Effect of intravenous atropine on gastric emptying, paracetamol absorption, salivary flow and heart rate in young and fit elderly volunteers

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1 The effects of atropine on gastric emptying, paracetamol absorption, salivary flow and heart rate were examined in young and elderly subjects.

2 Seven healthy young male subjects of age 23 ± 1.3 years (mean $\pm$ s.e. mean) and seven fit elderly subjects of age 70 ± 1.6 years received placebo (P), 300 μ g atropine (A300) or 600 μ g atropine (A600) in randomized order at weekly intervals. After 10 min they ingested a 500 ml orange drink containing 1 g paracetamol. Gastric emptying was measured by ultrasound, blood samples were taken to measure plasma paracetamol concentration by h.p.l.c., salivary flow was measured by dental cotton wool cylinder technique and pulse rate was recorded.

3 In young subjects, the gastric 5 min volumes were 260.1 ± 17.9 ml (s.e. mean) with P, 310.6 ± 10.5 ml with A300 and 317.9 ± 8.9 ml with A600. In elderly subjects, the gastric 5 min volumes were 166.7 ± 10.1 ml with P, 252.6 ± 13.7 ml with A300 and 266.0 ± 14.8 ml with A600. Thus the early adaptive phase of gastric emptying was more rapid in the elderly than the young with all treatments ($P < 0.05$). The gastric emptying half-lives were 18.8 ± 2.5 min with P, 30.0 ± 2.7 min with A300 and 34.5 ± 3.3 min with A600 in young subjects ($P < 0.01$). In elderly subjects, the gastric emptying half-lives were 16.1 ± 2.5 min with P, 23.7 ± 2.4 min with A300 and 30.0 ± 2.9 min with A600 ($P < 0.01$). Thus atropine intravenously in therapeutic dose (300 and 600 μ g) delayed gastric emptying in both young and elderly subjects. The inhibitory effect of atropine on the early adaptive phase of gastric emptying appeared to be greater in the elderly. The maximum plasma concentration ($C_{\max}$) of paracetamol was greater in the elderly than young with all treatments ($P < 0.05$). There was a close relationship between the early adaptive phase of gastric emptying and paracetamol absorption ($P < 0.05$). Atropine reduced salivary flow and increased resting heart rate in both young and old subjects. The effect of atropine on salivary flow was greater in the elderly.

4 The dose-response relationship varied in the three systems (stomach, salivary glands and heart rate) studied. Age had an effect on the magnitude of the response, but not on the slope of the dose-response curve for the two doses of atropine studied. There was no clear relationship between the magnitude of the effects of atropine on gastric emptying, salivary flow and heart rate in either young or elderly subjects.

Keywords atropine paracetamol gastric emptying autonomic function age

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Introduction

The rate of gastric emptying is the principal factor and the most important rate limiting step affecting the absorption of orally administered drugs (Gibaldi, 1979; Levine, 1970; Nimmo, 1976, 1979; Prescott, 1974a,b). Paracetamol has been widely used as a model drug for absorption studies and the pattern of absorption of oral paracetamol has been shown to be closely associated with the pattern of gastric emptying (Heading *et al.*, 1973). Atropine is known to have a pronounced effect on gastric emptying and to reduce the rate of absorption of concomitantly administered drugs (Gamble *et al.*, 1976; Gothani *et al.*, 1972; Wing *et al.*, 1980).

Age is also thought to be a factor affecting gastric emptying and subsequent drug absorption (Bender, 1968; Kendal, 1970). Previous studies do not seem to have investigated the effects of age on drugs absorbed by passive diffusion. Few studies have been undertaken specifically to investigate gastric emptying and drug absorption in different age groups. In addition, age itself may have influence on the effect of drugs modifying gastric emptying.

The present study had five objectives. Firstly to observe the effects of two different therapeutic doses of atropine on the two phases of gastric emptying of liquid which the ultrasound technique identifies. Secondly to investigate the relationship between gastric emptying (particularly the early adaptive phase) and absorption of paracetamol (a drug absorbed passively). Thirdly to compare these in young (<30 years) and elderly (>60 years) subjects after modifying gastrointestinal motility by two different doses of atropine. Fourthly to examine the anticholinergic effects of atropine on salivary flow and pulse rate, and investigate whether age modifies these effects, and fifthly to examine the dose-response relationships of the effects of atropine on the stomach, salivary flow and pulse rate and evaluate the effects of age on these relationships.

