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The influence of levodopa on gastric emptying in man

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1 Simultaneous radioisotopic (^{99}Tc-DTPA) gastric emptying measurements and paracetamol pharmacokinetic studies were performed in eight healthy male volunteers with and without levodopa (125 mg orally).

2 In the absence of levodopa gamma camera imaging showed rapid mono or biexponential emptying in all subjects and the plasma concentration-time curves for paracetamol displayed a single major peak.

3 In the presence of levodopa the time to 90% emptying was prolonged from 32 ± 24 min to 81 ± 20 min ($P < 0.01$). Gastric emptying was interrupted by a plateau phase in six subjects and this pattern of emptying was associated with double peaks in the plasma concentration-time curves of both levodopa and paracetamol. The time to the end of the plateau phase of emptying correlated with the time to the trough plasma concentrations of paracetamol and levodopa.

4 There was excellent agreement between the plasma concentration-time curves of levodopa and paracetamol, i.e. time to initial peak, $r = 0.946$, $P < 0.001$; time to trough concentration $r = 0.943$, $P < 0.01$; time to second peak $r = 0.974$, $P < 0.001$.

5 The results indicate that levodopa inhibits gastric emptying and thus influences its own absorption. Temporary inhibition of gastric emptying by levodopa (or a metabolite) is the cause of the multiple plasma peaks commonly observed following oral levodopa.

Keywords levodopa gastric emptying paracetamol multiple plasma peaks

Introduction

Levodopa is the principal drug used in the treatment of Parkinson's disease and relies on decarboxylation to dopamine within the central nervous system to produce its therapeutic effect. A peripheral decarboxylase inhibitor is usually prescribed with levodopa to reduce the formation of dopamine in the periphery; thereby reducing both the dose and the incidence of side effects (Pinder *et al.*, 1976). As the disease progresses many patients exhibit fluctuating clinical responses (the 'on-off' phenomenon). In these patients a stable clinical response can be achieved by infusing levodopa intravenously to maintain constant plasma concentrations (Quinn *et al.*, 1984). Levodopa has a short elimination half-life and stable concentrations are difficult to achieve with oral therapy. Multiple peaks commonly occur in the plasma concentration-time curve for levodopa following oral administration and further exaggerate the variability of plasma concentrations (Evans *et al.*, 1981; Robertson *et al.*, 1989; Wade *et al.*, 1974). It has been suggested that these multiple peaks reflect the manner in which levodopa is delivered from the stomach to the site of carrier-mediated absorption in the small intestine (Evans *et al.*, 1981). However, the precise aetiology of secondary peaks is unknown. Gastric emptying can be quantified

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by radioisotopic techniques or by the use of paracetamol as a pharmacological marker (Heading *et al.*, 1973). Unlike levodopa, paracetamol is absorbed passively in the upper small intestine and multiple plasma peaks do not usually occur following its oral administration.

The aim of this study was to define the effect of levodopa on gastric emptying and the relationship between the pattern of emptying and the occurrence of multiple plasma peaks. We have, therefore, undertaken simultaneous radioisotopic gastric emptying and paracetamol pharmacokinetic studies in healthy young male volunteers with and without levodopa.

Methods

The study was approved by the local Ethics Committee and all subjects gave written informed consent. Eight healthy male volunteers (19–22 years) were recruited. None of the volunteers had a history of gastrointestinal disease or were receiving regular medication. Smoking was prohibited on the study days. Subjects were studied after an overnight fast on two occasions, in random order, separated by at least a week. On both study days, subjects received a solution containing 12 MBq ^{99}Tc-diethylenetriaminepentaacetic acid (DTPA) and 1.5g of soluble paracetamol (in 100 ml of water). On one of the study days the subjects received 125 mg of levodopa in suspension with the DTPA/paracetamol solution. 100 mg of carbidopa was administered one h before the start of each gastric emptying study and subjects fasted until 4 h when a standard lunch containing 25 g of protein was administered. Gastric emptying was determined by serial scintigraphy with a gamma camera (Siemens LFOV with a 140 keV parallel hole collimator) using consecutive 1 min images until negligible activity was apparent in the stomach (equivalent to approximately 10% or less). The data were acquired on a link MAPS 2060 computer and transferred to a VAX 11/730 computer with P.I.C.S. medical imaging software (Fleming *et al.*, 1987) for subsequent analysis. A region of interest (ROI) was created defining the stomach from the gamma camera image in the first minute after dosing and images were corrected for any movement by the use of ^{57}Co markers attached to the subject's chest. A time-activity curve for the stomach ROI was calculated after correction for radioactive decay. Blood samples were taken prior to the DTPA/paracetamol/levodopa mixture and at 10, 20, 30, 40, 50, 60, 75, 90, 105, 120, 135, 150, 165, 180, 240, 360 and 480 min after the dose. Paracetamol and levodopa concentrations were measured by reverse phase h.p.l.c. using u.v. and electrochemical detection respectively (Ameer *et al.*, 1981; Robertson *et al.*, 1989).

