Cancer Chemother Pharmacol (1999) 44: 389–394

ORIGINAL ARTICLE

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Effect of gastric pH on the relative oral bioavailability and pharmacokinetics of temozolomide

Received: 15 December 1998 / Accepted: 16 March 1999

Abstract *Purpose*: Temozolomide is an imidazotetrazine alkylating agent which undergoes chemical conversion at physiological pH to the active species 5-(3-methyltriazene-1-yl)imidazole-4-carboxamide (MTIC) but is stable at acid pH. This study evaluated the effect of an increase in gastric pH, through the use of ranitidine, on the oral bioavailability and plasma pharmacokinetics of temozolomide and MTIC. *Methods*: Fifteen patients with advanced cancer were enrolled of which 12 were evaluable, all of whom had pharmacokinetic blood sampling. Each patient received temozolomide 150 mg m^{-2} day^{-1} for 5 days in cycle 1 and also received ranitidine 150 mg every 12 h either on days 1 and 2 or days 4 and 5. Gastric pH was monitored by the use of the Heidelberg capsule system. *Results*: Following the administration of ranitidine there was a rise in gastric pH by 1–2 pH units over the duration of the study period (pH range 2.2–5.2 without ranitidine and 3.5–6.0 with ranitidine). There was no difference in the pharmacokinetic parameters of temozolomide or MTIC with or without the concomitant administration of ranitidine. There was however, a lower C_{max} for temozolomide and MTIC for patients receiving ranitidine on day 1 and 2 versus day 4 and 5. Temozolomide was rapidly absorbed [time to maximum plasma concentration (t_{max}) 1.8 h] and eliminated [elimination half-life ($t_{1/2}$) 1.8 h] and MTIC followed a similar pattern with a t_{max} of 1.9 h and a $t_{1/2}$ of 1.9 h. Overall, the AUC of the MTIC represented about 2–4% of the AUC for temozolomide.

Key words Temozolomide · MTIC · Pharmacokinetics · Gastric pH · Phase I trial · Heidelberg capsule

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Introduction

Temozolomide is an oral imadazotetrazine derivative which is structurally related to dacarbazine (DTIC). Whereas DTIC requires metabolic activation through cytochrome P450 to MTIC, temozolomide is degraded by a pH-dependent chemical hydrolysis under neutral and basic conditions to the active metabolite monomethyl triazenoimidazole carboxamide (MTIC), which alkylates DNA predominantly at the O^6 position of guanine and to a lesser extent the N^7 position [6]. The activity of temozolomide is known to be schedule-dependent due to the depletion of alkyltransferase, the enzyme responsible for the repair of this toxic lesion [8]. The initial phase I trial studied a single dose of temozolomide and while establishing a maximum tolerated dose of 1000 mg/m^2, no responses were observed [10]. Subsequent phase I trials have been performed in the UK using hand-filled gelatin capsules and with machine-filled capsules in both the UK and the US on a daily times 5 schedule every 28 days [4, 5, 10]. The UK trial established an MTD of 200 mg m^{-2} day^{-1} times 5 and the US trial reported an MTD of 150 mg m^{-2} day^{-1} times 5 in previously treated patients and 250 mg m^{-2} day^{-1} times 5 in patients previously untreated, with the dose-limiting toxicity being thrombocytopenia. The pharmacokinetics of temozolomide have been investigated in all of these studies and similar conclusions have been reached in each study. The pharmacokinetics are linear, there is 100% oral bioavailability and there is no accumulation of temozolomide on day 5. Temozolomide is rapidly absorbed from the gastrointestinal tract with a time to maximum plasma concentration (t_{max}) of approximately 1 h (range

