THE INFLUENCE OF URINE PH CHANGES ON THE RENAL EXCREPTON

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MUTUROI S.K.

This project work was submitted in partial fulfilment for the award of a degree in Bachelor of Pharmacy of the University of Nairobi.

June. 1979



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I am greatly indebted to my supervisors Prof. C.K. Maitai and Dr. C. Muriuki, without whose guidance this work would not have been possible. I am particularly grateful to them for reading through the script and guiding so in any alterations and corr otions that had to be made.

I make grateful to the technical staff of the Pharmoology section for their unfailing assistance during the course of this project.

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UNNARY

This project was carried out to investigate the influence of urine pH change on the renal e cretion of drugs that are weakly asidic. In choosing the drugs to be used in the project the maticability of their asany in a common laboratory was considered. Hence four drugs were chosen, Appirin, Chlorothiaside alphathiasole and alphafurasole. Rats were used in all the experiments that were carried out. In each experiment the urine was collected over a period of 24 hours and analysed for rug in question. In this way, the uncunt of drug excreted in urine wher verying wrine pH condition, were determined. Jodium bicarbonate and Ammonium chloride were used to make the urine alkaline and acidic respectively. emilate of a filter mild the Bomer's Capally, with a hope along called a manal taipaire. This collections don't is s functionally and a summer by a vermin the angle is a source of the tabule are did and shall be the second s wat at white a sum of investing inter manageding as will. and a set of the set o and the state of the state sections and filler date the errorly and page date the the set of the set of the set of the set of the and a second these second and a second second and a second s the transferred to serve the larger of means to any site

INTRODUCTION

columns (drugs) and area a little espect of ellipsic pros-

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This project was assigned to estermine the effects of oral admini.tration of alkali and acid upon the renal excret.on of druge that are weakly scinic,

the same that sub tenuss cre-shearbed from the filtrate

The kidney is the most is ortant organ of excretion her thing the les are returned to the blood and a such most substances are excreted in urine, However, Fourthously the tubulo can be divided into three s some other substances are excreted in bile, sweat, saliva, he province former former and gastric juice, or from the lungs. The excretory unit of the kidney is the Nephron. In the human kidney there are millions of these units. The ne hron essentially consists of a filter called the Bosman's Capsule, with a long stem called a renal tubule. The collecting duct is also functionally a part of the nephron. The blood 15 vessels that supply the capalle gaand the tubule are also an essential part of the nephron. The Borman's Capsule is packed with a mass of branching inter connecting capillaries (glossrular tuft) which provides a large surface area of capillary endothelium through which fluid and small molecules may filter into the cap ule and pass down the tubule. The glomenular tuft together with the Bounnis capsule constitute the glomerula. The glomerular capillary endothelium and the supporting layer of Bowman's capule shore in also optive transport of arganic detines

und inn: into the lines (hateling scoretion), and by a

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nave pores ranging upwards to 40°A. Hence, unbound olutes (drug.) and even a little amount of albumin page into the glomerular filtrate.

The post-closerualr vessels which lie close to the tubules are critically important to renal function in the sense that substances re-absorbed from the filtrate by the tubules are returned to the blood along the • vessels. Functionally the tubule can be divided into three major part., the proximal convoluted tubule, the loop of Henle and the distal Convoluted tubule.

After filtration the glomerular filtrate passes through the proximal tubule, where some soluties may be re-absorbed through the tubular epithelium and teturned to the blood stream. Re-absorption occurs partly by passive diffusion and partly by active transport especially with odium and glucose. Consequently, by these processes the filtrate becomes diminished in volume by approximitely 60% in the Proximal tubule, although it is not concentrated. In the Proximal tubule, although it is not concentrated. In the diffusion of hydronium ion reacts with the biourbonate ion, which is converted to re-absorbable non-ionic carbon dioxide.

There is also active transport of organic outions and ion, into the lumen (tubular secretion), each by a

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a separate system. These active transport systems are extremely important in the excretion of a number of drugs for example Penicillin G is rapidly secreted by the anion transport system and tetraethylammonium by the cation transport system.