Methods

Seven healthy young subjects, aged 20–30 years and seven fit elderly subjects aged 64–76 years were studied on three occasions separated by at least a week in a double-blind manner. The subjects had no history of gastrointestinal or renal disease and were not on any medication concurrently. They were requested to refrain from taking any formulations containing paracetamol while at home between the study days.

All subjects had normal physical examination and ECG prior to entering the study. The study was approved by the Joint Ethics Committee of the University of Newcastle upon Tyne and the Newcastle Health Authority.

Subjects were asked to avoid alcoholic drinks and smoking for 48 h preceding the study and to attend after an overnight fast. After emptying the bladder, subjects were seated in an upright chair for the first hour of the study. After inserting an intravenous cannula into a forearm vein, the baseline samples for salivary flow measurement were taken in duplicate and pulse rate was recorded. A baseline 10 ml blood sample was drawn and put in an appropriately labelled heparinised blood collection tube. Saline (5 ml) containing no drug (placebo), atropine (300 µg) or atropine (600 µg) was infused intravenously over 5 min using an infusion pump. Due to variations of weights of the subjects the doses of atropine per kg body weight obviously differed but the mean dose per kg body weight was not significantly different between the young and elderly group of subjects.

After 10 min for stabilization had elapsed the patients drank 500 ml dilute orange cordial at 37° C (pH 2.6) containing 1 g paracetamol. The time of starting the drink was designated time zero. Ultrasound scans of the abdomen were obtained, using real-time ultrasound, at regular intervals of 5 min for 30 min and 10 min to 1 h. The scans obtained were recorded onto video tape and replayed subsequently for analysis and volume calculation (Bateman, 1982). Nothing further by mouth was allowed for 2 h. Blood samples (10 ml) were taken at 10, 20, 30, 40, 50, 60, 70, 80, 90, 120, 180 and 360 min after time zero. Following separation, plasma was stored at –20° C until assay.

Samples for the salivary flow measurement were taken at 15, 30, 45, 60, 75 and 90 min after the drug infusion. In addition to baseline data, pulse rate was recorded at time zero and immediately before withdrawing each blood sample.

The half-life of gastric emptying was estimated from the monoexponential fall in volume with time. Gastric emptying half-life, 5 min volume (gastric volume measured 5 min after time zero) and intercept volume (log linear decline of stomach volume with time back extrapolated to zero time) were considered as gastric emptying parameters. In addition, the amount of paracetamol emptied from the stomach at 30 min was also considered as a parameter of gastric emptying to relate it with paracetamol absorption. This was calculated from the volume change observed over 30 min, using the original con-

centration of paracetamol, and ignoring gastric secretion.

Plasma paracetamol concentrations were determined by high performance liquid chromatography (h.p.l.c.) using a slightly modified version of an existing technique (Adriaenssens & Prescott, 1978). β -hydroxyethyl theophylline was used as an internal standard. The maximum plasma paracetamol concentration ($C_{\max}$), the time to reach maximum plasma concentration ($t_{\max}$), area under the plasma paracetamol-time curve for the period of 6 h (AUC0–6) and for the first 30 min (AUC0–30) were considered as paracetamol absorption parameters. The parameters $C_{\max}$ and $t_{\max}$ were obtained by fitting the plasma concentration-time data to a three compartmental pharmacokinetic model. The AUC was calculated using the trapezoidal rule.

Salivary flow was measured by the dental cotton wool cylinder technique (Dollery *et al.*, 1975). The area under the salivary flow-time curve for the 90 min period of observation (AUC^{0–90}) was used for assessing the effect of atropine.

Pulse rate was recorded up to 370 min after infusion of the drug. For assessing effect of drug treatment on cardiovascular system, area under the pulse rate-time curve for this 370 min (AUC0–370) was calculated.

