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The Effect of the Mode of Administration on the Hypolipidaemic Activity of Niacin: Continuous Gastrointestinal Administration of Low-dose Niacin Improves Lipid-lowering Efficacy in Experimentally-induced Hyperlipidaemic Rats

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Abstract

The effect of different routes and modes of administration of niacin (nicotinic acid) on its hypolipidaemic activity has been evaluated. Our working hypothesis was that the major sites of niacin action are located presystemically (i.e. in the gut wall or the liver, or both) which would make niacin a gastrointestinal drug. For such drugs continuous administration to the gastrointestinal tract is expected to augment their efficacy compared with bolus oral administration or parenteral administration.

The hypothesis was examined in two rat models of experimentally induced hyperlipidaemia—Model A, based on a cholesterol-enriched diet, and Model B, in which acute hyperlipidaemia is induced by intraperitoneal administration of triton (225 mg kg^{-1}). Continuous administration of niacin into the duodenum at 1·66 mg h^{-1} (total dose 40 mg kg^{-1} day^{-1}) for up to 7 days (Model A) or at 2·22 mg h^{-1} over 18 h (Model B) had significantly greater lipid-reducing effects both on total cholesterol and on triglyceride levels (15–25%) and elevation of high-density lipoprotein (HDL) cholesterol levels than did bolus oral administration of the same dose. Continuous duodenal infusion of niacin also had an even greater lipid-reducing effect than continuous intravenous infusion of the drug at the same rate and dose.

The results indicate that the site(s) of action are located presystemically and that continuous duodenal administration of a low dose of niacin (40 mg kg^{-1}) has a greater lipid-lowering effect than a higher dose (200 mg kg^{-1}) administered by peroral bolus administration. These conclusions were validated by administration of a specially designed niacin sustained-release matrix tablet formulation that was non-invasively administered to hyperlipidaemic rats. The hypolipidaemic activity of the sustained-release tablet was of similar magnitude to that resulting from continuous duodenal administration, thus providing a pharmacodynamic rationale for this mode of administration.

Niacin, one of the oldest hypolipidaemic drugs available, has been in clinical use for over 40 years (Altschul et al 1955; LaRosa 1982; DiPalma & Thayer 1991; Drood et al 1991). It is used to reduce cholesterol and triglyceride levels and, in particular, to elevate high-density lipoprotein (HDL) cholesterol levels (Grundy et al 1981; LaRosa 1982; Luria & Sapoznikov 1993). Certain side-effects, mainly flushing and hepatotoxicity, are major drawbacks of niacin therapy (Luria 1988; Etchason et al 1991; Keenan et al 1991). Although slow-release administration of niacin can reduce flushing (Knopp et al 1985; Lavie et al 1992) it can increase hepatotoxicity (Henkin et al 1991; Dalton & Berry 1992; Rader et al 1992; Lawrence 1993). The general aim of this investigation was to assess the effect of the mode of administration of low-dose niacin on the magnitude of its hypolipidaemic effect. Hitherto, the consequences of reducing the

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rate of drug release and the importance of drug formulation on the pharmacodynamics of drugs in general, and niacin in particular, have received little attention (Castaneda-Hernandez et al 1994). Despite its long clinical use, the mechanism of action of niacin is uncertain (Mckenney et al 1994) and the location of its main sites of action remains unclear.

We hypothesized that niacin is a gastrointestinal drug, i.e. a medication that has one or more sites of action (biophase) within the gastrointestinal tract (i.e. the gut wall), the portal vein or the liver. Because these sites can be reached directly after oral administration of a drug, it was expected that continuous administration of a drug to the gastrointestinal tract at a slow rate would improve the magnitude of the pharmacological response. Because this mode of administration results in relatively low systemic concentrations of the drug, with a drug such as niacin it is expected to reduce the incidence of flushing. Although slow-release preparations of niacin have been associated with hepatotoxicity, this study seeks to ascertain if a much lower dose might be administered by this route and whether this lower dose might serve to minimize the risk of hepatotoxicity. This is particularly relevant because recent clinical evidence suggests that the hepatotoxicity of niacin is dose-dependent (Brown et al 1997). In this study we have compared the activity after continuous intraduodenal infusion with that after other modes of administration, and validated the results by comparing them with those observed after administration of an oral slow-release drug delivery system that is designed to release its content over 8–10 h, the expected transit time in the gastrointestinal tract of the rat.

