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GASTRIC EMPTYING FOLLOWING PREMEDICATION WITH GLYCOPYRROLATE OR ATROPINE

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SUMMARY

A double-blind study of the effects of glycopyrrolate or atropine i.v. on gastric emptying was undertaken in 30 non-pregnant and 30 pregnant women. Gastric emptying, which was assessed by the uptake of orally administered paracetamol, was decreased in the patients in the first trimester of pregnancy when compared with the non-pregnant patients. Following the administration of glycopyrrolate, gastric emptying was decreased in the non-pregnant patients and decreased further in the pregnant patients.

Various attempts have been made to provide prophylaxis against the development of the acid aspiration syndrome in pregnant women, including treatment with the anticholinergic agent, glycopyrrolate (Baraka et al., 1977).

Since anticholinergic agents delay or decrease the uptake of various drugs (Gothoni et al., 1972; Nimmo et al., 1973; Gibbons and Lant, 1975; Wing et al., 1980; Nimmo, 1981), it has been implied that they delay, or decrease, gastric emptying (Heading et al., 1973; Nimmo et al., 1975; Nimmo, 1981).

However, assessments of the effects of glycopyrrolate on gastric emptying are inconsistent. The subcutaneous administration of glycopyrrolate has been shown to decrease antral motility (Young and Sun, 1962) and gastric emptying (Saiphoo, Bingham and Cramp, 1968), whereas glycopyrrolate by mouth failed to influence gastric emptying (Young and Sun, 1962; Posey et al., 1965). Since different methods of assessment of gastric emptying were used it is difficult to compare results.

In the present study the effects of pretreatment with atropine or glycopyrrolate i.v. on gastric emptying were assessed in pregnant and non-pregnant patients. Gastric emptying was assessed by the rate of absorption of orally administered paracetamol (Heading et al., 1973; Nimmo et al., 1973; Nimmo, Wilson and Prescott, 1975; Nimmo et al., 1975).

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PATIENTS AND METHODS

Patients

Thirty patients undergoing first trimester termination of pregnancy, and 30 non-pregnant patients undergoing various gynaecological procedures gave informed consent for the study. The patients were aged between 18 and 40 yr and weighed between 40 and 90 kg (table I). No patient had a history of gastrointestinal, hepatic, cardiac or renal disease and none had received paracetamol, anticholinergic drugs or drugs known to affect gastrointestinal function in the 24 h preceding the investigation. Patients with glaucoma or known hypersensitivity to paracetamol, atropine or glycopyrrolate were excluded.

Patients were starved from 07.00 h and were investigated for a 2-h period commencing approximately 3 h before the scheduled operation on an afternoon operating list. An indwelling cannula was inserted in the antecubital fossa at the start of each investigation and 0.025 ml kg^{-1} of one of the following preparations (prepared in identical coded ampoules) administered i.v.: 0.9% sodium chloride injection; glycopyrrolate injection 0.2 mg ml^{-1}; atropine sulphate injection 0.4 mg ml^{-1}. The maximum volume administered was 1.5 ml, equivalent to glycopyrrolate 0.3 mg or atropine 0.6 mg. The drugs were administered double-blind, according to a randomized code which ultimately assigned 10 pregnant and 10 non-pregnant patients to each treatment group. Concurrent with the administration of the i.v. preparation, 0.5 ml kg^{-1} of a suspension of paracetamol 40 mg ml^{-1} was given orally. This suspension was prepared before each period of study by dissolving each Panadol (Winthrop) effervescent

TABLE I. *Details of patients (mean values ± SD)*

	Non-pregnant			First-trimester pregnancy		
	Atropine	Glyco.	Placebo	Atropine	Glyco.	Placebo
No. patients	10	10	10	10	10	10
Age (yr)	31.6	31.6	30.8	25.9	23.4	26.6
	±4.2	±5.2	±5.7	±7.4	±4.03	±5.8
Height (cm)	159.4	158.2	158.0	159.2	159.75	158.1
	±6.5	±7.9	±6.0	±7.6	±8.2	±4.5
Weight (kg)	58.3	60.9	64.4	57.4	55.1	55.4
	±10.5	±13.3	±17.3	±12.3	±5.9	±8.2

tablet in distilled water 12.5 ml. The suspension was not effervescent when administered. No other premedication was given.

Venous blood samples (6 ml) were obtained from the indwelling cannula before and 15, 30, 45, 60, 90 and 120 min after the administration of the i.v. preparation and the oral paracetamol, and were placed in heparinized tubes until the plasma could be separated by centrifugation at the end of the investigation. The plasma was stored at −20 °C pending estimation of plasma paracetamol concentration (gas–liquid chromatography).

