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NICOTINAMIDE PHARMACOKINETICS IN NORMAL VOLUNTEERS AND PATIENTS UNDERGOING PALLIATIVE RADIOTHERAPY

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The influence of nicotinamide formulation on absorption characteristics and incidence of adverse side-effects has been studied in normal volunteers and in patients undergoing radiotherapy. Escalating single or repeated oral doses of nicotinamide were administered in tablet or liquid form under fasting or non-fasting conditions. Drug absorption was slowed both by the presence of food in the stomach and by the administration of nicotinamide in tablet form compared with when it was dissolved in orange juice. Peak concentrations were generally slightly higher following the liquid preparation, but the incidence of adverse side-effects (chiefly nausea) was increased. A single dose of 9 g (88–97 mg/kg) nicotinamide in tablet form was well tolerated in two fasting normal volunteers, and in patients, doses of up to 133 mg/kg as tablets were tolerated twice/week for three weeks. Daily administration of 80 mg/kg nicotinamide was tolerated when given as tablets, but not in a liquid formulation. Neither the peak concentration nor the area under the concentration/time curve (AUC) of nicotinamide, nor the main metabolites of nicotinamide appeared to correlate with the incidence of toxicity.

Nicotinamide has been shown to radiosensitise murine tumours both after single radiation doses (1, 2) and in fractionated regimens (3, 4), although it is not a sensitiser using in vitro cell systems (2). Recent in vivo data would suggest that a dose of 100 mg/kg sensitises rodent tumours, and above this dose, little further increase in effect is seen, suggesting the existence of a threshold concentration for sensitisation (5, 6). Although the drug has been given clinically to relatively healthy patients in large doses of up to 12 g/day for prolonged periods in the treatment of a number of disorders (7–11), 6 g/day has been suggested as the maximum dose which could be safely administered over several months (11). Previous studies in man (5, 12) have shown that this dose gives peak plasma levels similar to those seen in mice after 100 mg/kg. The drug is now entering clinical trials, but while there is experimental evidence to suggest that sensitisation is maximal when radiation is given at the time of peak nicotinamide concentration (5), comparatively little is known about the factors which govern the rate at which the drug is absorbed, the influence of this upon the peak concentrations, and the maximum dose which can be given either as a single dose or on a daily basis. The aim of the present study was to investigate the tolerance of different formulations and to assess the factors which influence the maximum tolerated dose.

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Material and Methods

Studies were performed in both normal volunteers and patients receiving palliative radiotherapy. Nicotinamide (Cantassium Ltd, London) was administered orally using the two formulations described below. Blood samples were taken at intervals after administration of nicotinamide, the

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Table 1

Pharmacokinetics of nicotinamide in normal volunteers

Dose g	Vol No.	Sex wt kg	Dose mg/kg	Formulation	T_{max} h	C_{max} μmol/ml	$AUC_{(0-8\,h)}$ μmol/ml.h
6–9	1	M 103	88	Tablet fasted	1.3	1.00	6.29 (13.3, 0–24 h)
	2	M 93†	97	Tablet fasted	0.7	1.73	7.91 (16.6, 0–24 h)
	3	F 81.5	74	Tablet fasted	1.7	*1.05	6.43
	2	M 87†	69	Liquid fed	0.5	0.93	4.02 (6.51, 0–24 h)
	3		74	Liquid fed	0.75	1.08	6.41 (12.3, 0–24 h)
	4	M 76.2	79	Liquid fed	0.5	0.96	6.05
	6	F 58	103	Liquid fed	1.5	1.26	7.11
3	4		39	Liquid fed	0.5	0.43	2.40
	5	M 89	34	Liquid fed	2.0	0.34	1.60
	6		52	Liquid fed	1.13	*0.58	3.14
	4		39	Liquid fasted	0.75	0.55	2.68
	5		34	Liquid fasted	0.5	0.51	2.26
	6		52	Liquid fasted	1.25	0.64	3.25
	4		39	Tablet fed	3.0	0.38	2.05
	5		34	Tablet fed	3.0	0.28	1.42
	6		52	Tablet fed	1.75	*0.54	2.90
	4		39	Tablet fasted	1.5	0.28	1.81
	5		34	Tablet fasted	2.0	0.27	1.32
	6		52	Tablet fasted	0.88	*0.66	3.18

† Doses separated by >6 months.