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As the filtrate travels down the tubule through the loop of Hemle it become, concentrated, expecially at the bottom, as a result of notive reabsorption and the counter currect distribution offect of the renal apparatus. In the distal tubule modium re-absorption occur partly in exchange for Potessium and hydronium ion., amonia corotion may be either acidified or alkalinised according to the moid-base and electrolyte requirement.

and the pH of the unine here is extremely important in determining the rate of re-absorption and amount ro-absorbed. The pH of the tabular fluid also affects the tabular secretion of drugs. Then the drug in the tabule is highly include only a little of the drug can be reabsorbed. Hence no t of the drug is raidly excreted in unine. The unine pH and hence drug excretion may fluctuate widely according to the diet, exer ise, drugs, time of day and other factors.

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Obviouly, the excretion of week solds and bases can be partly controlled with soldifying or alkalinizing salts for excepts Assonium Caloride or odium bicarbonate respectively.

Comparative studies on petency and officiary of drugs in man have comparated the importance of controlling urinary pi. Urine pH is important only when the drug in question is a weak acid or base of which a significant fraction is expressed through the renal route. The plasma level: of the drug will be affected fue to the change, in the expression rate. This may have fir reaching effects on the therapeutic 1 effect of the drug.

bod hy the liver to thus, during which process lyin

The is ortunes of urine pi, in the expression of drugs has been illustrated by several workers. <u>Hilbs et al (1957)</u> found that necessylamine (basic) is exercised more than four times faster when the urine pH is less than 5.5 then when it is above 7.5. <u>Heag and largon</u> (1942) demonstrated that in the case of micrime the extent of urinary expression of the chemical may be related to the pH of the urine. They emphasized the importance of taking into consideration the dissociation constant of a drug and the relative reaborrbility of the free and dissociated base. Extending these studies to the urinary exercision of quimine in many. Hang, Lar on and churrts (1943) found that the urinary .' could be doubled by passing from an alkaline to an noidie urine and they ascribed the difference to greater

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re-absorption of quinine from the unimary tract when nivilar's securit of the urine is alkaline. Ever on and Dole (1943) found that renal clearance of quinacrine was subject to 100-fold variations due principally to two variable, the urinary pa and the renal plana flow. The army malaria research unit at Oxford (1945) supha ised the striking parallelion between excretion of Quinacrine and Amenonia.

collection of alkaline united. The affect of amonium Caloride and godium bicarbonate on the urine <u>到</u> DETAILS IN ADDRESS

After ingestion and absorption, the HH, ion is converted by the liver to Ures, during which process hyprogen ione are liberated.

> ts, 500 3.2 (leads deployed) HH. +Uren. ad shatistands why poner, July (lough aughund)

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The hydrogen ion so formed react, with bloarbon tes and other buffers in the extra-cellular fluid. Reduction in the bigarbonate concentration causes an increase in

ration (I CO, - ICO, + H) thus ouusing HCO.

an increase in the concentration of hydrogen ion in the extra-collular fluid, Consequently there is a fall in the pil, resulting in the formation of aoidic urine. The and result is that chloride ion displaces the bicarbonate ion.

the infter i. moverhod to cover dismine, that, the solution

the latter i wonverted to curbon dioxide. Thus, the chloride to the kidneys i, increased and appreciable occapes reabsorption along with an equivalent amount of oution (mainly Ma⁺) and i e-e motic quantity of water.