Materials and Methods

Evaluation of hypolipidaemic activity

Evaluation of the antilipidaemic activity of niacin was performed in two rat models of elevated total cholesterol and triglyceride levels. The effective dose of niacin in man is generally 1·5–6 g day^{-1}; in hyperlipidaemic rodents the equivalent dose was found to be 100–900 mg kg^{-1} day^{-1} (Shurr et al 1971; Ohata et al 1983; Olivier et al 1988; Krishnamurthy & Thapar 1991). In the current investigation the dose of niacin used (40 mg kg^{-1} day^{-1}) was relatively low in comparison with the regular dose (200 mg kg^{-1} day^{-1}).

Rats were obtained from the animal breeding unit of the Hebrew University Hadassah Medical School. They were housed individually with food and water freely available in a temperature-, light-, and humidity-controlled room.

Model A. Male Sabra rats, 200–230 g, were given a cholesterol- and coconut-rich diet containing 1·5% cholesterol, 0·5% cholic acid and 10% coconut oil in ground standard chow. The rats were fed the lipid-rich diet for 10 days and niacin administration was initiated on the fourth day of the enriched diet. The rats were divided into groups of 10. Two groups received peroral (stomach tube) niacin at 40 mg kg^{-1} day^{-1} once a day or in two doses of 20 mg kg^{-1} at 0800 h and 2000 h; another group received the dose by continuous infusion into the duodenum (2 cm below the portal sphincter) by means of an Alzet osmotic pump (Alza, Palo Alto, CA) implanted, under ether anaesthesia, under the skin in a dorsal position. Other groups received the drug by continuous infusion to the jugular vein. Respective control groups (10 rats each) received the equivalent volume of the vehicle (buffer carbonate solution). The effect of slow-release niacin tablets was assessed by giving the rats slow-release matrix tablets containing 4·3 mg niacin or placebo (controls) twice daily for 3 days (2 × 20 mg kg^{-1}, slow-release; equivalent to 40 mg kg^{-1} day^{-1}). Blood samples (0·7 mL) were taken from the tail under light ether anaesthesia 3 and 7 days after initiation of niacin administration.

The samples were held at room temperature for 30 min and then centrifuged at 4000 rev min^{-1}. The plasma was separated and stored frozen (−20°C) pending assay. Total cholesterol, triglycerides, HDL cholesterol and aspartate transaminase (AST) (for liver function assessment) were determined by means of the Kodak Ek, Clinical Chemistry Products dry method chemistry autoanalyser (Young et al 1975; Warnick et al 1983).

Model B. To examine the effect of niacin in an intense hyperlipidaemic model, male Lewis rats, 280–350 g, received an intraperitoneal injection of triton WR-1339 (Tyloxapol; Sigma, St Louis, MO) 225 mg kg^{-1} in normal saline solution. After the triton injection the rats were divided into groups of 10 that received different doses of niacin by different modes of administration. The groups were: one dose of 40 mg kg^{-1} or two doses of 20 mg kg^{-1} by either peroral administration or continuous duodenal infusion; 200 mg kg^{-1} either perorally or by continuous duodenal infusion; or as a 200 mg kg^{-1} slow-release matrix tablet (each rat received two tablets each containing 30 mg niacin, equivalent to 200 mg kg^{-1}). The control groups received the vehicle solution (carbonate–bicarbonate buffer solution, pH 10) either perorally

or by continuous duodenal infusion, or a slow-release placebo tablet. During the experimental period the rats were deprived of food but not water.

To administer the drugs continuously to unanaesthetized (and unrestrained) rats, a polyethylene cannula was implanted into the rats' duodena under anaesthesia, and exteriorized at the dorsal neck, 3 days before the pharmacodynamic experiment. The polyethylene cannula was protected by a light metal spring to prevent biting. Continuous duodenal administration of the drugs at a constant rate of 0·436 mL h^{-1} was performed by means of a microprocessor-controlled syringe pump (Pump 22; Harvard Apparatus, South Natick, MA).

Blood samples (0·7 mL) were obtained from the rats' tails, under light ether anaesthesia, 18 h after triton administration. Cholesterol, triglycerides and AST were determined and statistically analysed as specified for models A.

In-vitro evaluation

Small matrix tablets containing nicotinic acid (niacin) and hydroxypropylmethylcellulose Methocel K4M were directly compressed in a 5-mm punch. The rate of release of niacin from the tablets in phosphate buffer (pH 6·8) was tested according to the method specified in the USP. The tablets were designed to release the drug at a constant rate over approximately 10 h.

