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The bioavailability of sustained release nicotinic acid formulations

P. J. NEUVONEN, L. ROIVAS, K. LAINE & O. SUNDHOLM
Department of Pharmacology, University of Turku, SF-20520 Turku, Finland

1 The bioavailability of three nicotinic acid formulations was investigated in a randomized cross-over study.
2 Single doses of nicotinic acid (500 mg) were given to seven healthy volunteers. The concentrations of nicotinic acid and its main metabolite nicotinuric acid were measured in serum up to 8 h and in urine up to 24 h.
3 The relative bioavailability of unchanged nicotinic acid from two slow release formulations compared with a rapid-release form was only 1% and 25%, respectively. Relative values of AUC (0,8 h) for nicotinuric acid were 15% and 58%, and relative urinary recoveries were 18% and 59%, respectively. Facial flushing was less when slow release formulations were used.
4 The bioavailability of unchanged nicotinic acid is low and the ratio of nicotinuric acid to nicotinic acid in serum and urine is high when slow release formulations are used.

Keywords nicotinic acid nicotinuric acid slow release formulations bioavailability

Introduction

In high doses the vitamin nicotinic acid (niacin) is an effective antihyperlipidaemic agent. It inhibits hepatic cholesterol synthesis and the catabolism of high density lipoproteins. In daily doses of 3 to 6 g, nicotinic acid decreases plasma concentration of free fatty acids, low density lipoproteins and very low density lipoproteins. However, flushing of the face and neck occurs in most patients with implications for compliance.

Nicotinic acid is rapidly absorbed and metabolised after oral dosing, with an elimination half-life ranging from 20 to 45 min. Flushing seems to be associated with the rapid rise in plasma drug concentration and not with high concentrations as such (Svedmyr *et al.*, 1969). Various sustained-release preparations of nicotinic acid have been developed in an attempt to prevent the side-effects associated with the rapid drug absorption. Nevertheless serious hepatotoxic reactions have been reported in some patients receiving such preparations, despite having tolerated conventional dosage forms (Henkin *et al.*, 1990; Hodis, 1990). The potential hepatotoxicity associated with the use of sustained release preparations, their poorly characterized bioavailability and the dose-dependency of nicotinic acid kinetics (Mrochek *et al.*, 1976) prompted us to compare the bioavailability of three formulations with different rates of nicotinic acid release *in vitro*.

Methods

Subjects

Seven healthy volunteers, five males and two females, aged 20–32 years, and weighing 63–78 kg, participated in the study. The results of physical examination and routine laboratory tests before and after the study were normal. All subjects gave their written informed consent prior to the study.

Study design

The study protocol was approved by the local ethics committee. A randomized cross-over study design was employed with three phases at intervals of 1 week. The subjects were under direct medical supervision for the first 2 h after drug ingestion.

The nicotinic acid formulations I and II were experimental preparations (I = nicotinic acid in hard gelatine capsules; II = nicotinic acid preadsorbed onto a matrix and packed in hard gelatine capsules). Formulation III was a commercial formulation (Lipolyt Retard 500 mg, Lot OF4, Leiras Pharmaceuticals Ltd, Turku, Finland).

At 08.00 h after an overnight fast each subject ingested a single dose of 500 mg nicotinic acid as formulation I, II or III. The volunteers fasted for 3 h after the drug intake. Coffee and tea were not permitted until after 4 h. The

Correspondence: Professor Pertti J. Neuvonen, Department of Pharmacology, University of Turku, Kiinamyllynkatu 10, SF-20520 Turku, Finland

drugs were ingested with 150 ml of water and the subjects remained supine for the following 2 h. Venous blood samples (8 ml) were taken at 0, 0.25, 0.5, 0.75, 1, 1.5, 2, 3, 4, 6 and 8 h after drug ingestion. Serum was separated within 30 min for measurement of nicotinic acid and its main metabolite nicotinuric acid. Urine was collected from four subjects in 0–4, 4–8 and 8–24 h fractions. The serum and urine samples were stored at −20° C until analyzed.