After ingestion of odium biourbonate, the excess of carbonate load presented to the distal tubule is not completely autralized by the available hydrogon ion . Con equantly the presence of exce. biourbonates in the extra-collular fluid result in the production of alkaline urine,

MAT.RL.L . HD AFPAR TU:

(i) Alkalinising agent - Jodium bioarbonute - (BHI)
(ii) Acidifiging agent - Assonium chloride - Analytical reajunt
(iii) Jruge u.eds-

Aspirin Tablet, 300m, B.P (Jawa Pharmocuticals Ltd) ulphafurazole Tablets, 500mg, B.P (lough ingland) ulphat iszole Tablet, 500mg, B.P.C (lough ingland) ulphatiszole Tablets, 500mg, B.P.C (lough ingland) ulphatiszole Tablets, 500mg, B.P.C (lough ingland)

(iv) Animal - Rate

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Determination of amount of acidifying and alkalinizing agents

The purpose of the e set of experiment was to determine the approximate amount of either Ammonium chloride or of the order mo mo odium bicarbonate required to achieve acidic and alkaline urine pH values respectively in rate. In each case 100 charcol. The 1 inc easing amounts of either Ammonium Chloride or edium for the drug under t bicerbonate were orally fed to the rate and the urine stips apostro di collected over a period of 24 hours. The pH of the urine 8,17 Lotion byim obtained was determined using a pl meter. Thi exerci . contains the al was repeated until the minimum amount of either Ammonium chloride or odium bicarbonate required to produce expected urine pH was obtained. (In this case the expected urine TT mod 1 pH was either acidio or alkaline) The results are shown on Table I.

Urine pH

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Tables IT and T.

Three group of rate each consisting of 3 animals were chosen and starved for at le st 24 hours. Three rate were used for each experiment to ensure enough wrine was

obtained. The rate were hydrated to ensure reasonable amount of urine was collected within the experimental period. To one of the groups odium bicarbonate was given orally and to the second group Amonium Chloride was given. The The third group was used as a control. Then equal amounts of the drug were given orally to the three groups of rats. The three groups of rate were then placed in three different metabolic cages and the urine collected in measuring cylinder over a eriod of 24 hours. The pH of the urine was noted to ensure it was within the expected range. The urine was filtered and decolourised with charcol. The wrine was then quantatively analyzed for the drug under test. This was done by obtaining an absorption spectra for the drug. I ulphuric soid 100mas/ and 0.1N odium hydroxide vere used as the solvents to obtain the absorption spectra of Aspirin and Chlorothiazide respectively. Typical absorption spectra are shown on figures 1 and 2. The results obtained are shown on Tables II and III.

20m1.

quantative estimation of "ulphafuramole and alphathiasole in Urine The experimental set up was the same a for Aspirin and Chlorothiazide just described except that the method of analysis was titrimetric. A titration was carried out with 0.1M standard Sodius Eitrite solution at a temperature below 15°C until a drop of solution immediately gives a blue colour on starch-lodide paper. The end point was complete when the and point could be reproduced after the titrated solution was allowed to standard for one minute. The titre was noted. The results obtained are shown on Tables IV and V.

RESULTS

for both drugs at thear A and in them, it is possible to

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	ODIUM BICARBOHATS			ANNORIUM CHLORIDZ		
Anount given to each rat	7 0mg/ 0.25Kg.	bance -1 140mg/ 0.25Lg.	210mg/ 0.25Kg.	300mg/ 0.25Kg.	60mg/ 0.25Xg.	90mg/ 0.25Kg.
Volume of urine collected	1911.	2 3ml	21 1	21ml	<u>22m1</u>	20m 1

9.6] = 50.0 2 #11

Jailer, J.W, Rosenfeld, J. and hannon, J.A in their work on renal excretion of quinacrine, Chloroquine and Santaquine used sodium biourbonate and Annonium Chloride to make urine alkaline and acidic respectively.

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Table I: Determination of amount of acidfying and alkalinising agents

Collection of trag in wrine from absorbance:

The spectrophotometric method was used to analyse the urine for Aspirin and Chlorothiaside, ince the extinction Coefficients for both drugs at their A max is known, it is possible to calculate their concentration in urine using the Berr-Laubert relationship.

A TO BIS CX1

0,92

Khere

1.120

A = Absorbance at max Artinotion Coefficient at Bar - 25100

c/100n3

0 = Concentration in g/100 ml

1 = Path length of the cell in Continetres.

