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The dependence of paracetamol absorption on the rate of gastric emptying

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Summary

1. The rate of gastric emptying was measured directly in 14 convalescent hospital patients and paracetamol absorption was studied following an oral dose of 1·5 g.

2. Rapid gastric emptying was associated with the early appearance of high peak plasma paracetamol concentrations whereas peak concentrations were low and occurred late when gastric emptying was slow.

3. There was a significant correlation between the rate of gastric emptying and the 0–4 and 0–24 h urinary excretion of paracetamol and its metabolites.

4. In five patients with abnormally slow gastric emptying the mean maximum plasma concentration and 0–4 and 0–24 h urinary excretion of paracetamol were significantly lower than in seven patients with normal gastric emptying rates while the time taken to reach maximum plasma concentrations was longer.

5. Individual differences in the rate of gastric emptying may contribute to variable absorption of many drugs.

Introduction

There is often considerable individual variation in the rate at which orally administered drugs are absorbed in man. Physiological factors such as intestinal motility, the rate of gastric emptying, splanchnic blood flow and the volume, composition and pH of alimentary secretions are known to alter the rate of drug absorption in experimental animals (Levine, 1970; Diamond, Doluisio & Crouthamel, 1970), but their clinical significance is uncertain since few relevant studies have been carried out in man.

For a drug absorbed predominantly from the small intestine, the rate of gastric emptying will determine the time taken to reach the absorption site, and thus influence its rate of absorption. According to the pH-partition hypothesis, weakly basic lipid soluble drugs are absorbed much more rapidly from the small intestine than from the acid contents of the stomach (Brodie, 1964) and absorption should be limited by the rate of gastric emptying. However, acidic drugs such as barbiturates and aspirin are also absorbed much more slowly from the stomach than from the small intestine, presumably because of the greater relative surface area of the latter (Magnussen, 1968; Siurala, Mustala & Jussila, 1969; Kojima, Smith & Doluisio, 1971). The absorption of many drugs is therefore likely to be dependent on the rate of gastric emptying.

In the present investigation, the relationship between gastric emptying rate and paracetamol absorption was studied in hospital patients. Paracetamol was chosen because it is a safe widely used drug, and variation in its absorption has previously been described in normal volunteers under standard conditions (Gwilt, Robertson, Goldman & Blanchard, 1963 ; Prescott & Nimmo, 1971).

Methods

Patients

Fourteen convalescent hospital patients age 38–77 years (mean 60 years) were studied. One patient had a duodenal ulcer with pyloric stenosis and gastric surgery had been carried out previously in two patients for chronic peptic ulceration. There was no clinical evidence of malabsorption or cardiac, hepatic or renal failure in any of the patients. All other drugs were withheld during the period of investigation.

Paracetamol absorption

After an overnight fast, the patients were given 1·5 g of paracetamol as 3 Panadol (Bayer, Batch No. 1EE 588) tablets with 50 ml of water. Fluids were withheld for 2 h and no food or tobacco was allowed for 3 hours. Blood samples were taken at 0, 0·5, 1, 1·5, 3, 5 and 8 h and in 11 patients urine was collected from 0–4, 4–12 and 12–24 hours. Plasma and urine samples were stored frozen until the time of analysis. Total unchanged and conjugated paracetamol in urine and unchanged paracetamol in plasma were estimated by gas-liquid chromatography (Prescott, 1971a ; 1971b).

Gastric emptying

The gastric emptying rate was measured directly without intubation within 6 days of the drug absorption study by a sequential scintiscanning technique using 113 M indium diethylenetriaminepenta-acetic acid chelate. After an overnight fast 200 μCi of tracer was ingested in a standard meal of 20 g cornflakes, 15 g sucrose and 150 ml of milk (Heading, Tothill, Laidlaw & Shearman, 1971). Since gastric emptying is an exponential process, results are expressed as half times.

