THE INFLUENCE OF URINARY pH
ON THE ELIMINATION OF MEXILETINE

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1   The plasma elimination half-life of mexiletine was measured in four subjects when the urine was rendered (a) acidic and (b) alkaline.

2   Urinary acidification (pH 5.0) was associated with a plasma elimination half-life of 2.8 h and 57.5% of the intravenous dose was excreted in the urine within 48 hours. When the urine was alkaline (pH 8.0) the half-life increased to 8.6 h with negligible amounts of drug appearing in the urine.

3   Urinary pH varies widely in cardiac patients and should be controlled or monitored to provide better therapeutic precision with mexiletine.

Introduction

In therapeutics, a standard dosage of drug may produce very different degrees of response in individual patients. Much of this variation is due to differences in the tissue drug concentrations achieved by the dosage (Koch-Weser, 1972). These differences can be due to factors such as the patient's size, variable absorption of oral doses, the state of tissue perfusion and disease of the organs which eliminate the drug. These factors are well known and often taken into account when dosage is chosen, but the handling of a drug can sometimes be considerably influenced by other variables, whose significance may be overlooked.

Many drugs are weak acids or bases and exist in both ionized and unionized forms. The extent to which the drug is ionized depends on the dissociation constant and the pH of the medium (Gibaldi, 1971). Ionized organic molecules usually diffuse poorly across biological membranes whereas unionized molecules will diffuse rapidly if the drug is lipid soluble (Goldstein, Aronow & Kalman, 1968). Variation in pH, by altering the degree of ionization, can therefore effect passive reabsorption in the renal tubules since this process involves passage of drug molecule across a membrane.

We have examined the effect of urinary pH on the elimination of mexiletine, a new anti-arrhythmic agent recently found to be effective in

the treatment of ventricular arrhythmias (Allen, Kofi Ekue, Shanks & Zaidi, 1970; Talbot, Clark, Nimmo, Neilson, Julian & Prescott, 1973; Campbell, Chaturvedi, Kelly, Strong, Shanks & Pantridge, 1973).

Methods

Mexiletine hydrochloride, 200 mg (Kö 1173: Boehringer Ingleheim), equivalent to 166 mg mexiletine base, was given intravenously over 15 min to four healthy volunteers (age 25-33 years, weight 53.5-74.9 kg). The drug was given on two occasions, once when the urine was being acidified with oral doses of ammonium chloride (1 g every 3 h with 2 g before sleep, beginning 21 h before the experiment) and once when the urine was alkalinized by sodium bicarbonate (4 g every 4 h beginning 21 h before the experiment). A period of one week separated the doses to permit elimination of the first dose. The injection was given at approximately the same time of day on each occasion. The subjects remained ambulant during the experiment and fluids were taken *ab libitum*. Blood samples for mexiletine assay were taken via an indwelling venous catheter. Urine was collected in aliquots for 48 h after the dose for measurement of pH and mexiletine concentration.

Specimens of urine were also collected from unselected patients in a coronary care unit.

The pH of the urine aliquots was measured

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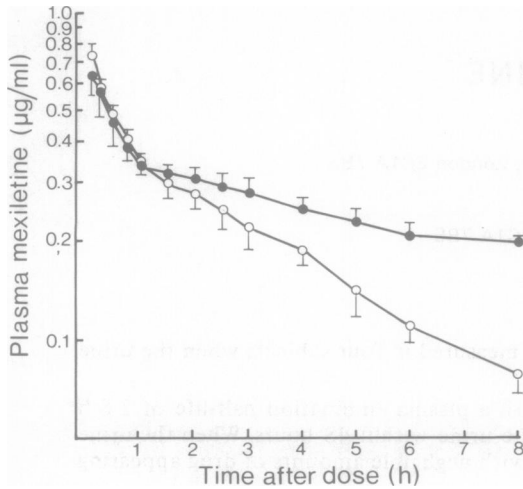
Fig. 1   Plasma mexiletine concentrations and elimination half-lives with urine pH acidic ($t_{1/2}$ 2.8 h; o) or alkaline ($t_{1/2}$ 8.6 h; •). Results are mean ± s.e. for four subjects.
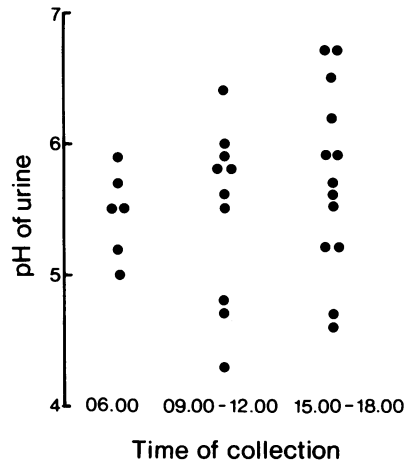

Fig. 2   pH values of urines from coronary care unit patients ($n = 20$).

using a potassium chloride electrode (Radiometer, Copenhagen).

Mexiletine was assayed by gas liquid chromatography by a method described elsewhere (Kiddie, Royds & Shaw, 1973; Kiddie & Kaye, 1974). The method is specific for the unchanged drug.