For example, the amount of Aspirin excreted in urine under alkaline conditions was calculated as shown below :-

> C X 1 E1%lon 0.63 - 05.5 X CX1 0.63 g/100ml a similarly enheatstat as shown above, The Postlin of is hiblds IS and ITL. 65.5 = 0.00962g 0 = 9.62mg of aspirin C

Similarly, the amount of Chlorothiazide expreted in alkaline urine can be calculated :-

1.81a 11				
	= E1% los	CX1		
0.92	- 700 X C X 1			
C	= <u>0,92</u> g/10	OCml		
1999	700		1	
C	= 0.001314g	at	we as of	-
c	= 1.314mg of G	hlorothiazide.	trag	25
-		and a grant the G	and heaterman in	10.00
	Contra Co	10 mm	excitation .70	
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	ince a dilution of ysi then concentr		de during the	-
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anal	ince a dilution of	tion of Chloroth	de during the	-
The	ince a dilution of ysi then concentr - <u>13.1498</u>	tion of Chloroth	de during the deside in urine	·B.
anal,	ince a dilution of ysi then concentr - 13.1438. other value: were result. are shown i	tion of Chloroth	de during the disside in urine ted as shown abov	·B.
The	ince a dilution of ysi then concentr - <u>13.1498</u> other values were result, are shown i	tion of Chloroth inilarly calcula in tables II and	de during the disside in urine ted as shown abov	3.0 3.0 9.

Table II

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ASPIRTY

	225 3	inours p	a descharge	design of	
akalun Lanationada	PH	Anount of Drug Siven	Absorbance at Amax 276 m	inc.nt of irug excreted in	Average amount or arug exoreted
initia initia	3.7	4005	0,60	11,485.	in urine
bic rbonate	8.7	300mg	0.70 0.56	10.69mg 55mg	9 . 2206.
Aumonium Culoride	5.6	300mg	0.15 0.135	2.2)mg. 2.069mg	2.18mg.
Control (no agent)	7.1	300mg	0.29 0.395	4.43mg 6.03mg	5.23mg.

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Toble III

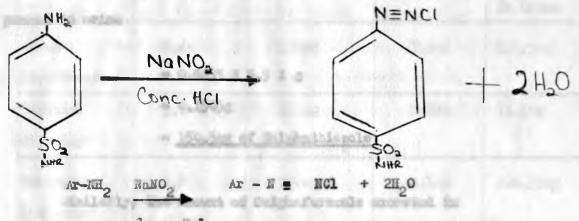
N.M.	PE	amount of	bsorbane	Amount of
-	NaNO	drug givon	.tλ εα 228	drug excreted in urine 24.0
icarbonate	8.5	40mg	0.92	13.14Mg.
Annonium Ciloride	5.7	4 Omg	0.80	11.446.
Control (no agent)	7.2	4úng	0.89	12.7Mg.

A ten-fold dilution was made

1 al af 0.12 Isto, a 0.0250g of 0.1. T. 0.

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i solur solution of $1000_2 = 1207.30$ of $0_{11}0_{13}0_{3}0_{3}^{-1}$ 2000al of 10 $100_2 = 207.30$ of $0_{11}0_{13}0_{3}0_{3}^{-1}$ 1 al of 10 $000_2 = 0.00705$ of $0_{11}0_{13}0_{3}^{-1}$ 1 al of 0.15 $000_2 = 0.00705$ of $0_{11}0_{13}0_{3}^{-1}$ In calculating the amount of ulphathiasole or -ulphafurasole excreted the followin relationship was derived. From the titration reaction, 1 mole of odium Hitrite is required for every mole of either ulphathiasole or sulphafurasole.



Conc. Hol

Therefore

1 molar solution of NaNO = 255g of $G_{H_{2}H_{3}O_{2}}$ (...lphathiazole) 1000ml of lN NaNO₂ = 255g of $G_{2}H_{2}H_{3}O_{2}-2$ 1 ml of lN NaNO₂ = 0.255g of $G_{2}H_{2}H_{3}O_{2}O_{2}$ 1 ml of 0.1N NaNO₂ = 0.0255g of $G_{2}H_{2}H_{3}O_{2}-2$

255g = Molocular weight of alphathiagole imilarly, a imilar relationship can be derived for alphafurazole:-

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267.3g = Nolecul r weight of alpha unasolo.