Results

Plasma paracetamol concentrations

The maximum plasma paracetamol concentrations varied from 7·4 to 37·0 μg/ml and the time taken to reach peak concentrations ranged from 30–180 min after ingestion. Similarly the gastric emptying rate varied widely, and the half time values ranged from 20–86 minutes. There were statistically significant correlations between the half time of gastric emptying and both the maximum plasma paracetamol concentrations and the time taken to reach the peak (Table 1: Figs. 1 and 2). Thus rapid gastric emptying was associated with the early appearance of high peak plasma paracetamol concentrations whereas peak concentrations were low and occurred late when gastric emptying was slow.

There were also statistically significant correlations between the half time of gastric emptying and the plasma concentration at 30 min (Table 1) and at 60 min ($r=-0{\cdot}65$, $P<0{\cdot}005$).

TABLE 1. *Gastric emptying rates, plasma concentrations and urinary excretion of paracetamol in* 14 *patients*

Patient	Gastric emptying half time (min)	Maximum plasma concentration (μg/ml)	Time to maximum plasma concentration (min)	Plasma concentration at 30 min (μg/ml)	Unchanged paracetamol in urine (mg) 0–4 h	Total unchanged and conjugated paracetamol in urine (mg) 0–4 h	4–12 h	12–24 h	0–24 h
1	42	25·7	90	13·2	9·5	333	473	213	1,019
2	34	21·3	60	15·9	13·3	373	—	—	—
3	50	30·9	90	3·4	—	—	—	—	—
4	68	24·6	60	15·5	4·8	384	621	163	1,168
5	37	17·7	90	3·2	12·8	567	518	76	1,161
6	20	34·0	30	34·0	24·9	522	568	146	1,236
7	59	21·0	90	3·3	—	178	494	218	890
8	81	7·4	180	0·4	1·3	61	588	233	881
9	39	28·2	30	28·2	37·5	390	578	146	1,114
10	33	37·0	60	21·7	—	—	—	—	—
11	26	33·8	60	18·7	8·1	254	833	229	1,316
12	84	18·3	90	2·5	6·7	281	409	339	—
13	86	10·3	180	2·6	4·9	247	556	161	964
14	41	25·0	60	13·7	14·1	386	563	185	1,134
Correlation with half time of gastric emptying r		−0·77	+0·76	−0·72	−0·59	−0·62	−0·38	+0·46	−0·73
P		<0·005	<0·005	<0·005	<0·05	<0·05	N.S.	N.S.	<0·01

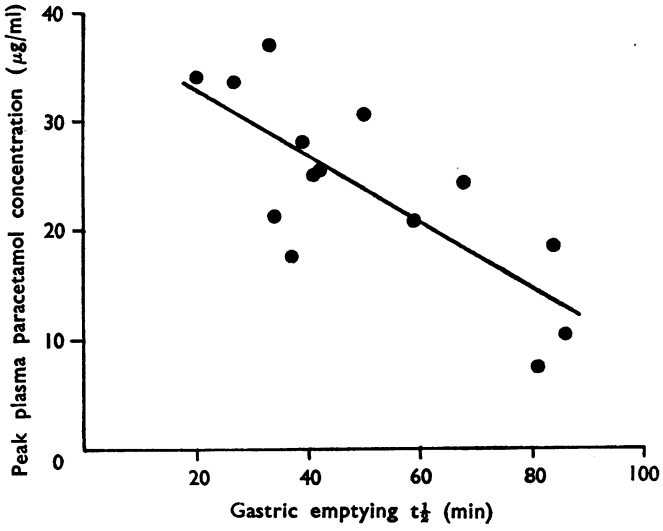

FIG. 1. Relationship between gastric emptying half time ($t_{\frac{1}{2}}$) and the peak plasma paracetamol concentration ($r = -0{\cdot}77$, $P < 0{\cdot}005$).

Urinary excretion of paracetamol

The mean 24 h urinary recovery of paracetamol and its conjugates ranged from 58·7% to 87·8% of the ingested dose (mean 71·5%). There were statistically significant correlations between the half time of gastric emptying and the urinary excretion of total unchanged and conjugated paracetamol during the periods 0–4 and 0–24 hours. No such correlation could be demonstrated from 4–12 or 12–24 hours. The urinary excretion of unchanged paracetamol during the 4 h after ingestion was also correlated with the rate of gastric emptying (Table 1).

