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Administration of nicotinamide during a five- to seven-week course of radiotherapy: pharmacokinetics, tolerance, and compliance

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Abstract

Background and purpose: Nicotinamide was administered daily as a liquid formulation to head and neck cancer patients receiving a 5- to 7-week course of radiotherapy. The pharmacokinetics, compliance, and tolerance of this drug formulation were studied.

Materials and methods: Blood samples were drawn and nicotinamide levels determined in 40 head and neck cancer patients. On the first treatment day serial samples were obtained followed by daily samples at the time of irradiation during the first and last full weeks of the treatment. Side-effects of nicotinamide were monitored.

Results: In all patients peak concentrations greater than 700 nmol/ml could be obtained 0.25–3 h (mean 0.83 ± 0.73 h) after drug intake. During the first week of treatment plasma levels at the time of irradiation were adequate in 82% of the samples. This decreased to 59% in the last week of treatment which can be partly attributed to reduced compliance. The most important side-effect of nicotinamide was nausea with or without vomiting occurring in 65% of the patients. Severe side-effects were associated with high plasma concentrations over subsequent days. Tolerance improved after a 25% reduction of dose in six of seven patients but plasma levels at the time of irradiation fell below 700 nmol/ml in four out of six of these patients.

Conclusions: Peak plasma concentrations above the 700 nmol/ml level were obtained in all patients but these concentrations could not be reproduced during the entire course of the treatment in a significant portion of the subjects. Side-effects of nicotinamide are associated with plasma concentrations and tolerance can be improved by a moderate reduction of dose. © 1997 Elsevier Science B.V. All rights reserved

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1. Introduction

Nicotinamide is currently being assessed in clinical trials as a modifier of acute perfusion-limited tumour-hypoxia. This compound can reduce the intermittent closure of blood vessels in experimental rodent tumours [2,7] and consequently decrease hypoxic-cell radioresistance [6,10]. In addition, nicotinamide has been shown to enhance the sensitising effect of carbogen [1,12,13], which overcomes the sparing effect of chronic diffusion-limited hypoxia [16]. With fractionated radiation schedules to mouse tumours, relative to radiation treatments

in air without the drug, enhancement ratios in the order of 1.3–1.9 have been obtained for the combination of carbogen and nicotinamide [3,12,14,15]. Experimentally, plasma levels of 700 nmol/ml of nicotinamide are required at the time of irradiation to obtain a sensitising effect [8,15]. Initial studies in healthy human volunteers showed that peak plasma levels of 800–1600 nmol/ml could be obtained after oral intake of 6 g [8,19]. Horsman et al. showed that for maximal radiosensitization tumours should be irradiated at the time of peak drug levels [8].

The current clinical practice is to prescribe the drug on a weight adjusted basis and adequate plasma levels can be obtained in patients with oral doses of 80 mg/kg/day [9,18]. In a recent study performed on a small number of

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patients undergoing CHART and given this dose of nicotinamide over 12 consecutive days, the drug was well tolerated but large inter-patient variations were seen both with regards to the maximum plasma concentration (C_{\max}) obtained and the time taken to reach this peak (T_{\max}). Peak levels were reported to range from 400 to 1400 nmol/ml with T_{\max} values from 0.8 to 4 h, but in the four patients in which repeated assessments were made at various times during the course of radiotherapy the kinetic parameters were reproducible [9]. However, there are no reliable pharmacokinetic and toxicity data with prolonged daily administration of high doses of nicotinamide during a 5- to 7-week course of radiotherapy and information on patient compliance is also lacking.

Although nicotinamide was suggested as a relatively non-toxic agent with a low incidence of side-effects even at the dose levels required for tumour radiosensitization [20], in our experience gastrointestinal complaints occur frequently. In a previous study 60% and 36% of the patients had nausea and vomiting respectively and in 26% this was reason to discontinue drug intake [11]. Till now clinical studies have failed to demonstrate a relationship between side-effects and nicotinamide plasma levels [18].

We therefore decided to investigate if adequate nicotinamide plasma levels could be obtained in head and neck cancer patients enrolled in a study combining radiotherapy with carbogen breathing and nicotinamide and whether such levels were maintained throughout the course of treatment. We also aimed to study whether the use of a liquid formulation of the drug improves the pharmacokinetic parameters of C_{\max} and/or T_{\max} and whether there is a relationship between plasma levels and the incidence and severity of toxic side-effects. This paper reports on data obtained in 40 patients undergoing either conventional or accelerated radiotherapy.

2. Materials and methods

2.1. Patients

In our institute head and neck cancer patients with Stage III–IV disease and also Stage II hypopharyngeal cancer are currently being enrolled in a study combining radiotherapy with carbogen breathing and nicotinamide, details of which have been described previously [11]. Inclusion criteria are: age over 18 years, WHO performance status of 0–2, no severe heart or lung disease, no severe liver or kidney dysfunction, no severe stridor, no distant metastases, and written informed consent. From February 1995 to March 1996, after approval from the local ethical committee, 40 consecutive patients consented to have plasma samples drawn for determination of nicotinamide levels. There were 28 men and 12 women. Mean age was 61 years with a range of 41–82 years.

