Br. J. clin. Pharmac. (1992), **33**, 309–312

The effect of pirenzepine on gastric emptying and salivary flow rate: constraints on the use of saliva paracetamol concentrations for the determination of paracetamol pharmacokinetics

F. KAMALI, C. EDWARDS & M. D. RAWLINS
Wolfson Unit of Clinical Pharmacology, University of Newcastle upon Tyne, NE1 7RU

1 The effects of pirenzepine on gastric emptying, salivary flow and saliva paracetamol concentrations were investigated in healthy volunteers.

2 Pirenzepine significantly reduced the area under the saliva flow-time curves (7.29 ± 3.30 g min^{-1} h without pirenzepine; 4.19 ± 2.59 g min^{-1} h with pirenzepine, $P < 0.01$). Pirenzepine had no significant effect on plasma paracetamol C_{max} (17.5 ± 7.8 μg ml^{-1} without pirenzepine; 12.6 ± 7.7 μg ml^{-1} with pirenzepine), plasma t_{max} (0.2 h (0.2–0.8 h) without pirenzepine; (0.2 h 0.2–0.8 h) with pirenzepine) and plasma AUC(0,6 h) (32.3 ± 7.2 μg ml^{-1} h without pirenzepine; 30.3 ± 6.5 μg ml^{-1} h with pirenzepine).

3 Mean ratios of saliva:plasma paracetamol AUC (1.06 ± 0.24 without pirenzepine; 1.84 ± 0.48 with pirenzepine, $P < 0.001$) and saliva:plasma paracetamol C_{max} (1.7 ± 1.0 without pirenzepine; 6.5 ± 2.7 with pirenzepine, $P < 0.01$) were significantly increased by pirenzepine pretreatment, but there was a poor correlation between the percentage change in the area under the saliva flow-time curve and the percentage change in saliva paracetamol AUC ($r = 0.47$, $P = 0.21$).

4 The findings suggest that a) pirenzepine is a more selective antagonist of the muscarinic receptors in salivary glands than those in gastric smooth muscle and b) caution is required when using saliva paracetamol concentrations to determine the pharmacokinetics of the drug in the presence of other agents which may influence salivary flow rate.

Keywords antimuscarinic salivary secretion paracetamol (acetaminophen) pirenzepine pharmacokinetics

Introduction

Antimuscarinic drugs such as atropine (Hilton & Lewis, 1955; Kay & Smith, 1956), propantheline (Kraines, 1957; Schwartz *et al.*, 1953) and mepenzolate (Kleckner, 1957; Kraines, 1957) have been shown to reduce gastric emptying and salivary flow rates. Pirenzepine (a pyridobenzodiazepine compound) is an antimuscarinic drug used in the treatment of peptic ulceration. It has been shown to be a selective inhibitor of high affinity muscarinic receptors *in vitro* (Hammer *et al.*, 1980) but, in contrast to the action of the classical antimuscarinic drugs, there is a wide disparity between the potency of pirenzepine in different tissues. Whilst very low doses inhibit gastric secretion, higher doses are required to inhibit salivation, and only very high doses have an effect on gastric smooth muscle and on the heart (Jennewein, 1979; Matsuo & Seki, 1979).

Gastric emptying is rate limiting in the absorption of many orally administered drugs (Gibaldi, 1979; Levine, 1970; Nimmo, 1976; Prescott, 1974a,b). The rate of paracetamol (acetaminophen) absorption depends mainly on the rate of gastric emptying (Heading *et al.*, 1973) and drugs with antimuscarinic properties such as propantheline (Nimmo *et al.*, 1973), desmethylimipramine (Hall, 1976) and atropine (Rashid & Bateman, 1990) which reduce the rate of gastric emptying have all been shown to delay paracetamol absorption. Paracetamol is also present in saliva after drug administration and a close correlation between saliva and

Correspondence: Dr F. Kamali, Wolfson Unit of Clinical Pharmacology, University of Newcastle upon Tyne, NE1 7RU

plasma paracetamol concentrations has been described (Glynn & Bastain, 1973; Kamali *et al.*, 1987a). Saliva paracetamol concentrations have therefore been used to determine the pharmacokinetics of the drug (Kamali *et al.*, 1987b, 1988; Miners *et al.*, 1983; Mucklow *et al.*, 1980).