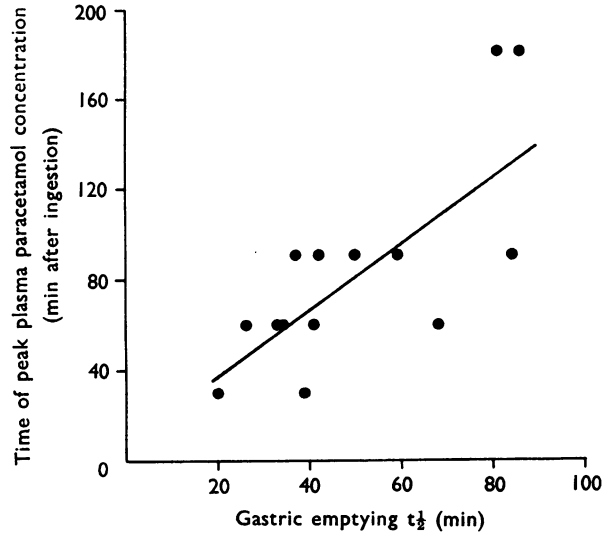

FIG. 2. Relationship between gastric emptying half time ($t\frac{1}{2}$) and the time of the peak plasma paracetamol concentration ($r=0{\cdot}76$, $P<0{\cdot}005$).

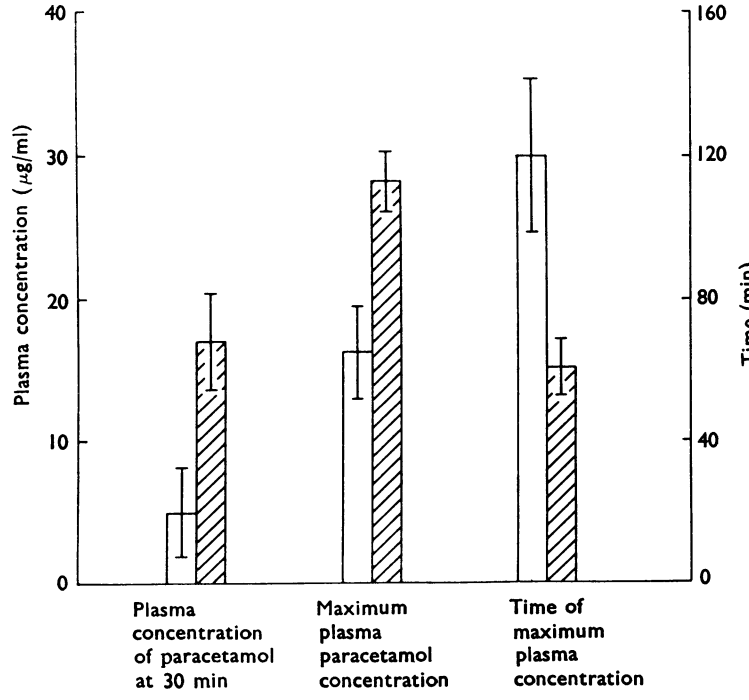

FIG. 3. Mean 30 min and maximum plasma concentration of unchanged paracetamol and time of maximum plasma concentration in patients with normal and prolonged gastric emptying rates (means ± S.E.). Open columns—5 patients with gastric emptying half time>55 min (mean 76 min). Cross-hatched columns—9 patients with gastric emptying half time<55 min (mean 36 min).

Abnormally slow gastric emptying

Gastric emptying was abnormally slow in 5 of the 14 patients (half time>55 minutes). (Heading, *et al.*, 1971). The mean maximum and 30 min plasma paracetamol concentrations were lower, and the time taken to reach maximum concentration was longer in these patients than in those with normal gastric emptying rates (Fig. 3). These differences are all statistically significant.