2.2. Radiotherapy

Nine patients were treated by a conventional schedule and 31 by an accelerated fractionation schedule. Conventional radiotherapy was given in fractions of 2 Gy, five times a week to a total dose of 68 Gy. Overall treatment time was 46–48 days. With the accelerated schedule the total dose was 64–68 Gy while dose per fraction remained the same and treatment time was reduced by 10 days by giving two fractions per day during the last 1.5 weeks of the treatment. The interval between the two fractions per day was 6 h. Some patients were hospitalised when they were treated twice daily because of travelling distance.

2.3. Nicotinamide administration

Nicotinamide (Pharmachemie, Haarlem, The Netherlands), dissolved in fruit juice was administered orally 1.5 h before irradiation. After the pharmacokinetic data of the first 22 patients were analysed, the interval was changed to 1 h for the following 18 patients. A light meal, if taken at least 1 h before drug intake, was allowed. On days when two fractions were given, only one dose of nicotinamide was administered before the first treatment. The daily dose was 80 mg/kg to a maximum of 6 g. Since November 1995 a dose reduction to 60 mg/kg was introduced for patients with severe side-effects. Sixteen patients have been treated with this approach. If a dose reduction was applied, nicotinamide was discontinued during one day prior to this to allow complete elimination of the drug in case accumulation had occurred.

2.4. Sample acquisition and analysis of nicotinamide concentrations

On the first treatment day serial samples were taken usually through an intravenous cannula inserted in the arm. An initial 5 ml of blood was discarded before the actual sample was collected. On subsequent days blood was drawn by way of a venous puncture. Five-ml samples were collected in heparinized tubes and immediately stored at 4°C. Plasma was separated by centrifugation (3000 × g; 10 min) within 8 h of sampling and then stored at –20°C prior to analysis. Nicotinamide concentrations were determined in methanol extracts of plasma using high performance liquid chromatography [17]. From all patients a full profile was obtained on the first day of treatment. Sampling times on the first day were at 0, 0.25, 0.5, 1, 1.5, 2, 3, 4, 6, and 12 h after nicotinamide ingestion and the residual level was measured after 24 h (C_{res}). One or 1.5 h after intake of the second dose another sample was collected. Because of the frequent sampling on these first 2 days, patients were hospitalised during this time. Thereafter samples were obtained daily during the first and last full weeks of the treatment at the time of irradiation, i.e. 1 or 1.5 h after nicotinamide intake. In

addition, if nicotinamide dose was reduced, plasma samples were collected on at least 3 consecutive days starting on the first day of dose reduction.

2.5. Monitoring during treatment

At each time of sampling blood pressure and heart rate were recorded. During the course of treatment the patients were seen by both the attending radiotherapist and, separately, by the research assistant at least once a week and more frequently if necessary, e.g. when side-effects occurred. Patients were asked if any adverse events had occurred and they were specifically asked if they had experienced nausea and/or vomiting. If they reported vomiting they were asked to specify when this occurred and how often. Anti-emetics (metoclopramide, ondansetron) were prescribed when necessary. Side-effects of nicotinamide were considered severe if they led to a discontinuation of the drug or a reduction of the daily dose. Gastrointestinal bleeding in one patient and renal dysfunction in another patient were felt to be possibly related to nicotinamide and also scored as severe.

2.6. Statistics

For each patient the plasma levels obtained at the time of irradiation during the first full week were plotted and a linear least-squares regression fit was done. If there was a positive and significant ($P < 0.05$) correlation of plasma levels with time, the patient was considered to accumulate nicotinamide with daily administration. A discriminant analysis was done to examine which pharmacokinetic parameters predicted best for nicotinamide toxicity. All statistical analyses were done on a Macintosh computer using the Statistica 4.0 software package.

3. Results

3.1. Tolerance

The reported side-effects are listed in Table 1. Nausea with or without vomiting was reported by 65% of the patients. Often these complaints were unresponsive to

Table 1

Nicotinamide side-effects in 40 patients

Side-effect	No. of patients
Nausea	26
Vomiting	13
Flushing	7
Dizziness	6
Epigastric pain	3
Gastrointestinal disturbances	1
Renal dysfunction	1

