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THE EFFECT ON PARACETAMOL ABSORPTION OF STIMULATION AND BLOCKADE OF β-ADRENOCEPTORS

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1 The effect of drugs acting on β-adrenoceptors on the absorption and excretion of paracetamol was studied in 26 volunteers and nine patients with mild hypertension, each subject acting as his/her own control.

2 Isoprenaline given 30 min before paracetamol significantly slowed absorption, the effect being dose related, and blocked by prior administration of propranolol.

3 When isoprenaline was given immediately before the paracetamol, absorption was not altered, although a cardiovascular response was seen.

4 Oral salbutamol also delayed paracetamol absorption.

5 Propranolol given alone increased the rate of paracetamol absorption.

6 These results correlate with the changes in the rate of gastric emptying produced by these agents.

Introduction

Drugs whose actions are through stimulation or blockade of β-adrenoceptors are widely used in the treatment of respiratory and cardiovascular diseases. However, similar receptors are found throughout the body and are involved in regulating a variety of physiological functions, any of which might be modified by the action of drugs which alter the response of these receptors to adrenergic stimuli, e.g. such drugs significantly alter the rate of gastric emptying by this means (Rees, Barber, Clark, Holdsworth & Howlett, 1978). Such actions may influence the pharmacokinetics of drugs taken together with the adrenergic agents and this might have therapeutic signifcance.

The present study investigates the effects on the absorption and excretion of paracetamol of the two β-adrenoceptor stimulators, isoprenaline and salbutamol and of the β-adrenoceptor blocking agent, propranolol. The paracetamol was administered after a standard meal, which formed part of a simultaneous gastric emptying study, allowing comparison of the effect on absorption with that on gastric emptying.

Method

Twenty-six healthy volunteers and nine patients with mild hypertension, aged 18–55 years, were studied. Their informed consent was obtained. Each patient acted as his/her own control. Only trial drugs were taken for the duration of the investigation. Paracetamol alone was given for the control study and at least one further investigation conducted while receiving selected trial drugs. The order of the studies was randomised.

After fasting for 8 h the patients were given a meal of meat, potatoes and peas, followed by 1.5 g of paracetamol (three crushed tablets) with 10 ml of water. Venous blood (10 ml) was withdrawn through an indwelling cannula before and at 20, 40, 60, 80 and 100 min after receiving the paracetamol. The blood was immediately centrifuged and the plasma frozen to await analysis.

In four cases two 24 h urine collections were made, divided into six-hourly periods, 0–6 h, 6–12 h, 12–18 h and 18–24 h after paracetamol. The first collection was on paracetamol alone and the repeat after taking 168 mg propranolol daily for 1 week. After measuring the 6 hourly volume a 20 ml sample was frozen to await analysis. The plasma and urine samples were analysed for free and conjugated paracetamol using the gas chromatographic method described by Prescott (1971a, 1971b).

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Drugs studied

Isoprenaline (10 or 20 mg tablets dissolved sublingually) Six subjects were given 10 mg and six subjects 20 mg 30 min before the paracetamol and a further three subjects were given 20 mg of isoprenaline immediately before the meal. Four patients received 20 mg isoprenaline 30 min before one meal and on another occasion had repeated 20 mg doses of isoprenaline given at 30, 15 and 5 min before the paracetamol.

In five patients 20 mg isoprenaline was given 30 min before the paracetamol and the same procedure repeated after 1 week on propranolol 40 mg four times daily, the last dose being taken less than 2 h before the meal.

After each administration of isoprenaline the pulse rate was recorded for up to 40 min to assess cardiocascular response.

Salbutamol (4 mg tablets) Four subjects took 4 mg salbutamol four times daily for 1 week, the last dose being taken between 1 and 2 h before the paracetamol.

Propranolol (20 or 40 mg tablets) Nine patients were given 20 mg propranolol four times daily for 24 h, then 40 mg four times daily for 1 week, the last dose being taken less than 2 h before the paracetamol.