Results

The cumulative amounts of mexiletine in the urine are given in Table 1. When the urine was acidic (mean pH 4.9), 57.5% of the dose had been excreted in the urine within 48 h, compared to

Table 1   Cumulative total amounts of mexiletine base excreted in the urine at intervals up to 48 h after an intravenous dose of 200 mg mexiletine hydrochloride (166 mg mexiletine base) in four subjects

| | Time since dose (h) | | | | | | | | |
	0-2	0-4	0-6	0-8	0-10	0-12	0-24	0-36	0-48
Acid urine									
Cumulative amount of mexiletine in urine (mg) (mean ± s.e.)	27.4 ±5.0	40.3 ±5.5	51.3 ±5.6	58.4 ±6.1	64.0 ±7.2	68.5 ±7.9	90.0 ±9.5	94.5 ±11.2	96.2 ±12.0
pH of urine (mean ± s.e.)	4.9 ±0.1	4.9 ±0.2	4.9 ±0.1	4.9 ±0.1	5.0 ±0.0	5.2 ±0.1	5.0 ±0.1	4.9 ±0.1	5.0 ±0.1
Alkaline urine									
Cumulative amount of mexiletine in urine (mg) (mean ± s.e.)	0.1 ±0.0	0.2 ±0.0	0.2 ±0.0	0.3 ±0.0	0.3 ±0.1	0.3 ±0.0	0.7 ±0.2	0.9 ±0.2	1.1 ±0.3
pH of urine (mean ± s.e.)	8.0 ±0.1	8.1 ±0.1	8.2 ±0.2	8.1 ±0.1	8.2 ±0.2	7.8 ±0.2	7.9 ±0.2	8.2 ±0.1	7.9 ±0.2

0.64% when the urine was alkaline (mean pH 8.1). These differences are statistically significant ($P < 0.01$, paired t test).

The plasma mexiletine levels recorded up to 8 h after the dose are shown in Figure 1. The elimination half-life was calculated for the interval 2-8 h and was 2.8 h (s.e. mean ± 0.3) with an acidic urine and 8.6 h (s.e. mean ± 0.1) when the urine was alkalinized. This is also significant ($P < 0.001$, paired t test).

Transient symptoms of drowsiness, paraesthesia of the face and tongue, and tinnitus were experienced during and just after the injection in all subjects.

The pH levels of the urine samples of patients in the coronary care unit are shown in Figure 2.

Discussion

Our results show that mexiletine is much more rapidly eliminated from the body when the urine is acidic than when it is alkaline, as predicted from a preliminary study (Kiddie & Kaye, 1974). At a pH of about 8.0, urinary excretion of mexiletine virtually ceases, whereas at pH 5.0 more than half of the dose appears as unchanged drug in the urine. These findings can be explained by the influence of pH on the amount of unionized drug in the renal tubules. Such an effect on elimination can be expected when a drug has an appropriate pKa value, high lipid solubility, and significant excretion via the urinary tract (Melmon & Morelli, 1972). The partition coefficient of mexiletine between octanol and phosphate buffer (pH 7.4) suggested that this drug has a high degree of lipid solubility (Kaye, unpublished observation). Its pKa· is 9.05 (Bohn Sohn Analytical Research, personal communication), and from this it can be calculated that at pH 5.0, 0.01% of the drug would be unionized, compared to 8.23% at pH 8.0. Since only unionized drug is able to diffuse easily out of the renal tubule, reabsorption by diffusion could occur to a very small degree at pH 5.0, but to a much greater extent at pH 8.0. As reabsorption of unionized molecules takes place, part of the ionized fraction would become unionized to maintain the equilibrium of the dissociation ratio, thus providing more drug for diffusion. Reabsorption could then continue until all the drug had been reabsorbed or the end of the nephron was reached.

Even when the urinary excretion was minimal, plasma mexiletine levels fell during the 2-8 h period with a half-life of 8.6 hours. This probably reflects metabolism of the drug and excretion by other routes. It has been found that in the dog mexiletine is metabolized by the liver (Bohn Sohn Analytical Research, personal communication).

Urinary pH has been shown to be an important factor in the excretion of several drugs (Weiner & Mudge, 1964). These include amphetamine (Beckett, Rowland & Turner, 1965), phenylbutazone (Gutman, Dayton, Yü, Berger, Chen, Sicam & Burns, 1960), some of the salicylates and barbiturates (Goldstein et al., 1968), and propranolol (Kaye, Robinson & Turner, 1973).

Changes in drug elimination rate have important clinical implications. The rate of elimination is one of the factors determining the blood and tissue levels achieved during constant intravenous infusion or repeated oral dosing (Melmon & Morelli, 1972). A prolongation of elimination half-life from 3 to 6 h will result in a doubling of the mexiletine concentration finally obtained during intravenous infusion. Changes in urinary pH could therefore cause the development of drug toxicity or clinical ineffectiveness during infusion at a rate previously found satisfactory. The pH of urine of normal subjects varies considerably and there is a nyctohemeral rhythm (Elliott, Sharp & Lewis, 1959) but this rhythm may be absent in patients with heart failure (Goldman, 1951). The large range of urinary pH found in the coronary care unit patients illustrates the individual differences which are present in cardiac patients and may help to explain the wide range of mexiletine plasma levels found in similar patients (Campbell et al., 1973).

We would suggest that factors likely to alter urinary pH should be avoided during mexiletine treatment, and that the measurement of urine pH may help in the adjustment of its dosage.

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