0.33–2.5 h), followed by a rapid decline in plasma levels with a $t_{1/2}$ of 109 min. There were no differences in the pharmacokinetic parameters between those patients who had received previous nitrosoureas and those who had not. The metabolites of temozolomide, MTIC, 4-amino-5-imidazole carboxamide (AIC) and 3-methyl-2,3-dihydro-4-oxoimidazotetrazine-8 carboxylic acid (AM; Fig. 1) are detected in the plasma soon after the oral administration. AIC peak levels are observed at 150 min after administration of temozolomide and AIC has an elimination half-life ($t_{1/2}$) of 114 min. Trace amounts of AM are seen representing 0.8% of the exposure to temozolomide. The mean 24-h urinary excretion of temozolomide was 5.6% of the administered dose with 92% of this occurring in the first 8 h after administration [5]. In phase II trials using 150–200 mg m^{-2} daily for 5 days every 28 days, temozolomide has demonstrated activity in recurrent or progressive high grade gliomas with a response rate of 11%, 47% with stable disease and a median response duration of 4.6 months [3]. In metastatic melanoma, the response rate in chemotherapy naive patients was 21%, with three patients achieving a complete response, nine partial responses and eight no change, with an overall median survival of 5.5 months [2]. In 18 patients with heavily pre-treated low grade non-Hodgkin's lymphoma there was only one partial response [15].

The elimination of temozolomide is predominantly through the pH-dependent chemical hydrolysis to MTIC which occurs at a neutral (physiological pH) or basic environment, but at acid pH temozolomide is stable [13, 14]. Ranitidine is an aminomethyl-furan derivative which acts as an H_2-receptor blocking agent that is widely used in the overall management of cancer patients. It produces its therapeutic effect by decreasing gastric acid secretion leading to a rise in the gastric pH which may compromise the stability and hence alter the oral absorption of temozolomide from the gastrointestinal tract. The gastric pH can be measured by a non-invasive technique using a Heidelberg capsule system [11]. This technique involves the patient swallowing a capsule containing a pH-sensitive radio frequency transmitter encased in an inert non-digestible shell. The radiotransmitter is able to send a signal to a receiver worn by the patient which then displays a reading between 1.0 to 8.0 pH units. This system was employed during this study to evaluate the changes of gastric pH with and without ranitidine. This study was designed to evaluate the oral bioavailability and pharmacokinetics of temozolomide and MTIC in the presence and absence of ranitidine in the patients with advanced cancer.

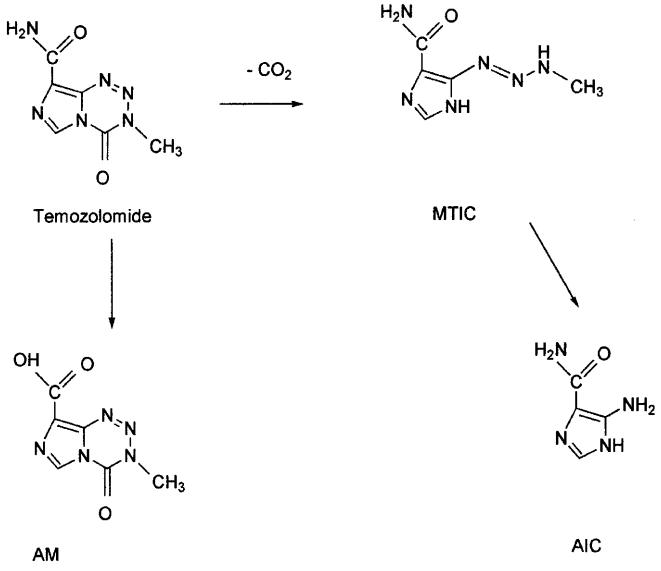

Fig. 1 Metabolic pathways of temozolomide. *MTIC* 5-(3-methyltriazene-1-yl)imidazole-4-carboxamide, *AM* 3-methyl-2,3-dihydro-4-oxoimidazotetrazine-8-carboxylic acid, *AIC* 4-amino-5-imidozole-carboxamide

Patients and methods

The study was approved by the Research Ethics Committee of the Royal Marsden NHS Trust and written consent was provided by all patients. Patients with solid tumours not amenable to curative therapy or significant palliation were recruited into the trial. Eligibility for the trial included age ≥18; treatment-free interval of 4 weeks and 6 weeks for prior nitrosourea and Mitomycin C; no radiotherapy within the previous 4 weeks or prior radiotherapy to greater than 50% of bone marrow; measurable or evaluable disease; adequate bone marrow function (haemoglobin ≥10 g/dl, neutrophil count $\geq 1.5 \times 10^9$/l, platelet count $\geq 100 \times 10^9$/l); adequate liver function [bilirubin within upper limits of normal (ULN), ALT, ALT $\leq 2 \times$ ULN, ALP $\leq 1.5 \times$ ULN]; life expectancy >12 weeks and performance status (PS) 0–2. Patients were ineligible if: gastroenterological abnormalities were likely to compromise absorption; they required the use of antacids or H_2 blocking agents, proton pump inhibitors or sucralfate, if CNS metastases were present; and if severe toxicities from previous therapy were still present.