* Where the concentration prior to the peak was <5% below the peak, the times and concentrations quoted are the respective means.

plasma separated within 2 h and stored at −20°C until analysis. In the normal volunteer studies, samples were typically taken every 15 min for the first 2 h, at 3 and 4 h, at 8 h and generally at 24 h. Patient samples were taken less frequently, but typically hourly over the first 3 hours. Concentrations of nicotinamide were determined in methanol extracts of plasma by high performance liquid chromatography (HPLC) using a reverse phase ion-pairing technique which separates nicotinamide from its major metabolites (13). Volunteers received single doses of nicotinamide up to 9 g, both after an overnight fast and following a light meal, to assess the effects of fasting upon the pharmacokinetic profile of orally administered nicotinamide. Two nicotinamide formulations were also evaluated in this series of volunteers: tablets (0.5 g) (a commercially available vitamin supplement), and a solution made up in orange juice (~150 ml) to disguise taste. Also studied were multiple administrations of nicotinamide to patients undergoing palliative radiotherapy to assess the influence of repeated doses upon the pharmacokinetics. The physical parameters of the normal volunteers and the patients are included in Tables 1 and 2 respectively. Pharmacokinetic parameters were calculated using computer-based weighted non-linear least squares regression analysis, and AUCs were determined using the trapezium rule.

Results

Two fasting normal volunteers (Nos. 1 and 2) received 9 g nicotinamide, administered as 0.5 g tablets, corresponding to doses of 88 and 97 mg/kg. No adverse symptoms were reported. Table 1 summarizes the pharmacokinetic parameters obtained in these and in one other subject (No. 3) following a lower dose of 74 mg/kg (6 g) under the same conditions. In both individuals receiving the higher dose there was relatively rapid absorption, with peak levels occurring within 75 min. The elimination half-lives for the linear (on a semi-logarithmic plot) portion of the curve (i.e. between 2 and 24 h) were calculated for

Table 2

Pharmokinetics of nicotinamide in patients

Patient no. (sex)	Dose g	wt kg	Dose mg/kg	Dose schedule	Formulation	T_{max} h	†C_{max} μmol/ml	†$AUC_{(0-24\ h)}$ μmol/ml.h	Toxicity
1(F)	6	>100	<60	× 2/week (Mon/Thurs) over 3 weeks	Tablet	2.3–2.4	0.81	13.1	None
2(F)	6	79	76	× 2/week (Mon/Thurs) over 3 weeks	Tablet	1–3	1.00	7.9	None
3(F)	6	45	133	× 2/week (Mon/Thurs) over 3 weeks	Tablet	2.2–3.1	1.77*	28.1	None
4(F)	5	59	85	1/day × 5 (first week)	Tablet	4	0.87	8.9	None
				1/day × 1 (second week)	Liquid	4	0.86	11.6	Day 2: severe anorexia moderate nausea itching mild headache
5(F)	6	81	74	1/day × 5 (first week)	Liquid	0.5–0.8	1.46	14.4	Day 4, 5: severe flushing
6(M)	5	63	79	1/day × 5 (first week)	Tablet	4	0.66	9.0	Day 4: mild anorexia, nausea
				1/day × 1 (second week)	Liquid	2	0.99	11.9	§

† After first dose.
§ Refused more than one dose because of unpalatability.
* Previous time point <5% less.

volunteers No. 1 and No. 2 to be 10.8 and 12.4 h respectively; after 24 h, elimination became more rapid. In the subsequent volunteer studies described below, also included in Table 1, we were primarily interested in the factors controlling drug uptake, and samples were generally only taken to 8 h. Because of this and the non-linear rapid terminal clearance of the drug, $AUC_{0-\infty}$ could not reliably be extrapolated. Previous experience with 2 and 4 g doses would suggest that the additional AUC beyond 8 h would be relatively small (12).