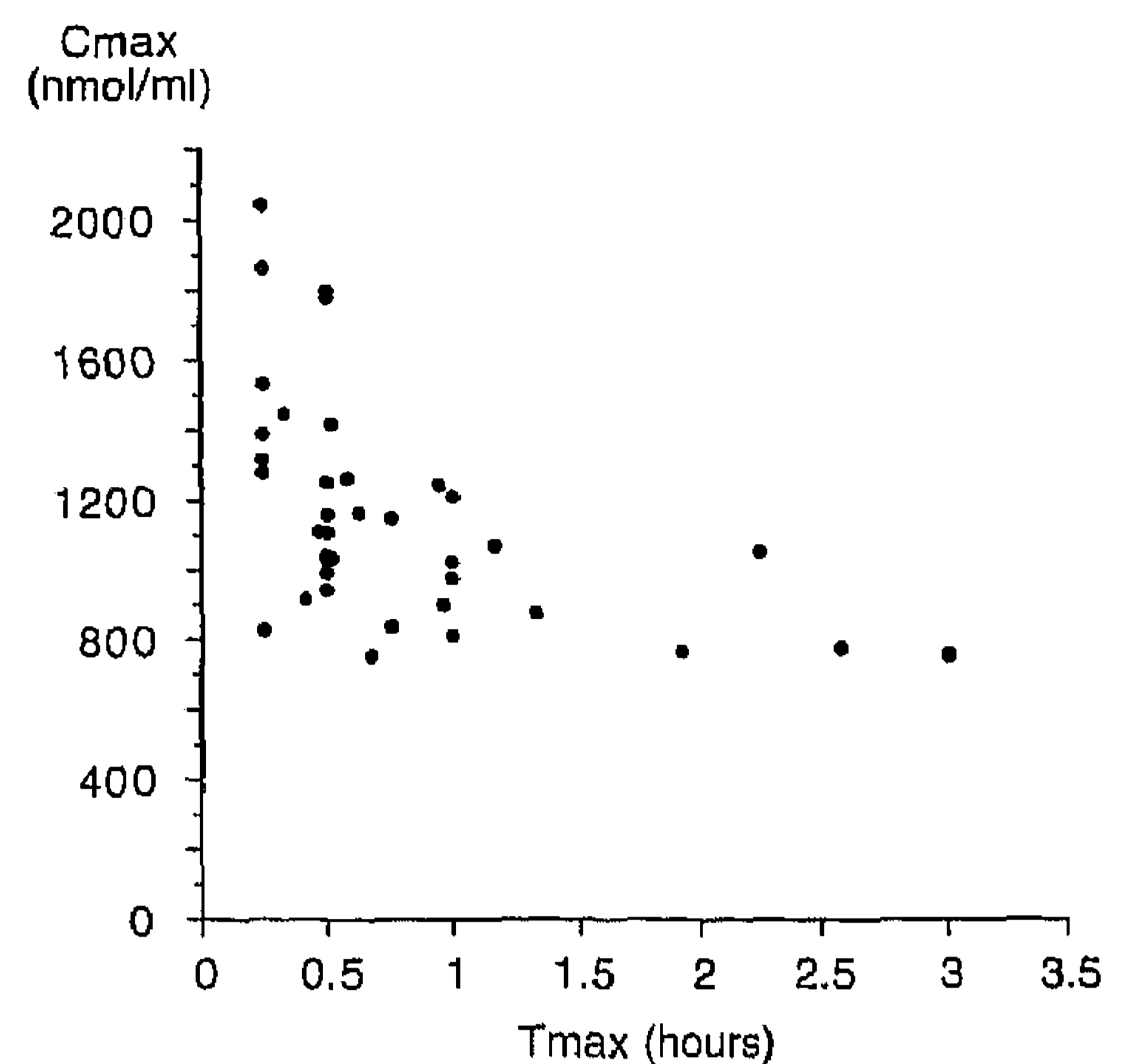


Fig. 1. Scatterplot of C_{max} versus T_{max} including all 40 patients.

anti-emetics including ondansetron. Eight patients experienced no side-effects at all while 16 patients had side-effects that were considered as severe. Nine patients discontinued nicotinamide intake because of side-effects, eight because of nausea and one because of renal toxicity. Five patients discontinued intake of the drug for other reasons: three patients went off study because of very poor compliance with the treatment protocol, one patient stopped nicotinamide in the fourth week of treatment because of the poor taste and dysphagia due to irradiation-mucositis, and in one case it was decided to stop at day 4 because of pre-existent renal disturbances. Of the 16 patients treated since November 1995, seven had a dose reduction to 60 mg/kg because of severe nausea. Only one of these 16 patients finally discontinued nicotinamide intake because of the side-effects in contrast to eight of the 20 patients treated previously (excluding the five patients that stopped nicotinamide for other reasons).

There was no indication of an effect of nicotinamide on blood pressure or pulse.

3.2. First day nicotinamide plasma profile

C_{max} and T_{max} for each individual are shown in Fig. 1. Mean and median C_{max} were 1154 nmol/ml and 1088 nmol/ml with a standard deviation (SD) of ± 326 nmol/ml and a range of 752–2041 nmol/ml. Thus, in all patients a minimal level of 700 nmol/ml could be obtained. Mean and median T_{max} were 0.83 h and 0.51 h (SD ± 0.73 h, range 0.25–3 h). T_{max} was equal or less than 1 h in 33 of the 40 cases. Fig. 2 illustrates the mean of the pharmacokinetic profiles obtained on the first day of treatment of all 40 patients. The profiles of two individual patients are added in the figure to illustrate the inter-individual variability which is largest during the first hour after nicotinamide intake. One patient has a very high C_{max} with short T_{max} whereas the other has a relatively low C_{max} and long T_{max} . With the accelerated radiation schedule the second treatment of the day is given 7–8 h after nicotinamide

