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EFFECT OF INNATE LIPID SOLUBILITY ON BUCCAL ABSORPTION OF BASIC DRUGS

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This study is designed, to find out the effect of innate lipid solubility on buccal absorption of basic drugs with similar pka values. Allopurinol hydrochloride, nortriptyline hydrochloride and procainamide hydrochloride with Pka values 9.4, 9.7 and 9.2 respectively were selected for in vivo (buccal absorption test) and in vitro (I-octanol/buffer partitioning coefficient) study at pH range 6-10. Results found that the mean percentage of buccal partitioning and/I-octanol partitioning of allopurinol hydrochloride was decreased with the increase in pH from 6.0-10. On the other had mean percentage of buccal partitioning and I-octanol partitioning of procainamide hydrochloride and nortriptyline hydrochloride was increased with the increase in pH from 6.0-10. It is concluded that although the drugs studied have nearly similar Pka values their lipid solubility is widely variable. A good correlation between buccal and I-octanol partitioning excluded the possibility of interaction between these drugs and I-octanol. Decrease in lipid solubility of allopurinol hydrochloride with increase in pH needs further evaluation.

Drug absorption is a very complex process that manifests itself through potential interaction with a host of physiochemical and physiological variables. Some factors that may affect the absorption processes include presystemic metabolism/cefflux, the "absorption window" along the gastrointestinal tract, disease states, demographics (gender, age, ethnicity), and biopharmaceutical classification of solid dosage forms.[1,2] The oral absorption of any chemical entity reflects a complex spectrum of events. Factors influencing product bioavailability include drug solubility, permeability, and the rate of in vivo dissolution.[3] A drug after being administered crosses various aqueous and lipid barriers before it reaches the site of action. Physiochemical properties of drugs suggest that the water soluble drugs with molecular weight less than 200 dalton may diffuse passively through aqueous channel of cell membrane.[4] It is evident that pharmacologically active drug must be soluble to some extent both in lipid and water.[5]

Higaki and coworkers proposed[6,7] the mechanism of drug absorption. They observed that the drug binds to proteins of mucosa. The drug then diffuses across the lipid membrane of the mucosa, passing through its various layers and then enters the body fluids. It is found that protein binding within the membrane would influence but there may be some loss of drug from oral cavity. They found that although protein binding is not involved in buccal absorption, it does serve to concentrate the drug at or near the surface of the buccal mucosal membrane, thus increasing the rate of absorption.[8]

Drugs used in clinical practice are mostly weak electrolytes. They are present in various tissues and body fluids in ionized or unionized state depending upon pH of the tissue. Their transmembrane diffusion mainly depends upon their Pka values, degree of ionization and relative lipid/water solubilities.[10] Antidepressant drugs are extensively metabolised prior to elimination from the body. These metabolites usually have biological and chemical properties different from of the parent drug.[11]

Allopurinol acts on purine catabolism without disrupting the biosynthesis of purines. It reduces the production of uric acid by inhibiting the enzyme xanthine oxidase and thus inhibits the conversion of xanthine to uric acid. The use of allopurinol blocks the formation of urates and avoids the hazard of hyperuricaemia of uric acid posed by uricosuric drugs. Allopurionol is approximately 90% absorbed from the gastrointestinal tract. Its renal clearance rate is rapid and approximates that of glomerular filtration rate.[12]

Procainamide hydrochloride is an anti-arrhythmic drug. It is free base with Pka 9.23. It increases the effective refractory period of the atria, and to a lesser extent, the bundle of Hiss, Purkinje system and ventricles of the heart. It reduces impulse conduction velocity in the artia, Hiss-Puakinje fibers and ventricular muscle, but has variable effects on the atrioventricular (A-V) node, a direct slowing action and weaker vagolytic effect which may

produce slight acceleration of heart rate, while high or toxic concentrations may prolong A-V conduction time or induce A-V block, or even cause abnormal automaticity and spontaneous firing by unknown mechanisms. The elimination half life of procainamide, is three to four hours in patients with normal renal function.[13]

Nortriptyline hydrochloride is water soluble practically insoluble in most organic solvents. The mechanism of mood elevation by tricyclic anti-depressants is at present unknown. However it inhibits the activity of diverse agents such as histamine, 5-hydroxytrypamine, and acetylcholine. Studies suggest that nortriptyline interferes with the transport, release, and storage of catecholamines. Operant conditioning techniques in rats and pigeons suggest that nortriptyline has a combination of stimulant and depressant properties.[16]

The present study is designed to find out effect of innate lipid solubility on buccal absorption of basic drugs with similar Pka values.