A pilot study in 3 patients receiving palliative radiotherapy was undertaken using the tablet formulation. Nicotinamide (6 g as 0.5 g tablets) was taken twice/week (Mondays and Thursdays) for 3 weeks. Blood samples were taken during the course of treatment, and the plasma concentrations for one of the patients are shown in Fig. 1; data for all three patients are summarized in Table 2 (Nos. 1–3). This, and all subsequent plots are on linear scales, since this facilitates seeing any differences in the rate or extent of absorption. As would be expected with the rapid terminal clearance of nicotinamide mentioned above, there was no accumulation of the drug when administration was separated by three to four days, although two out of the three patients showed significant residual drug remaining at 24 h (data not shown); the patient receiving the highest dose (No. 3) showed the highest peak plasma nicotinamide concentration (C_{max}) of 1.8 μmol/ml. In the two patients for whom complete profiles were obtained, peak plasma concentrations were quite reproducible, and there was no major change in the pharmacokinetics during the course of the treatment. The time for the drug concentration to reach a peak showed some inter- and intra-patient variation, ranging from one to three hours.

To investigate some of the factors that could influence the rate of absorption, plasma nicotinamide concentrations were determined in three volunteers (Nos. 4, 5 and 6)

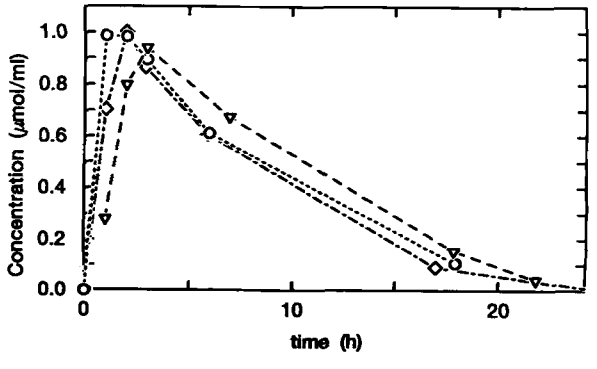


Fig. 1. Plasma concentrations of nicotinamide in a patient (No. 2) receiving repeated administrations of 6 g nicotinamide (76 mg/kg) as 0.5 g tablets; first dose ◇, third dose, ○, sixth dose, ▽;

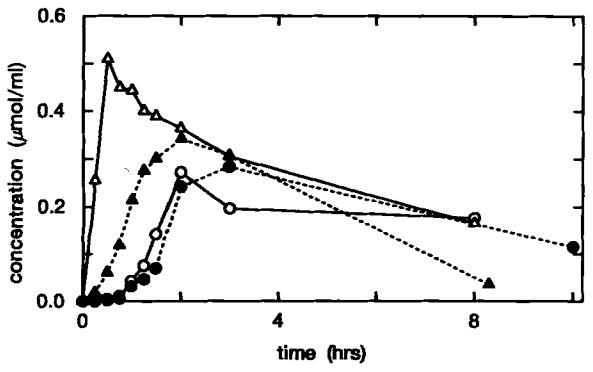


Fig. 2. Plasma concentrations of nicotinamide in volunteer No. 5 under different conditions after 3 g (34 mg/kg); liquid fasted △; liquid fed ▲; tablet fasted ○; tablet fed ● (see Table 1).

under either fed or fasted conditions, using a 3 g dose of either the liquid or tablet formulation (Fig. 2, Table 1). For each of the three subjects, under fed conditions, the time to peak concentration (T_{max}) was slowest with the tablet formulation, ranging from 1.8 to 3 h; fasting resulted in more rapid uptake, but still with considerable variability. With the liquid preparation, under fasting conditions, absorption was more consistent in all three volunteers with maximum concentrations being reached in 0.5–1.25 h. Only in one (No. 5) was the effect of food marked, with the time to peak increasing from 0.5 to 2 h.

In the light of the more rapid absorption of nicotinamide using the liquid formulation, the tolerance and plasma pharmacokinetics following a dose of 6 g nicotinamide, (our target dose), was investigated in 4 volunteers using this vehicle. These studies were performed with nicotinamide administration following a light breakfast.

