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Short communication

Salivary passage of 5-fluorouracil during continuous infusion

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Summary. Plasmatic and salivary concentrations of 5-FU were investigated in ten patients given 5-day continuous infusions of 5-fluorouracil (5-FU) (1 g/m^2/day). Measurable concentrations of salivary 5-FU were scattered ranging from 6 to 100 ng/ml. Between individual 5-FU concentrations in saliva and plasma the coefficient of correlation was low. The theoretically predicted ratios of 5-FU concentrations in saliva over those in plasma, calculated as a function of salivary pH, did not correlate with the observed ratios, the majority of which ranged between 0.1 and 0.5. Noteworthy, 8 of 10 patients exhibited a more or less pronounced increase in 5-FU salivary excretion during 5-day continuous i.v. infusions.

Compared with bolus injections, the continuous infusion of 5-fluorouracil (5-FU) significantly improves hematological tolerance in treated patients [10]. However, digestive intolerance and, particularly, the occurrence of oral mucositis remain the major limiting toxicities during prolonged 5-FU infusions [1, 2]. The salivary passage of 5-FU has been advocated by Gudauskas et al. [7], partially studied by Celio et al. [3], and recently explored by Watenabe et al. [13] in beagle dogs. A direct, prolonged contact of 5-FU with the oral epithelium could at least partly explain the development of stomatitis. This represented a substantial rationale for acquiring a greater understanding of the salivary pharmacology of 5-FU. Theoretically, for a given drug, a satisfactory salivary/plasmatic ratio can only be correctly appreciated at steady state [9]. Thus, sampling saliva in patients receiving a continuous infusion of 5-FU represents a more appropriate method than studying patients who have been given an i.v. bolus. Plasmatic and salivary concentrations of 5-FU were investigated in ten patients given 5-day continuous infusions of the drug (1 g/m^2/day). In all, 34 individual, coupled saliva-plasma samples were analyzed during successive days of the cycle.

Methods

Table 1 gives the characteristics of the patients studied, whose mean age was 64.8 years (range, 50–77 years). Saliva samples (at least 0.5 ml) were taken by sublingual aspiration with a plastic pipette (Poly Labo Paul Bock 3013150; Strasbourg, France) before patients had eaten and 15 min after the thorough use of a mouthwash. At the same time, 5-ml blood samples were drawn into EDTA tubes, which were rapidly moved to the laboratory. After centrifugation (2,000 rpm for 10 min), particle-free saliva and plasma were stored at −20° C until analysis (within 10 days). A high-performance liquid chromatographic (HPLC) technique (UV detection at 254 nm) was used for 5-FU measurements [5]. The mean recovery from blank saliva spiked with 5-FU ($n = 4$) was 65.5% (CV, 6.5%); the limit of detection was 6 ng/ml. pH values for saliva samples were systematically recorded (pH microelectrode, Corning MD 00311306 L; Corning, Halstead, England). The predicted saliva/plasma (CS/CP) concentration ratio was calculated as:

$$CS/CP = \frac{1+10^{8.2-x}}{1+10^{8.2-7.4}},$$

where 8.2 is the pK_a of 5-FU, 7.4 is the pH of plasma, and x is the pH of the saliva sample, assuming that the percentage of 5-FU protein binding in plasma was negligible [3].

Results and discussion

Measurable concentrations of salivary 5-FU were scattered, ranging from 6 to 100 ng/ml; an identical dispersion was found for plasmatic 5-FU. The relationship between individual 5-FU concentrations in saliva and plasma is shown in Fig. 1. The coefficient of correlation ($r = 0.35$) was relatively low but statistically significant ($P < 0.05$). The theoretically predicted ratios of 5-FU concentrations in saliva over those in plasma (CS/CP), calculated as a function of salivary pH, did not correlate with the observed CS/CP ratios, the majority of which ranged between 0.1 and 0.5. The day-to-day evolution of individual salivary 5-FU concentrations is shown in Fig. 2. Eight of ten patients exhibited a more or less pronounced increase in 5-FU salivary excretion during 5-day continuous i.v. infusions.