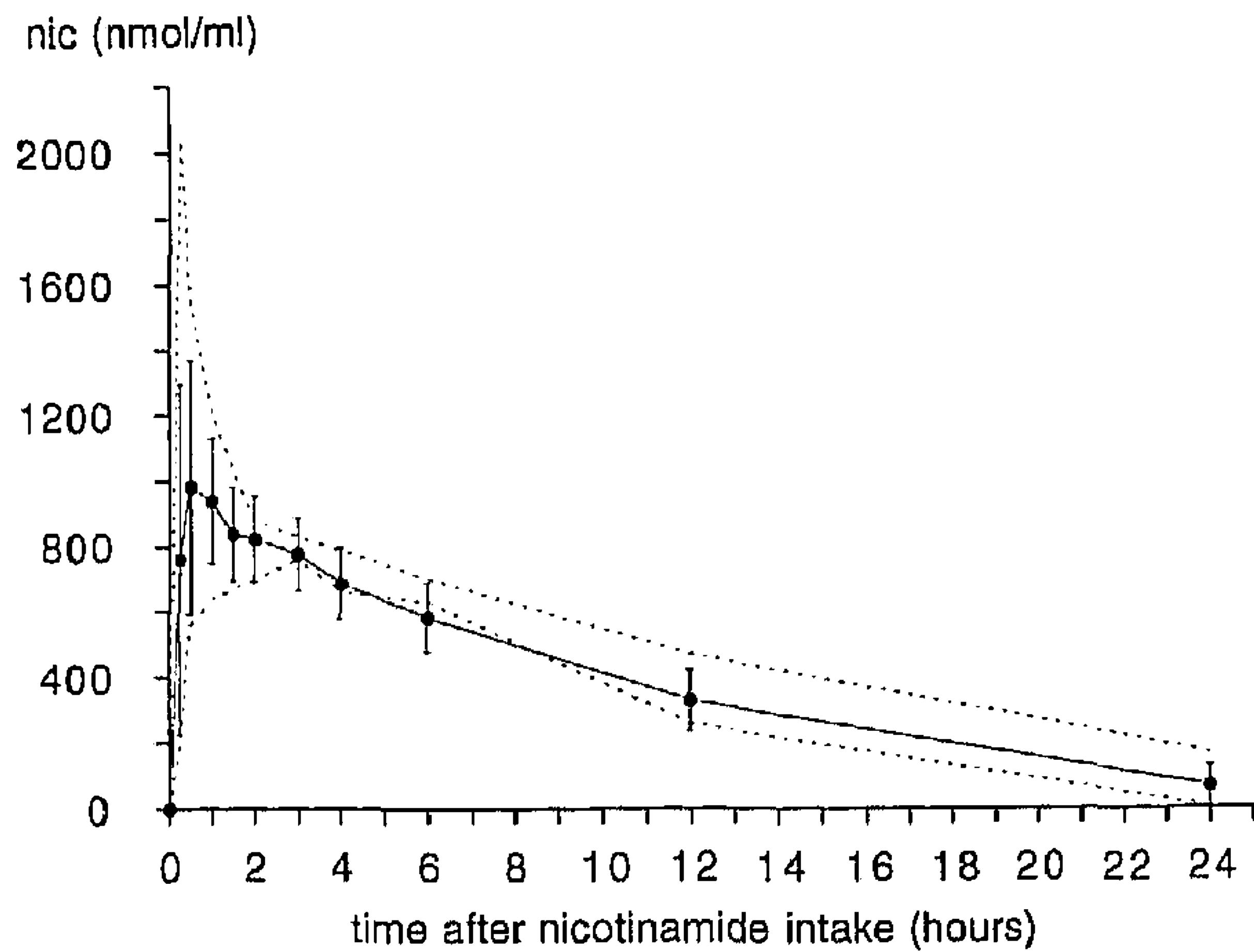


Fig. 2. Nicotinamide plasma concentrations as a function of time after intake. Mean of 40 patients with standard deviations. The dotted lines represent two individual patients: one with high C_{max} and short T_{max} and the other with low C_{max} and long T_{max} .

intake at which time the interpolated mean plasma level was about 500 nmol/ml. Mean and median C_{res} were 66 nmol/ml and 53 nmol/ml (SD ± 62 nmol/ml, range 0–221 nmol/ml).

3.3. Nicotinamide plasma levels during first and last weeks of treatment

Fig. 3 shows the individual and mean plasma levels at the time of irradiation during the first and last full weeks of the treatment. Some patients started radiotherapy on a Thursday; in those cases nicotinamide levels were determined in the first full week but also on the first 2 treatment days before and these are also shown in the figure. Nico-