Data analysis

The concentration of the initial plasma peak (C_{max_i}) and the time of C_{max_i} (t_{max_i}) are the observed values. The area under the plasma concentration-time curve (AUC) was calculated by the trapezoidal rule with extrapolation to infinity as described by Gibaldi & Perrier (1982). The paracetamol and levodopa assays had coefficients of variation of approximately ± 5% and a peak in the plasma concentration-time curve was defined as a rise in plasma concentration of > 10% (or a smaller rise if this was present in both the paracetamol and levodopa curves simultaneously). Results are expressed as mean ± s.d. Statistical analysis was by Wilcoxon's signed rank test. Correlations were determined by linear least squares regression analysis.

The initial phase of gastric emptying determined by gamma camera imaging was analysed by log-linear least squares regression and the half-life of emptying derived from the rate constant. The time to the end of the plateau phase detected in some studies was determined by visual inspection of the data (see Figures 1 and 2).

Results

^{99}Tc-DTPA

In all subjects the stomach ROI could be clearly recognised. The time-activity curves for two representative individuals are shown in Figures 1 and 2. Without levodopa there was a rapid mono or bi-exponential gastric emptying pattern with 94 ± 5% of the initial activity having left the stomach at the end of the period of observation.

Levodopa caused a small but significant increase in the half-life of the initial rapid emptying phase (6.2 ± 3.3 min without levodopa; 16.1 ± 9.8 min with levodopa $P < 0.05$). This was followed by a plateau phase of slow or negligible emptying in seven of the eight subjects prior to a second period of rapid emptying. In subject 8 there was an initial lag phase followed by rapid and apparently complete emptying. A mean of 91 ± 3% of the initial activity had left the stomach at the end of the period of observation. In two subjects (numbers 5 and 7) a loop of intestine containing ^{99m}Tc-DTPA lay