MATERIALS AND METHODS

Allopurinol hydrochloride, nortriptyline hydrochloride and procainamide hydrochloride with Pka values 9.4, 9.2-9.7 and 9.2 respectively were selected for in vivo and in vitro study. Base powder of drugs was received from Glaxo Welcome Pharmaceutical company Limited, Pakistan, and Bristol-Meyer-Squibb Pharmaceutical Company. Innate lipid solubility of drugs were determined by buccal absorption test (in vivo study) and by I-octanol/ buffer partitioning coefficient at various pH from 6-10 (in vitro study).[15,16]

Buccal absorption test

The study was carried out on 18 volunteers of either sex with ages 20-60 years. The volunteers were divided into three groups. Group A, group B, and group C. Each group consists of 6 volunteers.

An individual having any disease of oral cavity either acute or chronic was excluded from the study. Habitual user of pan, cigarette, snuff or alcohol was also not included in the study and to eliminate any possible effects of extraneous factors use of toothpaste, miswak, mouth freshener etc, was not allowed two hours prior to the buccal test.

Volunteers were asked to rinse their mouth with plain water to remove any food particles etc. The mouth was then rinsed with 20 ml of freshly prepared Sorensen phosphate buffer (pH 6.0) for 30 seconds (to adjust the pH of the oral cavity) and discarded. The volunteers of group A, B and C were given 20 ml of allopurinol hydrochloride, procainamide hydrochloride and nortriptyline hydrochloride respectively dissolved in pH 6 buffer (100 μg/ml) to keep in mouth for five minutes. They were asked to swirl it around the oral cavity approximately once per 5 seconds. After 5 min, they expelled the fluid in a beaker. To wash out any unabsorbed drug adhering to oral mucosa and teeth, immediately after this they rinsed their mouth with 20 ml of blank buffer of pH 6.0 for 10 sec. This fluid was expelled in the same beaker. Quantitation of drug expelled in buccal fluid was done on Schimadzu ultraviolet spectrophotometer. Buccal absorption test of drug at pH -10 was estimated using the same procedure.

I-octanol/buffer partitioning test

Study was carried out on 9 test samples. The test samples were divided into three groups i.e. group A. group B and group C. Each group consisted of 3 test samples. Fifty ml of allopurionol hydrochloride, procainamide hydrochloride and nortriptyline hydrochloride respectively each (50 μg/ml) dissolved in sorensen buffer (pH 6.0 was added to equal volume of I-octanol. It was then shaken for 20 min. After separation of I-octanol and buffer phases, amount left in buffer phase was determined spectrophotometerically. I-octanol / buffer partition coefficient of drug at pH 7-10 was determined similarly. Percentage of drug partitioned in I-octanol and partition coefficient was calculated by formulation.

Statistical analysis

Data was analysed by regression analysis and "p" value was found out. Correlation coefficient "r" between percentage buccal partitioning and percentage of drug under study at different pH was calculated.

RESULTS

Table 1 shows the mean percentage of buccal partitioning of allopurinol hydrochloride was decreased from 37.12 to 13.089 with the increase in pH from 6.0-10. On the other mean percentage of I-octanol partitioning was sharply decreased from 41.28 to 5.88 with the increase in pH from 6.0-10. The correlation coefficient "Y" between mean percentage buccal partitioning of allopurinol hydrochloride over the pH range 6-10 was highly significant ($r= 0.89$, $P<0.001$).

Table 2 shows that mean percentage of buccal partitioning of procainamide hydrochloride was increased from 3.99 to 24.08 with an increase in pH from 6.0-10. Mean percentage of I-octanol partitioning sharply increased from 5.6 to 55.1 with an increase in pH from 6.0-10. Correlation coefficient "Y" between mean percentage buccal partitioning and I-octanol partitioning of procainamide hydrochloride over the pH range 6-10 was very highly

significant (r = 0.98, P < 0.001).

Table 3 shows the mean percentage of buccal partitioning nortriptyline hydrochloride was increased from 12.12 to 97.258 with an increase in pH from 6.0-10 increased from 78 percent to 100 percent. Correlation coefficient "Y" between mean percentage buccal partitioning and I-octanol partitioning of nortriptyline hydrochloride over the pH range 6-10 was highly significant (r = 0.90, p < 0.001).