Drug measurement in saliva may offer an advantageous alternative to blood analysis [9, 11]. As 5-FU is not protein-bound to a great extent in plasma [3], this drug is theoretically an appropriate candidate for salivary investigations. Moreover, the limiting toxicity of 5-FU during increasingly used continuous-infusion protocols [12] arises

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Table 1. Patient characteristics

Patients (patient number)	Sex, age	Tumor site	Chemotherapy protocol	Day of 5-FU sampling (blood and saliva)[a]		
Lam (1)	F 69	Metastasis colon	5-FU 1,500 mg/day days 1–5	day 1 (6.91)		day 2 (6.39)
Mar (2)	M 50	Oesophagus	Cisplatin 170 mg day 1	day 3 (8.25)	day 4 (7.63)	day 5 (7.13)
			5-FU 1,700 mg/day day 2–6			
Gio (3)	M 64	Colon	5-FU 1,800 mg/day days 1–5	day 1 (7.13)		day 4 (6.80)
Ber (4)	M 62	Bladder	Cisplatin 150 mg day 1	day 2 (8.12)		day 3 (8.36)
			5-FU 1,500 mg/day days 2–6			
Fou (5)	F 68	Breast	5-FU 1,000 mg/day days 1–5	ND: day 1 (7.10)		day 4 (7.73)
Pou (6)	M 64	Bladder	Cisplatin 140 mg day 1	day 1 (7.25)	day 3 (6.35)	day 4 (6.51)
			5-FU 1,500 mg/day[b] days 2–6/C1			
			days 2–6/C2		day 2 (7.84)	
Bru (7)	M 76	Oesophagus	Cisplatin 150 mg day 1	day 2 (6.63)	day 4 (7.07)	day 5 (7.96)
			5-FU 1,400 mg/day days 2–6			
Bas (8)	M 77	Metastasis, colon	5-FU 1,400 mg/day[b] days 1–5/C1	day 1 (7.79)	day 2 (7.69)	day 3 (8.23)
			5-FU 1,400 mg/day day 1–5/C2	day 1 (7.90)	day 2 (7.66)	day 3 (8.14)
			5-FU 1,400 mg/day days 1–5/C3	day 1 (7.03)		day 2 (7.05)
Gan (9)	M 57	Adenocarcinoma origin unknown	5-FU 200 mg/day days 1–5	ND: day 1 (6.24)	ND: day 2 (6.82)	day 3 (6.28)
				day 4 (6.57)		day 5 (7.11)
Ber (10)	M 71	Metastasis colon	5-FU 1,700 mg/day days 1–5	day 1 (7.91)	day 2 (7.72)	day 3 (8.25)

[a] Coupled blood and saliva samples were taken at 5 p.m. (numbers in parentheses indicate pH values for saliva samples)
[b] C1, C2, C3: three different cycles at 3-week intervals; ND, 5-FU concentration in saliva was below the detection limit

from digestive intolerance and, particularly, oral mucositis [1, 2]. Thus, a local toxic effect of 5-FU on the oral epithelium may be involved. These arguments, as well as previous reports on the pharmacokinetics of 5-FU in saliva [7], led us to carry out the present study.

Gudauskas et al. [7] have reported 5-FU salivary levels of between 150 and 300 ng/ml in patients receiving 30 mg/kg per day for 4 or 5 days. Chabner [4] has shown that 1 μM (130 ng/ml) is the appropriate threshold for the cytoxic effect of 5-FU on normal tissue [4]. Allopurinol given as a mouthwash can reduce oral toxicity induced by 5-FU [6], although such an effect was not found with systemic administration of allopurinol [8]. This provides an indirect argument in favor of a more or less preponderantly local origin for mechanisms implicated in 5-FU-induced oral mucositis.

We found a significant correlation between individual concentrations of 5-FU in saliva and plasma; a similar observation has been made by others in beagle dogs [13]. However, the values were scattered, and we consider that a salivary measurement is not accurately predictive of the corresponding blood concentration. As 5-FU (pK_a, 8.2) is ionized in plasma, observed ratios between 5-FU concentration in saliva and plasma were compared with the pre-

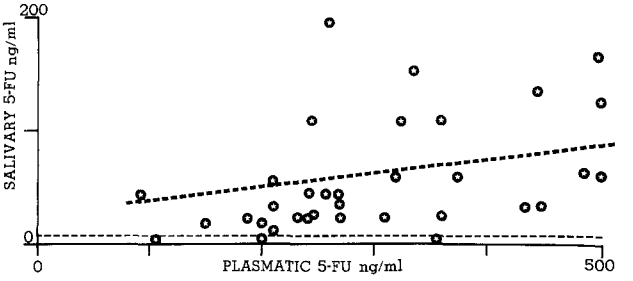

Fig. 1. Individual correspondence between salivary and plasmatic 5-FU concentrations

