RESEARCH IN PHARMACEUTICAL SCIENCES

Effect of some Drugs on Bioavailability of Oxytetracycline Hydrochloride in Rabbits

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Biological availability of Oxytetracycline hydrochloride was significantly decreased in presence of paramethasone acetate, Acetyl barbromal, Hydroxyzine Hydrochloride, cephalothin Sodium, Clindomycin hydrochloride, mefenamic acid and Iron. Whereas meprednisone caused only slight decrease, while Ascorbic acid, tartaric acid. Tybamate, and Triamcinolone diacetate were not found to affect the bio-availability of oxytetracycline in experimental animals.

Implications of large difference in the absorption characteristics of oxytetracycline by formation variables have been well emphasized by several reports; which has demonstrated bio-inequivalence among chemically equivalent products from different manufacturers[1-3]. The metal ions such as calcium, magnesium, aluminium and iron have been found to be capable, of retarding the absorption of tetracyclines through the formation of complex-4. Milk containing calcium antacids containing calcium and magnesium salts, and the preparations containing Iron could therefore inflict on impairment in the absorption of oxytetracycline from gastrointestinal tract following oral administration.5-6. As the consequence of calcium was earlier not known, no explanation could be sought as to why the earlier capsules formulations containing dicalcium phosphate as the filler showed poor absorption characteristics for tetracyclines. Relatively higher blood levels circumvented by combination of glucosamine, citric acid or sodium etaphosphate with tetracyclines were then interpreted as adjuvant effects. However, the alleged claims were from comparisons between formulations having dicalcium phosphate and those containing adjuvants without calcium.7

Unfortunately there is no information on whether other therapeutic agents might interact with tetracyclines and alter their usual absorption. The present investigation deals with this aspect.

EXPERIMENTAL

The drugs and adjuvants selected for studying their influence on biological availability of oxytetracycline hydrochloride (Pfizer) were as following:

Hormones: meprednisone (Parke Devis); Paramethasone Acetate (LillY); Triamcinolone diacetate (Lederle)

Hypnotics: Acetyl carbromal (Riker); Hydroxyzine Hydrochloride (Roerig). Tybamate (Robins)

Antibacterial agents: cephalothin Sodium (Lilly); Clindamycin Hydrochloride (Upjohn).

Miscellaneous: Tartaric acid; Ferrous Sulphate:— Ascarbic acid; mefenamic acid (Park-Devis).

The materials used were of the highest purity. Aqueous solutions of the materials were prepared before use.

Bioavailability Studies

Healthy male rabbits (1.5 to 2.0 kg) were divided into various groups of five each. They were fasted overnight prior to receiving the drugs. The dose of oxytetracycline hydrochloride (10mg/kg) was first given orally in 5ml water which was immediately followed by the test material (10mg/kg) dissolved in 10ml of water. Additionally about 25ml of water were given as washings. Blood samples were collected through the central artery of the rabbit at 1,2,3,4,5,6 and 9th hours and the oxytetracycline content in the blood was determined. The blood concentration time curve was constructed and the areas under curves (AUC) were calculated by numerical integration method employing the trapezoidal rule[8] to represent the total amount of drug available in blood upto the last sample at 9th hour. The area obtained (Sq.cm.) from the administration of play oxytetracycline Hcl was treated as standard for comparison with those obtained with the conjoint trials. The comparisons were also made between different groups with regard to the peak concentration and peak time.

Estimation of oxytetracycline in blood

The assay was based on the formation of yellow complex between oxytetracycline and quadrivalent thorium and its spectrophotometric measurement at 395mu[9]. The concentration of oxytetracycline in the blood samples was determined by comparison with a linear standard curve prepared by adding the known amounts (1 to 10 ug) of oxytetracycline Hcl to blood (1ml).

In general, the method[10] adopted for extraction and estimation was as follows:—

In a ten ml gass stoppered tube were placed in order 1.0 ml whole blood, 1.0ml water, 1.0ml o.IN Hcl and 1.0ml trichloroacetic acid (30%). The mixture was thoroughly shaken for 2 min.on a vortex mixer and centrifuged for 10 min. at 3000 r min.$^{-1}$ The supernate was placed in a 30ml tube and the traces of trichloacetic acid were removed by extracting with 2 ten ml. Portions of ether. After the last traces of ether were aspirated, the pH of the aqueous phase was adjusted to 4.0 by means of 0.1 Sodium hydroxide. The aqueous phase was then extracted with 5×5 ml portions of ethyl acetate. After centrifugation, two 3 ml aliquots were taken into two separate test tubes. One ml of alcoholic thorium nitrate (0.5%) was added to one of these tubes with shaking and after 20 min. absorbance of the oxytetracycline—thorium complex was measured at 395mu in a Beckman model DU2 Spectrophotometer against a blank prepared by adding all the chemicals omitting thorium nitrate.