Trial design

Patients were admitted to hospital for the first cycle of treatment and received temozolomide at a dose of 150 mg/m^2 daily for 5 days in this randomized open-label crossover study. Patients were fasted for 2 h prior to dosing and for 4 h post-dosing. A routine oral antiemetic ondansetron 8 mg was administered prior to dosing on days 2 and 5. Prior to dosing patients were randomized to receive ranitidine 150 mg every 12 h for three doses either on days 1 and 2 or days 4 and 5. On days 2 and 5 patients swallowed a Heidelberg capsule which contained a disposable radiotransmitter 15 min prior to dosing with temozolomide. The capsule transmits a signal from the gastrointestinal tract to an antenna embedded in a belt worn by the patient and displays a reading between 1.0 and 8.0 ± 0.5 pH units. Gastric pH was monitored prior to pharmacokinetic blood sampling for 4 h post-dosing or until the pH rose by >3 pH units, as measured by two measurements, which indicated the monitor had passed into the duodenum.

Patients were reviewed on a weekly basis for signs and symptoms of toxicity, and disease was assessed after two courses and responses recorded according to the World Health Organization (WHO) criteria. Toxicity was graded according to the Common Toxicity Criteria (CTC). Patients who experienced acceptable toxicity without disease progression went on to receive further cycles of treatment with a dosage interval of 28 days. For subsequent cycles of treatment patients were given 200 mg m^{-2} daily if they had not experienced CTC grade 3 or 4 toxicities during cycle 1. Patients with CTC grade 3 or 4 haematological toxicities which had resolved received a reduced dose for subsequent cycles.

Drug supply

Temozolomide was supplied by Schering Plough, Kenilworth, N.J., USA as a machine-filled white opaque preservative-free two-piece hard gelatin capsule in four strengths, 5 mg, 20 mg, 100 mg and 250 mg. Ranitidine was supplied by the pharmacy of the Royal Marsden NHS Trust.

Pharmacokinetics

Pharmocokinetic evaluations were done on days 2 and 5 for each patient during cycle 1. Blood samples were taken prior to dosing and at 15, 30, 45, 60 min and 90 min and 2, 3, 4, 6, 8 h and 12 h post-dosing to determine levels of temozolomide and MTIC. Blood samples were collected with pre-cooled syringes into pre-cooled heparinised tubes and placed immediately into an ice water bath. Samples for MTIC levels were immediately separated by centrifugation in a refrigerated centrifuge maintained at 4 °C for 10 min and immediately placed in a methanol dry ice bath and then transferred to a −80 °C freezer. Within 30 min of collection samples for estimation of temozolomide were centrifuged and plasma was placed in a plastic tube containing 0.1 ml of 8.5% phosphoric acid, vortexed and then placed in a −20 °C freezer. Plasma temozolomide and MTIC concentrations were determined using validated HPLC assays with limits of quantification of 0.1 μg/ml and 0.01 μg/ml, respectively [7, 12]. The plasma temozolomide and MTIC concentration-versus-time data on days 2 and day 5 were used to determine maximum plasma concentration (C_{max}), time to maximum plasma concentration (t_{max}), area under the plasma concentration-versus-time curve to the final sampling time (AUC_{0-t}), and from time zero to infinity ($AUC_{0-\infty}$), volume of distribution (Vd), elimination rate constant (k), half-life ($t_{1/2}$) and total body clearance using a model-independent method. C_{max} and t_{max} were the observed values, the $t_{1/2}$ was 0.693/k, the AUC_{0-t} was calculated using the linear trapezoidal method and the $AUC_{0-\infty}$, was calculated using $AUC_{0-\infty} = AUC_{0-t} + C/k$ where C is the concentration at the last time point. The total body clearance was calculated as: $CL_{T/F} = Dose/AUC_{0-\infty}$. The apparent volume of distribution ($V_{d/F}$) was calculated as $V_{d/F} = [Dose/AUC_{0-\infty}]/k$. The k, $AUC_{0-\infty}$ and $t_{1/2}$ could be determined in both phases in ten patients for temozolomide and only three patients for MTIC.

