gastrointestinal side effects (Uthgenannt & Letzel 1980; Sloboda et al 1980). Fenbufen does not inhibit the synthesis of prostaglandins (PG), but its active anti-inflammatory metabolite biphenylacetic acid does (Tolman & Partridge 1975). In the short time we allowed the drugs to be in contact with the gastric mucosa, it is reasonable to suppose that they cause gastric irritation by a direct 'barrier breaking' action, rather than by a systemic effect on the gastric mucosa via inhibition of enzyme PG cyclo-oxygenase. Thus we were able to distinguish between the relative effect on the stomach of a local as opposed to a systemic action. In the case of the pro-drug fenbufen, the local gastric irritation as measured by blood loss was minimal, unlike that caused by aspirin. It may be postulated that when fenbufen is metabolized by the liver, only the active metabolite will be available to act via a systemic action to cause gastric irritation, via PG cyclo-oxygenase; however a primary NSAID such as aspirin will act both locally and systemically in this respect. The systemic effect will presumably depend not only on the specificity of the drug to inhibit PG cyclo-oxygenase but will also depend on the consistency of the blood levels maintained during the course of long-term treatment. Thus, a slow release preparation of a drug which has a low specificity for the inhibition of PG cyclo-oxygenase may cause more damage to the gastric mucosa than a drug given at a dose that produces high but interrupted blood levels which are allowed to fall to a low value between doses.

With gastric aspiration after taking NSAID by mouth over a short period coupled with a sensitive assay for haemoglobin in stomach contents, it is possible to distinguish between the immediate local and long-term systemic effects of drugs upon the gastric mucosa.

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Some cardiovascular effects of LG 13979: comparison with nicotinic acid and other nicotinic acid derivatives

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2-(3-Pyridinecarbonylamino)-2-deoxy-1,3,4,6-dihydrogen-D-glucose tetrapyridinecarboxylate LG 13979 (Murmann & Ponchiroli 1982), is a new nicotinic acid derivative having more intense and longer lasting lipid-lowering activity than nicotinic acid and its derivatives in rats (Subissi et al 1983). One of the most common and troublesome side effects of nicotinic acid in man is flushing of the face and upper part of the body (Altschul 1964). As this effect is reproducible in the guinea-pig (Andersson et al 1977), we wished to find out whether LG 13979 induces flush and, if so, to what extent. Its effects in the guinea-pig were therefore compared with those of an equidose of nicotinic acid and of its derivatives niceritrol and sorbinicate. As the cholesterol-lowering and antiatherogenic effect of a drug might be secondary to a hypotensive effect (Carrier et al 1968), we also assessed the effects of LG 13979 on arterial pressure and heart rate of the conscious rabbit, in comparison with an equidose of nicotinic acid and sorbinicate.

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Materials and methods

Male Dunkin-Hartley guinea-pigs (n = 10), 265–570 g, from the Rodentia breeding station, Torre Pallavicina (BG) and female New Zealand White rabbits (n = 20), aged 95–115 days, 2·0–3·1 kg from our own breeding quarters were used. All the animals were fed on Altromin MS/K (A. Rieper, Vandoies, BZ) and had free access to water. They were kept in constant environmental conditions (temperature 18–19 °C, relative humidity 50–60%, 12 h light and 12 h dark). At the beginning of each experiment the animals had been fasted for 16 h.

The drugs used were: nicotinic acid (Merck, Darmstadt, GFR), niceritrol (Bofors Nobel Kemi, Sweden),

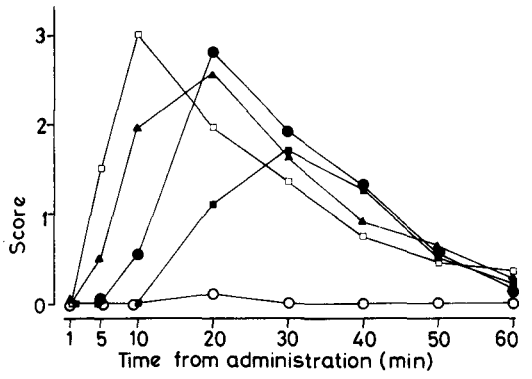

FIG. 1. Guinea-pig ear flush assessed on an arbitrary 0–4 scale. Nicotinic acid (□), niceritrol (▲), sorbinicate (●), LG 13979 (■), at the dose of 10 mg kg^{-1} in nicotinic acid, or vehicle (○) were given orally. Each point is the mean of 10 values.

sorbinicate and LG 13979 (Laboratori Guidotti S.p.A., Pisa, Italy).