RESULTS

Figures 1—4 represents mean blood levels versus time profiles in rabbits, after oral administration of identical doses of oxytetracycline with and without other drugs or adjuvants. Oxytetracycline when given as such was rapidly absorbed producing peak blood level (3.88ug/ml) at 2nd hour post administration.

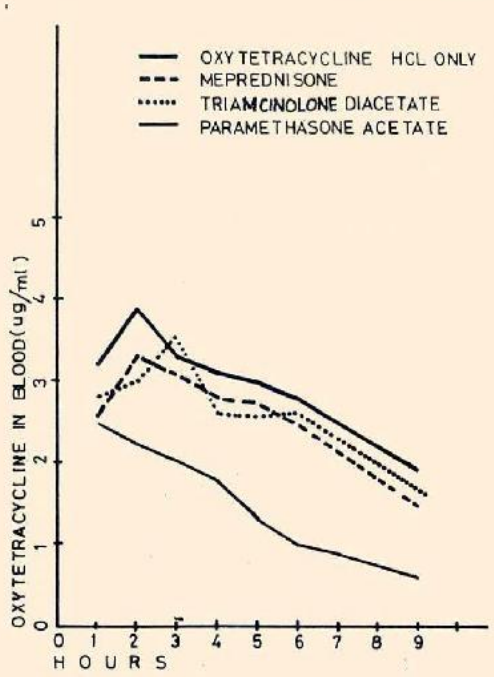

Fig. 1
Effect on Bioavailability of Oxytetracycline Hcl with and without harmones.

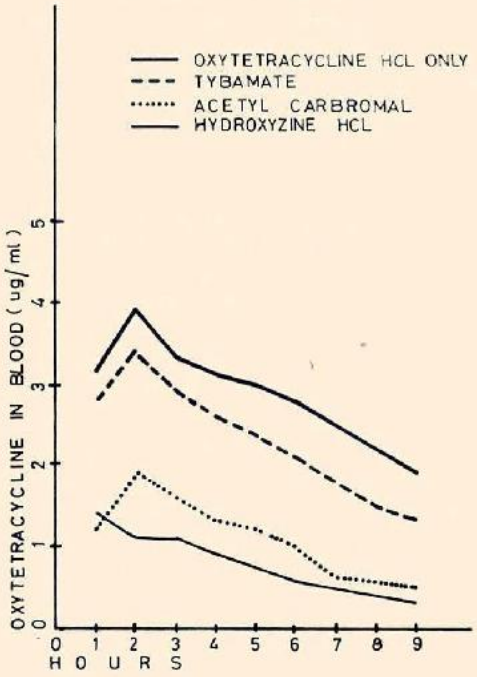

Fig. 2
Effects on Bioavailability of Oxytetracycline Hcl. with and without Hypnotics Drugs.

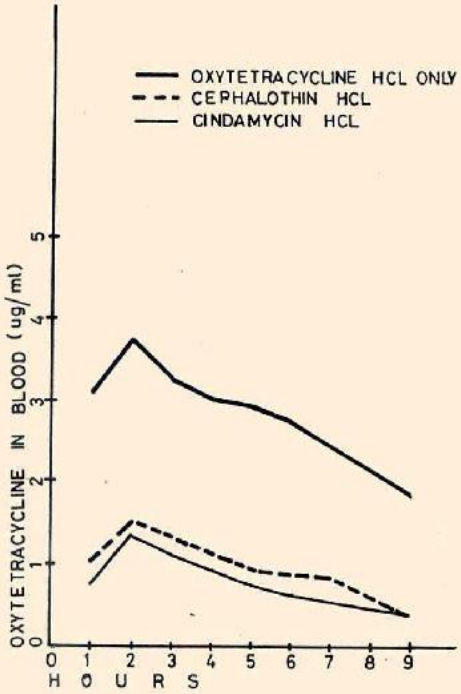

Fig. 3
Effects on Bioavailability of Oxytetracycline Hcl. with and without miscellenom Drugs.

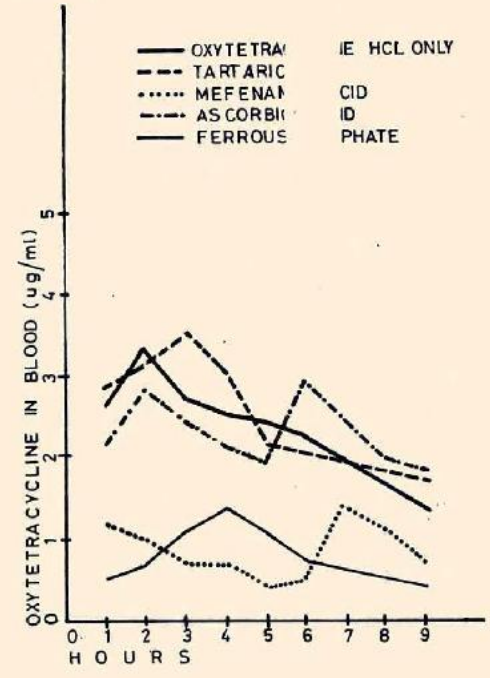

Fig. 4
Effects on Bioavailability of Oxytetracycline Hcl. with and without vitamins and other drugs.