Statistical methods

Gastric emptying and paracetamol absorption parameters between the treatments within the young or elderly groups were analysed by analysis of variance (for paired data). Student's unpaired *t* test was used to compare these parameters between the young and the elderly with different treatments. The Wilcoxon signed rank test was performed to compare the percentage differences of dose-response within the groups and the Mann-Whitney *U* test was used to compare the same data between the groups. In each of the above tests, the level considered to be significant was $P < 0.05$.

Results

Gastric emptying

The results of drug treatment on the gastric emptying parameters in young subjects are shown in Table 1a. The half-lives of gastric emptying were 18.8 ± 2.5 min (s.e. mean) with placebo (P), 30.0 ± 2.7 min with atropine-300 μ g (A300) and 34.5 ± 3.3 min with atropine-600 μ g (A600). Both doses of atropine produced highly

significant lengthening of gastric emptying half-life compared with placebo ($P < 0.01$). Furthermore there was a significant dose effect of atropine ($P < 0.05$). Both doses of atropine resulted in a significantly larger 5 min volume when compared with placebo ($P < 0.05$), but the effects of the two doses were not significantly different from one another. Only A300 produced significantly higher intercept volume in comparison with placebo ($P < 0.05$).

The results of drug treatment on the gastric emptying parameters in elderly subjects are shown in Table 1b. Both doses of atropine produced a significantly longer gastric emptying half-life compared with placebo ($P < 0.01$) and the effects of the two doses of atropine were significantly different from one another ($P < 0.01$). Both doses of atropine resulted in a significantly larger 5 min volume (P vs A300 $P < 0.01$; P vs A600 $P < 0.001$) and intercept volume (P vs A300 $P < 0.05$; P vs A600 $P < 0.001$) but the doses were not significantly different from one another for either 5 min or intercept volume.

When comparing the results of the young to the elderly subjects the gastric emptying half-life tended to be less in the elderly subjects for all treatments but the difference was not statistically significant for any single treatment. Five-minute volume was significantly less in elderly subjects than the young with all treatments (P $P < 0.01$; A300 $P < 0.01$; A600 $P < 0.05$) but this difference was most marked under control conditions (young 260.1 ± 17.9 ml; elderly 166.7 ± 10.1 ml). Intercept volume was significantly less in elderly subjects with placebo and A600 (P $P < 0.01$; A600 $P < 0.05$).

For examining dose-response relationship, percentage differences (from placebo) of the effects of low and high doses of atropine on gastric emptying parameters were calculated. Figure 1a and 1b represent the dose-response curves of the effect of atropine on gastric emptying half-life in the young and the elderly. In young subjects, the percentage differences of the effects of atropine on gastric emptying half-life were 68.4 ± 17.9 with A300 and 93.1 ± 19.5 with A600 (A300 vs A600 $P < 0.01$), on 5 min volume were 21.3 ± 6.2 with A300 and 25.6 ± 8.9 with A600 and on intercept volume were 12.4 ± 4.1 with A300 and 12.3 ± 6.9 with A600. In elderly subjects, the percentage differences of the effects of atropine on gastric emptying half-life were 56.3 ± 14.3 with A300 and 100.7 ± 24.7 with A600 (A300 vs A600 $P < 0.01$), on five-minute volume were 54.1 ± 12.0 with A300 and 60.0 ± 2.8 with A600 and on intercept volume were 45.6 ± 15.1 with A300 and 38.0 ± 6.2 with A600. The effect of A600 on gastric emptying

Table 1 a) Effects of drug treatment on gastric emptying parameters (young subjects)

	Placebo (P)	Treatment Atropine 300 µg (A300)	Atropine 600 µg (A600)	P
Gastric emptying half-life (min)	18.8 ± 2.5	30.0 ± 2.7	34.5 ± 3.3	P vs A300 <0.01 P vs A600 <0.01 A300 vs A600 <0.05
5 min volume (ml)	260.1 ± 17.9	310.6 ± 10.5	317.9 ± 8.9	P vs A300 <0.05 P vs A600 <0.05 A300 vs A600 >0.05
Intercept volume (ml)	308.9 ± 18.6	343.6 ± 10.9	336.3 ± 8.5	P vs A300 <0.05 P vs A600 >0.05 A300 vs A600 >0.05

b) Effects of drug treatment on gastric emptying parameters (elderly subjects)