Statistical analysis

The pharmacokinetic parameters listed above were analysed using a crossover analysis of variance (ANOVA) model. The effects due to sequence, period and treatment were determined. The 90% confidence intervals for the mean difference between the two treatments for the primary parameters, log transformed AUC and C_{max}, were calculated using the pooled residual error and associated degrees of freedom from the analysis of variance. The mean difference and the 90% confidence intervals were expressed as a percentage and these represent an estimate of the relative bioavailability. The power to detect a 20% difference in treatment

Table 1 Patients' characteristics ($n = 15$)

Characteristic	Number
Age (median, range)	44 (18–72)
Gender (male/female)	9/6
PS	
0	1
1	9
2	5
Tumour types	
Sarcoma	5
Melanoma	4
Astrocytoma	3
Oligodendroglioma	1
Ovary	1
Lung	1

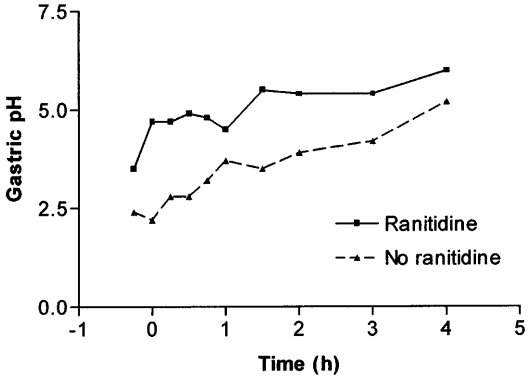

Fig. 2 Mean gastric pH values after administration of temozolomide to patients with and without ranitidine

Table 2 Pharmacokinetic parameters for temozolomide and MTIC with and without ranitidine. C_{max} maximum plasma concentration, t_{max} time to maximum plasma concentration, AUC_{0-t} area under the plasma concentration-versus-time curve to the final sampling time, $AUC_{0-\infty}$ area under the plasma concentration-versus-time curve from time zero to infinity, $t_{1/2}$ elimination half-life, CL/F total body clearance, $V_{d/F}$ apparent volume of distribution

	With ranitidine	Without ranitidine	Treatment P value
	Temozolomide ($n = 12$)		
	Mean (% CV)	Mean (% CV)	
C_{max} (μg/ml)	7.76 (48)	8.22 (37)	0.45
t_{max} (h)	1.79 (88)	1.85 (97)	0.904
AUC_{0-t} μg h ml^{-1}	23.3 (19)	23.3 (22)	0.915
$AUC_{0-\infty}$ μg h ml^{-1}[a]	24.3 (18)	24.1 (22)	0.757
$t_{1/2}$ (h)	1.81 (10)	1.82 (19)	0.201
CL/F (ml min^{-1} kg^{-1})	2.85 (16)	2.87 (20)	NS
$V_{d/F}$	0.44 (18)	0.45 (22)	NS
	MTIC ($n = 11$)		
C_{max} (ng/ml)	181 (43)	211 (48)	0.202
t_{max} (h)	1.92 (83)	1.88 (97)	0.940
AUC μg h^{-1} ml^{-1}	516 (25)	530 (23)	0.396

[a] $n = 11$

means for a level of 0.05 (two-tailed) was determined. The original scale data were used to analyse t_{max} and $t_{1/2}$.

Results

Patients and doses

Between September 1995 and July 1996, 15 adult patients with advanced cancer were treated at the Royal Marsden NHS Trust. The patients' demographic details are presented in Table 1. All patients had received prior chemotherapy with radiotherapy and/or surgery. Three patients were not considered evaluable for the pharmacokinetics of temozolomide and MTIC with and without ranitidine for the following reasons: in one patient the Heidelberg capsule was not functioning, in another the plasma samples inadvertently thawed and another received ranitidine on days 1 and 2 and days 4 and 5.