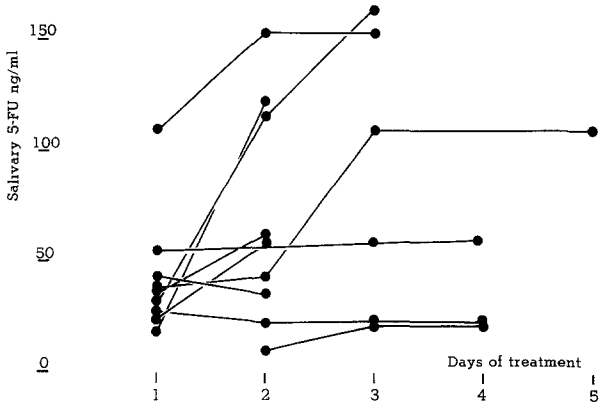

Fig. 2. Day-to-day evolution of individual salivary concentrations

dicted ratios, taking into account the individual salivary pH values. At steady state, most of the observed CS/CP ratios ranged between 0.1 and 0.5 and were much lower than those predicted. This can be explained by the secretory mechanisms of 5-FU in saliva, which are different from the simple, passive diffusions guided by the Henderson-Hasselbach equation.

Of particular interest was the progressive increase in 5-FU salivary concentrations in most of the patients studied during a 5-day cycle. This may strengthen the hypothesis that 5-FU has a local and directly contributory cytotoxic effect on oral mucosa during prolonged drug infusions. In conclusion, this study may contribute to a better knowledge of the clinical pharmacology of 5-FU; it suggests that a local effect of 5-FU on oral mucosa may be enhanced by prolonged infusion. This can stimulate and justify further pharmaco-clinical studies for a deeper understanding and/or the clinical management of salivary 5-FU.

References

1. Caballero GA, Ausman TK, Quebbeman EJ (1985) Long term, ambulatory, continuous i.v. infusion of 5-FU for the treatment of advanced adenocarcinomas. Cancer Treat Rep 69: 13–15
2. Carlson RW, Sikic BI (1983) Continuous infusion or bolus injection in cancer chemotherapy. Ann Intern Med 99: 823–833
3. Celio LA, Digregorio GJ, Ruch E, Pace J, Piraino AJ (1983) Doxorubicin and 5-fluorouracil plasma concentrations and detectability in parotid saliva. Eur J Clin Pharmacol 24: 261–266
4. Chabner BA (ed) (1982) Pyrimidine antagonists in pharmacologic principles of cancer treatment. Saunders, Philadelphia, pp 183–212
5. Christophidis N, Mihaly G, Vajda F, Louis W (1979) Comparison of liquid- and gas-liquid chromatographic assays of 5-fluorouracil in plasma. Clin Chem 25: 83–86
6. Clark PI, Slevin ML (1985) Allopurinol mouthwashes and 5-fluorouracil induced oral toxicity. Eur J Surg Oncol 11: 267–268
7. Gudauskas G, Goldie JH (1978) The pharmacokinetics of high dose continuous 5-fluorouracil infusions. ASCO Proc 364: 230C
8. Howell SB, Pfeifle CE, Wung WE (1983) Effect of allopurinol on the toxicity on high-dose 5-fluorouracil administered by intermittent bolus injection. Cancer 51: 220–225
9. Ritschel WA, Thompson GA (1983) Monitoring of drug concentrations in saliva: a non invasive pharmacokinetic procedure. Methods Find Exp Clin Pharmacol 5: 511–525
10. Seifert P, Baker LH, Reed ML, Vaitkevicius VK (1975) Comparison of continuously infused 5-fluorouracil with bolus injection in treatment of patients with colorectal adenocarcinoma. Cancer 36: 123–128
11. Svensson CK, Woodruff MN, Baxter JG, Lalka D (1986) Free drug concentration monitoring in clinical practise. Rationale and current status. Clin Pharmacokinet 11: 450–469
12. Vogelzang NJ (1984) Continuous infusion chemotherapy: a critical review. J Clin Oncol 2: 1289–1304
13. Watanabe J, Hayashi Y, Iwamoto K, Ozeki S (1985) Salivary excretion of 5-fluorouracil. Fluctuation of the saliva/plasma concentration ratio and salivary clearance in beagle dogs following bolus intravenous administration. Chem Pharm Bull (Tokyo) 33: 1187–1194

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