THE GASTRIC SECRETION OF DRUGS: A pH PARTITION HYPOTHESIS[1]

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The secretion of drugs and other foreign compounds into gastric juice is a route of drug disposition which has been generally ignored by pharmacologists and toxicologists. Various investigators have reported the presence of organic bases in the stomach after parenteral administration. A number of workers have shown that basic dyes are secreted by the gastric mucosa of the dog, while acidic dyes are not (Kobayashi, 1926; Dawson and Ivy, 1925; Ingraham and Visscher, 1935; Ray *et al.*, 1953; Cambel *et al.*, 1954). There are a number of reports stating that morphine is secreted into the gastric juice but other reports are in conflict. Sumwalt (1941) has reviewed the data of various investigators and concluded that "the best available work denies its gastric transfer except in traces." Davenport (1942) found certain sulfonamides in low concentration in the gastric juice after parenteral administration. Sung and Way (1954), in studying the fate of parenterally administered acetylmethadol in the rat, found rather large amounts of the drug in the stomach contents.

Our own interest in gastric secretion of drugs was instigated by the observation that levorphan (Dromoran) intravenously administered to dogs appeared in the gastric juice in high concentration (Shore *et al.*, 1955a).

The present paper describes the gastric secretion of a variety of basic and acidic drugs of heterogeneous structure and shows that the extent of gastric secretion of weak organic electrolytes is dependent upon the ionization constant of the compound. The results allow the formulation of a model of a lipoid barrier between blood and gastric juice that is in accord with experimental data.

METHODS AND MATERIALS. *Analytical methods.* The methods employed for the estimation of the various compounds in biological materials have been previously described with the exception of *p*-hydroxypropiophenone; acetanilide and aniline (Brodie and Axelrod, 1948); theophylline (Brodie, Axelrod and Reichenthal, 1952); antipyrine (Brodie *et al.*, 1949); aminopyrine (Brodie and Axelrod, 1950); quinine (Josephson *et al.*, 1947); levorphan (*l*-Dromoran) (Shore *et al.*, 1955); tolazoline (Priscoline) (Brodie, Aronow and Axelrod, 1952); salicylic acid (Brodie *et al.*, 1944); probenecid (Beyer *et al.*, 1951); phenylbutazone (Butazolidin) (Burns *et al.*, 1953); thiopental (Brodie *et al.*, 1950); and barbital (Goldbaum, 1948).

p-Hydroxypropiophenone was estimated as follows: The compound was extracted from acidified plasma or gastric juice into five volumes of benzene. An aliquot of the benzene phase was then shaken with 2.5 *N* sodium hydroxide, and the optical density of the alkaline

[1] A preliminary report on this work was presented before the American Society for Pharmacology and Experimental Therapeutics, Atlantic City, N. J., April, 1954.

phase measured at 325 mμ with a Beckman spectrophotometer. Recoveries of the drug added to plasma and gastric juice were satisfactory (95 ± 3 per cent).

Determination of dissociation constants. Since most reported dissociation constants for the drugs used in these experiments have been determined in partially nonaqueous systems, they were redetermined in an aqueous medium of constant ionic strength. Several methods were used. The pKa values of aminopyrine, levorphan, acetanilide, quinine, theophylline, antipyrine and probenecid were determined by distribution between an organic solvent and buffers of various pH values as described by Butler (1953). The spectrophotometric method of Flexser, Hammett and Dingwall (1935) was used for thiopental, barbital, *p*-hydroxypropiophenone and phenylbutazone. For both these methods the drugs were dissolved in 0.1 *M* buffer. Microtitration in 0.1 *M* saline was used for tolazoline, aniline and salicylic acid. All values are expressed as pKa.

Determination of drug binding to plasma proteins. The extent to which the various drugs at the appropriate plasma concentration are bound to proteins has been previously published in the above references to analytical methods, with the exception of salicylic acid, aniline, quinine, levorphan, antipyrine, *p*-hydroxypropiophenone, probenecid and theophylline. Salicylic acid is bound to the extent of about 75 per cent (Smith *et al.*, 1947). The values for the other compounds were determined by the ultrafiltration technique of Rehberg (1943) and are listed in table 1.