Pharmacokinetics

The gastric pH was increased by 1–2 pH units in the presence of ranitidine and the gastric pH time profiles were similar with and without ranitidine (Fig. 2). The mean pharmacokinetic parameters and the mean concentration-time profiles for temozolomide and MTIC with and without ranitidine are presented in Table 2 and Fig. 3 respectively. There were no statistically significant differences in any of the pharmacokinetic parameters for either temozolomide or MTIC when temozolomide was administered with or without ranitidine. For temozolomide the (C_{max}) was 7.7 versus 8.2 μg/ml; the mean t_{max} was 1.8 versus 1.9 h; the mean AUC_{0-t} was 23.3 μg h ml^{-1} for both, the mean $AUC_{0-\infty}$ was 24.3 versus 24.1 μg h ml^{-1}, and the mean $t_{1/2}$ 1.8 h for both, with and without ranitidine, respectively. The clearance and Vd were similar to previously published results [5, 10].

For MTIC, the mean C_{max} was 181 ng/ml and 211 ng/ml; the mean t_{max} was 1.92 versus 1.88 h; and the AUC_{0-t} 516 versus 530 ng h ml^{-1} with and without ranitidine, respectively. MTIC appeared in the plasma soon after the administration of temozolomide and the PK profile was similar to that of temozolomide (Fig. 3). The AUC of MTIC was 2–4% of the AUC for temozolomide with and without ranitidine.

To determine the treatment effect of the various parameters, the effects of sequence, phase and treatment were analysed using ANOVA. Treatment is defined as ranitidine or no ranitidine; phase is day 2 versus day 5; and sequence is ranitidine on day 1 and 2 versus ranitidine on days 4 and 5. There were no significant treatment or phase effects for the AUC and C_{max} for temozolomide and MTIC. However, there was a statistically significant sequence effect for C_{max} for both temozolomide and MTIC. For unexplained reasons, the average C_{max} of temozolomide and MTIC was slightly lower for subjects receiving ranitidine on days 1 and 2 compared with those receiving ranitidine on days 4 and 5 (P values 0.023 and 0.002, respectively). The individual data for both C_{max} and AUC are presented in Fig. 4, and demonstrate similar values in each patient given temozolomide with and without ranitidine. This suggests that the sequence effect on C_{max} on days 1 and 2 versus days 4 and 5 is unlikely to be clinically significant. The point estimates of relative oral bioavailability (C_{max} and AUC) for temozolomide and MTIC were 89–100%, indicating that the change in gastric pH due to ranitidine had no effect on the oral bioavailability (Table 3).

