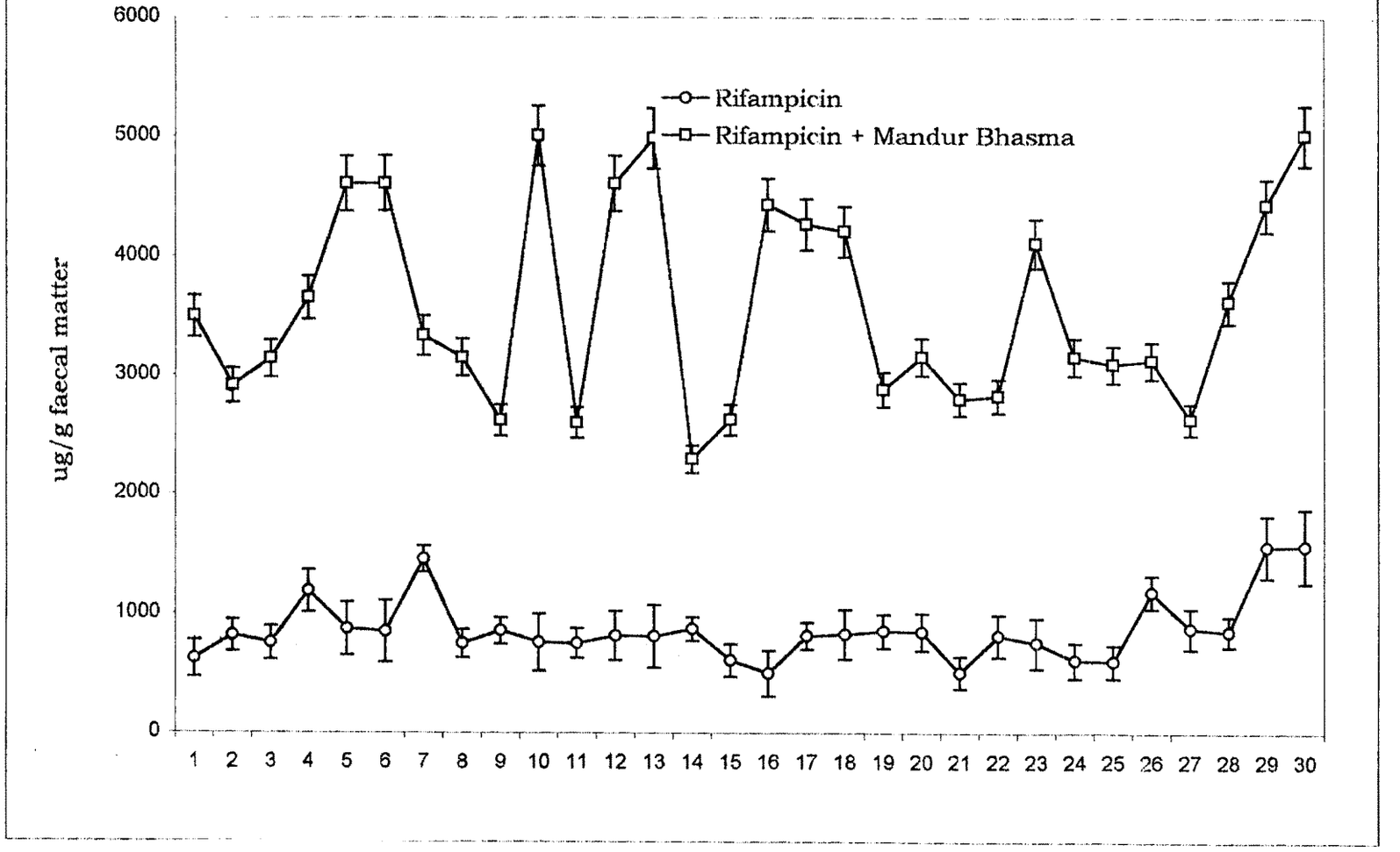
(Conc. µg/gm of faecal matter)