Saliva concentrations of a number of drugs such as phenytoin (Paxton *et al.*, 1977), carbamazepine (Westenberg *et al.*, 1977) and lithium (Groth *et al.*, 1974) have been found to be independent of salivary flow stimulation, but the effect of salivary flow rate on saliva paracetamol concentrations has not been investigated. It is possible that paracetamol concentrations in saliva are altered by changes in salivary flow rate and that the use of saliva paracetamol concentrations could result in misinterpretation of paracetamol pharmacokinetics. The present study was designed to investigate the effects of pirenzepine on gastric emptying and salivary secretion, by monitoring plasma paracetamol concentrations and salivary flow rate. The effect of pirenzepine on the salivary secretion of paracetamol was also studied and paracetamol pharmacokinetics were assessed from saliva drug concentrations and compared with those determined from plasma paracetamol concentrations.

Methods

Protocol

Eight healthy male volunteers aged 19–25 years took part in the study which was approved by the Joint University and Newcastle Health Authority Ethics Committee. After an overnight fast each volunteer received two treatments A and B in a randomised cross-over design, with a 1 week washout period between each treatment. Treatment A comprised paracetamol 1 g (2 × 500 mg Panadol soluble tablets) in 100 ml water. For treatment B, each volunteer received paracetamol (1 g) after 4 × 50 mg doses of pirenzepine (Gastrozepin) with three doses on day 1 and one dose on day 2, 1 h prior to paracetamol ingestion. Blood and saliva were collected at times 0 (pre-paracetamol dose), 15, 25, 35, 50, 65, 95, 125, 190, 240 and 360 min (post-dose). Saliva was collected by spitting directly into plastic vials for 3 min and blood samples were collected through a cannula inserted into a forearm vein. Salivary flow was measured 1 min after saliva collection at each time point, using dental cotton wool cylinders (Dollery *et al.*, 1975). A standard light breakfast (toast and a drink) was given after withdrawal of the 95 min sample and a standard lunch (sandwiches) was provided after withdrawal of the 240 min sample. Paracetamol concentrations in plasma and saliva were measured by high performance liquid chromatography (Adriaenssens & Prescott, 1978). The coefficient of variation for all assays was less than 6% and the limit of assay was 0.1 $\mu g\ ml^{-1}$.

Data analysis

Paracetamol absorption was assessed from the maximum plasma paracetamol concentration (C_{max}), the time to reach maximum plasma concentration (t_{max}) and the area under the plasma paracetamol concentration-time curve for the 6 h period, AUC(0,6 h). The areas under the plasma and saliva paracetamol concentration-time and salivary flow rate-time curves (AUC) were calculated by the linear trapezoidal rule. Paracetamol half-life was determined by the method of least squares regression, using five data points in the terminal elimination phase. Data were compared, using Students paired *t*-test and one way analysis of variance (ANOVA) as appropriate.

Results

The mean plasma paracetamol concentrations are shown in Figure 1. Pirenzepine pretreatment had no significant effect on plasma paracetamol C_{max}, t_{max} or AUC(0,6 h) (Table 1). The area under the salivary flow rate-time curves was significantly reduced (7.29 ± 3.3 g min^{-1} h without pirenzepine; 4.19 ± 2.59 g min^{-1} h with pirenzepine; $P < 0.01$) (Figure 2).

Saliva:plasma paracetamol concentration ratios were greater than unity during the first 50 min (Figure 3), but saliva paracetamol AUC was not significantly different from plasma paracetamol AUC without pirenzepine (Table 1). These findings are consistent with previous reports (Glynn & Bastain, 1973; Kamali *et al.*, 1987a; Miners *et al.*, 1983). However, saliva:plasma paracetamol concentration ratios were significantly increased by pirenzepine pretreatment and this was amplified during the absorption phase of paracetamol, when paracetamol concentrations were higher than those during the terminal phase of the drug (Figure 3). The mean ratio of saliva:plasma paracetamol AUC calculated

Table 1 Pharmacokinetic parameters of paracetamol calculated from plasma and saliva paracetamol concentrations with and without pirenzepine pretreatment. All figures represent mean ± s.d., except for t_{max} values (median (range))