Similarly the mean 0–4 and 0–24 h urinary excretion of total free and conjugated paracetamol was significantly lower in the 5 patients with slow gastric emptying

TABLE 2. *The mean urinary excretion* (±S.E.) *of paracetamol in patients with normal and delayed gastric emptying*

	Unchanged paracetamol 0–4 h (mg)	Total unchanged and conjugated paracetamol (mg)			
		0–4 h	4–12 h	12–24 h	0–24 h
7 patients with normal gastric emptying (half time<55 min)	17·2 ±4·0	404 ±41	589 ±51	166 ±23	1,164 ±42
5 patients with slow gastric emptying (half time>55 min)	4·4 ±1·1	230 ±54	534 ±38	223 ±32	986 ±53
P	<0·05	<0·05	N.S.	N.S.	<0·05

(Table 2). The amount excreted in the period 4–12 h was essentially the same in the two groups, but the patients with slow gastric emptying excreted more total paracetamol in the period 12–24 hours.

Discussion

The plasma concentration of paracetamol and the kinetics of its urinary excretion depend not only on absorption, but also on the rates of distribution and metabolism. However, paracetamol absorption is apparently related to the rate of gastric emptying since fast gastric emptying was associated with the rapid appearance of high peak plasma concentrations, while the peaks occurred late and were lower in patients with delayed gastric emptying. Not only did patients with delayed gastric emptying appear to absorb paracetamol more slowly, but the total amount of paracetamol and its conjugates excreted in the urine in 24 h was significantly reduced. The mechanisms involved in paracetamol absorption are unknown, but it is apparently absorbed much more rapidly from the small intestine than from the stomach. Paracetamol is a weakly acidic drug (pKa 9·5) which is largely unionized both in the stomach and small intestine. It should therefore be absorbed readily from both sites and the more rapid absorption from the small intestine is presumably due to the greater relative surface area. Gastric emptying probably influences paracetamol absorption directly by controlling the rate at which the drug is delivered to the small intestine. It is conceivable that rapid gastric emptying was associated with increased gastrointestinal motility and that absorption was enhanced as a result of more rapid tablet disintegration and dissolution of the drug. However, this is an unlikely explanation since the absorption of paracetamol from suspensions is also related to gastric emptying rate, and gross impairment of paracetamol absorption has been observed in patients with pyloric stenosis (Nimmo, unpublished observations).

It is often stated that low molecular weight neutral compounds and weakly acidic lipid soluble drugs are rapidly absorbed from the stomach. This is not always the case since aspirin and warfarin are absorbed much more rapidly from the small intestine than from the stomach in man (Siurala, *et al.*, 1969; Kekki, Pyörälä, Mustala, Salmi, Jussila & Siurala, 1971) and similar findings have been described with phenobarbitone, pentobarbitone and ethanol in rats (Magnussen, 1968; Kojima, *et al.*, 1971). The absorption of organic bases and drugs which are absorbed by small intestinal active transport or metabolized in the stomach must be even more dependent on the rate of gastric emptying. The clinical importance of this effect is illustrated by the therapeutic failure of L-DOPA in patients with delayed gastric emptying (Bianchine, Calimlim, Morgan, Dujuvne & Lasagna, 1971). Gastric emptying is abnormal in many disease states and is influenced by endocrine and autonomic activity and the volume, composition, tonicity, temperature and pH of the stomach contents (Hunt, 1958). Furthermore, many drugs have intrinsic pharmacological effects on gastrointestinal motility. For example, paracetamol absorption in man is slowed by propantheline and accelerated by metoclopramide—drugs which reduce and increase the rate of gastric emptying respectively (Nimmo, Heading & Prescott, 1971). Similarly, propantheline delays the absorption of riboflavin in man (Levy, Gibaldi & Procknal, 1972).

Striking individual variation has been observed in the rates of absorption of various drugs (Prescott & Nimmo, 1971; Koch-Weser, 1971). Despite the clinical importance, little attention has been given to elucidation of the mechanisms involved. In the present study, the plasma concentrations of paracetamol 60 min after administration ranged from 0·4 to 37·0 μg/ml, i.e. almost a hundred fold variation at a time when therapeutic effects might reasonably be expected. Individual variation in the rate of drug absorption may be due largely to differences in the rate of gastric emptying.

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