The mean percentage of buccal partitioning of allopurinol hydrochloride was decreased with an increase in pH. Its mean percentage of I-octanol partitioning also sharply decreased with an increase in pH. The correlation coefficient "Y" between percentage buccal partitioning and I-octanol partitioning of allopurinol hydrochloride over the pH range 6-10 was highly significant. This shows a decrease in partitioning of allopurinol in lipid phase or in other words decreased in lipid solubility of the unionized form of drug. Considering these observations the drug does not fall in any group of Beckett and Triggs classification[16] for the rank order of their lipid solubility. A study suggested that decrease in lipid solubility of unionized form of some drugs (both in vitro and in vivo) may be because of ion pair distribution kinetics of basic drugs and frankected 1999 this phenomenon provides a possible basis for drug interaction in clinical treatment.[17,18]

Mean percentage of buccal partitioning of procainamide hydrochloride increased with an increase in pH. On the other the mean percentage of I-octanol partitioning was sharply increased with an increase in pH. Correlation coefficient "r" between mean percentage buccal partitioning and I-octanol partitioning of procainamide hydrochloride over the pH range 6-10 was very highly significant. Percentage of unionized moiety as calculated by Headerson Hasselblach equation at pH range 6-10 was that the unionized moiety of drug increased from 0.07%-86.30%. It is suggested that non-ionic diffusion of a drug should cross the lipid membrane and their crossing is dependent on the pH of the tissue fluid. However it is thought that unionized moiety of most of the drugs did not show 100% absorption.[10] It is found that following oral administration every 6 hours procainamide hydrochloride extended release tablets achieve a mean steady state of procainamide. About 15 to 20 percent of procainamide hydrochloride is reversibly bound to plasma proteins, and considerable amounts are more slowly and reversibly bound to tissues of the heart, liver, lung and kidney.[14]

Table 1: *Relationship between percentage of unionized allopurinol and its mean percentage buccal and I-octanol partitioning over the pH range 6-10.*

pH	**6**	**7**	**7.4**	**8**	**9**	**10**	
Percentage of unionized drugs.	0.04	0.04	1	3.83	28.48	79.94	R. 0.90
Mean percentage of buccal partitioning	3.12	36.24	32.58	24.58	24.37	13.08	
Mean percentage of I-I-octanol partitioning	41.28	36.48	21.54	14.8	7.84	5.88	

Table 2: *Relationship between percentage of unionized nortriptyline and its mean percentage buccal and I-octaual partitioning over the pH range 6-10.*

pH	**6**	**7**	**7.4**	**8**	**9**	**10**	
Percentage of unionized drugs.	0.02	0.2	0.5	2	16.7	66.66	R. 0.96
Mean percentage of buccal partitioning	12.12	65.56	71.95	81.45	96.87	97.25	
Mean percentage of I-octanol partitioning	78.0	90.25	96.82	99.65	100	100	

Table 3: *Relationship between percentage of unionized procainanide and its mean percentage buccal and I-octaual partitioning over the pH range 6-10.*

pH	**6**	**7**	**7.4**	**8**	**9**	**10**	
Percentage of unionized drugs.	0.07	0.63	1.56	5.93	38.66	38.30	R. 0.98
Mean percentage of buccal partitioning	3.99	5.4	8.54	13.04	23.37	24.08	
Mean percentage of I-I-octanol partitioning	5.6	7	9.48	15.32	3.5	55.1	

The mean percentage of buccal partitioning of nortriptyline hydrochloride was highly increased with an increase in pH. Mean percentage of I-octanol partitioning was also sharply increased with the increase in pH. Correlation coefficient "r" between mean percentage buccal partitioning and I-octanol partitioning of nortriptyline hydrochloride over the pH range 6-10 was highly significant. The study is in agreement with a study of group of workers who also observed the same results. It was confirmed that the input time of the some drugs be higher for pH 6 infusion than for pH 4.[21]

However other studies showed that in normal subjects a higher apparent oral drug clearance is nevertheless perfect as compared to see the oral clearance in patients.[22]

It is **concluded** that although the drugs studied have nearly similar Pka values, their solubility is varied widely. A good correlation between buccal and octanol partitioning excluded the possibility of interaction between these drugs and octanol. Decrease in lipid solubility of allopurinol hydrochloride needs further evaluation.

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