Treatment	C_{max} *(plasma)* ($\mu g\ ml^{-1}$)	C_{max} *(saliva)* ($\mu g\ ml^{-1}$)	AUC *(plasma)* ($\mu g\ ml^{-1}\ h$)	AUC *(saliva)* ($\mu g\ ml^{-1}\ h$)	t_{max} *(plasma)* (h)	t_{max} *(saliva)* (h)	$t_{½}$ *(plasma)* (h)	$t_{½}$ *(saliva)* (h)
Without pirenzepine	17.5 ± 7.8	23.2 ± 10.6	32.3 ± 7.2	33.9 ± 10.3	0.2 (0.2–0.8)	0.2 (0.2–0.4)	2.7 ± 0.6	2.5 ± 0.9
With pirenzepine	12.6 ± 7.7	43.1 ± 15.4*	30.0 ± 6.5	54.7 ± 12.3**	0.2 (0.2–0.8)	0.2 (0.2–0.4)	2.5 ± 0.5	2.4 ± 1.4

Where indicated, saliva paracetamol AUC (**$P < 0.001$) and C_{max} (*$P < 0.01$) were significantly higher with pirenzepine pretreatment (paired Student's *t*-test).

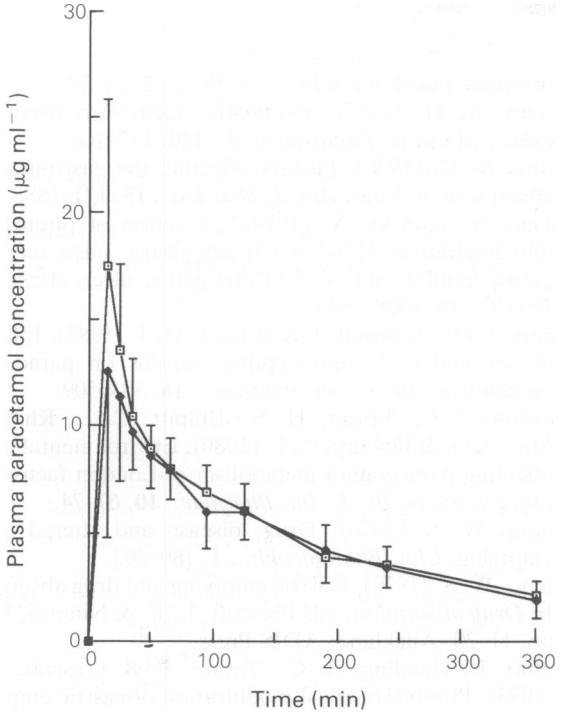

Figure 1 Mean (± s.d.) plasma paracetamol concentrations without (□) and with (◆) pirenzepine pretreatment.

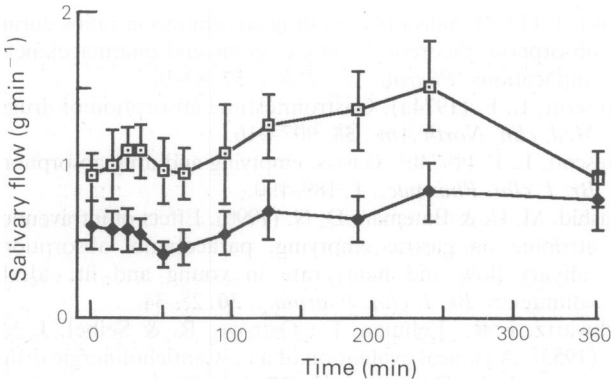

Figure 2 Salivary flow rate (mean ± s.d.) before (□) and after (◆) pirenzepine pretreatment.

from the sum of the individual ratios was significantly increased by pirenzepine pretreatment from 1.06 ± 0.24 to 1.84 ± 0.48; $P < 0.001$. The saliva:plasma paracetamol concentration ratios during the period of the study were also significantly higher following pirenzepine pretreatment ($F = 16.1$, $P < 0.001$; ANOVA). Similarly the mean ratio of saliva:plasma paracetamol C_{max} was also significantly increased from 1.7 ± 1.0 to 6.5 ± 2.7; $P < 0.01$. However, there was a poor correlation between the percentage change in saliva flow rate AUC and the percentage change in saliva paracetamol AUC ($r = 0.47$, $P = 0.21$). Paracetamol half-life calculated from saliva paracetamol concentrations after pirenzepine pretreatment was not significantly different from that calculated from saliva paracetamol concentrations without pirenzepine treatment and those calculated