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The above relation hipsware u od to calculate the anount of

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drug emersted in urine as follows -

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Service:

For example in, alkaline condition the amount of sulphat insole

- 0.0255 X 5.9 X 6

• 0.1505g

0.0

= 150.5mg of Hilphothiazole

initally, the amount of Sulph furazole excreted in alkaline condition: can be calculated:

- 0.02673 X 6.8 8

= 101.76mg of ul shafurazole

and the second s	os vero similarly nown in table.	colculated as a	abom above.	drug erstet
nitim biotroida	8.7	23,0mg	0,010	2.01. Yong
annin Giatie	5.5	21.04	3.54	113,56
Enviral (no agent)	7,1	Zion;	3.64	366300

Table IV

DISCUSSION

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the date addag in direct th	indian anthat.	Date agreent 1.	in urine
odius contrate 6.4 their to	100ng	5.911	150.5ag
bicarbonate da la cad a lieve	in rate to not the	all in the	
Armonium 5.7	180mg	2. Sail	71.503
Chloride " the solution.			
Control 7.0	1,005	4.1-1	104.55mg
(To agent)	amoist in write	ante attests	

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odium	11, id. scluble		6.821	181.76mg
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Ammoniam	5.5	21 Gaig	3.5ml	113.56
Glaria				
Control	7.1	21.0mg	5.402	144.34 5
(no agant)	street, As an	h how suciria s	111 appost in	pine.

DISCUSSION

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ASPIRIN

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In the body Aspirin (acetylcalic,lie acid) is hydrolysed to mlicylic acid. Hence, due to the presence of this actabolite in urine the estimation of a pirin in urine could not be done using a direct titration method. Consequently a spectrophotometric method was adopted to discriminate between the two. Aspirin and salicylic acid do not absorb at the same Amar in UV, aspirin **absorbs** at Amar 76mm, .11 alpharic acid used as the solvent.

From the results obtained, shown on table II, it is apparent that more Aspirin is excreted in urino under alkaline conditions compared to the amount excreted under acidic or normal conditions. This is in keeping with what would be expected the least amount being excreted under acidic conditions.

This result can be exclaimed by considering the Chemistry of the acetyl Salicylic acid molecule and the mochanisms of excretion in the kidney. Aspirin being an acidic drug will readily ionize under alkaline conditions. In this state, the A pirin is less lipid soluble and hence not readily absorbed through biological membrane. Therefore, alkalinizing the tubular fluid by inge ting sodium bioarbonate the a pirin will be ionized to some extent. Consequently, in this form, very little of the a pirin in the tubules will be reabsorbed back into the blood stream. As such more aspirin will appear in urine. Conver ely, under acidic conditions very little of the drug will be in the ionized form, resulting in more drug being reabsorbed back into the blood stream from the renal tubules. Hence there will be a decrease in the amount of drug appearing in urine.

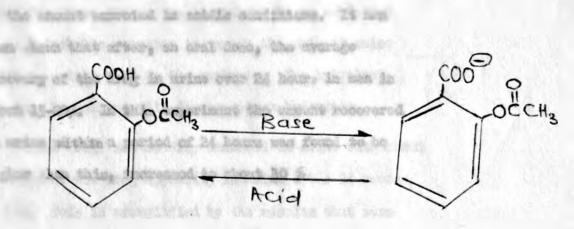
vi Asta 201 (S. das 700) uning 0.18 million hydrograda on

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By alkalinising the urine the amount of aspirin excreted in urine increases to about 2 - 4%, whereas the amount excreted in acidic condition is about 1%. A pirin and other alicylate are rapidly distributed to all body tis uss. This may explain why whay a mall amount is excreted in urine. The rate of excretion of aspirin varies with the pH of the urine, increasing as the pH rises and being greatest at pH 7.5 and above.