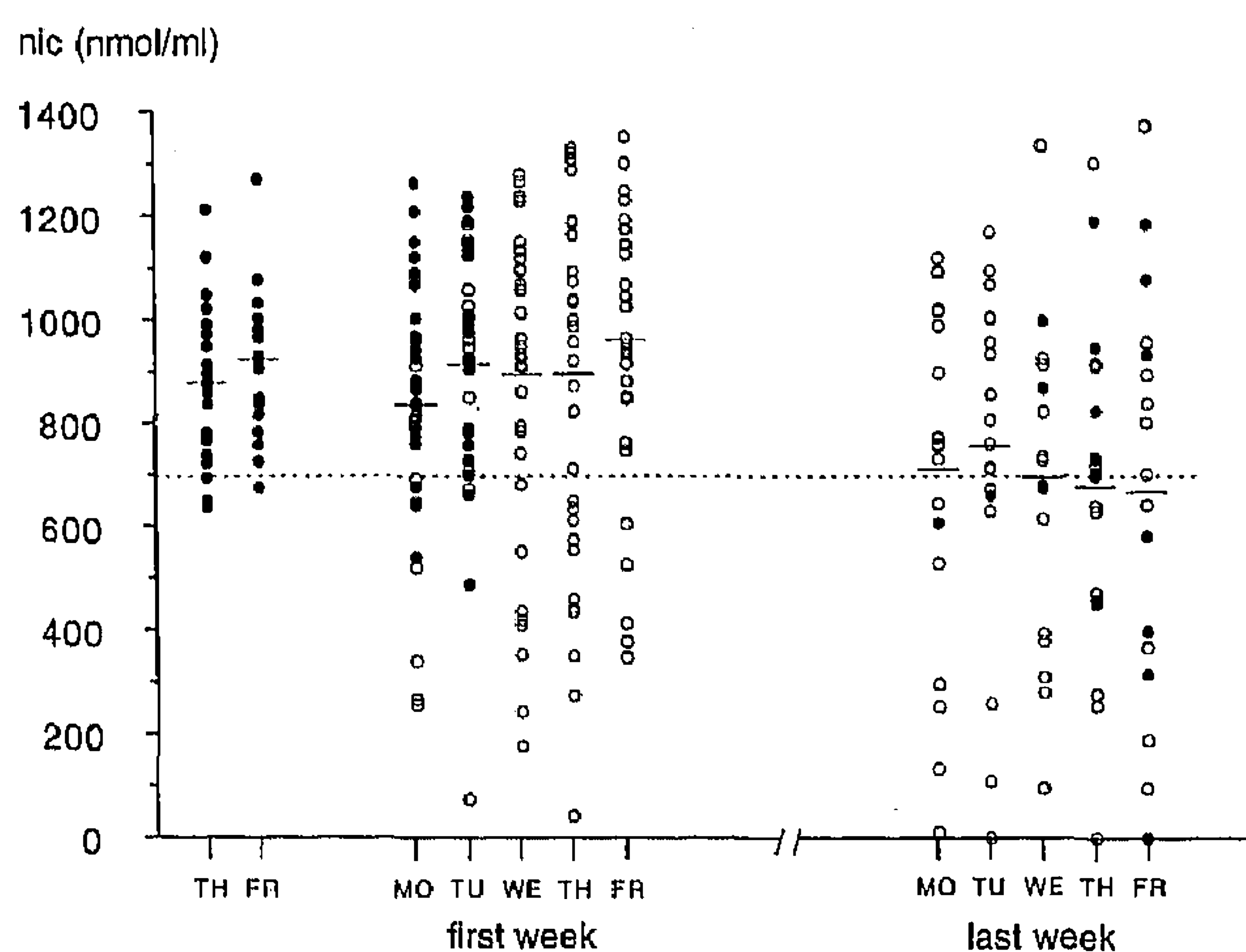


Fig. 3. Nicotinamide plasma concentrations at the time of irradiation during the first and last week of the treatment. Individual values of 40 patients are represented by the circles. Closed and open symbols represent values obtained during hospitalisation (●) and at the outpatients' department (○). Horizontal bars indicate mean values. Dashed horizontal line indicates 700 nmol/ml level.