Assay methods

Concentrations of nicotinic acid and nicotinuric acid were measured using modifications of reported h.p.l.c. methods for serum (Hengen *et al.*, 1978) and urine (Figge *et al.*, 1988). To 0.5 ml of serum 0.05 ml distilled water and 3 ml acetone were added. After agitation with a Vortex mixer, the tube was centrifuged and 3 ml of the supernatant was transferred to a second tube containing 3 ml chloroform. After agitation and centrifugation 0.3 ml of the supernatant was evaporated using a centrifugal evaporator and the residue was dissolved in water. The mobile phase consisted of water:methanol (4:1) with tetrabutylammonium bromide (30 mmol l^{-1}) as ion-pair reagent. The mobile phase for the urine samples consisted of water:methanol:acetonitrile (18:1:1) with tetrabutylammonium dihydrogenophosphate (20 mmol l^{-1}) as ion-pair reagent. The column used was a μ-Bondapak C18 with a GuardPak precolumn (Waters Ass, Milford, USA). The recoveries of nicotinic acid and nicotinuric acid were about 75%. The assay limits for nicotinic acid and nicotinuric acid were 0.1 mg l^{-1} in serum and 0.5 mg l^{-1} in urine. The interassay coefficients of variation were less than 10%.

Determination of bioavailability

Peak concentrations (C_{max}) and times to peak (t_{max}) were the observed values. The areas under the serum drug concentration-time curves (AUC) from 0 to 8 h were calculated using the linear trapezoidal rule. Cumulative 24 h urinary recoveries of nicotinic and nicotinuric acids were determined.

Side effects

The intensity of flush was registered at the times of blood sampling on an arbitrary scale (0 = no effect, 1 = a slight flushing on the face, 2 = a moderate flushing and pruritus of the face and neck, 3 = an intensive flushing and pruritus of the face, arms and trunk). The observer was blind to the formulation a particular subject had taken but the blindness was compromized by the intense flushing seen after formulations I and II.

In vitro *studies*

The release of nicotinic acid from the formulations was determined *in vitro* by placing them in 100 ml 0.05 M phosphate buffer (pH 7) at 37° C with continuous mixing. Samples of 5 ml were drawn from the medium through filters every 2 min, replaced with fresh medium and analyzed spectrophotometrically. The cumulative release of nicotinic acid from the formulations was calculated and the time for 50% release was determined. Each formulation was tested three times.

Statistics

Means ± s.e.mean are given. The bioavailability parameters were analyzed statistically by two-way analysis of variance. Whenever significant differences between the products were found, the Tukey test was applied to find the sources of the difference. The intensity of flushing was analyzed by the Wilcoxon matched-pairs signed-ranks test.

Results

Pharmacokinetics

There were considerable differences between the formulations with respect to their bioavailability (Figure 1, Table 1). The concentrations of serum nicotinic acid were significantly ($P < 0.05$) higher from 45 min to 2 h after the ingestion of formulation I than after II or III. Both the C_{max} and AUC of nicotinic acid were, on average, about 70 times greater after formulation I than III ($P < 0.01$), and about four times greater after I than II ($P < 0.05$). The value of t_{max} was longer after formulation III than after I or II but the difference was not significant statistically.

The serum concentrations of nicotinuric acid were lower ($P < 0.05$) after ingestion of formulation III than after I or II but the differences were not as striking as those in nicotinic acid concentrations (Figure 1). Values

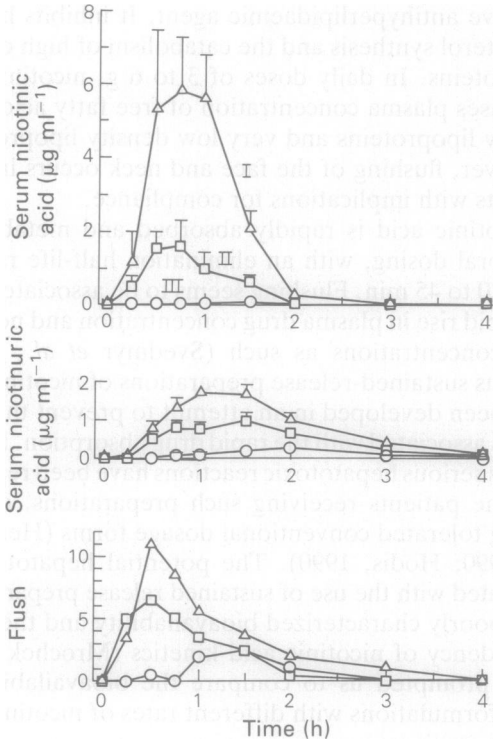

Figure 1 Serum concentrations of nicotinic and nicotinuric acids (means ± s.e. mean, $n = 7$) and the intensity of flush (sum of data for seven subjects) after single doses of nicotinic acid 500 mg in formulations I (Δ), II (□) and III (○).