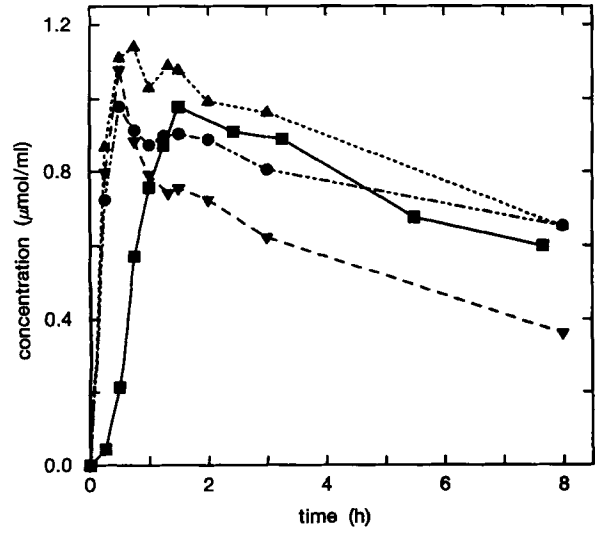
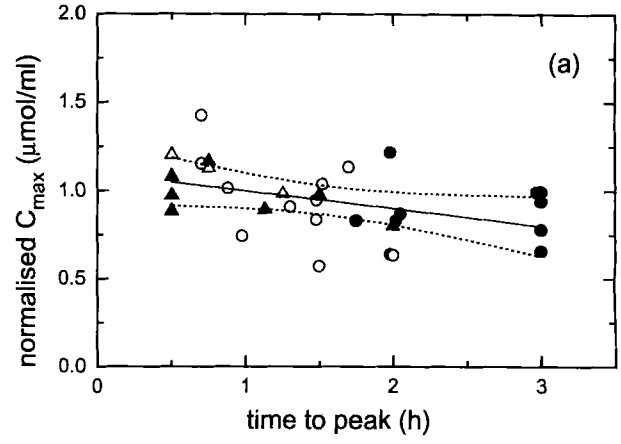


Fig. 3. Plasma concentrations of nicotinamide in four fed volunteers (No. 2, ▼; No. 3, ▲; No. 4, ●; No. 6, ■) after 6 g liquid formulation normalised to a dose of 80 mg/kg body weight.



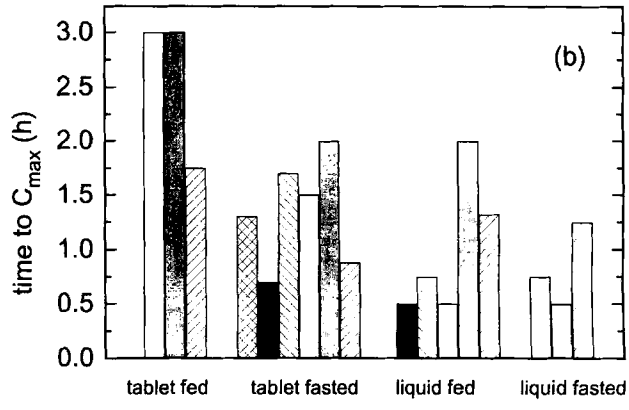


Fig. 4. Relationship between nicotinamide formulation, absorption and peak concentration in volunteers. (a): Effect of time to reach peak concentration against the peak concentration normalised to a dose of 80 mg/kg. Line is a best fit with 95% confidence limits to all the volunteer data from this paper and (12), intercept 1.10 ± 0.07 (std. dev.), slope -0.100 ± 0.040, correlation coefficient 0.42, $p = 0.02$. tablet fasted ○; tablet fed ●; liquid fasted △; liquid fed ▲. (b) Effect of drug formulation on rate of nicotinamide uptake in normal volunteers. ■ No. 1, ■ No. 2, ▧ No. 3, ▤ No. 4, ▩ No. 5, ▨ No. 6.

The plasma pharmacokinetics are summarized in Table 1, and illustrate the rapid uptake of the nicotinamide in three out of four subjects, the concentration peaking within 0.75 h; in the fourth, the peak was not reached until after 1.5 h. Although the subject showing the slowest absorption appeared to give rise to the highest level, adjusting for the differences in body weight (Fig. 3) revealed curves which suggested that a delay in reaching the peak may result in some loss in the maximum concentration achievable. In Fig. 4a plasma concentrations, normalized to that which would have been obtained by a dose of 80 mg/kg, classified according to nutritional status and formulation, are plotted against the time to peak concentration for all the volunteer data in this paper, and also our previously published work (12). In general more rapid absorption gave rise to higher peak concentrations, underlining the importance of achieving rapid absorption in order to at-