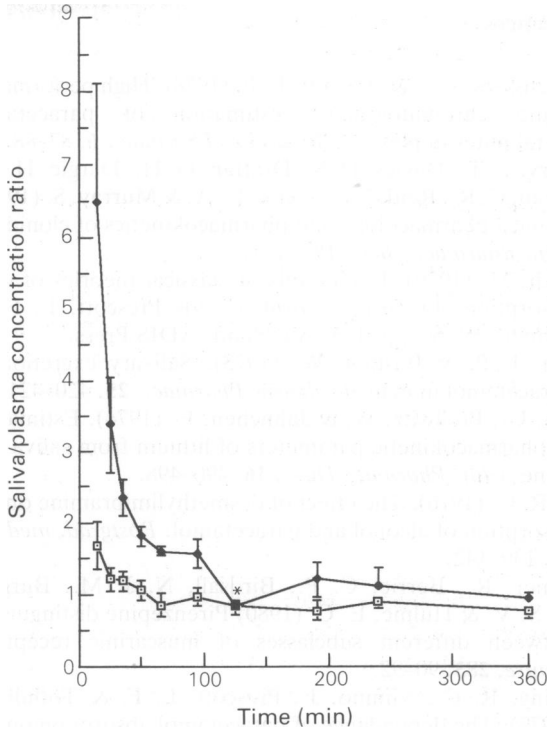

Figure 3 Saliva/plasma paracetamol concentration ratio (mean ± s.d.) before (□) and after (◆) pirenzepine pretreatment.

from plasma paracetamol concentrations with and without pirenzepine treatment (Table 1).

Discussion

Paracetamol concentrations in saliva reflect those in arterial blood (Kamali *et al.*, 1987a; Posti, 1982). Thus the differences between saliva and venous plasma paracetamol concentrations during the first hour following drug ingestion are due to initial arterio-venous differences in paracetamol concentrations (Kamali *et al.*, 1987a; Posti, 1982). Paracetamol pharmacokinetic parameters, except half-life, determined from saliva drug concentrations were markedly different from those obtained from plasma drug concentrations following pirenzepine pretreatment. Paracetamol concentrations in saliva were shown to increase when salivary flow rate was decreased by pirenzepine, although there was a poor correlation between the percentage change in saliva flow rate AUC and the percentage change in saliva paracetamol concentration AUC. Caution is therefore required when using saliva paracetamol concentrations as a means of determining the pharmacokinetics of the drug in circumstances where salivary secretion rate is altered.

Although pirenzepine significantly reduced salivary flow, it had no significant effect on the rate of paracetamol absorption. This indicates that in man pirenzepine shows selective antimuscarinic activity in salivary glands compared with gastric smooth muscle and is in agreement with previous findings (Jaup & Dotevall, 1981).

References

Adriaenssens, P. I. & Prescott, L. F. (1978). High performance liquid chromatographic estimation of paracetamol metabolites in plasma. *Br. J. clin. Pharmac.*, **6**, 87–88.

Dollery, C. T., Davies, D. S., Draffan, G. H., Dargie, H. G., Dean, C. R., Reid, J. L., Clare, R. A. & Murray, S. (1975). Clinical pharmacology and pharmacokinetics of clonidine. *Clin. Pharmac. Ther.*, **19**, 11–17.

Gibaldi, M. (1979). Limitations of classical theories of drug absorption. In *Drug absorption*, eds Prescott, L. F. & Nimmo, W. S., pp. 1–5. Auckland: ADIS Press.

Glynn, J. P. & Bastain, W. (1973). Salivary excretion of paracetamol in man. *J. pharm. Pharmac.*, **25**, 420–421.

Groth, U., Prellwitz, W. & Jahnchen, E. (1974). Estimation of pharmacokinetic parameters of lithium from saliva and urine. *Clin. Pharmac. Ther.*, **16**, 490–498.

Hall, R. C. (1976). The effect of desmethylimipramine on the absorption of alcohol and paracetamol. *Postgrad. med. J.*, **52**, 139–142.

Hammer, R., Berrie, C. P., Birdsall, N. J. M., Burgen, A. S. V. & Hulme, E. C. (1980) Pirenzepine distinguishes between different subclasses of muscarinic receptors. *Nature*, **283**, 90–92.

Heading, R. C., Nimmo, J., Prescott, L. F. & Tothill, P. (1973). The dependence of paracetamol absorption on the rate of gastric emptying. *Br. J. Pharmac.*, **47**, 415–421.

Hilton, J. M. & Lewis, G. P. (1955). The cause of vasodilatation accompanying activity in the submandibular gland. *J. Physiol.*, **128**, 235–248.

Jaup, B. H. & Dotevall, G. (1981). The effect of pirenzepine and L-hyoscyamine on gastric emptying and salivary secretion in healthy volunteers. *Scand. J. Gastroenterol.*, **16**, 769–773.