Table 1 Peak concentrations (C_{max}), times to peak (t_{max}) and area under the concentration-time curve (AUC) of nicotinic acid and nicotinuric acid in serum (mean ± s.e. mean) and the intensity of flush (median and range) after single doses of 500 mg nicotinic acid given as formulations I, II and III to seven subjects

	Formulation I	*Formulation II*	*Formulation III*
Nicotinic acid			
C_{max} (μg ml^{-1})	7.4 ± 2.0	2.1 ± 0.6*	0.08 ± 0.02**
t_{max} (h)	0.8 ± 0.1	0.8 ± 0.2	1.1 ± 0.2
AUC (μg ml^{-1} h)	6.4 ± 1.6	1.6 ± 0.5**	0.1 ± 0.03**,^{0}
Nicotinuric acid			
C_{max} (μg ml^{-1})	1.8 ± 0.3	1.0 ± 0.2*	0.3 ± 0.1**,^{0}
t_{max} (h)	1.2 ± 0.1	1.3 ± 0.2	1.6 ± 0.2
AUC (μg ml^{-1} h)	3.3 ± 0.4	1.9 ± 0.3*	0.5 ± 0.2**,^{0}
Flush			
Peak intensity	2.0 (0.5–2.5)	1.5 (0.5–2.0)	0.5 (0–1.5)
t_{max} (h)	0.5 (0.5–0.75)	0.5 (0.25–1.5)	1.25 (0.5–2.0)*,^{0}

Significant differences from formulation I (* $P < 0.05$, ** $P < 0.01$) and between formulations II and III (^{0} $P < 0.05$) are indicated.

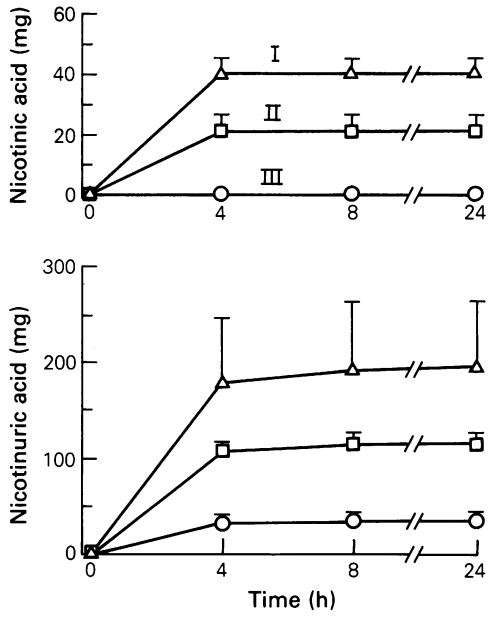

Figure 2 Cumulative urinary excretion of nicotinic and nicotinuric acids after single doses of 500 mg nicotinic acid in formulations I (Δ), II (□) and III (○). Means ± s.e. mean, $n = 4$.

of C_{max} and AUC were about six times greater after formulation I than after III ($P < 0.01$) and nearly two times greater after I than after II ($P < 0.05$).

The 24 h cumulative urinary excretion of unchanged nicotinic acid after formulation I was 40 ± 5 mg and after II it was 21 ± 6 mg. No unchanged nicotinic acid was found in urine after formulation III. The cumulative excretions of nicotinuric acid after formulations I, II and III were 193 ± 72 mg, 114 ± 12 mg, and 34 ± 9 mg, respectively (Figure 2).

Side effects

With formulations I and II flushing was obvious within 15 min and the peak intensity occurred at about 30 min (Figure 1, Table 1). Even after ingestion of formulation III, a recognizable flush appeared in all but one subject within 1–2 h, although the nicotinic acid concentrations in serum were hardly detectable. After the intake of formulations II and III but not after formulation I, one of the seven subjects complained of gastro-intestinal discomfort at the t_{max} value of nicotinic acid.

In vitro *studies*

The times for 50% dissolution of nicotinic acid at pH 7 from formulations I, II and III were 10 min, 2 h and 5 h, respectively.