Table 3

Effect of formulation and nutritional status on uptake of nicotinamide

	Tablet		Liquid	
	Fed	Fasted	Fed	Fasted
Half-life of absorption (h)	0.145 ± 0.017†	0.183 ± 0.013	0.125 ± 0.009	0.142 ± 0.021
Lag time (h)	0.924 ± 0.010	0.174 ± 0.006*	0.014 ± 0.003*	0.174 ± 0.009*

Values quoted are the weighted means of the individual non-linear regression fits.
† Standard error.
* significantly different from tablet fed ($p < 0.05$). All other values are not significantly different from each other.

tain the maximum plasma level. Fig. 4b highlights the role of gastric content and drug formulation on the rate of nicotinamide uptake for the data in Table 1, while Table 3 shows the relative importance of the delay in absorption and the subsequent rate of uptake of nicotinamide for the same data.

Some nicotinamide-induced toxicity in the form of nausea was observed in two of the four volunteers (Nos. 4, and 6) receiving the liquid formulation. The concentrations of the main metabolites of nicotinamide (nicotinamide N-oxide, 1-methyl nicotinamide, and the 2- and 4-pyridones) were compared but no significant differences were observed between volunteer No. 3 who exhibited no toxicity and No. 4 who experienced nausea which persisted for some hours (data not shown). This toxicity with 6 g nicotinamide in single doses using the rapidly absorbed liquid formulation suggested that we were close to the maximum tolerated dose (MTD). A fixed dose of 80 mg/kg, which corresponds to 5.6 g for a 70 kg person, was therefore chosen for further studies in patients. A planned regimen of 10 doses over 12 days (1 dose/day over 5 days with either tablets or liquid followed after a 2 day break by the alternative formulation) was therefore initiated. Because of the size of tablet available to us (0.5 g), the actual dose administered ranged from 74 to 85 mg/kg (Table 2). This regimen was given to three patients but none of them completed the schedule because the liquid formulation was not tolerated on a daily basis.

Patient No. 4 (Fig. 5a) took 5 daily doses of tablets with no significant side-effects. Although 24 h after the first dose there was no detectable drug, by day 4 there was some residual drug from the previous day which resulted in a higher peak concentration. After the weekend there was no detectable drug prior to the administration of nicotinamide in orange juice. Initial absorption appeared rapid, but peak concentrations were not seen till 2–4 h. The patient refused to take further doses owing to nausea.

Patient No. 5 (Fig. 5b) took nicotinamide in liquid form for 5 days. The drug was rapidly absorbed, and high concentrations were observed with some residual drug at 24 h even after the first dose. The drug appeared fairly well

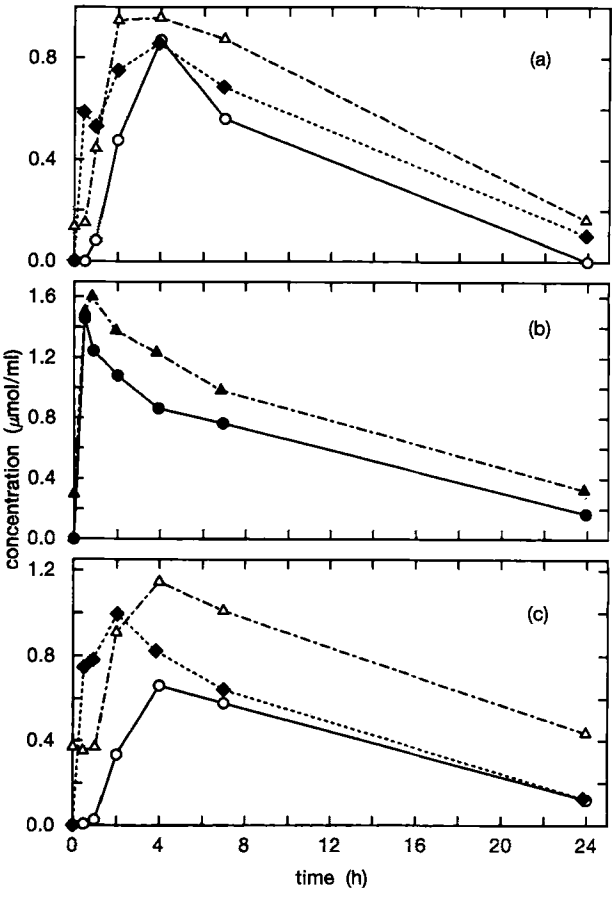


Fig. 5. Plasma concentrations of nicotinamide in three patients (a, No. 4; b, No. 5; c, No. 6 in Table 3) after 80 mg/kg nicotinamide daily for 5 days/week. week 1 day 1 (●, ○); week 1 day 4 (▲, △); week 2 day 1 (◆). Open symbols, tablets, closed symbols, liquid formulation.

