Influence of Acid-base Balance on Efficacy and Toxicity of Drugs

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Abstract
Changes in acid-base balance have a profound influence on many aspects of the action of drugs. This is illustrated by data on the absorption of drugs from the stomach and intestine, in changes in distribution of drugs between plasma and cells, and the effect of change in urinary pH.

As a general principle, these changes in the pharmacology of weak acids and bases are governed by physicochemical principles, which influence the proportion of the ionized and unionized components according to the pH of the medium and also to the peculiar property of biological membranes which allow the free passage of the lipoid-soluble unionized component and impede transfer of the water-soluble ionized fraction.

Lipoid-soluble weak acids are excreted at higher clearances in alkaline urine, and conversely weak bases in acid urine. This is shown to be of practical importance in the treatment of poisoning, in the diagnosis of addiction to drugs and in studies of drug metabolism. In general, the excretion of natural metabolites is less likely to be influenced by urinary pH, as these substances are usually less lipoid-soluble than many widely used drugs. pH-dependent excretion is, however, of practical importance in relation to the urinary content of many indolic metabolites and also in the excretion of pigments derived from the degradation of hæmoglobin. Urobilinogen excretion is certainly pH-dependent, a higher clearance rate occurring in alkaline urine. However, work is necessary to decide whether some of the porphyrins also show this important physiological property.

Changes in acid-base balance have a profound influence on many aspects of the action of drugs. Many such compounds are weak acids or bases in which the proportion of the ionized and unionized components is dependent on the pH of the medium according to the well-known Henderson-Hasselbalch equation. The main pharmacological action may be due to that of either the ionized or the unionized fractions alone or to a combination of both. In addition, the unionized component is usually lipoid-soluble and thus diffuses freely across cellular membranes, whereas the ionized fraction is predominantly water-soluble and therefore transfer across the membrane is either zero or negligible. This profoundly affects the distribution of the drug within the body, or alters the speed of transfer and attainment of equilibrium concentration at the site of action.

Absorption of Drugs from the Stomach
Shore *et al.* (1957) proved that absorption of weak acids and bases from the stomach is governed by the physicochemical laws of diffusion. A weak acid within the gastric contents, e.g. salicylic acid, is almost entirely unionized and therefore diffuses freely across the gastric mucosal cells into the capillary blood. The pharmacological action may, therefore, be almost as rapid as if the compound was given by injection. The distribution between gastric juice and plasma is dependent on the dissociation constant (pKa) of the acid, e.g. an acid with a moderately low pKa such as salicylic acid (pKa 3·0) would be expected to have a high plasma/gastric juice ratio at equilibrium, and therefore the amount in the juice is virtually zero, whereas a very weak acid such as barbitone (pKa 7·8) would have a ratio of only 1·67, and therefore absorption would be correspondingly less rapid.

Conversely, weak bases are highly ionized in gastric juice and therefore are absorbed by diffusion through the stomach wall in negligible amount. If given by injection they will, however, rapidly diffuse in the reverse direction giving gastric juice/plasma concentration ratios of up to 40 to 1. Extremely weak bases with pKa values below 2·0, e.g. acetanilide, theophylline and antipyrine, attain lower concentration ratios, but the vast majority with pKa values above 3·0 reach the maximum ratio of about 40 to 1. This limiting value is explained by the rate of gastric blood flow, as at high values only negligible amounts of base remain in the plasma within the capillaries supplying the mucosal cells. In medico-legal cases analysis of gastric juice is often as useful as examination of urine in cases of suspected poisoning by a weak base, but would be valueless in the case of a weak acid. Most observations on the distribution of drugs between gastric juice and plasma have been made on animals, and many problems remain unanswered in the case of man. In particular, the effect of achlorhydria on the rate of absorption of weak acids might well be a profitable field of research.

Absorption from the Intestine
Similar principles occur in intestinal absorption, but here hydrogen ion gradients between the lumen and the capillary blood are much less extreme (Schanker *et al.* 1958, Hogben *et al.* 1959, Schanker 1959). The rate of absorption is proportional to lipoid solubility and can occur both in the small and large intestines. Identical principles affect the absorption of lower fatty acids, rate of transfer increasing with greater molecular size and increased lipoid solubility (Dawson *et al.* 1964).