Anaesthesia was induced according to the preference of the anaesthetist who was not involved in the study, and who had access to the identity of the drug used if required for clinical reasons.

Gas–liquid chromatography

This was a modification of the method described by Prescott (1971). Serum samples were thawed and 2 ml of the sample transferred to a glass stoppered tube. One millilitre of phosphate buffer 0.5 mol litre^{-1} pH 7.4 unit was added and mixed, followed by ethyl acetate 5 ml containing the internal standard, N-butyryl-p-aminophenol 5 μg ml^{-1}. Organic extraction was obtained by mechanical shaking for 10 min. Following centrifugation the organic phase was removed with a pipette and transferred to a 5-ml glass stoppered tube. The contents were evaporated to dryness. The dry residue was acetylated by adding acetyl chloride 10 μlitre and incubating at 40 °C for 15 min. Excess acetyl chloride was removed by passing a stream of nitrogen over the contents of the tube. The residue was dissolved in ethyl acetate 10 μlitre and 0.8-μlitre aliquots were injected to the column.

A Pye Unicam 104 gas chromatograph with flame ionization detector was used. The column was a 5-ft coiled 0.25" i.d. glass tube filled with 3% OV17 on Gaschrom Q. Column temperature was 220 °C, nitrogen carrier gas flow 40 ml min^{-1} and detector oven temperature 300 °C.

A calibration curve was constructed using aqueous standard solutions of paracetamol and drug concentrations obtained by using peak height ratios of drug to internal standard. Twenty samples of paracetamol either 20 μg ml^{-1} or 10 μg ml^{-1} in plasma were assayed before patient sample assay to check the precision of the assay. For 20-μg ml^{-1} samples the standard deviation was 0.64 μg ml^{-1} and for 10-μg ml^{-1} samples the standard deviation was 0.2 μg ml^{-1} corresponding to 3% and 2% respectively.

Statistics

Statistical analyses were performed using a three-way analysis of variance and the sum of squares simultaneous test procedure (Gabriel, 1964) to compare plasma concentrations of paracetamol and a two-way analysis of variance to compare the areas under the plasma paracetamol concentration curves. The statistical technique used allowed the simultaneous analysis of more than one variable. As a result of this smaller subgroups for each variable could be studied.

RESULTS

Patients in the pregnant group were younger and had a slightly lower body weight than the non-pregnant group (table I).

Mean plasma paracetamol concentrations were smaller in the first-trimester pregnant patients than in non-pregnant patients when comparing groups receiving placebo or atropine ($P < 0.02$) or glycopyrrolate ($P < 0.01$) (table II, fig. 1).

TABLE II. *Plasma paracetamol concentrations (μg ml^{-1}) (mean values ± SD)*

		Time after drug administration (min)					
	0	15	30	45	60	90	120
Non-pregnant							
Placebo	0	7.5 ±3.2	15.4 ±5.7	19.3 ±5.7	19.6 ±5.1	14.9 ±5.5	11.6 ±5.3
Atropine	0	8.1 ±4.0	12.2 ±5.5	17.9 ±5.7	16.4 ±4.5	14.0 ±3.7	12.5 ±4.1
Glycopyrrolate	0	5.7 ±3.0	9.7 ±3.3	12.2 ±3.6	14.2 ±4.7	12.7 ±5.2	10.7 ±4.9
First-trimester pregnancy							
Placebo	0	7.3 ±3.2	14.1 ±5.9	14.1 ±7.0	15.5 ±4.5	11.1 ±3.4	9.4 ±3.0
Atropine	0	6.0 ±3.1	9.1 ±4.1	14.0 ±6.8	13.5 ±4.5	11.7 ±4.6	8.6 ±4.7
Glycopyrrolate	0	3.3 ±1.8	5.2 ±2.5	7.7 ±4.5	8.9 ±3.3	9.2 ±3.0	5.2 ±4.3

When all first-trimester pregnant patients were compared with all non-pregnant patients, mean plasma paracetamol concentrations were smaller in the former group ($P<0.01$).