The general pattern of its bioavailability was in excellent quantitative agreement with the earlier reports[11]. Marked differences in the area under curve (AUC) could be noted, even by visual inspection of the blood curves after giving oxytetracycline alone and that with other materials. The relative bioavailabilities of oxytetracycline Hcl in presence of other materials were as follows: Mepredrisone 90% Paramethasone acetate 67% Triamcinolone diacetate 99%, Acetyl carbromal 39% Hydroxyzine Hcl 28%, Tybamate 99%, Cephalothin Sodium 30% clindamycin Hcl 33% Tartaric acid 103% Ferrous Sulphate 50% Ascarbic acid 100% Mafenamic acid 50%. In keeping with this, the variability in the maximal blood concentrations in above order were 3.28, 2.55, 3.42, 1.90, 1.48, 3.40, 1.46, 1.59, 4.10, 1.93, 3.38. (3.46 second peak), 1.73 (1.93 second peak). ug/ml of blood respectively. (Table 1). From among various drugs tested ascarbic acid (100%) tartaric acid, (103%). Triamcinolone diacetate (99%) did not affect the bioavailability of oxytetracycline significantly. The bioavailability profile after giving oxytetracycline hydrochloride together with ascarbic acid was characterized by the bimodal patterns showing peaks at 2nd and 6th hours. Similar pattern was also observed in case of mefenamic acid exhibiting peaks at 1st and 7th hours.

The variability in peak time was evident in some case like that of paramethasone acetate, Hydroxyzine hydrochloride and mefenamic where peak was noted at 1st hour, whereas in case of ferrous sulphate it was 4th hour from the time of oxytetracycline administration with these drugs.

TABLE—1EFFECT OF DRUGS AND ADJUVANTS ON THE PEAK TIME, PEAK CONCENTRATIONS AND PERCENTAGE BIOAVAILABILITY OF OXYTETRACYCLINE Hcl.

Combinations	Peak blood level(ug/ml)	Peak time (Hours)	%Bioavailability[a]
Oxytetracycline Hcl (OTC)	3.88± 11	2	100.00
OTC + Meprednisone	3.28± 0.14*	2	90.62
OTC + Paramethasone Acetate	2.25± 0.17*	1	67.09
OTC ± Triamcinolone diacetate	3.42± 0.12	3	99.82
OTC ± Acetyl carbromal	1.90± 0.18	2	39.52
OTC ± Hydroxyzine Hydrochloride	1.48± 0.11	1	28.10
OTC ± Tybamate	3.40± 0.11	2	99.15
OTC ± Cephalothin Sodium	1.46± 0.20*		30.29
OTC ± Clindamycin hydrochloride	1.59± 0.20*	2	33.89
OTC ± Tartaric acid	4.10± 0.12	3	103.11
OTC ± Ferrous Sulphate	1.93± 0.15*	4	50.13
OTC ± Ascorbic acid	3.38± 0.22 3.46± 0.11	2 & 6	100.03
OTC ± Mefenamic acid	1.73± 0.24* 1.93± 0.15*	1 & 7	50.12

[a] Relative to plain oxytetracycline Hcl (control)
± Standard error of the mean of 5 animals
* Significantly different from the control ($P<.05$)

DISCUSSION

The present findings exemplifying significant reductions in the bioavailability of oxytetracycline after giving this antibiotic along with Paramethasone acetate, Acetyl carbromal, Hydroxyzine hydrochloride, cephalothin sodium, clidomycin hydrochloride, mefenamic acid and Ferrous Sulphate as evidenced by the decrease in AUC are suggestive of incomplete absorption of oxytetracycline from the gastrointestinal tract. If elimination characteristics have not been altered the decrease in are under curve realistically accounts for impaired absorption of the drug.

Decreased absorption of tetracyclines due to complex formation with calcium[4] and mucin[12] has been well documented. Although the invitro interactions of tetracyclines with several vitamins[13] and Surfactants[14] have been reported the implications of such interactions on systemic availability of the antibiotics are obscure. Although Higuchi[13] reported complexation between ascorbic acid and tetracycline, we could not record a change in overall bioavailability of oxytetracycline presumably due to weak complexation that may be reversed readily. Sugimoto[15] has demonstrated a relevant change in absorption rates of drugs in accordance with the equilibrium constants of the complexes determined by physiochemical methods.

Bioavailability of 102% of tartaric acid may be due to the pH effect on solubility. The reason for impaired absorption of oxytetracyclines in presence of mefenamic acid can not be found out. Our results for Iron are compatible with that of Neuvonen p. et al 16.

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