Changes in Distribution between Plasma and Cells
Similar factors govern the entry of lipoid-soluble weak bases and acids into cells and particularly

into the central nervous system. The intracellular and cerebrospinal fluids are considerably more acidic than is plasma. The partition of diffusing acids and bases will therefore result in a higher intracellular concentration of weak bases, and conversely a lower value for weak acids. In general, bases are more active than acids weight for weight because of their greater intracellular concentration. Substances which have a high lipoid solubility at pH 7·4 will penetrate well into body cells and particularly into the central nervous system and cerebrospinal fluid. In the case of bases, amine drugs are much more lipoid-soluble than are the highly ionized quaternary ammonium compounds. This is well illustrated by ganglion-blocking drugs; mecamylamine and pempidine have an important toxic effect on the brain in high dosage (Harington & Kincaid-Smith 1958), whereas quaternary compounds, e.g. hexamethonium and pentolinium, have no such action.

Sudden external changes of acid-base balance, e.g. breathing CO_2 during anæsthesia or ingestion of large doses of sodium bicarbonate, will alter extracellular pH more rapidly than that of the intracellular fluid. Equilibration is more rapid after respiratory than after metabolic changes of acid-base balance, but in either case there will be a temporary change in the gradient of hydrogen ions between the two phases with consequent alteration of the distribution of diffusible weak bases and acids. Breathing CO_2 will lower the concentration of phenobarbitone in plasma and excess sodium bicarbonate will have the reverse effect (Waddell & Butler 1957). Since the drug owes its sedative action to the intracellular fraction, acidosis increases the potency of the drug and bicarbonate reduces it. Similar principles affect the hypotensive effect of mecamylamine (Payne & Rowe 1957). As this drug is a base, CO_2 inhalation increases the concentration in plasma. There is a simultaneous fall in blood pressure, suggesting that the concentration in extracellular fluid, which is only a small fraction of the total amount of the drug within the body, is the active agent in ganglion blockade. This has later been confirmed by Blackman & Ray (1964), who found that the quaternary homologue of the drug, which is almost wholly confined to extracellular fluid and plasma, is also a potent ganglion-blocking agent.

Effect of Urinary pH Changes

Changes in urinary pH induced by ingestion of ammonium chloride, sodium bicarbonate and carbonic anhydrase inhibitors, e.g. acetazolamide, may have a profound influence on the excretion of weak acids and bases. In general, an acidic or basic drug may be expected to show the phenomenon of pH-dependent excretion if the unionized fraction is lipoid-soluble and if the pKa is within a favourable range of 7·5–10·5 for weak bases and 3·0–7·5 for weak acids. A few extremely lipoid-soluble bases, e.g. mecamylamine and pempidine, are excreted in this fashion although the pKa is higher than 10·5. Weak acids are excreted at a higher clearance in highly alkaline urine, and weak bases in acidic urine. Drugs which are known to show the phenomenon of pH-dependent excretion include the weak acids, salicylic acid, phenobarbitone, nitrofurantoin, nalidixic acid and some sulphonamides, and the weak bases mepacrine, chloroquine, nicotine, procaine, mecamylamine, pempidine, pethidine, levorphanol, quinine, amphetamine, imipramine and amitryptiline. The phenomenon of pH-dependent excretion is of practical importance for at least four reasons:

(1) *Treatment of poisoning:* Elimination of potentially toxic drugs may be expedited by appropriate adjustment of urinary pH. This has already proved useful in phenobarbitone and salicylate intoxications, and may be valuable in therapy of pethidine and amphetamine poisoning.

(2) *Diagnosis of addiction to drugs:* Recognition and identification of the unchanged drug may often be easier and more definitive than of the metabolites, which are in general more water-soluble and are not usually excreted in a pH-dependent manner. Acidification of urine in the certain diagnosis of pethidine and amphetamine addiction is of especial importance in this respect.

(3) *Studies on drug metabolism:* Reports on the metabolism and elimination of drugs showing pH-dependent excretion are misleading and incomplete unless studies are made at the extreme range of urinary pH. Pethidine was thought to be a case in which urinary excretion of the unchanged drug was negligible, until studies were made at low urinary pH (Asatoor *et al.* 1963). By contrast, amphetamine was thought to be excreted by man largely unchanged until studies were made in highly alkaline urine (Asatoor *et al.* 1965). Here excretion of the unchanged drug is almost negligible (Figs 1 and 2) proving that metabolism must play a major role in the elimination of the drug. In man, this is probably by oxidative deamination to phenylacetone with subsequent further degradation of this metabolite.