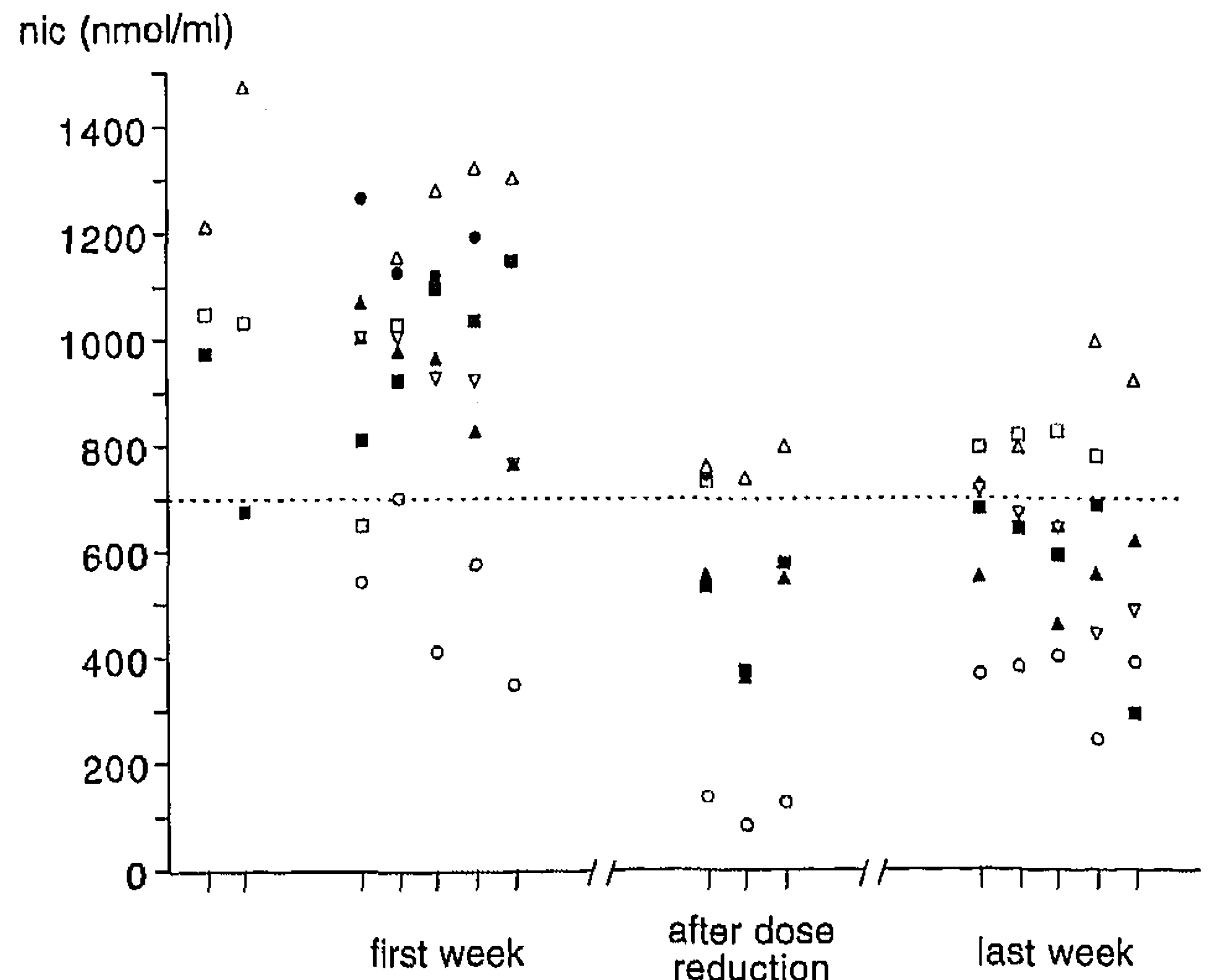


Fig. 4. Nicotinamide plasma concentrations at the time of irradiation in seven patients. Data obtained before dose reduction (first week), on 3 consecutive days directly after dose reduction, and during the last week of treatment. Different symbols represent different patients (○, patient with assumed poor compliance; ●, patient discontinued nicotinamide intake). Dashed horizontal line indicates 700 nmol/ml level.

tinamide levels measured after dose reduction are not included. At the start of the treatment 179 of 219 values (82%) were above the desired 700 nmol/ml and nine of 40 patients had lower values more than once. In 11 of 37 patients a linear least-squares regression fit to the values obtained at the time of irradiation during the first full week indicated that accumulation of nicotinamide occurred with daily administration. In three cases the regression analysis could not be carried out because drug intake was already discontinued in the first week. Accumulation was not correlated with C_{res} , i.e. patients with a relatively high residual 24-h level after the first drug dose did not necessarily show drug accumulation.

On average, plasma concentrations decreased towards the end of the treatment. During the last week 55 of 94 (59%) values were above the 700 nmol/ml level and nine of the 19 patients who continued nicotinamide intake until the end of the treatment and without a dose reduction had values that fell below this level more than once.

Fig. 4 shows the nicotinamide plasma concentrations for the seven patients who had a dose reduction. It includes the levels obtained in the first week with doses of 80 mg/kg, the levels directly after reduction to 60 mg/kg, and those obtained in the last week of the treatment. One patient continued having severe side-effects and stopped nicotinamide intake. In two patients levels greater than 700 nmol/ml were obtained and reproduced daily with the 60 mg/kg dose, three others produced levels in the 400–700 nmol/ml range, and in one patient the levels were clearly inadequate which, we believe, was largely due to poor compliance. In fact this patient had already insufficient levels at the beginning of the treatment.