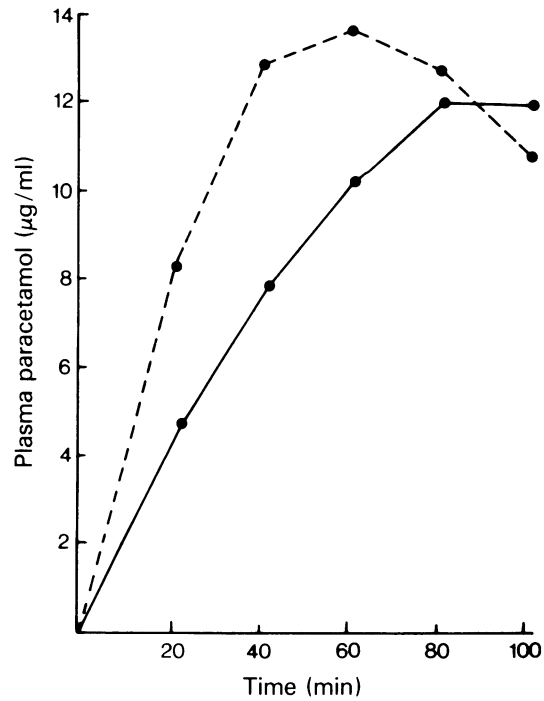

Figure 1 Mean plasma paracetamol curves for the twelve patients given isoprenaline 30 min before the paracetamol (—) and their control studies (- - -).

Results

There were wide variations in the results between individuals but as each acted as his/her own control, the matched differences were analysed using standard statistical methods (Student's *t*-test), and the standard errors quoted refer to these differences (Industrial Experimentation, H.M.S.O., 1956).

Response to isoprenaline

As there was no difference between the effect of the 10 mg and 20 mg doses the mean plasma paracetamol curves for the 12 patients given isoprenaline 30 min before the paracetamol and corresponding control studies are shown together in Figure 1. Isoprenaline produced significant lowering of the 20 min ($P<0.05$) and maximum ($P<0.01$) paracetamol levels and delay in the time needed to reach peak levels ($P<0.001$).

The mean results for the three cases given isoprenaline immediately before the paracetamol showed no significant alteration in the 20 min or maximum paracetamol levels nor in the peak times e.g. control 2.5 and 10 μg/ml and 80 min, post-isoprenaline 3.2 and 10.4 μg/ml and 80 min respectively.

Increasing the dose of isoprenaline produced progressive lowering of the mean 20 min paracetamol levels (control 10.7 μg/ml, single dose 4.8 μg/ml, and triple dose 1.7 μg/ml) with a delay in the mean peak times (control 50 min, single dose 85 min and triple dose greater than 100 min). The mean maximum level was lower following the single dose, but peak levels were not attained following the triple dose.

In every case there was a significant increase in the pulse rate within a few minutes of isoprenaline administration.

The effect of prior administration of propranolol on the isoprenaline response (Table 1)

The mean results for the five cases studied confirm that while isoprenaline significantly lowered the 20 min paracetamol levels ($P<0.05$) and delayed peak times ($P<0.01$); prior administration of propranolol not only completely blocked this effect, but appeared to increase the 20 min plasma level and to shorten the time needed to reach peak levels.

Response to salbutamol

The 20 min paracetamol levels were consistently lower (mean control 7.1 μg/ml, mean salbutamol 3.5 μg/ml) and the peak times delayed (mean contol 45 min, mean salbutamol longer than 85 min) but as two

Table 1 Modification of the isoprenaline effect by prior administration of propranolol

Study	*20 min paracetamol levels (μg/ml)*	*Peak times (min)*
1. The effect of isoprenaline		
(a) Control	7.2	60
(b) On isoprenaline	5.6	92
	($P<0.05$; s.e. 0.39)	($P<0.01$; s.e. 4.89)
2. The effect of isoprenaline while on propranolol		
(a) Control	7.2	60
(b) On isoprenaline and propranolol	11.9	48
	(NS: s.e. 2.78)	(NS: s.e. 7.99)

There were no significant differences in the maximum concentrations (s.e. = Standard error of the matched differences)