Gastric emptying half-life (min)	16.1 ± 2.5	23.7 ± 2.4	30.0 ± 2.9	P vs A300 <0.01 P vs A600 <0.01 A300 vs A600 <0.01
5 min volume (ml)	166.7 ± 10.1	252.6 ± 13.7	266.0 ± 14.8	P vs A300 <0.01 P vs A600 <0.001 A300 vs A600 >0.05
Intercept volume (ml)	217.6 ± 19.0	303.1 ± 20.8	293.9 ± 13.1	P vs A300 <0.05 P vs A600 <0.001 A300 vs A600 >0.05

*Young vs elderly**Gastric emptying half-life*Placebo $P > 0.05$ Atropine 300 µg $P > 0.05$ Atropine 600 µg $P > 0.05$ *5 min volume*Placebo $P < 0.01$ Atropine 300 µg $P < 0.01$ Atropine 600 µg $P < 0.05$ *Intercept volume*Placebo $P < 0.01$ Atropine 300 µg $P > 0.05$ Atropine 600 µg $P < 0.05$

Values quoted mean ± s.e. mean. The significance of differences within groups were calculated using analysis of variance and between groups were calculated using Student's unpaired t -test.

half-life was statistically greater than A300 in both young and elderly group of subjects ($P < 0.01$) but there was no statistically significant effect of age. In contrast, there was no significant effect of atropine dose on 5 min volume in the young or elderly. However, overall atropine had a statistically greater effect on 5 min volume in the elderly group than the young one. Dose-response of the intercept volume to atropine was similar to 5 min volume.

Paracetamol absorption

Table 2a shows the effects of drug treatment on paracetamol absorption parameters in young subjects. Both doses of atropine produced significantly lower $C_{\max}$ (P vs A300 $P < 0.05$; P vs A600 $P < 0.01$) and later $t_{\max}$ ($P < 0.05$) when compared with placebo but there was no significant dose effect on either $C_{\max}$ or $t_{\max}$. The areas under the plasma paracetamol-time curves (see

Figure 2a) over the entire 6 h (AUC0–6) were $39.94 \pm 1.91 \mu\text{g ml}^{-1} \text{ h}$ with P, $36.68 \pm 1.66 \mu\text{g ml}^{-1} \text{ h}$ with A300 and $35.83 \pm 1.57 \mu\text{g ml}^{-1} \text{ h}$ with A600. The AUC0–6 was significantly less with A300 ($P < 0.01$) and A600 ($P < 0.05$) when compared to placebo but that with A300 was not significantly different from that with A600.

Table 2b shows the effects of drug treatment on paracetamol absorption parameters in elderly subjects. Both doses of atropine produced significantly lower $C_{\max}$ (P vs A300 $P < 0.05$; P vs A600 $P < 0.01$) and later $t_{\max}$ (P vs A300 $P < 0.01$; P vs A600 $P < 0.001$) when compared with placebo. In addition, there was a significant effect of dose on both $C_{\max}$ and $t_{\max}$ ($P < 0.01$). The areas under the plasma paracetamol-time curves (see Figure 2b) over the entire 6 h (AUC0–6) were: $59.87 \pm 3.47 \mu\text{g ml}^{-1} \text{ h}$ with P, $54.75 \pm 2.76 \mu\text{g ml}^{-1} \text{ h}$ with A300 and $48.35 \pm 2.85 \mu\text{g ml}^{-1} \text{ h}$ with A600. The AUC0–6 was significantly less with A300 ($P < 0.05$) and

Figure 1 Dose-response curve for gastric emptying half-life in a) young subjects and b) elderly subjects.

A600 ($P < 0.01$) when compared with placebo and the doses were significantly different from one another ($P < 0.05$).

When comparing the results of young to the elderly subjects $C_{\max}$ was significantly higher in the elderly subjects with all treatments ($P < 0.05$; A300 $P < 0.01$ and A600 $P < 0.01$). There was no statistically significant effect of age on $t_{\max}$. AUC0–6 was greater in elderly subjects and significantly different with all treatments ($P < 0.001$; A300 $P < 0.001$; A600 $P < 0.01$).