Flush of guinea-pig ear. Each animal was subjected to five tests with an interval of one week between tests, each receiving the four drugs and the vehicle in randomized order. At the times indicated in Fig. 1, flush was assessed, independently, by two observers unaware of the treatment scoring the redness of the ears on an on an arbitrary scale ranging from 0 = no reddening to 4 = very intense reddening. Before each test the two observers were shown two other guinea-pigs, treated 10 min before, one with the vehicle and the other with nicotinic acid 30 mg kg^{-1} orally, for standardizing scores 0 and 4. The time x score areas were calculated in arbitrary units by the trapezoidal method. The statistical comparisons were done with the Mann-Whitney U test (Armitage 1971).

Arterial pressure and heart rate in the conscious rabbit. A sound-attenuated room was used. Blood pressure was measured from a polypropylene catheter, introduced into the central ear artery under local anaesthesia (lidocaine 2%), by means of an HP 1280 C pressure transducer, and heart rate, triggered by the pulse pressure, by means of an HP 8812 rate computer. Both parameters were recorded on an HP 7758 D polygraph. One h after the end of the operation the animals received LG 13979 or sorbinicate or nicotinic acid, at the dose equivalent to 300 mg kg^{-1} orally of nicotinic acid, in gelatin capsules. The parameters studied were checked for 6 h. The results were evaluated statistically by means of the paired Student's *t*-test.

Results

Flush of guinea-pig ear (Fig. 1). There was good agreement between the two observers. The scores were the same in 338 out of 400 observations, differed by one point in 59 and by two points in the remaining three observations. Among the control animals only one animal presented slight reddening (score = 1) and only at one of the times tested. Nicotinic acid, sorbinicate

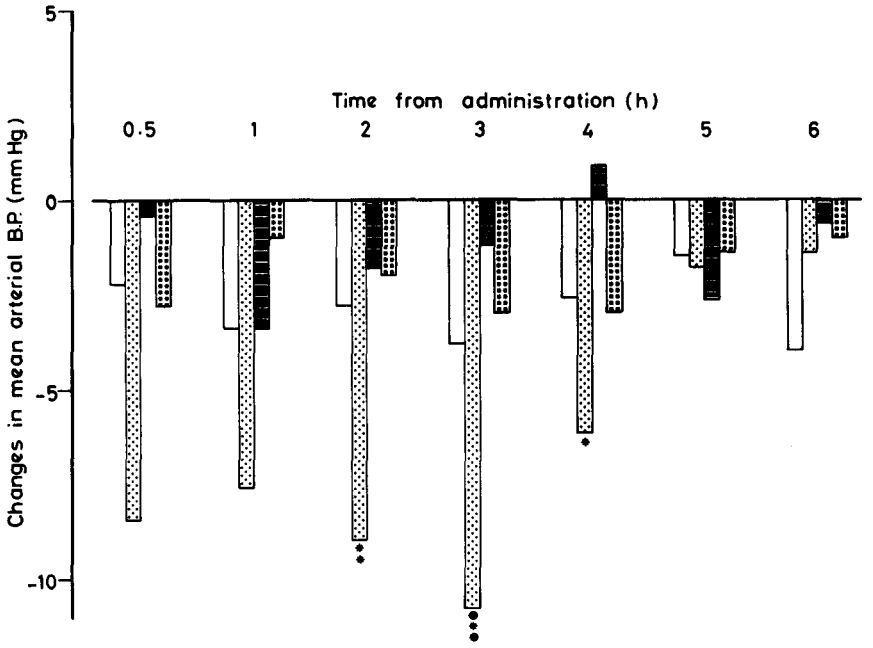

FIG. 2. Effects in columns of an oral dose (300 mg kg^{-1} in nicotinic acid) of nicotinic acid (dotted), sorbinicate (striped), LG 13979 (squared) or vehicle (open) on arterial pressure in the conscious rabbit. Mean values of 5 animals are given. Paired Student's *t*-test was used for statistical analysis (* $P < 0.05$; ** $P < 0.01$; *** $P < 0.001$).