Dogs, of either sex, with a vagally denervated Heidenhain fundic pouch were used several weeks after operation. The animals were fasted for about 16 hours prior to each experiment. Histamine, dissolved in 0.9 per cent saline, was infused intravenously into a superficial leg vein at a rate of 0.25 mgm. per kgm. per hour, using a Bowman infusion pump, and the infusion was continued throughout the experimental period. This rate of histamine infusion elicits a maximal secretory rate and acidity of gastric juice (Öbrink, 1948). When the juice was flowing freely through the cannula, a priming dose of the drug under investigation was injected intravenously followed by a constant intravenous infusion of the drug to maintain a relatively constant blood level. Only the priming dose of probenecid and the barbiturates was necessary since the plasma levels of these drugs declined at a sufficiently slow rate following a single injection. After waiting about one-half hour to ensure approximate equilibrium distribution of the drug throughout the body, simultaneous gastric juice and venous (jugular) blood samples were taken. After another one-half hour the sampling was repeated. The concentrations of drug in plasma and in gastric juice were determined and the values expressed as the concentration ratio, R, that is, the concentration of drug in gastric juice divided by the concentration in plasma.

Results. The average concentration ratio (R) for each drug is shown in table 1, which summarizes the experimental findings. It is evident that for the basic compounds, R increased with increasing basicity until a limiting value of about 40 was reached for compounds with a pKa of 5 or higher. For these stronger bases, an increase of pKa above 5 had no effect on R. For example, aniline (pKa 5) had the same R value as the much stronger base levorphan (pKa 9.2). Tolazoline was an exception, repeatedly confirmed, to the otherwise striking constancy of R for stronger bases.

The concentration ratios for the acids also increased with increasing pKa. Strong acids such as salicylic acid, probenecid and phenylbutazone with pKa's ranging from 3 to 4.4 could not be detected in the gastric juice, while the weaker acids *p*-hydroxypropiophenone, thiopental and barbital were all secreted.

A possible explanation for the limiting concentration ratio for stronger bases is that these compounds are completely cleared from the blood as they pass through

TABLE 1

Gastric secretion of drugs

Drug	Plasma protein binding	pKa	Priming dose	Infusion dose	Drug concentrations and R value at one-half hour			Drug concentrations and R value at one hour			Average R value
					Plasma*	Gastric juice	R	Plasma*	Gastric juice	R	
Bases	%		mgm./kgm.	mgm./kgm/hr.	mgm./l.	mgm./l.		mgm./l.	mgm./l.		
Acetanilide	0	0.3	33	66	78	78	1	126	126	1	1
Theophylline	15	0.7	30	30	54	81	1.5	81	118	1.5	1.5
Antipyrine	0	1.4	66	66	138	575	4.2	230	938	4.1	4.2
Aniline	25	5.0	20	10	9.5	350	38	8.5	358	42	40
Aminopyrine	15	5.0	20	10	25	1050	42	24	1010	42	42
Quinine	75	8.4	50	24	4.0	144	36	4.7	189	40	38
Levorphan	50	9.2	2	1	0.2	7.8	39	0.2	8.3	42	40
Tolazoline	23	10.3	15	5	12.0	125	11	13.2	135	10	10.5
Acids											
Salicylic acid	75	3	75	38	270	0	0	338	0	0	0
Probenecid	75	3.4	25	—	14	0	0	14	0	0	0
Phenylbutazone	90	4.4	30	10	185	0	0	195	0	0	0
p-Hydroxypropiophenone	75	7.8	17	9	6.4	0.95	0.15	5.5	0.62	0.11	0.13
Thiopental	75	7.6	44	—	23	3.2	0.14	20	2.0	0.10	0.12
Barbital	0	7.8	200	—	268	164	0.6	254	152	0.6	0.6

* Plasma values represent total (bound + unbound) drug.

the gastric epithelium. This hypothesis was tested by the following experiment. The stomach of a normal male dog under pentobarbital anesthesia was ligated at the cardiac and pyloric ends. The jugular vein and a gastro-epiploic vein were cannulated with polyvinyl tubing. The stomach itself was cannulated with a short length of rubber tubing and was flushed clean with saline. Aniline and histamine were administered as described above. When the flow of gastric juice was copious, and aniline had been infused for one-half hour, simultaneous samples of jugular blood and gastro-epiploic venous blood were taken. The aniline content of whole blood and plasma of each sample was measured. Table 2 summarizes the data obtained and indicates that about 64 per cent of the aniline in the whole blood was removed by passage through the stomach. The aniline removed from blood was more than was originally present in the plasma. Thus it might appear that all of the plasma and a portion of the red cells were cleared of aniline, followed by a subsequent rapid reestablishment of equilibrium of the drug between plasma and red cells. An alternative and more likely possibility, however, is that all of the drug was completely cleared from the blood serving the gastric epithelium. This is not unreasonable since the gastro-epiploic venous sample represents blood from not only the epithelium but also the muscle wall and anastomoses. Accordingly, two-thirds of the blood contacted the epithelium where clearance was complete and the remaining one-third passed through the muscle and arterio-

venous anastomoses where no removal of drug would take place. Complete clearance of substances by the epithelium would explain the apparent limit of concentration ratios that occurs when the stronger bases are secreted.