Ionization Builibrium of Amirin

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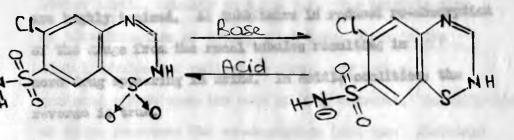
chlorothiazile was also spectrophotonstrically analyzed at $\lambda = 288$ ($\Delta_{1} = 700$) using 0.1H odium hydroxido as the solvent.

The malphanido is group in chlorothingile makes the molecule lightly acidic. Consequently, andar very alkaline conditions it will ionize to some extent by lossing a proton. This ionization takes place only to a limited extent. Hence very little of the rug will be in the ionized form. This exclaims shy there was only a small variation in the mounts of the rug extrated in urino by varying urine pli.

hy claiming the unine there is only a small increase in the asount of the drug expreted in unine compared to the amount excreted in asidic conditions. It has been hows that efter, an oral does, the everage recovery of the drug in unine over 24 hours in man is -bout 15-20,. In this experiment the amount recovered in units mithin a period of 24 hours was found to be higher has this, increased to about 30 p

one. This is complified by the regulty that uses

interior in the second in the second in the second



<u>Sulphafursole and Sulphathiazole</u>

The quintative estimation of these drugs involves a diasotization reaction which involve the reaction of a primary aromatic unine with Nitrou acid to form a diasonium salt.

white bitting for shield of a

In the body these drugs are readily acetylated, to form conjugated derivatives. Hence in analysing the urine for these drugs, the drugs have to be subjected to an hydrolytic reaction to unmask the primary amine which is made use of in the analysis. The hydrolysis was done by boiling with dilute sodium hydroxide.

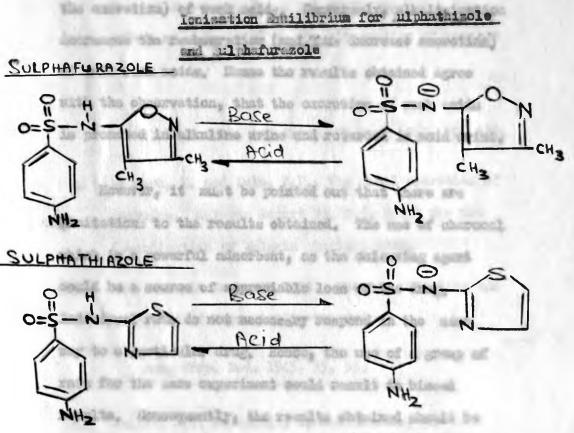
These drug, are readily exoreted in urine with about 90 - 95% of the drug appearing in urine after 24 hours in man. This is exemplified by the results that were

theories in gutresimuting trust on his been

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obt ined in this experiment. By alkalinising the urine there was an approxiable increase in the amount of the drug, emersted in urine. This can be explained by the fact that under these condition the drugs are highly i nized. As each takes is reduced re-absorption of the rule from the renal tubules resulting in more drug appearing in arine. In solicio condition, the r verse is true.

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It must be noted, that explanations advanced for the results obtained only apply for the area that has been absorbed from the gastro-intestinal traot and has been filtered in the kidney into the real tubule.

CONCLU-ION

The pH of urine is normally maint ined wi him fairly trict limit, usually pH 6.8 - 7.4. The moidific tion or alkalinization of urine, which takes place in the distal tubulos and collecting ducts, may have a profound effect upon the r to of drug exercised. Addification of urine increases the ro-absorption (and thus diminishe the expression) of weak acids. Conversely, alkalinization decreases the reabsorption (and thus increase excretion) of such weak acids. Hence the results obtained agree with the observation, that the excretion of weak acids is monoted in alkaline urine and rotarded in acid urine.

However, it must be pointed out that there are initation to the results obtained. The use of charcoal which is a overful adsorbout, as the colouring agent could be a source of appreciable loss of the drug. Individual rate do not necessary respond in the same way to a particular drug. Hence, the use of a group of rate for the same experiment could result to biased results. Consequently, the results obtained should be accessed in the light of these factors.

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