To relate gastric emptying and paracetamol absorption 5 min volume was correlated to $C_{\max}$, $t_{\max}$ and the area under the plasma paracetamol-time curve to 30 min (AUC0–30). There were significant correlations between 5 min volume and $C_{\max}$ in the young ($r = 0.46$, $P < 0.05$) and the elderly ($r = 0.57$, $P < 0.01$). The correlations between 5 min volume and $t_{\max}$ were significant in elderly ($r = 0.68$, $P < 0.001$). There were also significant correlations between 5 min volume and AUC0–30 in the young ($r = 0.44$, $P < 0.05$) and the elderly ($r = 0.64$, $P < 0.01$). In addition, AUC0–30 was correlated to the amount of paracetamol emptied from the stomach in the first 30 min. The correlation coefficients were significant in both the young ($r = 0.72$, $P < 0.001$) and

Figure 2 Plasma paracetamol-time curve in a) young subjects and b) elderly subjects.

the elderly ($r = 0.67$, $P < 0.001$). The AUC0–30 plotted against the amount of paracetamol that emptied from stomach at 30 min for each young and elderly subject on each treatment is shown in Figure 3 and a highly significant correlation was obtained overall ($r = 0.8$, $n = 42$, $P < 0.001$).

Salivary flow

In young subjects, the areas under the salivary flow-time curves (AUC0–90) were 80.50 ± 10.28 g min⁻¹ min with P, 43.02 ± 4.42 g min⁻¹ min with A300 and 33.07 ± 3.46 g min⁻¹ min with A600 (see Figure 4a). Both doses of atropine produced significantly lower AUC0–90 when compared with placebo (P vs A300 $P < 0.05$; P vs A600 $P < 0.01$) and there was a significant dose effect ($P < 0.05$). In elderly subjects, the AUC0–90 (see Figure 4b) were 60.28 ± 9.28 g min⁻¹ min with P, 23.88 ± 4.39 g min⁻¹ min with A300 ($P < 0.01$) and 16.33 ± 2.72 g min⁻¹ min with A600 ($P < 0.01$). There was a significant dose effect of atropine in the elderly ($P < 0.05$).

When comparing the salivary flow in young and elderly groups of subjects with placebo, the AUC0–90 was not significantly different, whereas the young group had significantly greater AUC0–90 than the elderly group following both

Table 2 a) Effects of drug treatment on paracetamol absorption parameters (young subjects)

	Placebo (P)	Treatment Atropine 300 µg (A300)	Atropine 600 µg (A600)	P
$C_{\max}$ (µg ml ⁻¹)	14.1 ± 1.12	10.74 ± 0.9	10.0 ± 0.54	P vs A300 <0.05 P vs A600 <0.01 A300 vs A600 >0.05
$t_{\max}$ (min)	28.3 ± 3.1	48.1 ± 7.5	72.3 ± 13.9	P vs A300 <0.05 P vs A600 <0.05 A300 vs A600 >0.05
AUC ⁰⁻⁶ (µg ml ⁻¹ h)	38.94 ± 1.91	36.68 ± 1.66	35.83 ± 1.57	P vs A300 <0.01 P vs A600 <0.05 A300 vs A600 >0.05

b) Effects of drug treatment on paracetamol absorption parameters (elderly subjects)

$C_{\max}$ (µg ml ⁻¹)	20.07 ± 1.62	16.81 ± 1.33	12.67 ± 0.59	P vs A300 <0.05 P vs A600 <0.01 A300 vs A600 <0.01
$t_{\max}$ (min)	36.6 ± 7.6	54.9 ± 7.9	77.1 ± 8.2	P vs A300 <0.01 P vs A600 <0.001 A300 vs A600 <0.01
AUC ⁰⁻⁶ (µg ml ⁻¹ h)	59.87 ± 3.47	54.75 ± 2.76	48.35 ± 2.85	P vs A300 <0.05 P vs A600 <0.01 A300 vs A600 <0.05

Young vs elderly

$C_{\max}$	$t_{\max}$	AUC ⁰⁻⁶
Placebo $P < 0.05$	Placebo $P > 0.05$	Placebo $P < 0.001$
Atropine 300 µg $P < 0.01$	Atropine 300 µg $P > 0.05$	Atropine 300 µg $P < 0.001$
Atropine 600 µg $P < 0.01$	Atropine 600 µg $P > 0.05$	Atropine 600 µg $P < 0.01$

Values quoted mean ± s.e. mean. The significance of differences within groups were calculated using analysis of variance and between groups were calculated using Student's unpaired *t* test.

doses of atropine (A300 $P < 0.05$; A600 $P < 0.01$).

