Salivary concentrations of pirmenol as a possible cause of unpleasant taste

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Salivary concentrations of the anti-arrhythmic, pirmenol, were compared with plasma concentrations in six patients. Group mean salivary values tended to be higher despite high plasma protein binding, suggesting the possibility of an active transport process. The observed salivary concentrations are reasonably close to those detectable in healthy volunteers as tasting unpleasant.

Keywords pirmenol saliva concentrations

Introduction

Pirmenol is a pyridine-methanol derivative, which has been shown to be effective against both supraventricular and ventricular arrhythmias in a variety of animal models (Steffe *et al.*, 1980; Reder *et al.*, 1980; Kaplan *et al.*, 1983). Early evidence of clinical efficacy after intravenous or oral administration has also been reported (Hammill *et al.*, 1982; Sanders *et al.*, 1983). Its electrophysiological properties are like those of quinidine, but it appears to have a more favourable therapeutic index (Kaplan *et al.*, 1983). Major side effects have rarely been noted by patients taking oral pirmenol, but it appears that 12–14% have complained of a persistent bad taste in completed clinical trials (Dr R. E. Weber, Warner-Lambert, personal communication). It was decided to investigate the relationship between salivary and plasma concentrations of the drug, and determine the concentration at which pirmenol can be detected as an unpleasant taste.

Methods

Six patients who were enrolled in a long-term study of the capacity of oral pirmenol to suppress premature ventricular contractions (PVC) were asked to undergo an ancillary study. Ages ranged from 57 to 75 years, and body weight from 73 to 95 kg. There were four men and two women, and all were white. Most had no well-defined cardiac

disease other than ventricular ectopy. All had demonstrated average PVC counts in excess of 160 per hour throughout the non-sleeping day, and all had shown an initial response of at least 70% inhibition of PVC counts to the first course of pirmenol. None was taking digitalis, β -adrenoceptor blockers, other anti-arrhythmics, reserpine, sulphonylureas or insulin. All had continued to receive oral pirmenol as outpatients for at least 6 months. Half of the patients (J.M., E.Y. and N.A.) had a mild complaint of a persistent bad taste.

All patients reported to the research clinic 1 h after a light breakfast. The last dose of pirmenol had been taken during the previous evening. After collecting initial samples of venous blood and saliva, the established morning dose of pirmenol was administered by mouth, and further blood and saliva samples were collected 1, 2 and 3 h later. Patients chewed upon pieces of Latex tubing for 5 min periods before collection time to stimulate salivary flow. Saliva was expelled into beakers, pH was immediately determined with a pH meter, and after centrifugation the supernatant was stored frozen. Plasma was also rapidly separated from venous blood and stored frozen. Pirmenol concentrations were determined by a modification of the high performance liquid chromatography method of Shand *et al.* (1981). In our laboratories, the assay between-run variation averages 5%.

A panel of 10 healthy volunteers aged 25 to 50 years underwent a double-blind assessment of the taste of pirlmenol. Prepared solutions with concentrations of 0, 2.5, 5, 10 and 50 $\mu\text{g ml}^{-1}$ of pirlmenol in tap water were compared, with sequence of testing randomized by Latin Squares. Volunteers swilled their mouths first with tap water and then with 0.5 ml of the test solution. Most of the solution was then expelled, but the residual was swallowed. The severity of any unpleasant taste experienced either immediately or as an after taste over the next 5 min was recorded. A minimum of 4 h separated testing of each solution.

Results

Table 1 shows that plasma pirlmenol concentrations were fairly consistent between patients, with peak concentrations usually occurring at 1 or 2 h after dosing. Salivary pirlmenol concentrations were more variable between patients. In individual patients, fluctuations tended to follow those in plasma concentration, though there were too few data for formal statistical testing. Whereas plasma and salivary concentrations were similar in three patients, salivary concentrations were consistently higher in the others. The two highest salivary concentrations occurred in patients with complaints of persistent bad taste. Saliva pH was uniformly close to 7, and appeared unrelated to saliva plasma ratios of pirlmenol.

In the taste experiment, only three subjects could differentiate between tap water, and the 2.5 and 5 $\mu\text{g ml}^{-1}$ solutions. However, eight of the eleven subjects reported mild to moderate unpleasant taste with the 10 $\mu\text{g ml}^{-1}$ solution. All experienced an unpleasant taste with the 50 $\mu\text{g ml}^{-1}$ solution, and seven subjects reported that it was markedly unpleasant.

Discussion

As reviewed by Mucklow (1982), salivary drug concentrations are rarely helpful in therapeutic drug monitoring. Salivary concentrations can be used to monitor dosage regimen changes only if consistently well correlated with those in plasma (as for some anticonvulsants). Despite the small sample of patients in our study, between-patient variability seems likely to be too high for this purpose.