Data analysis

The effects of the treatment on lipid constituents were determined as the difference between the mean serum level of each lipid component in the niacin-treated group and its respective control group, normalized to the control value, and presented as a percentage. This approach, of having a parallel control group for every treatment group was adopted to overcome the effect on lipid levels of the delivery system and of the differences between different groups of rats.

The statistical significance of differences between the groups was determined by the non-parametric Mann–Whitney test and the Kruskal–Wallis test.

Results

In-vitro evaluation

The dissolution-rate profile of niacin from the slow-release tablets was determined under sink conditions. Over 80% of the drug was released in a continuous and steady rate over 10 h; the same results were obtained for both types of matrix tablet containing either 4·3 or 30 mg niacin. These in-vitro findings demonstrate that the matrix formulation, specially designed with small dimensions to enable non-invasive administration in rats, releases its drug content in a slow-release fashion during its transit along the gastrointestinal tract.

In-vivo evaluation

Model A. The effects after 3 days of niacin, administered by various routes, on the serum lipid concentrations in Sabra rats with enriched-diet-induced hyperlipidaemia are shown in Table 1. It was found that when niacin was given by continuous duodenal infusion serum lipid levels of cholesterol were reduced more than after peroral administration. The reduction in cholesterol level after 3 days was found to be 17% (from 2·48 to 2·06 mg mL^{-1}) after continuous duodenal administration, whereas after peroral or intravenous administration any differences were not statistically significant. The most significant effect was found for the slow-release group—niacin slow-release tablets reduced cholesterol by 25% (from 2·23 to 1·67 mg mL^{-1}). In comparison with the control group the triglyceride-reducing effect was found to be 14% after continuous duodenal infusion. The reduction of 13% in triglyceride levels after peroral administration of both single and divided doses was not statistically significant. Similarly, continuous intravenous infusion of the same dose had no apparent effect. The largest effect was found for slow-release niacin tablets; these reduced cholesterol by 20% (from 2·73 to 2·18 mg mL^{-1}). HDL levels were only significantly altered by the administration of the slow-release formulation; this resulted in a 25% elevation (from 0·27 to 0·35 mg mL^{-1}). The HDL/cholesterol ratio, which might be a more meaningful clinical parameter, was found to be significantly changed by continuous duodenal infusion and slow-release administration (see Table 1).

The antilipid effects of niacin after treatment for 7 consecutive days showed the same trend as after 3 days.

Model B. The effects of niacin given via various modes of administration on serum lipid concentrations in Lewis rats with acute experimentally-induced hyperlipidaemia are shown in Table 2. Serum levels of both cholesterol and triglycerides were reduced after both continuous duodenal infusion and slow-release administration of niacin, but not after peroral administration. The reduction in serum cholesterol level after a dose of 40 mg kg^{-1} was found to be 25% (from 2·32 to 1·74 mg mL^{-1}) when the drug was given by continuous duodenal administration whereas no

Table 1. The reduction of cholesterol and triglyceride levels and the increase in high-density-lipoprotein cholesterol and the ratio between high-density-lipoprotein cholesterol and total cholesterol after administration of niacin, given in different forms for 3 days, to male Sabra rats fed a cholesterol-enriched diet (Model A).

Treatment	Cholesterol (mg mL^{-1})			Triglycerides (mg mL^{-1})		
	Control	Niacin	Δ (%)†	Control	Niacin	Δ (%)
2 × 20 mg kg^{-1} day^{-1} peroral doses	2·23 ± 0·16	2·01 ± 0·14	−10	2·73 ± 0·30	2·38 ± 0·22	−13
40 mg kg^{-1} day^{-1} peroral dose	2·10 ± 0·13	2·25 ± 0·18	7	2·54 ± 0·21	2·21 ± 0·20	−13
40 mg kg^{-1} day^{-1} by continuous intraduodenal infusion	2·48 ± 0·30	2·06 ± 0·27*	−17	1·44 ± 0·17	1·24 ± 0·17*	−14
40 mg kg^{-1} day^{-1} by continuous intravenous infusion	2·32 ± 0·30	2·67 ± 0·52	15	1·41 ± 0·26	1·47 ± 0·28	4
2 × 20 mg kg^{-1} day^{-1} slow-release tablets	2·23 ± 0·16	1·67 ± 0·12*	−25	2·73 ± 0·30	2·18 ± 0·25*	−20