(4) *Excretion of natural metabolites:* Natural metabolites are usually less lipoid-soluble than drugs and therefore pH-dependent excretion is less common. Ammonium, which is excreted in much higher amount in acid urine, is a specialized

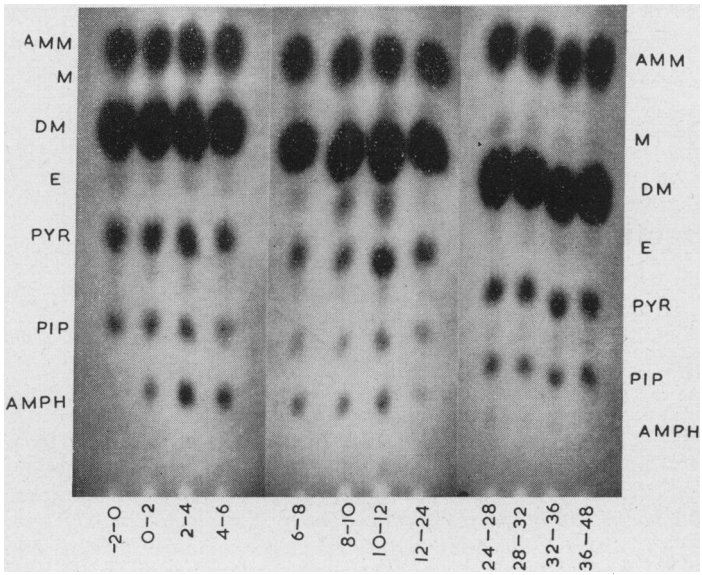

Fig 1 *Chromatogram of twelve urine fractions before, and up to forty-eight hours after, ingestion of 10 mg amphetamine sulphate during acidosis with highly* alkaline *urine. Output of amphetamine is high during the first twelve hours and progressively falls up to thirty-six hours after ingestion of the drug. Reversed-phase chromatography of dinitrophenyl derivatives of urinary amines and ammonia extracted by cyclohexane. Chloroform : methanol : water : liquid paraffin as solvent. Dinitrophenyl derivatives photographed in ultraviolet light. From the origin the spots are dinitrophenyl derivatives of amphetamine* (AMPH), *piperidine* (PIP), *pyrrolidine* (PYR), *ethylamine* (E), *dimethylamine* (DM) *methylamine* (M), *and ammonia* (AMM). *Figures under the chromatogram refer to times in hours*

example as urinary ammonia is entirely synthesized from glutamine and various amino acids in renal tubule cells and is not derived from blood ammonia. Indolic metabolites are unusually lipoid-soluble and therefore indolyl-acetic acid is excreted in greater amount in alkaline urine and, conversely, tryptamine and serotonin in acid urine. This is of importance in assays of monoamine oxidase inhibitors which increase excretion of tryptamine and lessen that of the metabolite indolyl-acetic acid after injection of small amounts of tryptamine. Unless variations resulting from change of urinary pH are allowed for, such assays may be misleading or even valueless. We have recently shown that urobilinogen is excreted in greater amount in highly alkaline urine. Urinary urobilinogen estimations are used in diagnosis of hæmolytic states and of hepatic cell function. Again, the results will be misleading if the effect of urinary pH is neglected. It is not yet known whether porphyrin excretion is similarly increased in alkaline urine. There is, however, a diurnal variation in porphyrin output, the lowest excretion occurring in the night when the urine is most acidic. These metabolites are known to be highly lipoid-soluble weak acids with pKa values within the favourable range for pH-dependent excretion to occur. If further investigation confirms these suspicions, alkalinization of the urine will obviously be valuable in diagnosis, and possibly in therapy, of the porphyrias.

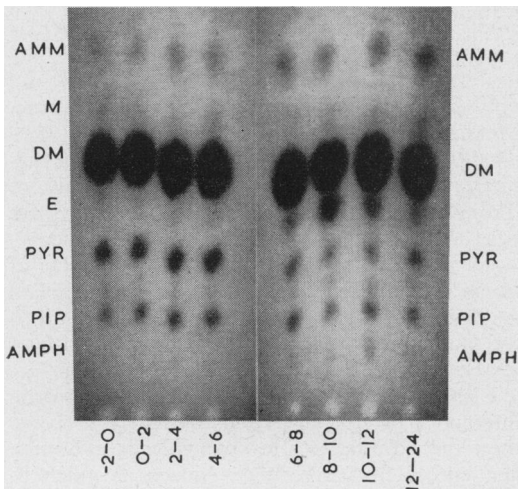

Fig 2 *Chromatograms of eight urine fractions before, and up to twenty-four hours after, ingestion of 10 mg amphetamine sulphate during alkalosis with highly* alkaline *urine. Technique and abbreviations as in Fig 1. Excretion of both amphetamine and ammonia but not of endogenous urinary amines is much less than in acid urine (Fig 1). Only a trace of amphetamine is excreted unchanged under these conditions*

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