DISCUSSION. The weak electrolytes used in the study of gastric secretion possess greatly varying structures and dissociation constants and include compounds with a diversity of pharmacologic effects. The diversity of chemical structures of the compounds secreted into the gastric juice makes it unlikely that this secretion is the result of an "active" transport mechanism involving specific chemical reactions. From the data summarized in table 1 it is apparent that the only variable that changes consistently with the observed concentration ratio is the pKa of the compounds. Except for the stronger bases, those with pKa > 5, an increase in the pKa of bases and acids results in an increased concentration ratio.

This pK dependence may be explained by the concept that plasma and gastric juice are separated by a membrane having the characteristics of a lipoid barrier, across which only the undissociated molecule can pass. At equilibrium, the concentration of undissociated drug would be equal on both sides of a lipoid membrane. However, in gastric juice and plasma the unionized moiety must also be in equilibrium with the ionized moiety. Since the pH of the two phases differs markedly, the concentration of ionized drug may differ markedly in the two phases, the difference depending on the pKa of the drug. If, as pictured diagrammatically in figure 1, the gastric juice has a pH of 1 and the plasma a pH of 7 with an oil layer separating the two, parenterally administered bases would be

TABLE 2

Clearance of aniline by the gastric mucosa

	Systemic Blood	Gastric Blood
Hematocrit	0.54	0.53
Aniline whole blood conc. (microgm. per ml.)	16.8	6.0
Aniline plasma conc. (microgm. per ml.)	15.9	5.8
Calculated aniline in plasma of 1 ml. whole blood	7.3	2.8

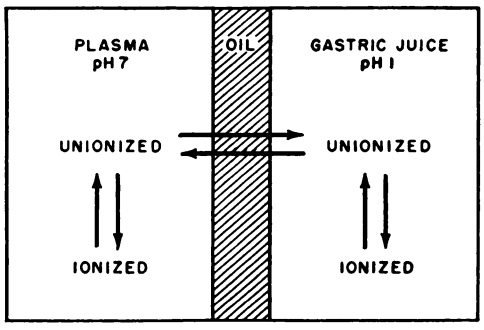

FIG. 1. Model illustrating pH partition mechanism of gastric secretion of weak electrolytes.

expected to be concentrated on the gastric juice side while acids would remain concentrated on the plasma side.

It is possible to derive a formula which will express mathematically the concentration ratios which should theoretically obtain at equilibrium[2].

$$R(\text{for bases}) = \frac{1 + 10^{(pKa-1)}}{1 + 10^{(pKa-7)}}$$

$$R(\text{for acids}) = \frac{1 + 10^{(1-pKa)}}{1 + 10^{(7-pKa)}}$$

where R is the theoretical concentration ratio, and pKa is the negative logarithm of the acid dissociation constant for each drug. Thus if the pKa is known, R may be calculated.

[2] Let U and I be concentrations of unionized and ionized moieties respectively and subscripts g and p indicate gastric juice and plasma respectively. From the Henderson-Hasselbalch equation for a base we have

$$pH = pKa + \log U/I \qquad \text{or } I = U.10^{(pKa - pH)}$$

The concentration ratio,

$$R = \frac{U_g + I_g}{U_p + I_p}$$

Thus

$$R = \frac{U_g + U_g.10^{(pKa-pHg)}}{U_p + U_p.10^{(pKa-pHp)}}$$

but it is postulated that the concentration of the unionized moieties in gastric juice and plasma become equal, or

$$U_g = U_p$$

thus

$$R = \frac{1 + 10^{(pKa-pHg)}}{1 + 10^{(pKa-pHp)}}$$

when

$$pH_g = 1 \text{ and } pH_p = 7$$

then

$$R = \frac{1 + 10^{(pKa-1)}}{1 + 10^{(pKa-7)}}.$$

A comparable equation for an acid is obtained from the form of the Henderson-Hasselbalch equation for a weak acid,

$$pH = pKa + \log I/U$$

For reason of simplicity the distinction has been drawn between the ionized and unionized moieties. It must be recognized, however, that dissociation of an ionizable group of a polyvalent compound of large molecular weight may result in a lipoid-soluble ion.

Quantitative aspects of the movement of weak electrolytes across cell membranes have been considered previously (Osterhout, 1925; Jacobs, 1940; Clowes, Keltch and Krahl, 1940; Orloff and Berliner, 1956; Hogben, 1954).

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