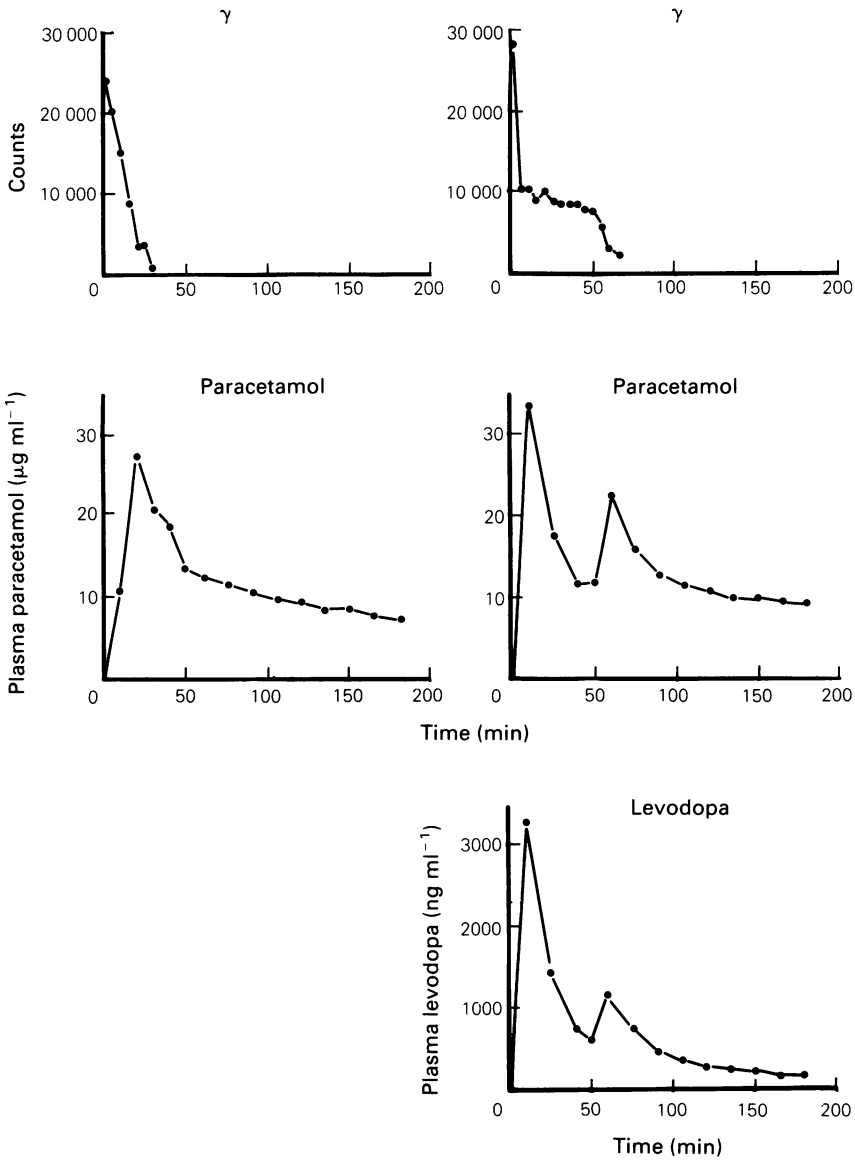

Figure 1 (a) Control day without levodopa: Gamma camera time-activity curve (top left); Paracetamol plasma concentration-time curve (middle left). (b) With levodopa: Gamma camera time-activity curve (top right); Paracetamol plasma concentration-time curve (middle right); levodopa plasma concentration-time curve (bottom right).