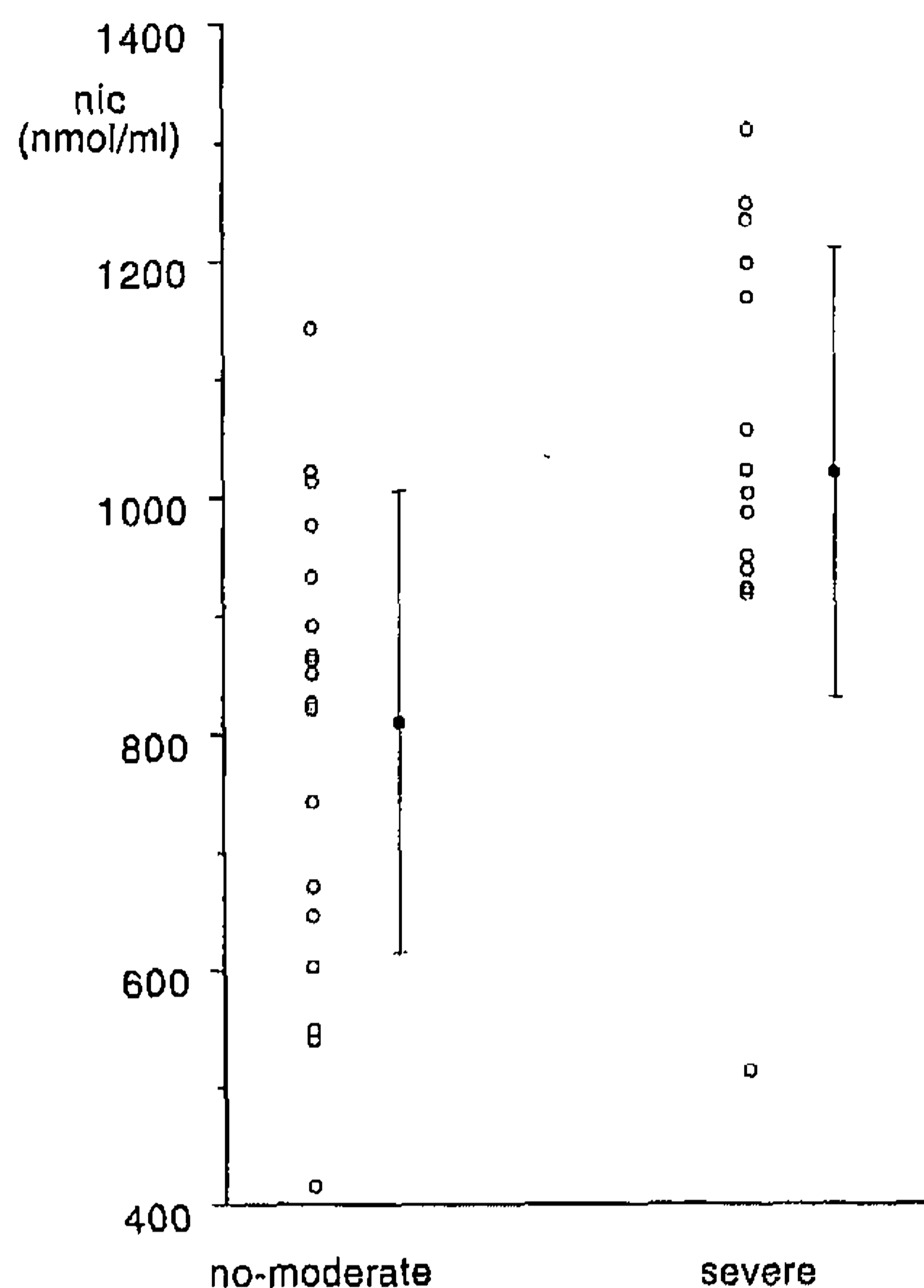


Fig. 5. Mean of nicotinamide plasma concentrations measured at the time of irradiation during the first week of treatment. Open symbols represent mean per patient (35 patients). Patients are divided in two groups by severity of nicotinamide side-effects (no-moderate versus severe). Closed symbols indicate mean values of the two groups with standard deviations.

3.4. Correlation between nicotinamide side-effects and plasma levels

Adequate assessment of the severity of side-effects was not possible in five cases: three patients were taken out of the study because of very poor compliance with the treatment protocol, in one case it was decided to stop at day 4 because of pre-existing renal disturbances, and in one case reporting of side-effects was very inconsistent and unreliable and therefore not interpretable. Thus, 35 patients were evaluable for this analysis of which 16 patients experienced side-effects that were considered as severe. We investigated if the pharmacokinetic parameters could predict for nicotinamide toxicity by discriminant analysis. The following parameters were included: absolute daily dose, C_{max} , area under the curve (AUC) derived from the first day profile, C_{res} , the mean of the plasma concentrations measured at the time of irradiation during the first week (C_{mean}), and whether or not accumulation occurred. There was no correlation between side-effects and absolute daily dose or C_{res} or AUC. High C_{max} ($P = 0.03$) and high C_{mean} ($P = 0.008$) were correlated with the occurrence of severe side-effects. There was a positive correlation between drug accumulation and severe side-effects but this did not reach statistical significance ($P = 0.10$). Eight of the 11 patients who showed drug accumulation had severe side-effects as compared to seven of the 23 patients in whom there was no indication of accumulation. The most powerful single predictor for severe nicotinamide toxicity was C_{mean} (Fig. 5).

4. Discussion

4.1. Tolerance

Gastrointestinal symptoms, flushing, dizziness, sweating, fatigue, and headache were already recognised as side-effects of nicotinamide [5,8,9,20]. In a previous report we associated renal failure with nicotinamide intake as a relatively infrequent event but one that can have serious consequences [11]. In our total experience this occurred in three of 61 patients that were treated with nicotinamide. All three had received nephrotoxic medication previously (cisplatin) or concomitantly (ACE-inhibitor, carbasalatcalcium). Consequently we withheld nicotinamide in patients with pre-existing renal dysfunction and it was not administered concomitantly with nephrotoxic medication. Since then we have treated 41 other patients and no renal toxicity has been observed. One patient had a gastric bleeding. He also used carbasalatcalcium for analgesia which is a salicylate and known to cause gastric irritation which may have been enhanced by nicotinamide. One patient reported emotional lability and depressive moods. This was also noted in another patient treated previously. It remains unclear whether this relates to nicotinamide use.

The most frequent adverse effect is nausea with or without vomiting. With prolonged daily administration it occurred in 65% of the patients and was often unresponsive to anti-emetics confirming the findings from our previous study [11]. In 14 patients drug intake was either discontinued or the dose was reduced because these symptoms were severe and we did not allow these side-effects to significantly interfere with nutritional intake as this was already impaired in most of our patients. We observed a significant correlation between side-effects and some pharmacokinetic parameters. In particular high plasma concentrations over subsequent days are associated with severe side-effects whereas absolute daily dose was not. This indicates that, apart from direct topical irritation of the gastrointestinal mucosa, there is probably also a systemic effect. Thus, alternative routes of drug administration may not circumvent the problem of nausea.

Severe clinical effects were reported with daily doses higher than 6 g or 80 mg/kg administered over a few subsequent days [4,9]. This was associated with high residual 24-h plasma levels and significant drug accumulation. It was suggested that accumulation can become of a particular concern when residual levels are higher than 300 nmol/ml [9]. With the 80 mg/kg dose we observed relatively low residual values after the first drug intake (mean 66 nmol/ml) which did not predict for accumulation or side-effects.