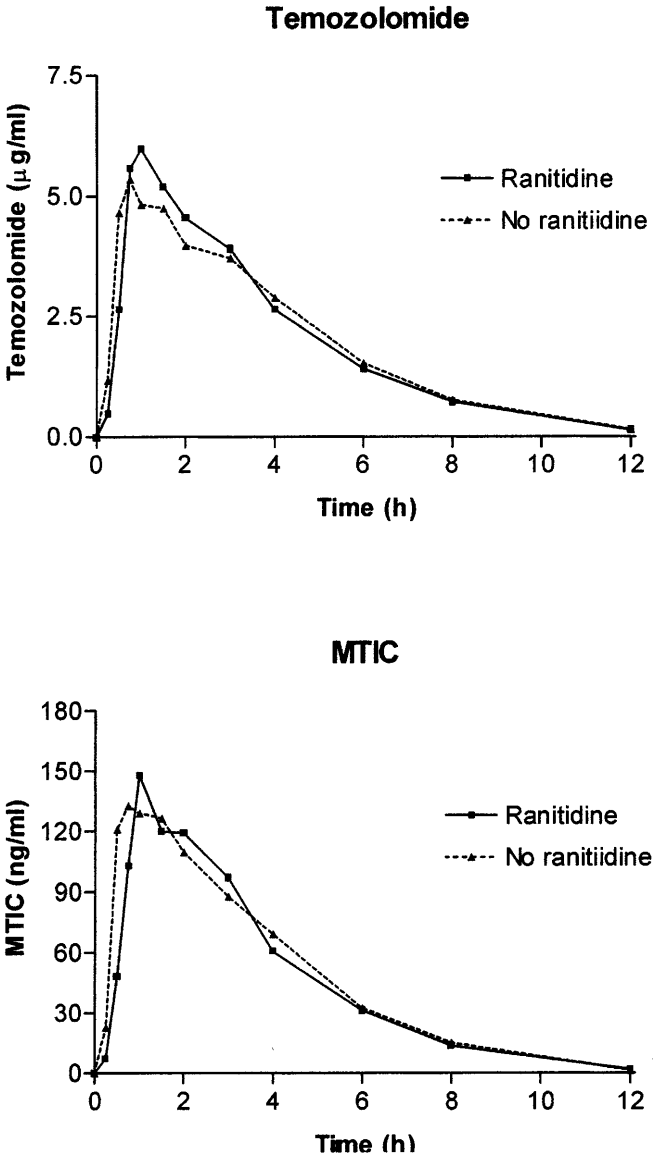

Fig. 3 Mean concentration-versus-time curves for temozolomide and MTIC in patients with and without ranitidine

Tolerability/responses

The 15 patients received a total of 34 cycles of treatment (range 1–6 cycles per patient). No patient achieved a

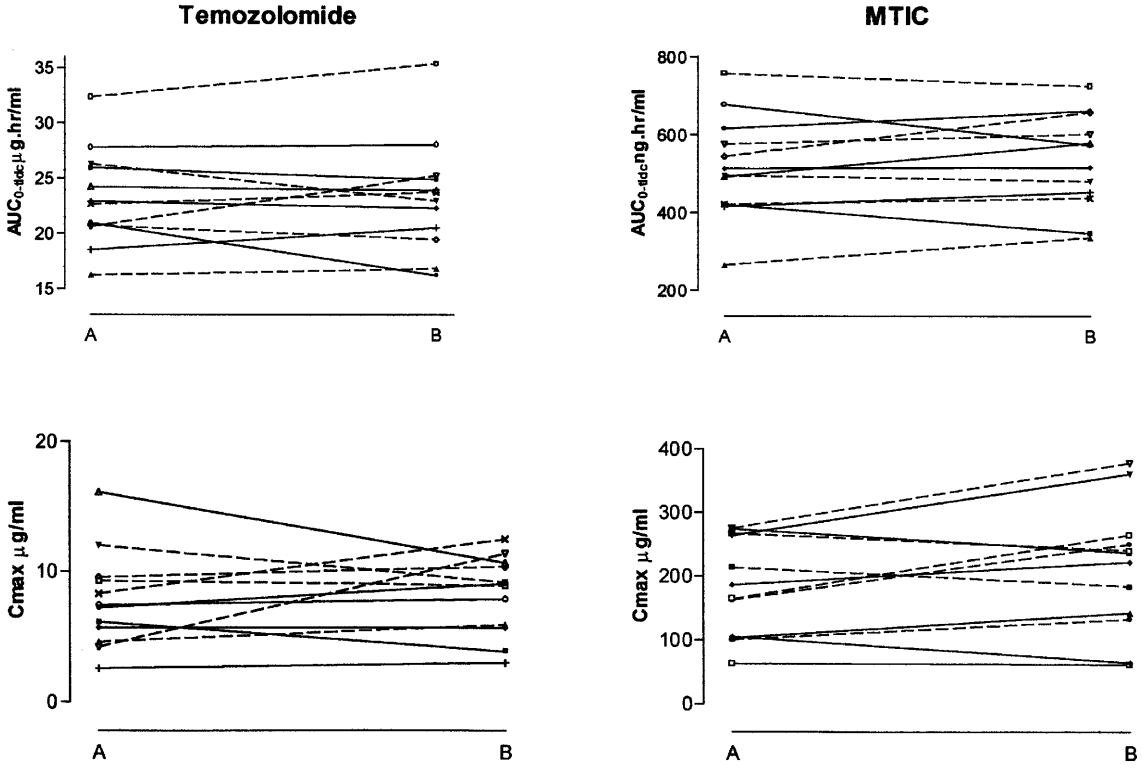

Fig. 4 Individual values for plasma temozolomide and MTIC; C_{max} and AUC values with (**A**) or without (**B**) ranitidine and sequence (*solid line* ranitidine/no ranitidine sequence, *broken line* no ranitidine/ranitidine sequence). C_{max} maximum plasma concentration, AUC_{0-t} □

response, although four patients achieved stable disease and received multiple cycles of treatment. Toxicity was mild, although one patient did experience grade 4 thrombocytopenia and neutropenia after receiving 200 mg m^{-2} per day for 5 days and subsequently had a 25% dose reduction (Table 4).