Day	Rifampicin	Rifampicin + Mandur Bhasma
1	623.00 ± 42.71	3496.34 ± 153.54
2	815.38 ± 56.38	2912.41 ± 133.33[c]
3	754.43 ± 34.52	3136.29 ± 140.09[c]
4	1189.00 ± 60.79	3652.62 ± 178.15[c]
5	872.15 ± 36.10	4608.43 ± 221.47[c]
6	850.24 ± 39.45	4612.05 ± 258.71[c]
7	1456.67 ± 76.19	3333.33 ± 108.32[c]
8	750.12 ± 31.08	3148.73 ± 117.00[c]
9	856.37 ± 41.72	2621.60 ± 109.35[c]
10	757.83 ± 33.33	5008.25 ± 241.28[c]
11	751.44 ± 38.11	2600.00 ± 125.04[c]
12	814.19 ± 45.28	4611.28 ± 206.18[c]
13	810.08 ± 40.00	4987.96 ± 263.57[c]
14	872.71 ± 49.34	2292.17 ± 100.24[c]
15	608.95 ± 28.93	2623.54 ± 136.52[c]
16	500.00 ± 22.49	4435.19 ± 192.63[c]
17	811.45 ± 39.78	4270.61 ± 113.10[c]
18	827.03 ± 50.32	4209.23 ± 208.53[c]
19	853.72 ± 46.47	2879.56 ± 142.91[cc]
20	846.19 ± 43.37	3154.12 ± 156.74[c]
21	505.67 ± 23.16	2800.00 ± 133.33[c]
22	813.91 ± 40.58	2826.47 ± 176.09[c]
23	752.74 ± 34.00	4109.38 ± 211.82[c]
24	606.67 ± 27.38	3153.40 ± 149.36[c]
25	598.87 ± 28.67	3093.85 ± 138.20[c]
26	1182.35 ± 62.81	3125.14 ± 137.68[c]
27	875.00 ± 43.51	2629.18 ± 169.47[c]
28	848.79 ± 48.06	3618.36 ± 127.22[c]
29	1563.14 ± 80.79	4430.80 ± 258.46[c]
30	1567.58 ± 75.23	5015.23 ± 307.25[c]

Values are mean ± SE of 6 animals

p values are as in Table 1

Figure 2 - Effects of Rifampicin and rifampicin + mandur bhasma on rifampicin in faecal matter of albino rats



Rifampicin content from faecal matter :

The changes in rifampicin content of faecal matter are demonstrated in Figure 2 and Table 2.

The faecal matter of the rats treated with only rifampicin showed average of 800 μg/kg of rifampicin in most of the days (50 %). Then 29 % of the days showed rifampicin content in the range of 500 - 700 μg/kg. During 17 % of the days rifampicin content never attained 1600 μg/kg faecal matter. During first week two peaks on day 4 and day 7 were noted. From day 8 to day 25 of treatments rifampicin concentration was in the range of 500 - 872 μg/kg. On day 26, 29 and 30 of the treatment the concentrations were high (the highest were on days 29 and 30. More frequent 30 % of the days showed 3000 μg concentration of rifampicin. 30 % of the days showed 4000 μg concentrations. 30 % of the days-showed 2500 % mg. 0.6 % of the days showed 5000 μg and 0.3 % of the days exhibited 600-μg rifampicin.

DISCUSSION

The low content of rifampicin in oesophagus may be due small time exposure during swallowing. In case of other organs may be their metabolic specificity and physiological status, which may be

influencing the accumulation. High levels of rifampicin in liver be explained, as it is the main organ of enteric route and drug detoxication. The accumulation in different organs was altered by mandur bhasma. The results indicated that the presence of mandur bhasma significantly influences accumulation of rifampicin content in organs. The absorption of rifampicin may have altered due to the presence of mandur bhasma. The metabolism of rifampicin may have altered in the presence of mandur bhasma. Assandri *et al* (1978) studied deposition of a series of rifamycin in rat. pH seems to influence the absorption of rifampicin in *in vitro* models (Patel *et al*, 1981). All these reasons together may have influenced absorption, metabolism and clearance.

The results indicated that excreted rifampicin in faecal matter was in the range of 300 to 5000 μg/kg. Treatment of mandur bhasma concurrent with rifampicin increased 6 fold rifampicin excretion in faecal matter. The alterations are the cumulative effects of both rifampicin and mandur bhasma. The bile clearance is coupled with the reabsorption cycles. If the pH is influential in intestinal and in other soft parts then mandur bhasma may be modulating the same in gastrointestinal tract.