and niceritrol induced flush (score ≥ 1) in 10/10 animals and LG 13979 in 8/10. The times at which the effect reached its peak were $8 \pm 0{\cdot}8$ min (mean ± standard error) for nicotinic acid, $13 \pm 2{\cdot}4$ min for niceritrol, $23 \pm 2{\cdot}1$ for sorbinicate and $29 \pm 2{\cdot}3$ min for LG 13979. The maximum effect was the same for nicotinic acid, niceritrol and sorbinicate (mean value: 3·0–3·1), lower, though not significantly so for LG 13979 (mean value 2·2). The time per score area, expressed in arbitrary units, was also practically the same for nicotinic acid (100), niceritrol (95) and sorbinicate (93), but significantly lower for LG 13979 (62) than for the acid ($P < 0{\cdot}05$).

Arterial pressure and heart rate in the conscious rabbit. In the controls the parameters tested remained constant throughout the experiment. The baseline values were 89 ± 3 mm Hg for mean arterial pressure and 246 ± 8 beats min^{-1} for heart rate. As is clear from Fig. 2, nicotinic acid induced a slight fall in arterial pressure (−10 mm Hg), significant from the 2nd to the 4th h after administration. Sorbinicate and LG 13979 did not affect this parameter. None of the drugs tested significantly affected heart rate.

Discussion

Nicotinic acid and the three derivatives tested, each presented a different pharmacokinetic profile in the rat (Subissi et al 1983). The peak plasma concentration of free nicotinic acid after nicotinic acid was twice that after niceritrol, 15 times that after sorbinicate and 36 times that after LG 13979. Notwithstanding this, the flush induced in the guinea-pig ear by the four drugs was similar in intensity and duration, thus confirming the observation of Svedmyr et al (1969), namely that flush does not correlate with the plasma nicotinic acid concentrations but comes on while the plasma level of the acid is rising then disappearing when the level become relatively constant. The most marked difference between the effects of the four drugs was in the flush latency time (nicotinic acid < niceritrol < sorbinicate <LG 13979), probably in step with the absorption rate of the drugs. These results obtained in the guinea-pig cannot necessarily be extrapolated to man. In clinical trials flush varies in incidence from 92% for nicotinic acid (Coronary Drug Project Research Group 1975) to 47% for niceritrol (Vessby et al 1979) and 10% for sorbinicate (Avogaro et al 1980) and so the incidence of this effect with LG 13979, still to be tested, may be markedly lower than for nicotinic acid, the vasodilator effect of which is thought to be due to increased vascular formation of prostaglandins (Andersson 1977; Eklund et al 1979; Kaijser et al 1979), but seems to be dissociated from that on lipolysis (Kaijser et al 1979).

In addition to the vasodilator effects in the guinea-pig, nicotinic acid at higher doses induced a slight but significant fall in blood pressure in the conscious rabbit but had no effect on heart rate. Its cardiovascular effects in anaesthetized animals are conflicting (hypertensive in guinea-pig, Abdel Aziz & Karrar 1969, and rabbit, Abdel Aziz 1966, hypotensive in dog and cat, Abdel Aziz & Karrar 1969). In line with our data, however, in man the acid induces a slight fall in blood pressure, due to a reduction in total peripheral resistance (Ekström-Jodal et al 1970). The other two derivatives tested did not affect arterial pressure or heart rate in the conscious rabbit. This rules out any possibility of relating their cholesterol-lowering (Subissi et al 1983) and antiatherogenic action (Subissi et al 1980 and unpublished results) in any way to a hypotensive effect.

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