Table 3 Relative bioavailability[a] for temozolomide and MTIC (expressed as a ratio of ranitidine/no ranitidine). C_{max} maximum plasma concentration, AUC_{0-t} □, $AUC_{0-\infty}$ area under the plasma concentration-versus-time curve from time zero to infinity

Parameter	Relative bioavailability (%)	90% Confidence interval
	Temozolomide	
C_{max}	91.9	76–112
AUC_{0-t}	100	94–107
$AUC_{0-\infty}$	100	93–108
	MTIC	
C_{max}	89.0	76–104
AUC_{0-t}	96.7	90–104

[a] The mean difference in the log transformed AUC and C_{max} values expressed as a percentage is an estimate of the relative oral bioavailability

Table 4 Drug-related toxicity for all cycles ($n = 36$)

Toxicity	Grade 1–2	Grade 3–4
Anaemia	4	1
Thrombocytopenia	4	3
Leucopenia	1	1
Neutropenia	1	1
Vomiting	1	0
Lethargy	1	0

Discussion

Temozolomide is an imidazotetrazine derivative with schedule-dependent activity in glioma and melanoma. It is converted by pH-dependent chemical hydrolysis to MTIC under neutral and basic conditions and this metabolite exerts a cytotoxic action by DNA alkylation preferentially at the O^6 position of guanine [13]. MTIC is itself metabolized to AIC, which is detectable in plasma, although the appearance in plasma is delayed compared with that of temozolomide and MTIC. Hepatic metabolism appears to play only a minor role in the clearance of temozolomide, with only trace amounts of AM appearing in plasma, and renal clearance of the parent compound contributes to only 6% of the total clearance [5].

The aim of this study was to determine the effect of altering the gastric pH by the use of ranitidine, an H_2-receptor blocker, on the oral bioavailability of temozolomide and the plasma pharmacokinetics of temozolomide and MTIC. Given the decreased stability of temozolomide at neutral or alkaline pH, it was pos-

tulated that elevation of gastric pH by ranitidine might result in reduced oral bioavailability. Ranitidine is commonly used in cancer patients and therefore the two drugs may be given concomittently. The gastric pH was measured by a Heidelberg capsule, which transmitted a signal to a receiver on a belt worn by the patients. The pH was seen to rise by 1–2 pH units with use of ranitidine, with each patient acting as their own control. The range of pH throughout the study was 2.2–6.0. The pharmacokinetics of temozolomide and MTIC were not altered by altering the gastric pH within this physiological range. The C_{max}, t_{max}, or AUC values for temozolomide and the metabolite MTIC were similar following temozolomide administration with and without ranitidine. The C_{max} values of both temozolomide and MTIC, however, were lower in the patients who received ranitidine on day 1 or 2 rather than day 4 or 5 (sequence effect) but this was not reflected in a change in the AUC. The reason for this difference is not known and is unlikely to be clinically significant. The oral bioavailability of temozolomide and MTIC were similar, with or without ranitidine.

The results of this study are in keeping with the temozolomide pharmacokinetics reported from the previous phase I trials [4, 5, 10]. Temozolomide is rapidly absorbed and eliminated following oral administration. Peak plasma temozolomide concentrations are observed 1–2 h after dosing and the $t_{1/2}$ is 1.8 h. Conversion of temozolomide to MTIC was rapid, with MTIC appearing in the plasma soon after temozolomide administration with a t_{max} of 1–2 h and a $t_{1/2}$ of 1.9 h. Overall, the exposure to MTIC (AUC) represented 2–4% of the AUC of the parent compound. Additionally, the drug is well tolerated, with the only significant toxicity being myelosuppression seen at the higher dose level of 200 mg/m^2 per day.

The successful use of the Heidelberg capsule to determine gastric pH has been demonstrated in this study. While this system has been used previously [1, 9], this is the first report of its application in cancer drug pharmacology and it was shown to be well tolerated by the patients, all of whom had advanced disease. This study confirmed that the rise in pH following the administration of ranitidine had no effect on the stability of temozolomide, which in turn did not affect the oral bioavailability or the pharamocokinetics of temozolomide and MTIC.