For examining dose-response relationships, percentage differences (from placebo) of the effects of low and high doses of atropine on area under the salivary flow-time curve (AUC0-90) were calculated. Figure 5a and 5b represent the dose-response curves of the effects of atropine on salivary flow in the young and the elderly. In young subjects, the percentage differences of the effects of atropine on AUC0-90 were 42.4 ± 7.5 with A300 and 57.1 ± 4.7 with A600 (A300 vs A600 $P < 0.01$). In elderly subjects, the percentage differences of the effects of atropine on AUC0-90 were 61.0 ± 3.6 with A300 and 72.7 ± 2.9 with A600 (A300 vs A600 $P < 0.01$). The effects of atropine in the elderly were greater than those in the young with A600 ($P < 0.05$) but not with A300.

Pulse rate

In young subjects, the area under the pulse rate-time curve (AUC0-370) were 25557.1 ± 901.1 beats min⁻¹ min with P, 25670.0 ± 1019.8 beats min⁻¹ min with A300 and 2693.41 ± 1058.8 beats min⁻¹ min with A600. The AUC0-370 with A600 was significantly greater than that with placebo ($P < 0.01$) but did not reach the level of statistical significance with A300. There was a significant difference between the two doses ($P < 0.05$) of atropine.

In elderly subjects, AUC0-370 were 22544.3 ± 740.0 beats min⁻¹ min with P, 23224.3 ± 788.8 beats min⁻¹ min with A300 and 23831.4 ± 700.1 beats min⁻¹ min with A600. The AUC0-370 with both the doses of atropine was significantly greater than with placebo (P vs A300 $P < 0.01$; P vs A600 $P < 0.001$) and in addition the doses

Figure 3 Linear regression analysis of the relationship between area under the plasma paracetamol concentration time curve at 30 min and amount of paracetamol emptied from stomach at 30 min. The regression line is shown ($r = +0.8$, $P < 0.001$). The equation of the line is $y = 0.944x + 474$.

Figure 4 Salivary flow-time curve in a) young subjects and b) elderly subjects.

Figure 5 Dose-response curve for salivary flow in a) young subjects and b) elderly subjects.

were significantly different from one another ($P < 0.05$).

When comparing the pulse rate between young and elderly group of subjects, the AUC0-370 were significantly greater in the young than the elderly with placebo and the high dose of atropine ($P < 0.05$).

Percentage differences (from placebo) of the effects of low and high doses of atropine on area under the pulse rate-time curve (AUC0-370) were calculated. In young subjects, the percentage differences of the effects of atropine on AUC0-370 were 0.5 ± 1.4 with A300 and 5.6 ± 1.1 with A600 (A300 vs A600 $P < 0.05$). In elderly subjects, the percentage differences of the effects of atropine on AUC0-370 were 3.0 ± 0.5 with A300 and 5.9 ± 0.7 with A600 (A300 vs A600 $P < 0.05$). There was no effect of age on the percentage change in pulse rate with atropine.

Discussion

Atropine is well-known to inhibit gastric emptying (Botts *et al.*, 1985; Chernish *et al.*, 1982; Clark & Seager, 1983) but studies addressing the effects of age on gastric emptying are very few and no study has been previously performed to evaluate the effects of age on the inhibitory actions of atropine on the stomach.

Gastric emptying of liquid can be described in two different phases, an early adaptive phase reflected by the gastric volume at 5 min or the intercept volume, and a subsequent mono-exponential phase of liquid emptying (Bateman, 1982; Bateman & Whittingham, 1982).

In the present study both 5 min volume and intercept volume were significantly lower in the elderly subjects, compared with young subjects under control conditions. The gastric emptying half-life also tended to be shorter under control conditions in the elderly than in the young, but this was not statistically significant. These findings are consistent with the study by Kupfer *et al.* (1985) who also determined gastric emptying by ultrasound. However, these findings differ from the studies by Moore *et al.* (1983) and Evans *et al.* (1981) who measured gastric emptying by a radioisotope technique. Studies with radioisotope techniques suggest that the emptying of liquids by the stomach could be slower in the elderly (Evans *et al.*, 1981; Moore *et al.*, 1983), whereas the ultrasound technique suggests that the initial rate of gastric emptying of liquids was significantly higher in elderly subjects than in young controls (Kupfer *et al.*, 1985).