Table 1. *Continued*

Treatment	High-density-lipoprotein cholesterol (mg mL^{-1})			High-density-lipoprotein cholesterol/total cholesterol		
	Control	Niacin	Δ(%)	Control	Niacin	Δ(%)
2 × 20 mg kg^{-1} day^{-1} peroral doses	0·27 ± 0·02	0·30 ± 0·04	11	0·120 ± 0·02	0·138 ± 0·03	15
40 mg kg^{-1} day^{-1} peroral dose	0·36 ± 0·04	0·362 ± 0·05	1	0·171 ± 0·02	0·189 ± 0·03	11
40 mg kg^{-1} day^{-1} by continuous intraduodenal infusion	0·30 ± 0·05	0·32 ± 0·04	7	0·139 ± 0·04	0·162 ± 0·04*	17
40 mg kg^{-1} day^{-1} by continuous intravenous infusion	0·29 ± 0·07	0·29 ± 0·06	–	0·130 ± 0·04	0·123 ± 0·04	−5
2 × 20 mg kg^{-1} day^{-1} slow-release tablets	0·27 ± 0·02	0·34 ± 0·03*	26	0·119 ± 0·02	0·161 ± 0·02*	35

†Percentage change. *$P < 0·05$, statistically significant difference between results from the drug-treated group and its corresponding control group (n = 10).

appreciable effect was apparent after peroral administration of the same dose (whether administered as one dose or two). Similarly, serum triglycerides levels were reduced by approximately 39% (from 4·61 to 2·81 mg mL^{-1}) after continuous duodenal infusion of the drug (compared with the corresponding control group), whereas the drug had no apparent activity when it was given as a peroral bolus administration. The reduction in serum cholesterol levels after administration of a larger dose of niacin (200 mg kg^{-1}) was found to be 28% (from 2·32 to 1·67 mg mL^{-1}) when given by continuous duodenal administration whereas the effect after peroral administration was only 9% (from 2·19 to 1·99 mg mL^{-1}; not statistically significant). Serum triglycerides levels were reduced by 21% (from 4·61 to 3·64 mg mL^{-1}) after continuous duodenal infusion (in comparison with the control group), but again no effect was found after peroral administration of the same (high) dose. The slow-release tablets had lipid-lowering effects of similar magnitude to those found after continuous duodenal administration of the drug, with a reduction of 30% (from 2·16 to 1·51 mg mL^{-1}) in serum cholesterol levels and 29% (from 4·48 to 3·18 mg mL^{-1}) in serum triglycerides levels.

Liver function, as evidenced by AST levels, was not significantly changed by niacin administration (Tables 3 and 4).

Discussion

The mode of administration has an important impact on the magnitude of pharmacological response especially for drugs for which there is no direct correlation between systemic blood concentration and magnitude of effect. This is exemplified by targeting a drug directly at its site of action (biophase). Because the biophase of gastrointestinal drugs is located presystemically,

Table 2. The cholesterol- and triglyceride-reducing effect† of niacin administered by different routes for three days to male Lewis rats with hyperlipidaemia induced by intraperitoneal injection of 225 mg kg^{-1} triton (Model B).

Treatment	Cholesterol (%)	Triglyceride (%)
2 × 20 mg kg^{-1} day^{-1} peroral doses	−9	−5
40 mg kg^{-1} day^{-1} peroral dose	2	4
40 mg kg^{-1} continuous intraduodenal infusion for 18 h	−39*	−25**
200 mg kg^{-1} day^{-1} peroral dose	15	−9
200 mg kg^{-1} continuous intraduodenal infusion for 18 h	−21*	−28**
200 mg kg^{-1} day^{-1} slow-release tablets	−29*	−30**

†The magnitude of effect is presented as the ratio (%) of the lipid-reducing effect of the drug-treated group to that in the corresponding vehicle-treated control group normalized by the control lipid level. *$P < 0.05$, **$P < 0.005$, statistically significant difference between result from drug treated group and that from its corresponding control group ($n = 10$).

continuous administration of a drug to the gastrointestinal tract produces relatively high concentrations at the biophase with considerably lower blood concentrations.

Despite a long history of clinical use, the mechanism of action of niacin is not clearly defined, and the contribution of the gut wall and pharmacodynamic effect of the first pass in the liver have not been established (LaRosa 1982; DiPalma & Thayer 1991; Drood et al 1991). This investigation examined our hypothesis that niacin can be regarded as a gastrointestinal drug, an assumption based on the important role of the gut wall and the liver in lipoprotein regulation. Our findings indicate that in two experimental models administration of niacin by continuous duodenal infusion has greater hypolipidaemic effects than other less direct gastrointestinal routes, and thereby confirms our hypothesis. We compared the magnitude of lipid-lowering activity of continuous administration of niacin to the gastrointestinal tract with equal intravenous infusion of the drug (same rate and dose). No correlation was found between drug amounts in the systemic circulation and the magnitude of hypolipidaemic response. Furthermore, no apparent effect was detected after intravenous administration of the drug whereas continuous duodenal administration significantly affected all three lipid components measured (cholesterol, triglycerides and HDL serum levels).