The administration of atropine in both pregnant and non-pregnant patients failed to produce significant decreases in the plasma paracetamol concentrations during the 2 h of the study. Glycopyrrolate produced decreases in plasma paracetamol concentrations when compared with placebo ($P<0.01$)

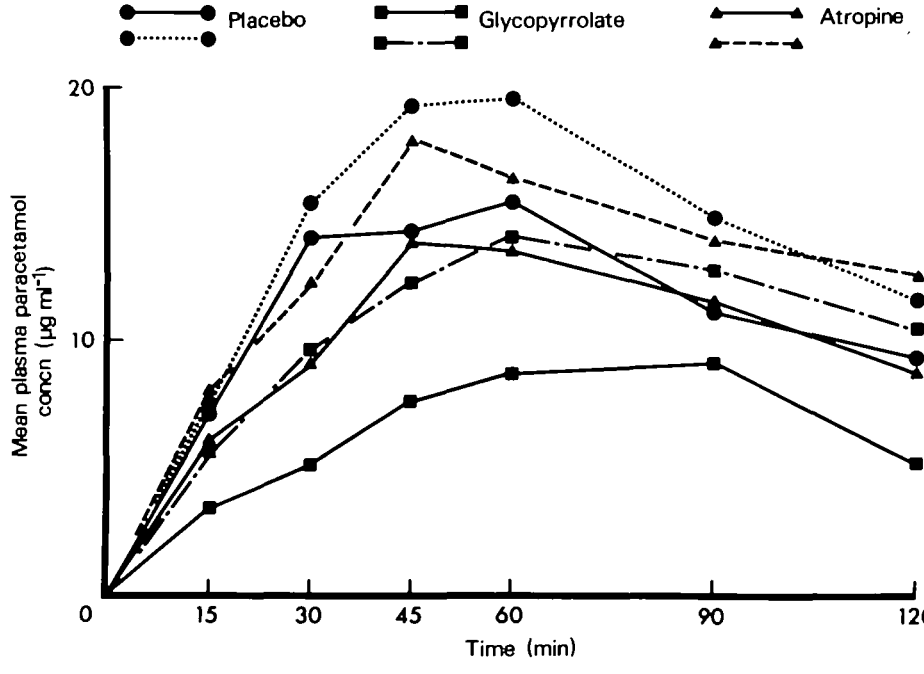

FIG. 1. Mean plasma paracetamol concentration following oral paracetamol 20 mg kg^{-1} at 0 min. Broken lines show concentrations in non-pregnant patients ($n = 10$ for each group); solid lines show concentrations in first-trimester pregnant patients ($n = 10$ for each group).

and patients treated with glycopyrrolate had smaller plasma paracetamol concentrations than those treated with atropine ($P<0.01$).

Paracetamol appeared in venous blood within 15 min of oral administration in all patients. The interval from administration of paracetamol to the time of peak plasma paracetamol concentration was not significantly different in any of the groups of patients.

The area under the plasma paracetamol concentration curve was less in pregnant than in non-pregnant patients after 45, 60 and 120 min ($P<0.05$), and was less in both pregnant and non-pregnant patients treated with glycopyrrolate compared with those treated with placebo after 45, 60 and 120 min ($P<0.01$) (table III). This contrasts with the insignificant difference at any time interval in patients treated with atropine when compared with placebo ($P>0.1$). The area under the plasma paracetamol concentration curve was less in both pregnant and non-pregnant patients when treated with glycopyrrolate compared with those treated with atropine at 45 min and 120 min ($P<0.05$), although at 60 min this difference was only apparent in pregnant patients ($P<0.05$).

TABLE III. *Area under paracetamol curve (arbitrary units) (mean values ± SD)*

	Time after drug administration (min)		
	45	60	120
Non-pregnant			
Placebo	32.6 ±11.0	53.7 ±16.5	114.9 ±33.6
Atropine	29.5 ±12.8	43.0 ±24.1	105.9 ±26.3
Glycopyrrolate	19.1 ±9.8	30.7 ±14.8	73.0 ±26.3
First-trimester pregnancy			
Placebo	29.9 ±8.8	44.7 ±12.2	91.8 ±23.1
Atropine	22.0 ±6.7	35.8 ±14.2	80.2 ±25.6
Glycopyrrolate	12.4 ±6.35	20.7 ±10.7	54.5 ±22.3

DISCUSSION

Even in early pregnancy there was a decrease in the uptake of paracetamol after oral administration. This is contrary to the findings of Nimmo, Wilson and Prescott (1975) who reported normal absorption in 12 women in labour and 10 post-partum women. However, no comparison was made with patients who had not recently been pregnant. The administration of glycopyrrolatate produced considerable decreases in the plasma paracetamol concentration and the area under the paracetamol concentration curve (total amount of paracetamol absorbed). Since the area under the curve 1 h after administration of paracetamol closely relates to gastric emptying (Nimmo et al., 1975), it would appear that glycopyrrolate i.v. decreased gastric emptying.