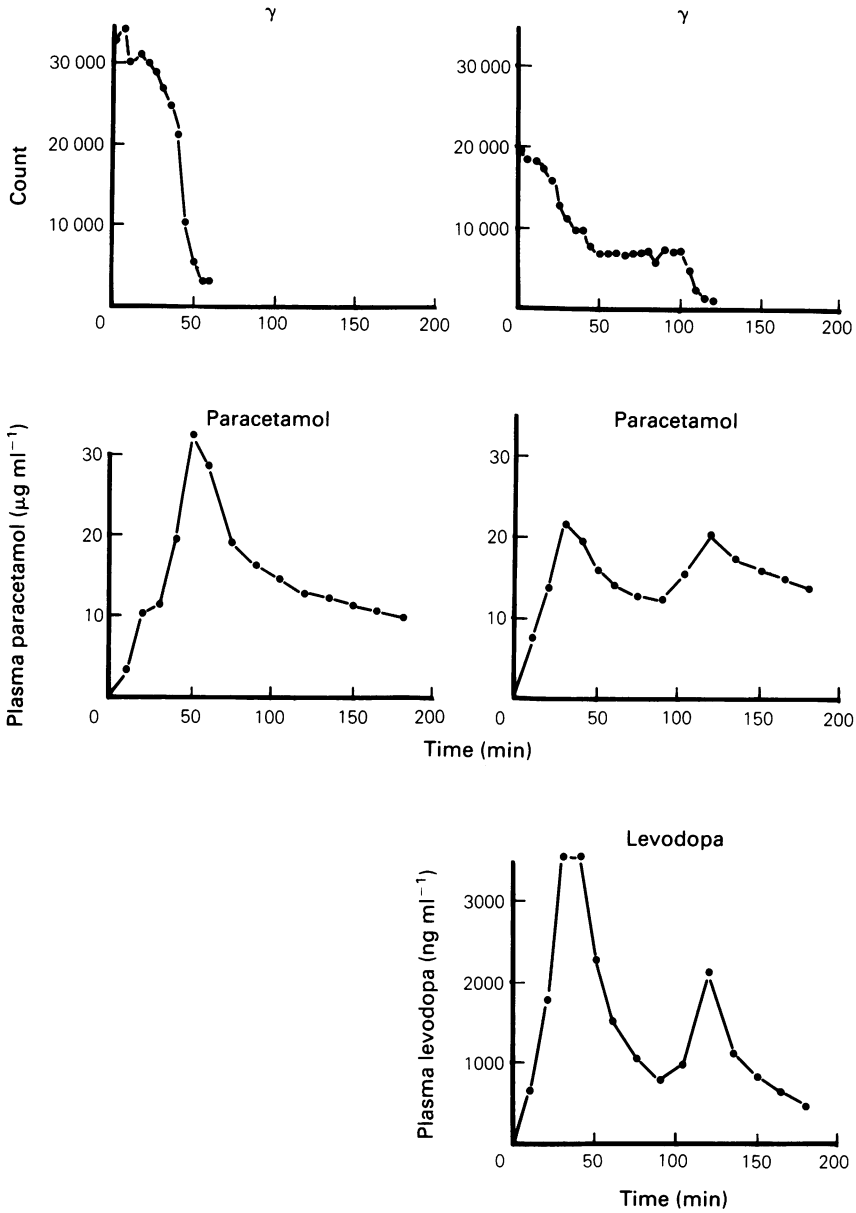

Figure 2 (a) Control day without levodopa: Gamma camera time-activity curve (top left); Paracetamol plasma concentration-time curve (middle left). (b) With levodopa: Gamma camera time-activity curve (top right); Paracetamol plasma concentration-time curve (middle right); levodopa plasma concentration-time curve (bottom right)

close to the area defined as the stomach so that some overlap probably occurred. Determination of the time to 50% emptying was difficult because of the presence of the plateau and we have therefore determined the time to 90% emptying as a more appropriate indication of the influence of levodopa on gastric emptying. In all cases levodopa prolonged the time to 90% emptying (32 ± 24 min without levodopa; 81 ± 20 min with levodopa, $P < 0.01$).

Paracetamol and levodopa

In the absence of levodopa, the paracetamol plasma concentration-time curve showed a single peak in all eight subjects. Subject 2, who showed a late peak at 50 min displayed the slowest gastric emptying by gamma camera imaging on the control day (Figure 2).

When given levodopa, subjects 1–5 (who showed clear evidence of a plateau phase interrupting gastric emptying on their gamma scans) had definite double peaks in both their levodopa and paracetamol plasma concentration-time curves (Figures 1 and 2). Subject 6 also showed a small increase (4–5%) in both paracetamol and levodopa plasma concentrations which corresponded with the end of the plateau phase of gastric emptying. In subject 7 interpretation of the isotope scan was difficult due to an artifact caused by an adjacent loop of small intestine. Secondary peaks were not detected in the plasma concentration-time curves for this subject. Subject 8 showed a single peak for both levodopa and paracetamol which occurred at the end of an initial plateau on the gamma scan and was not preceded by any measurable emptying.

For the group of eight subjects the t_{max} for paracetamol was not significantly affected by levodopa (22.5 ± 11.6 min without levodopa; 27.5 ± 19.1 min with levodopa). C_{max} for paracetamol was significantly lower in the presence of levodopa (33.1 ± 11.0 μg ml^{-1} without levodopa; 24.2 ± 6.5 μg ml^{-1} with levodopa $P < 0.05$) but the AUC was not affected (4589 ± 653 μg ml^{-1} min without levodopa; 4694 ± 822 μg ml^{-1} min with levodopa).

There was excellent agreement between the concentration-time curves for paracetamol and levodopa. This applied to temporal relationships i.e. the time to initial peak in all subjects ($r = 0.946$, $P < 0.001$) and, in the six subjects with evidence of double plasma peaks, the time to the trough concentrations ($r = 0.943$, $P < 0.01$); also for the time to the second peak ($r = 0.974$, $P < 0.001$) and the ratio of the concentration at the second peak to that of the initial peak ($r = 0.955$, $P < 0.01$).

The time to the end of the gamma plateau correlated with the time to the trough plasma concentrations of paracetamol ($r = 0.871$, $P < 0.05$) and levodopa ($r = 0.745$, $P = 0.089$). Finally, the ratio of the amount of emptying in the post plateau phase to that in the initial phase from the gamma camera data correlated well with the ratio of the concentration at the second peak to that at the initial peak for both paracetamol ($r = 0.925$, $P < 0.01$) and levodopa ($r = 0.916$, $P < 0.05$).