tolerated, but on day 4 and particularly day 5, the patient experienced severe flushing ~15–30 min after the drug which could have been associated with these very high levels; the plasma AUC was also higher than in the other patients (Table 2). Since this side-effect had not been previously seen in this study, we did not continue administration of this formulation to this patient. She was unable

to swallow because of her advanced malignancy, and so could not be given tablets.

Patient No. 6 took tablets for the first week without problem. Peak plasma concentrations were not reached until 4 h after administration (Fig. 5c); this slow absorption resulted in significant residual drug at 24 h, which after 3 doses of nicotinamide, was >0.4 μmol/ml. Despite this, the peak plasma level did not reach that seen for patient No. 5, possibly because of the slower absorption of the tablets compared to the liquid. In the second week, the orange juice preparation was well absorbed, although again the nicotinamide did not peak until 2 h after administration. However, this formulation was not acceptable to the patient and no further drug was given.

Discussion

The timing of administration of a sensitizer has been shown in mice to be an important factor in maximizing the radiosensitizing effect (5). The human data presented here show there can be considerable variation in T_{max}, both in normal volunteers and patients, which may be dependent on both food intake (5, 12) and drug formulation, although there are significant individual variations (Fig. 4b; Tables 1 and 2). The tablets and the presence of food in the stomach gave the slowest release, with a mean lag time of $\sim$1 h before absorption began (Table 3), but with individual variation between volunteers, even under fasted conditions. The presence of even a light meal can clearly have quite a marked effect, but it would be difficult to require that all patients were fasted before nicotinamide.

The previously published data (5) using capsules in fasted volunteers gave somewhat higher peak levels with relatively fast absorption compared to our tablet data (this paper, (12)), suggesting that although fasting is undoubtedly an important factor, the tablet formulation which we have used was not optimal with respect to achieving reproducible and rapid nicotinamide uptake. In this study, the liquid drug preparation, which in general showed faster uptake (Fig. 4b), was associated with greater toxicity, and it is noteworthy that using nicotinamide in capsules, all four individuals studied by Horsman et al. (5), where plasma concentration peaked in less than one hour, suffered some toxicity at doses of 76–92 mg/kg, while in our previous study using tablets only one out of four showed any toxicity at up to 78 mg/kg (12) and in this present study using tablets at 88–97 mg/kg, no toxicity was observed. It seems possible that the rapid attainment of high concentrations contributes in part to the nausea seen with nicotinamide, but other factors seem to be involved: the nausea persists for some hours after the peak plasma concentration is attained, and volunteers Nos. 3 and 4 received a similar dose of the liquid formulation but showed marked differences in toxicity despite having comparable plasma concentrations, T_{max} and AUCs.

In the patient study, there appeared to be some correlation between overall exposure to nicotinamide and toxicity, since the more rapid absorption conferred by the liquid formulation in the patients (Fig. 5) also gives rise to larger AUCs (Table 2), perhaps because of the non-exponential elimination which results in higher concentrations being more slowly cleared. However, in the study as a whole, no clear correlation between the incidence or severity of the side-effects and peak level, time to reach the peak, or metabolism of nicotinamide could be discerned.

We are currently investigating the use of alternative tablets with more rapid release characteristics since the liquid formulation of nicotinamide was unsatisfactory. Although one patient took this preparation for 5 days, the flushing seen on days 4 and 5 led us to discontinue treatment with this subject. The other two patients successfully took 80 mg/kg in tablet form for 5 days, but even after a weekend without treatment, found the nicotinamide dissolved in orange juice unacceptable. One other study has been published using a liquid formulation (14), where nausea and vomiting were also a problem, only partially alleviated by the use of a naso-gastric tube; however, this practice is not common in the U.K. Subsequently, we have carried out limited investigations with metoclopramide, which acts primarily on the gastro-intestinal tract, and dexamethasone or ondansetron, which act centrally, to control the nausea. Despite the late onset and persistence of the symptoms, which suggest an effect on the central nervous system rather than on the gastrointestinal tract, none were of benefit in reducing toxicity. In both volunteers and patients the majority of the toxicity experienced was gastro-intestinal with nausea being the main dose-limiting symptom; flushing occured in only one patient and in our experience this is not a frequent side-effect.