Saiphoo, Bingham and Cramp (1968) using a phenol-red test meal to measure gastric emptying in patients with gastric disorders, suggested that glycopyrrolate s.c. in doses similar to those used in the current study produced a decrease in gastric emptying.

However, Young and Sun (1962) and Posey and colleagues (1965), failed to demonstrate any decrease with glycopyrrolate by mouth. As glycopyrrolate is a quarternary ammonium compound, its gastrointestinal absorption would be poor, which might explain the lack of effect.

Certainly, Young and Sun showed a decrease in antral motility with either 0.2 mg or 0.5 mg of glycopyrrolate s.c., but gastric emptying was not assessed with parenteral treatment.

In the present study atropine, given in what is generally regarded as the dose equivalent to glycopyrrolate failed to produce any significant decrease in paracetamol absorption when compared with controls. This was a consistent finding in both pregnant and non-pregnant patients, but is surprising since atropine, in similar dosage, has been shown to delay the absorption of pivampicillin and tetracycline (Gothoni et al., 1972) and mexiletine (Wing et al., 1980). Another anticholinergic agent, propantheline has been shown to decrease the absorption of paracetamol (Nimmo et al., 1973) and ethanol (Gibbons and Lant, 1975).

Saiphoo, Bingham and Cramp (1968) found atropine and glycopyrrolate produced similar decreases in gastric emptying in dyspeptic patients.

The present results might suggest that the relative potency of glycopyrrolate and atropine varies according to the effect being observed. Such variable potency has been suggested for cardiovascular effects (Ostheimer, 1977; Mirakhur, Dundee and Clarke, 1977; Mirakhur, Jones and Dundee, 1980), antisialagogue activity (Mirakhur, Dundee and Jones, 1978) and protection against the effects of neostigmine (Mirakhur et al., 1981).

If the area under the venous paracetamol concentration curve relates closely to gastric emptying (Nimmo et al., 1975) the present results suggest that glycopyrrolate decreases gastric emptying by 40–50%. Since the dose of glycopyrrolate used by Baraka and colleagues (1977) was larger than that used in the present study, it might be expected that treatment with the drug to increase gastric pH in pregnant patients carries the risk of significantly decreasing gastric emptying and thus increasing the risk of regurgitation.

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LA VIDANGE GASTRIQUE APRES PREMEDICATION AU GLYCOPYRROLATE OU A L'ATROPINE

RESUME

Une étude en double aveugle des effets du glycopyrrolate ou de l'atropine i.v. sur la vidange gastrique a été entreprise chez 30 femmes enceintes et chez 20 qui ne l'étaient pas. La vidange gastrique, estimée grâce à la captation du paracétamol administré per-os était plus mauvaise au cours du premier trimestre de la grossesse qu'en dehors de toute grossesse. Après administration de glycopyrrolate, la vidange gastrique était également plus lente chez les femmes non enceintes et se ralentissait encore chez les femmes enceintes.

MAGENENTLEERUNG NACH PRÄMEDIKATION MIT GLYKOPYRROLAT ODER ATROPIN

ZUSAMMENFASSUNG

Bei 30 schwangeren und 30 nicht-schwangeren Frauen wurde eine Doppelblindstudie des Effekts von Glykopyrrolat und Atropin i.v. auf die Magenentleerung durchgeführt. Die Magenentleerung, die durch die Aufnahme oral verabreichten Paracetamols geprüft wurde, war bei Patientinnen im ersten Schwangerschaftsdrittel verzögert gegenüber nichtschwangeren Patientinnen. Nach Gabe von Glykopyrrolat war die Magenentleerung bei nicht-schwangeren Patientinnen verzögert, bei schwangeren Patientinnen noch mehr verzögert.

VACIADO GASTRICO A RAIZ DE PREMEDICACION CON GLICOPIRROLATO O ATROPINA

SUMARIO

Se sometió a 30 mujeres embarazadas y a otras 30 no embarazadas a un estudio de doble anonimato sobre los efectos del glicopirrolato o de la atropina intravenosa en el vaciado gástrico. El vaciado gástrico se evaluó mediante la absorción de paracetamol administrado oralmente y disminuyó en las pacientes con embarazo del primer trimestre cuando se las comparó con las no embarazadas. A raiz de la administración de glicopirrolato, el vaciado gástrico disminuyó en aquellas pacientes no embarazadas, disminuyendo aún más en las embarazadas.