Discussion

The absorption of unchanged nicotinic acid from sustained-release formulations has been poorly characterized. Some of the early studies used nonspecific analytic methods, and in some bioavailability studies aspirin had been given prior to nicotinic acid in order to minimize flushing (Figge *et al.*, 1988). Aspirin, however, greatly impairs the conjugation of nicotinic acid to nicotinuric acid (Ding *et al.*, 1989) causing an increase in the bioavailability of nicotinic acid. We have used specific h.p.l.c. methods which allow the determination of nicotinic acid and its main metabolite nicotinuric acid in serum and urine, and the subjects were not given aspirin prior to nicotinic acid ingestion.

The relative bioavailability of unchanged nicotinic acid from the commercial retard formulation (III) was only about 1%, compared with plain nicotinic acid (I). This low bioavailability was indicated both by the AUC of unchanged nicotinic acid and by a negligible urinary excretion. The bioavailability of the experimental retard formulation (II) was considerably higher but so also was the rate of nicotinic acid release *in vitro*. The differences between the formulations were less striking when the concentrations of the main metabolite were compared. After ingestion of the commercial retard formulation (III), the AUC and cumulative excretion of nicotinuric acid were 15% and 18%, respectively, of those after plain nicotinic acid (I). Thus, the contribution of nicotinuric acid to total drug absorption (nicotinic acid + metabolites) was much higher than from the plain formulation.

The results are consistent with dose-dependent first-pass metabolism of nicotinic acid. Thus, when the oral dose is low, nicotinic acid is metabolized almost completely and no unchanged drug can be detected in plasma or urine (Mrochek *et al.*, 1976). Conversely, when the rate of gastrointestinal absorption of nicotinic acid is slow, as from the retard formulation in the present study, nicotinic acid appears to undergo extensive first-pass metabolism, either in the gut or in the liver, resulting in very low systemic concentrations of parent drug but high metabolite-nicotinic acid ratios in plasma and urine.

Bechgaard & Jespersen (1977) have studied the absorption of nicotinic acid after instillation into the stomach and into the upper small intestine. The absorption rate from a 200 mg solution was at least as rapid

from the small intestine (peak plasma concentration at 5–10 min) as from the stomach (peak 10–20 min). They concluded that 'the physiological basis for the development of a sustained-release nicotinic acid preparation is established'. It should be emphasized, however, that what they demonstrated was the rapid absorption of the aqueous nicotinic acid from the small intestine and not the bioavailability of a sustained release formulation.

Using intravenous infusions, Svedmyr *et al.* (1969) have shown that flushing was present only while the plasma concentration of nicotinic acid continued to increase and disappeared when the concentration reached a constant, but in other respects active, pharmacological level. Similarly, in the present study, flushing was at its maximum during the time of the rapid increase in serum nicotinic acid concentration independent of the absolute concentrations, and started to disappear even before peak drug concentration was attained.

Hepatotoxic reactions have occurred in many subjects who have used sustained-release preparations some of whom have tolerated conventional nicotinic acid preparations without any problem (Christensen *et al.*, 1961; Henkin *et al.*, 1990; Hodis, 1990). The first-pass metabolism of nicotinic acid seems to be more extensive when sustained release formulations are ingested. Thus, it would appear that hepatotoxicity might be associated with extensive and prolonged metabolism of nicotinic acid.

Gastrointestinal discomfort has also been associated with the use of sustained-release formulations (Knopp *et al.*, 1985). In the present study, one subject had gastrointestinal pain when given the sustained release formulations but not when receiving the conventional capsule.

A serum concentration of nicotinic acid between 0.5 and 1 $\mu g\ ml^{-1}$ has been associated with efficient lipolysis (Carlson *et al.*, 1968; Svedmyr *et al.*, 1969) but the correlation between concentration and clinical antihyperlipidaemic effect is controversial (Kruse *et al.*, 1979). Nicotinic acid may exert part of its antihyperlipidaemic effect during the first-pass in the gut and liver (Cayen, 1985) and, despite their low systemic bioavailability, retard formulations may not be as deficient as indicated by the low bioavailability of nicotinic acid. On the other hand, at least in some clinical studies, the efficacy of a sustained release capsule has been less than that of the plain formulation (Knopp *et al.*, 1985).

In conclusion, the bioavailability of nicotinic acid from sustained release formulations is very low. Owing to extensive and dose-dependent first-pass metabolism, it may not be possible to develop a product with slow absorption and high bioavailability of nicotinic acid. However, knowledge of the extent of bioavailability alone may be insufficient to characterize the clinical performance of nicotinic acid formulations.

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