Discussion

Clements *et al.* (1978) investigated the pharmacokinetics of paracetamol absorption by simultaneous radioisotopic measurement of gastric emptying. Three different patterns of emptying were observed; Type 1, monoexponential emptying commencing immediately after ingestion or preceded by a lag phase, Type 2, biphasic emptying with a rapid initial phase and Type 3 in which two periods of monoexponential emptying were interrupted by an interval without emptying. A close relationship was found between the absorption of paracetamol (in solution) and the pattern of gastric emptying. The plasma concentration-time curve for paracetamol was smooth with the exception of one individual with a double plasma peak which appeared to be the result of Type 3 emptying.

In the present study gastric emptying in the absence of levodopa was consistent with a Type 1 or 2 pattern in all subjects and the plasma concentration-time curves for paracetamol showed a single major peak and only minor fluctuations. From the results in Figures 1 and 2 it is apparent that levodopa altered the gastric emptying pattern to predominantly Type 3, in which emptying was interrupted by a plateau phase with negligible emptying. This was associated with evidence of double peaks in the plasma concentration-time curves of both levodopa and paracetamol in six of the eight subjects, which coincided with the two rapid phases of emptying. This suggests that temporary inhibition of gastric emptying by levodopa is the cause of the multiple plasma peaks which have been commonly observed following oral levodopa.

Although gastric emptying of non-nutritive liquids is usually considered to be a volume dependent first order process (Hunt & Spurrell, 1951), gastric empyting patterns other than simple monoexponential empyting are well recognised in the literature (Clements *et al.*, 1978). Recent studies in dogs have indicated that

the emptying of small volumes is related to the background motility pattern of the stomach whilst larger volumes follow first order kinetics (Gupta *et al.*, 1986). We have shown that levodopa alters the pattern of gastric emptying and thereby influences its own absorption. The mechanism of this effect on gastric emptying is unknown and either central or peripheral mechanisms could be involved. The neural and hormonal mechanisms involved in the control of gastric emptying are complex and have not been fully elucidated. Relaxation of gastric musculature is mediated by inhibitory vagal neurones (Abrahamson, 1973). The post ganglionic transmitter of this nonadrenergic, noncholinergic system is uncertain and several different substances including dopamine have been implicated in animal studies (Andrews & Lawes, 1985; Burnstock, 1972; Valenzuela, 1976). Levodopa and dopamine have both been shown to inhibit gastric emptying in man (Berkowitz & McCallum, 1980; Muller-Lissner *et al.*, 1986; Valenzuela & Liv, 1982) and the ability of dopamine antagonists such as metoclopramide and domperidone to reverse this effect has been taken as evidence that levodopa exerts its effect via putative dopamine receptors in the stomach. However, delayed gastric emptying occurred in our study despite pretreatment with the decarboxylase inhibitor carbidopa using a regimen which we have found previously to produce 80% inhibition of decarboxylation (Robertson *et al.*, 1989). In addition, studies by Bateman (1985) suggest that dopamine antagonism is not the primary mechanism of action of metoclopramide and domperidone in man. Furthermore cisapride, a benzamide derivative devoid of anti-dopaminergic activity, also counteracts the dopamine induced inhibition of gastric emptying (Muller-Lisner *et al.*, 1986). Other possible mechanisms by which levodopa in the small intestine may inhibit gastric emptying include stimulation of osmoreceptors or of a more specific receptor such as has been described for tryptophan in animals (Minami & McCallum, 1984).

The relationship between plasma levodopa concentrations and effect is complex but appears to become more critical as the disease progresses. Administration of levodopa by intravenous infusion stabilises both levodopa concentrations and the clinical response (Quinn *et al.*, 1984). Similar effects can be obtained with the intraduodenal infusion of levodopa (Kurlan *et al.*, 1986, 1988; Sage *et al.*, 1988). Collectively, these findings suggest that the effects of levodopa on gastric emptying could be an important factor in the genesis of the 'on-off' phenomenon. Patients experiencing the 'on-off' phenomenon are often treated by giving small doses of levodopa more frequently. This policy, combined with periodic inhibition of gastric emptying, could lead to intermittent excessive plasma concentrations as a result of dose accumulation within the stomach. Further work is required to determine the contribution of erratic gastric emptying and delivery of levodopa to the small intestine to the fluctuating clinical response to oral levodopa therapy in Parkinson's disease.

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