The present study confirms a linear relationship between nicotinamide dose, expressed on a mg/kg basis, and peak plasma concentration (Fig. 6) (5, 12); also the non-linear (more rapid) clearance of nicotinamide when the concentration falls below 0.1 μmol/ml noted previously (12). Animal data suggest that plasma levels of at least 0.7–1.0 μmol/ml nicotinamide are required to achieve tumour sensitization in fractionated radiotherapy (6). A comparison of peak plasma levels in the current series of volunteers with previously published data (5, 12), indicates that this concentration is readily achievable in humans with single oral doses above 60 mg/kg. As could be expected, generally the earlier the peak was reached the higher the concentration achieved. In normal volunteers, doses up to 9 g ($\leqslant$97 mg/kg) nicotinamide as a single dose can be administered without undue toxicity, giving a peak concentration as high as 1.7 μmol/ml. In patients receiving repeated administration of nicotinamide, doses of $\leqslant$85 mg/kg gave variable but adequate peak levels (mean 1.07 μmol/ml $\pm$ 0.32 (SD), range 0.66–1.60 μmol/ml) (Fig. 5). Higher doses than this are likely to lead to drug

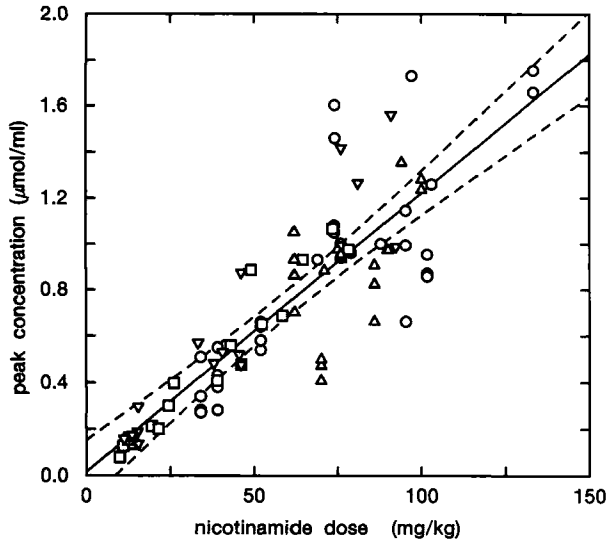


Fig. 6. Effect of nicotinamide dose on peak plasma concentrations. Line is best fit with 95% confidence limits, intercept 0.017 ± 0.054 (std. dev.), slope 0.0120 ± 0.0008, correlation coefficient 0.858, $p = 0.0001$. ○, this work; □, Stratford et al. 1992 (12); ▽, Horsman et al. 1993 (5), △, Hoskin et al. 1995 (15).

accumulation, requiring careful monitoring of plasma concentration, with dose adjustments which may be difficult to implement clinically.

Because of the variability in T_{max} and the relatively long half-life of nicotinamide, it may be advisable to extend the interval between nicotinamide and radiotherapy from the 1.5 h previously recommended and currently used in clinical trials (4, 14), to 2 h. Although this may be beyond the maximum plasma concentration in some patients, in the absence of a rapid method for determining this interval in patients, 2 h looks to be a better compromise at present. In very few cases, where the nicotinamide was taken up rapidly, would the plasma level have fallen by more than 10% by this time, while in only two out of the 15 profiles shown here where absorption was slow, was the concentration significantly higher at 4 h compared with 2 h.

In conclusion, a dose of 80 mg/kg administered as tablets 2 h before radiotherapy, preferably under fasting conditions, should achieve effective plasma levels with few side-effects. During fractionated radiotherapy residual plasma levels should however be monitored and the dose reduced if there is an indication of drug accumulation, especially in patients with renal and or hepatic dysfunction.

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