Jennewein, H. M. (1979). In *Die Behandlung des Ulcus Pepticum mit Pirenzepine*, eds Blum, A. L. & Hammer, R., pp. 41–48. Munich: Karl Detmeter.

Kamali, F., Fry, J. R. & Bell, G. D. (1987a). Salivary secretion of paracetamol in man. *J. Pharm. Pharmac.*, **39**, 150–152.

Kamali, F., Fry, J. R. & Bell, G. D. (1987b). Temporal variation in paracetamol absorption and metabolism in man. *Xenobiotica*, **17**, 635–642.

Kamali, F., Fry, J. R., Bell, G. D., Kitchingman, G. K., Standen, G. & Sokal, M. (1988). Hepatic drug metabolising ability and gastrointestinal absorption of drugs in patients undergoing high-dose methotrexate chemotherapy. *J. Drug Dev.*, **1**, 137–143.

Kay, A. W. & Smith, A. N. (1956). The action of atropine and hexamethonium on gastric secretion and motility. *Br. J. Pharmac.*, **11**, 231–235.

Kleckner, M. S. (1957). Therapeutic appraisal employing the double blind control technique of a new intestinal anticholinergic agent J.B-340 (Canti) in various types of obstinate diarrhoea. *Clin. Res. Proc.*, **5**, 19–20.

Kraines, S. H. (1957). Psychiatric factors in therapy of duodenal ulcers. *Illinois med. J.*, **110**, 157–160.

Levine, R. R. (1970). Factors affecting the gastrointestinal absorption of drugs. *Am. J. Dig. Dis.*, **15**, 171–188.

Matsuo, Y. & Seki, A. (1979). TI action of pirenzepine-dihydrochloride (LS-519 Cl) on gastric juice secretion, gastric motility and experimental gastric ulcer. *Arzneimittel Forsch.*, **29**, 1028–1035.

Miners, J. O., Attwood, J. & Birkett, D. J. (1983). Influence of sex and oral contraceptive steroids on paracetamol metabolism. *Br. J. clin. Pharmac.*, **16**, 503–509.

Mucklow, J. C., Fraser, H. S., Bulpitt, C. J., Khan, C., Mould, G. & Dollery, C. T. (1980). Environmental factors affecting paracetamol metabolism in London factory and office workers. *Br. J. clin. Pharmac.*, **10**, 67–74.

Nimmo, W. S. (1976). Drug, disease and altered gastric emptying. *Clin. Pharmacokin.*, **1**, 189–203.

Nimmo, W. S. (1979). Gastric emptying and drug absorption. In *Drug absorption*, eds Prescott, L. F. & Nimmo, W. S., pp. 11–20. Auckland: ADIS Press.

Nimmo, J., Heading, R. C., Tothill, P. & Prescott, L. F. (1973). Pharmacological modification of gastric emptying. Effects of propantheline and metoclopramide on paracetamol absorption. *Br. med. J.*, **1**, 587–589.

Paxton, J. W., Whiting, B. & Stephen, K. W. (1977). Phenytoin concentrations in mixed, parotid and submandibular saliva and serum measured by radioimmunoassay. *Br. J. clin. Pharmac.*, **4**, 185–191.

Posti, J. (1982). Saliva-plasma drug concentration ratios during absorption: theoretical considerations and pharmacokinetic implications. *Pharm. Acta Helv.*, **57**, 83–92.

Prescott, L. F. (1974a). Gastrointestinal absorption of drugs. *Med. clin. North Am.*, **58**, 907–916.

Prescott, L. F. (1974b). Gastric emptying and drug absorption. *Br. J. clin. Pharmac.*, **1**, 189–190.

Rashid, M. U. & Bateman, D. N. (1990). Effect of intravenous atropine on gastric emptying, paracetamol absorption, salivary flow and heart rate in young and fit elderly volunteers. *Br. J. clin. Pharmac.*, **30**, 25–34.

Schwartz, I. R., Lehman, E., Ostrove, R. & Seibel, J. M. (1953). A clinical evaluation of a new anticholinergic drug, probanthine. *Gastroenterol.*, **25**, 416–430.

Westenberg, H. G. M., De Zeeuw, R. A., Van der Kleijn, E. & Oei, T. T. (1977). Relationship between carbamazepine concentrations in plasma and saliva in man as determined by liquid chromatography. *Clin. Chim. Acta*, **79**, 155–161.

(Received 15 July 1991, accepted 1 October 1991)