The cause of the conflicting findings of gastric emptying under control conditions in elderly subjects may be due to different methods used for measuring gastric emptying. The findings of the present study and Kupfer *et al.* (1985) suggest that the control of adaptive relaxation (responsible for the early phase of liquid emptying) may be impaired in elderly subjects. This homeostatic response is not measured by the radioisotope technique used by other workers (Evans *et al.*, 1981; Moore *et al.*, 1983) and will not be readily detected using solid meals. Kupfer *et al.* (1985) showed that length of drink-time had no influence on gastric emptying of liquid. This confirms the previous observations on the reproducibility of gastric emptying measurements using ultrasound (Bateman & Whittingham, 1982) and lends weight to the hypothesis that the results of this study indicate a change in gastric physiology in the elderly.

Atropine in two different doses prolonged the gastric emptying half-life in both the young and the elderly. This effect appeared similar in

young and old. Thus, the effect of atropine on the second phase of gastric emptying is in agreement with the findings of Botts *et al.* (1985) and Chernish *et al.* (1978) although the methods for measuring gastric emptying were different. Atropine resulted in larger 5 min volumes in both groups of subjects when compared with placebo, but as observed under control conditions, this index of gastric adaptation was significantly impaired in the elderly when compared with the young. The effect of atropine on intercept volume was similar to the findings on 5 min volume but the magnitude of the effect was less.

The effects of atropine on 5 min volume and intercept volume were different to its effects on gastric emptying half-life, which did not appear to be altered by age. These findings suggest that in the elderly the inhibitory effect of atropine on the early adaptive phase of gastric emptying was increased. After atropine, adaptive relaxation in the elderly stomach appeared to be similar to that in the young stomach under control conditions.

The precise mechanisms underlying this pattern of gastric emptying in the elderly are not clear. The elderly could, theoretically, have more vagal tone. This hypothesis does not seem to be valid since gastric pH has been reported to be higher in the elderly due to reduction in basal and maximal histamine stimulated gastric acid output (Stevenson *et al.*, 1979). This has been suggested to be due to a gradual reduction of vagal tone with increasing age. If that were the case gastric emptying should be slower in the elderly. On the other hand a rise in gastric pH itself could lead to acceleration in gastric emptying.

This study showed that both the rate and the extent of paracetamol absorption were significantly decreased by atropine (see Tables 2a and 2b). The young did not demonstrate any significant dose effect on any parameter ($C_{\max}$, $t_{\max}$ and AUC0-6) of paracetamol absorption. In contrast, the elderly showed a significant dose effect in all the above parameters. These findings, taken together with the ultrasound findings suggest that in the elderly subjects atropine may have a different dose-response effect than in the young. This may indicate an age-related change in cholinergic function of the stomach.

The effects of age on paracetamol absorption appeared complex. $C_{\max}$ was significantly higher in the elderly, suggesting more rapid absorption, but $t_{\max}$ tended to be later, although this difference was not statistically significant. In addition, AUC0-6 was also greater in the elderly, but the exact reasons for this are not clear. It has been

reported that both splanchnic blood flow and small bowel mucosal surface area are reduced in the elderly (Stevenson *et al.*, 1979) which should lead to decreased drug absorption. However, the high AUC0-6 of paracetamol absorption in the elderly group may be due to a combination of factors, including gastric emptying, absorption and possible changes in paracetamol pharmacokinetics in the elderly (Forrest *et al.*, 1982). These studies, therefore illustrate the difficulties of using indirect measurements of gastric emptying.

Atropine produces its inhibitory effect on gastric motility by its well-known muscarinic cholinergic blocking effect. Although atropine can completely abolish the effects of acetylcholine (and other parasympathomimetic drugs) on the gastrointestinal tract, it incompletely inhibits the motor effects of vagal impulses (Weiner, 1985). The precise reasons for these observations are not known. It appears likely that this may be due to involvement of gastrointestinal hormones and neurotransmitters other than acetylcholine and noradrenaline. Changes in the relative activities of these systems in the elderly cannot be excluded as a cause of the observations in these experiments.