Salivary concentrations of pirlmenol were considerably higher than had been anticipated. As reviewed by Mucklow (1982), most drugs diffuse passively into saliva until equilibrium with free, unbound drug concentrations in plasma is achieved. As it has been reported that mean plasma protein binding is 83–90% (Hammill *et al.*, 1982), salivary concentrations would be expected to be much lower than those of plasma. Anti-arrhythmics are often weak bases with high pK_a value, so that salivary concentrations can vary greatly with salivary pH (Koup *et al.*, 1975). However, in the patients receiving pirlmenol salivary pH was not greatly different from the normal physiological pH of plasma, so it seems unlikely that different extent of drug ionization in saliva and plasma could explain the high salivary drug concentrations. It has been suggested that lithium (Groth *et al.*, 1974), penicillin (Borzelleca & Cherrick, 1965), and metoprolol (Dawes *et al.*, 1978) undergo active transport into saliva. Although active drug transport is much less common than passive diffusion into saliva, it is possible that pirlmenol undergoes active transport. The resultant high saliva concentrations may account for the frequent complaints of a bad taste while taking pirlmenol, as it appears that similar concentrations are capable of producing unpleasant taste sensations.

Table 1 Comparison of concentrations of pirlmenol in saliva and plasma

Patient	Dose (mg)	Dose interval (h)	Saliva concentration ($\mu\text{g ml}^{-1}$)				Plasma concentration ($\mu\text{g ml}^{-1}$)			
			Pre-dose	1	2	3 h	Pre-dose	1	2	3 h
E.Y.*	125	6	4.2	6.3	7.4	3.7	1.7	2.0	4.2	3.1
N.A.*	125	8	1.3	2.2	2.3	1.4	1.7	2.1	2.8	2.4
A.J.	150	8	0.8	1.7	2.1	1.1	1.1	2.6	2.3	1.3
I.M.	100	6	2.4	3.4	4.3	3.3	1.7	2.9	2.2	3.2
J.M.*	150	8	5.1	5.7	7.8	6.5	1.8	2.5	2.9	2.9
J.S.	125	8	1.1	1.2	1.6	1.6	0.9	1.6	1.4	1.5
		Mean	2.5	3.4	4.3	2.9	1.5	2.3	2.6	2.4
		($\pm$ s.d.)	($\pm$ 1.8)	($\pm$ 2.1)	($\pm$ 2.8)	($\pm$ 2.1)	($\pm$ 0.4)	($\pm$ 0.5)	($\pm$ 0.9)	($\pm$ 0.8)

*Experienced a persistent bad taste.

References

- Borzelleca, J. F. & Cherrick, H. M. (1965). The excretion of drugs in saliva: Antibiotics. *J. oral Ther. Pharmac.*, **2**, 180–187.
- Dawes, C. P., Kendall, M. J. & John, V. A. (1978). Comparison of plasma and saliva levels of metoprolol and oxprenolol. *Br. J. clin. Pharmac.*, **5**, 217–221.
- Groth, U., Prellwitz, W. & Jahnchen, E. (1974). Estimation of pharmacokinetic parameters of lithium from saliva and urine. *Clin. Pharmac. Ther.*, **16**, 490–498.
- Hammill, S. C., Shand, D. G., Routledge, P. A., Hindman, M. C., Baker, J. T. & Pritchett, E. L. C. (1982). Pirmenol, a new antiarrhythmic agent: Initial study of efficacy, safety and pharmacokinetics. *Circulation*, **65**, 369–374.
- Kaplan, H. R., Mertz, T. E., Steffe, T. J. & Toole, J. G. (1983). Pirmenol. In *New Drugs Annual: Cardiovascular Drugs*, ed. Scriabine, A. New York: Raven Press.
- Koup, J. R., Jusko, W. J. & Goldfarb, A. L. (1975). pH-dependent secretion of procainamide into saliva. *J. pharm. Sci.*, **64**, 2008–2010.
- Mucklow, J. C. (1982). The use of saliva in therapeutic drug monitoring. *Ther. Drug Monitoring*, **4**, 229–247.
- Reder, R. F., Danilo, J., Jr. & Rosen, M. R. (1980). Effects of pirmenol HCl on electrophysiologic properties of cardiac Purkinje fibers. *Eur. J. Pharmac.*, **61**, 321–333.
- Sanders, S. W., Nappi, J. M., Foltz, R. L., Lutz, J. R. & Anderson, J. L. (1983). Disposition of intravenous pirmenol. *J. clin. Pharmac.*, **23**, 113–122.
- Shand, D. G., Verghese, C., Barchowsky, A., Hammill, S. C. & Pritchett, E. L. C. (1981). High-performance liquid chromatographic analysis of a new antiarrhythmic drug, pirmenol, in biological fluids. *J. Chromatogr.*, **224**, 343–347.
- Steffe, T. J., Mertz, T. E., Hastings, L. G., Potoczak, R. E. & Kaplan, H. R. (1980). CI-845 (pirmenol hydrochloride): A new orally effective long-acting antiarrhythmic agent. *J. Pharmac. exp. Ther.*, **214**, 50–57.

(Received 29 July 1985,
accepted 9 July 1986)