References

1. Betalach CJ, Straughn AB, Meyer MC, Bailey M, Vashi VI, Lieberman P, Gonzalez MA (1991) The effect of raising gastric pH with ranitidine on the absorption and elimination of theophylline from a sustained-release theophylline tablet. Pharmacol Res 8: 1516
2. Bleehen NM, Newlands ES, Lee SM, Thatcher N, Selby P, Calvert AH, Rustin GS, Brampton M, Stevens MG (1995) Cancer research campaign phase II trial of temozolomide in metastatic melanoma. J Clin Oncol 13: 910
3. Bower M, Newlands ES, Bleehen NM, Brada M, Begent RH, Calvert AH, Colquhoun I, Lewis P, Brampton MH (1997) Multicentre CRC phase II trial of temozolomide in recurrent or progressive high-grade glioma. Cancer Chemother Pharmacol 40: 484
4. Brada M, Moore S, Judson I, Batra VJ, Quartey P, Dugan M (1995) A phase I study of SCH 52365 (temozolomide) in adult patients with advanced cancer (meeting abstract). Proc Annu Meet Am Soc Clin Oncol 14: A1521
5. Dhodapkar M, Rubin J, Reid JM, Burch PA, Pitot HC, Buckner JC, Ames MM, Suman VJ (1997) Phase I trial of temozolomide (NSC 362856) in patients with advanced cancer. Clin Cancer Res 3: 1093
6. Hartley JA, Gibson NW, Kohn KW, Mattes WB (1986) DNA sequence selectivity of guanine-N7 alkylation by three antitumour chloroethylating agents. Cancer Res 46: 1943
7. Kim KH, Lin CC, Parker D, Lim J, Likhari P, Statkevich P, Marco A, Nomeir AA (1997) High-performance liquid chromatography determination and stability of 5-(3-methyltriazene-1-yl)-imidazo-4-carboxamide, the biologically active product of the antitumour agent temozolomide, in human plasma. J Chromatogr B Biomed Sci Appl 703: 225
8. Lee S, Thatcher N, Crowther D, Marigson GP (1994) Inactivation of O^6 alkylguanine DNA alkyltransferase correlates with potentiation of temozolomide and CCNU toxicity in human tumour cells. Br J Cancer 69: 452
9. Meyer M, Straughn AB, Jarvi EJ, Wood GC, Vashi VI, Hepp P, Hunt J (1993) The effect of gastric pH on the absorption of controlled release theophylline dosage forms in humans. Pharmacol Res 10: 1037
10. Newlands ES, Blackledge GP, Slack JA, Rustin GS, Smith DB, Stuart NA, Quarterman CP, Hoffman R, Stevens MG, Brampton MH, Gibson AC (1992) Phase I trial of temozolomide (CCRG 81045: M and B 39831: NSC 362856). Br J Cancer 65: 287
11. Russell TL, Beradi RR, Barnett JL, Dermentzoglou LC, Jarvenpaa KM, Schmaltz SP, Dressman JB (1993) Upper gastrointestinal pH in seventy-nine healthy elderly North American men and women. Pharmacol Res 10: 187
12. Shen F, Decosterd LA, Gander M, Leyvraz S, Biollaz J, Lejeune FJ (1995) Determination of temozolomide in human plasma and urine by high-performance liquid chromatography after solid-phase extraction. J Chromatogr B Biomed Sci Appl 667: 291
13. Stevens MFG, Hickman JA, Langdon SP, Chubb D, Vickers L, Stone R, Baig G, Goddard C, Bigson N, Slack JA, Newton C, Lunt E, Fizames C, Lavelle F (1987) Antitumour activity and pharmacokinetics in mice of 8-carbamoyl-3-methylimidazo(5,1-d)-1,2,3,5-tetrazin-4(3*H*)-one; a novel drug with potential as an alternative to darcarbzine. Cancer Res 47: 5846
14. Tsang LL, Farmer PB, Gescher A, Slack JA (1990) Characterisation of urinary metabolites of temozolomide in humans and mice and evaluation of their cytotoxicity. Cancer Chemother Pharmacol 26: 429
15. Woll PJ, Crowther D, Johnson PM, Soukop M, Harper PG, Harris M, Brampton MH, Newlands ES (1995) Phase II trial of temozolomide in low-grade non-Hodgkin's lymphoma. Br J Cancer 72: 183