In this study significant correlations were found between 5 min volume, and $C_{\max}$, $t_{\max}$ and AUC0-30 in both groups of subjects irrespective of drug treatment (see Table 4a). These findings basically coincided with Heading *et al.* (1973) who found significant correlations between gastric emptying half-life ($t_{1/2}$) and $C_{\max}$ and $t_{\max}$ of paracetamol. The present study suggests that the early adaptive phase of gastric emptying may have an important effect on drug absorption. In addition, the correlation between AUC0-30 and the amount of paracetamol emptied from the stomach in first 30 min was highly significant irrespective of treatment and age (see Figure 3, $r = 0.8$, $P < 0.001$). This correlation therefore, tends to confirm a relation between the early adaptive phase of gastric emptying and paracetamol absorption. This extends the observations of Nimmo *et al.* (1975) who tested the correlations between the area under the plasma paracetamol concentration-time curve at 1 h and percentage of ingested solution emptied from the stomach at 1 h.

This study demonstrated that atropine produced significantly less salivary flow in both elderly and young subjects. The high dose produced a greater reduction in salivary flow than the low dose in both groups of subjects. When comparing the salivary flow under baseline conditions (by measuring AUC0-90), the elderly tended to have less salivation than the young,

but this did not reach statistical significance. The percentage differences (from placebo) of the effects of atropine on salivary flow were greater in the elderly and this difference was significant at the high dose. These findings suggest that age affects the salivary response to atropine (see Figures 4a and b).

Atropine produced significant increase in pulse rate. When comparing the pulse rate under baseline conditions, the elderly had significantly lower pulse rate than the young. The effects of atropine on pulse rate did not seem to be age dependent.

The overall results on pulse rate and salivary flow suggest that old age may result in a slower pulse rate but that the magnitude of the effect of atropine is similar in the young and the old. In contrast, salivary flow is more effectively decreased by atropine in the elderly than the young.

In this study, both baseline salivary flow and pulse rate tended to be less in the elderly than in the young. The cause of this difference is not clear. As mentioned earlier, old age may result in a reduction in vagal tone, and a reduction in cholinergic tone would explain the reduction in salivary flow in the elderly. In contrast, reduction in vagal tone should result in an increase in heart rate, not the decrease observed. Thus, direct parallels can not be drawn from these two different parameters which are under autonomic nervous system control.

Although only two doses of atropine were administered, these were within the dose range used in clinical medicine. Log dose-response curves were constructed to examine both the absolute effect of atropine and the differences in the effect of the two doses studied (see Figures 1a and b, 5a and b). Age appeared to affect the response of the stomach and salivary glands, as discussed above. The slope of the dose-response curve for atropine was not obviously altered by age although the elderly appeared to have a greater response to atropine *per se*. This may be due to the doses of atropine being towards the top of the dose-response curve for the effects being studied. Within individuals, in both the young and the old, there was no clear relationship between the effects of atropine on one organ system studied and any other.

The clinical implications of these experiments are that the fit elderly appear more likely to be at risk of certain adverse effects which are due to cholinergic blockade. These include dry mouth and impairment of gastric emptying. In contrast effects on the cardiovascular system did not appear materially different at rest in the elderly group.

In conclusion, atropine in two different doses (300 and 600 µg) reduced gastric emptying with effects on both adaptive relaxation and the subsequent mono-exponential phase. In this study the early adaptive phase of gastric emptying was more rapid in the elderly. The inhibitory effect of atropine on the early adaptive phase of gastric emptying appeared to be greater in the elderly. The rate of paracetamol absorption was greater in the elderly, and this probably directly reflects gastric emptying changes since the early

adaptive phase of gastric emptying clearly correlated to paracetamol absorption. The dose-response to atropine on the stomach, salivary flow and heart rate were found to vary. Age had an effect on the magnitude of the response, but not on the slope of the dose-response curve for the two doses of atropine studied. There was no clear relationship between the magnitude of the effects of atropine on gastric emptying, salivary flow or heart rate in either young or elderly subjects.

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