An important clinical advantage of niacin therapy is elevation of serum HDL levels in hyperlipidaemic patients (Luria 1988). To stress the impact of the mode of administration on this activity we used an experimental rat model with a lipid-enriched diet (Model A) that is associated with markedly reduced serum HDL levels. The data clearly show that elevation of HDL activity is closely associated with continuous administration of niacin into the gastrointestinal tract by duodenal infusion.

Administration of triton causes transient elevation of lipid levels owing to inhibition of lipoprotein lipase activity which reaches a peak about 18 h after its administration and disappears several days later (Shurr et al 1971; Sirtori et al 1978; Takeuchi et al 1987). This experimental model (Model B) has been previously used to screen the activity of antilipidaemic agents, including niacin (Krishnamurthy & Thapar 1991). With this model we found that differences between the hypolipidaemic effects after peroral and continuous duodenal administration followed the same trend noted for the cholesterol-rich diet-induced hyperlipidaemic model. There were no differences between the lipid-reducing effects of niacin at 40 or

Table 3. Aspartate transaminase serum levels after administration of niacin by different routes for 3 days to male Sabra rats fed a cholesterol-rich diet (Model A).

Treatment	Aspartate transaminase (Int. units mL^{-1})		
	Control	Niacin	Δ (%)*
2 × 20 mg kg^{-1} day^{-1} peroral doses	112 ± 16	140 ± 14	19
40 mg kg^{-1} day^{-1} peroral dose	104 ± 9	107 ± 16	3
40 mg kg^{-1} day^{-1} continuous intraduodenal infusion	84 ± 8	81 ± 10	−4
40 mg kg^{-1} day^{-1} continuous intravenous infusion	82 ± 5	63 ± 15	−23
2 × 20 mg kg^{-1} day^{-1} slow-release tablets	112 ± 16	122 ± 12	9

*Percentage change.

Table 4. Aspartate transaminase serum levels after administration of niacin by different routes to male Lewis rats with hyperlipidaemia induced by intraperitoneal injection of triton 225 mg kg^{-1} (Model B).

Treatment	Aspartate transaminase (Int. units mL^{-1})		
	Control	Niacin	Δ (%)*
2 × 20 mg kg^{-1} day^{-1} peroral doses	204±29	205±35	–
40 mg kg^{-1} day^{-1} peroral dose	205±75	210±35	3
40 mg kg^{-1} day^{-1} continuous intraduodenal infusion for 18 h	178±26	301±62	69
40 mg kg^{-1} day^{-1} continuous intravenous infusion for 18 h	208±29	294±55	41
200 mg kg^{-1} day^{-1} peroral dose	205±75	258±20	26
200 mg kg^{-1} day^{-1} continuous intraduodenal infusion for 18 h	178±26	162±18	−9
200 mg kg^{-1} day^{-1} slow-release	190±23	267±29	41
200 mg kg^{-1} da^{-1} continuous intravenous infusion for 18 h	170±52	220±33	29

*Percentage change.

200 mg kg^{-1}. Thus, there is no apparent dose–response relationship, and no clear advantage of the higher dose of niacin.

To verify that continuous administration of niacin to the gastrointestinal tract is the preferred route we administered slow-release tablets. This approach is based on the premise that drug absorption patterns are similar along the gastrointestinal tract. In contrast with continuous duodenal administration, which releases the drug exclusively to the upper part of the small intestine, the matrix tablet releases the drug along the entire gastrointestinal tract. Because the slow-release tablets had effects of equal magnitude in both models compared with continuous duodenal administration, our theory is confirmed and provides a pharmacodynamic rationale for a sustained-release formulation of the drug.

Although slow-release niacin formulations are already available on the market, this mode of administration can be hepatotoxic (Etchason et al 1991; Keenan et al 1991; Mckenney et al 1994). Although the hepatotoxic effect of slow-release niacin is beyond the scope of this work we did not note abnormal liver function as evidenced by AST levels during one week of continuous drug administration or after the acute treatment (Tables 2 and 3). The hypolipidaemic activity of low-dose niacin (500 mg per day) has been effective in hyperlipidaemic patients (Luria 1988). On the basis of the outcome of the current study it can be suggested that administration of this low dose by the slow-release mode will enable safe and effective niacin therapy while minimizing hepatotoxicity.

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