4.2. C_{max} and T_{max}

The nicotinamide plasma profiles obtained on the first treatment day show that, with a dose of 80 mg/kg, ade-

quate (>700 nmol/ml) levels could be obtained in all patients. Large inter-patient variations in C_{\max} were seen however. We used a liquid formulation which, on average, produced higher peak levels than tablets which were used in other studies [9,19] and also shorter T_{\max} with a mean of 0.83 h (SD ± 0.73) as compared to 2.1 h (SD ± 1.3) with tablets [9]. Apparently the drug is more rapidly absorbed when administered as a liquid formulation resulting in higher C_{\max} . Initially, irradiations were given 1.5 h after drug intake but when an interim-analysis showed this short T_{\max} , the interval was reduced to 1 h. Eighty-three per cent (33/40) of the patients had $T_{\max} \leq 1$ h and the inter-patient variability was less than with tablets which can be of advantage for the timing of irradiations. It has been suggested that absorption is also more rapid with higher peak concentrations when the drug is taken on an empty stomach [8,9]. Our patients were allowed to take a light meal at least 1 h before drug intake. We found it not advisable for them to skip or postpone meals as most have impaired nutritional intake because of the location of the tumour and, as treatment progresses, because of radiation mucositis.

4.3. Compliance

On the first 2 treatment days, when patients were hospitalised and nicotinamide was ingested in the presence of the nurse who was to obtain the plasma sample, nicotinamide levels at the time of irradiation were nearly always adequate. With progression of treatment there was an increasing proportion of values below 700 nmol/ml with some being very low or even zero. During the last week of the treatment nine of the 19 patients who continued nicotinamide intake until the end of the treatment and without a dose reduction had repeatedly low values at the time of irradiation. In some but not all cases this could be explained because the patient vomited shortly after nicotinamide intake. Alternatively, repeated administration of nicotinamide might possibly activate metabolic pathways resulting in a more rapid elimination of the drug. However, full kinetic profiles obtained in patients administered the same dose of nicotinamide daily, albeit over 12 days, showed no indication of this [9]. Furthermore, together with nicotinamide concentrations, we measured the plasma levels of the three major metabolites of nicotinamide (1-methyl nicotinamide, nicotinamide *N*-oxide, and 2-pyridones) in our patients at the start of treatment and 5–7 weeks later (data not shown). The metabolite levels gave no indication of a faster elimination of the drug with time, i.e. low levels of nicotinamide correspond with low levels of metabolites. We must therefore assume a decreased compliance, i.e. patients were not always taking the dose of nicotinamide they were supposed to. This may well be caused by the experience of side-effects and the bad taste which is a disadvantage of the liquid formulation. An additional argument is the often weak psychosocial status

of head and neck cancer patients with inadequate self-care including poor drug compliance. Other patient categories may do better in this respect.

4.4. Dose reduction

The high mean plasma concentrations shown in Fig. 5 suggest that a moderate dose reduction for those patients with severe adverse effects might still produce adequate plasma levels. All but one had mean plasma levels greater than 900 nmol/ml at the time of irradiations. It was shown that peak plasma levels are linearly dependent on the administered drug dose [8,18,19]. If levels of at least 900 nmol/ml can be obtained with 80 mg/kg, the expected minimum level after a 25% reduction of dose would be around 700 nmol/ml or slightly lower. We introduced a dose reduction to 60 mg/kg for patients who experienced severe nausea and/or intractable vomiting. Tolerance improved after this moderate reduction of dose in six of seven patients and they were able to continue nicotinamide intake until the end of the treatment. In five patients indeed plasma concentrations of about 75% of the initial values were obtained on some days but in only two patients this could be reproduced daily. This is probably not attributable to the reduced drug dose only but also to a reduced compliance as was argued above. Possibly, when the lower dose is administered from the start of treatment, better tolerance may also lead to improved compliance.

In rodent tumours, nicotinamide plasma levels between 700–1000 nmol/ml achieve significant increases in radiosensitization over that of carbogen alone [14]. In this current study we have demonstrated that these levels can be achieved in man with oral doses of 80 mg/kg but it is not always possible to reproduce such levels daily during a fractionated radiation treatment. Lower doses may improve tolerance and compliance but the question arises whether such doses can produce drug levels sufficient for significant radiosensitization. Further studies in experimental tumours are needed to determine the lower threshold dose for radiosensitization by nicotinamide. It may also be helpful to obtain a pharmacokinetic profile from each patient over the first 2 h after nicotinamide intake prior to the start of treatment for optimal timing such that patients are irradiated as close to their individual T_{\max} as possible. It has been shown that, with repeated drug administrations, the intra-patient variations of T_{\max} are small [9].

5. Conclusions

A nicotinamide dose of 80 mg/kg administered as a liquid formulation can produce peak plasma concentrations above the 700 nmol/ml level in all patients. Equivalent levels have been shown to be sufficient for radiosensitization in mice. However, due to adverse

effects and loss of compliance, these concentrations could not be reproduced during the full course of the 5- to 7-week treatment in a significant portion of the subjects. High plasma concentrations over subsequent days are associated with severe side-effects and a 25% dose reduction can improve tolerance. The question remains whether drug concentrations obtained after such dose reduction are still effective. Timing of irradiations may become more critical with the lower dose and further studies are needed to assess the threshold dose for radiosensitization by nicotinamide.

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