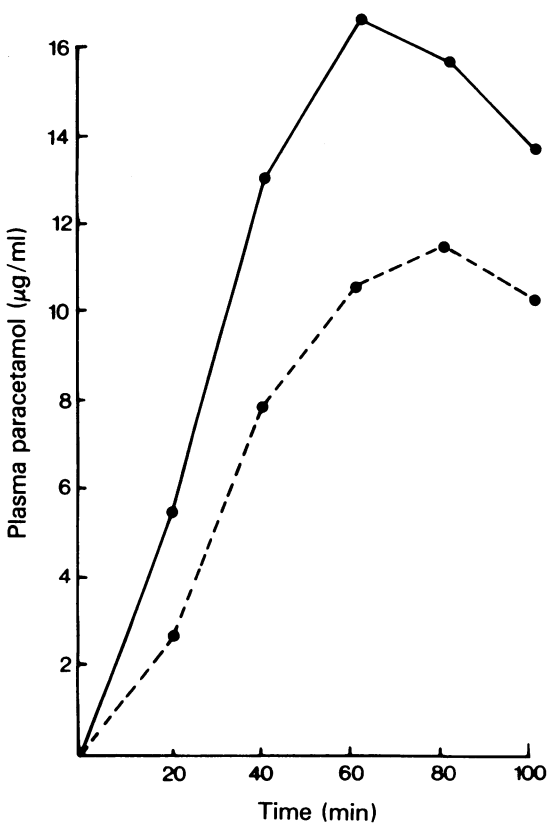

Figure 2 Mean plasma paracetamol curves for the nine patients given propranolol (—) and their control studies (---).

cases on salbutamol had not peaked by 100 min the mean maximum concentrations were not attained. The pattern resembles that observed with isoprenaline

The effects of propranolol

The mean plasma paracetamol curves for the nine patients taking propranolol alone and corresponding control studies are shown together in Figure 2. Propranolol significantly increased the 20 min ($P<0.01$) and maximum ($P<0.01$) paracetamol levels and shortened the peak time ($P<0.05$).

Urinary excretion of paracetamol while taking propranolol

Propranolol had no significant effect on the mean 24 h excretion of free (control 19.2 mg, propranolol 21.5 mg) or conjugated (control 631 mg, propranolol 1,016 mg) paracetamol in the four cases studied.

Discussion

Earlier studies have shown a relationship between the speed of gastric emptying and the rate of absorption for drugs absorbed from the upper small bowel, e.g. paracetamol (Rivera-Calimlin, Casteneda & Lasagna, 1973; Prescott, 1974). Drugs which alter the rate of gastric emptying can affect drug absorption through this mechanism, e.g. propantheline and tricyclic antidepressants slow gastric emptying and delay the absorption of paracetamol, alcohol and phenylbutazone (Nimmo, Heading, Tothill & Prescott, 1973;

Consolo, Morselli, Zaccala & Garattini, 1970; Hall, Brown, Carter & Kendall, 1976) while metoclopramide by stimulating gastric emptying increases the rate of paracetamol absorption (Nimmo *et al.*, 1973).

Recent work has shown that adrenergic stimulation significantly slows while β-adrenoceptor blockade speeds up gastric emptying and that under physiological conditions the β-adrenoceptor system exerts an inhibitory action on gastric emptying (Rees *et al.*, 1978). The changes in paracetamol absorption observed in our studies correlate well with the alterations in gastric emptying produced by these drugs. Slower absorption reflected in the lower 20 min plasma levels, and a decreased rate of gastric emptying occurred with β-adrenoceptor stimulation whether this was generalised (isoprenaline) or through the β receptors (salbutamol) while β-adrenoceptor blockade with propranolol speeded up both absorption and the rate of gastric emptying.

The role of the β-receptors is indicated by the action of propranolol in blocking the effect of isoprenaline on absorption. Of special interest is the time lag necessary to initiate the response to isoprenaline both with respect to absorption and gastric emptying, 30 min appearing optimal from our pilot studies. In contrast the rise in the pulse rate occurred immediately and some intermediate mechanism seems likely for the effect on the gastric emptying.

The bioavailability of paracetamol is not affected by its passage through the stomach and the drug is rapidly absorbed in the upper small bowel. Other drugs, i.e. levodopa, are inactivated in the stomach and the slower rate of gastric emptying the smaller the amount available for absorption (Bianchine, Calimlim, Morgan, Dujuvne & Lasagna, 1979). Conversely drugs, e.g. digoxin and riboflavin which have either specific absorption sites or incomplete absorption in the small bowel benefit from slower gastric emptying with better absorption and higher plasma levels (Manninen, Melin, Apajalahti & Karesoja, 1973; Levy, Gibaldi & Procknal, 1972). Alterations in adrenergic activity with the effects on gastric emptying might have a significant effect on both the total absorption and bioavailability of these drugs.

It is likely that the drugs active on adrenoceptors also influence small bowel mobility and the splanchnic blood flow although this has not been studied in man. Animal studies suggest that changes in these parameters are of secondary importance compared to variations in gastric emptying for drugs which are passively absorbed (Levine, 1970; Marcus & Lengemann, 1962).

These functions are likely to be of greater importance in the absorption of drugs using an active transport mechanism, i.e. if adrenergic stimulation slows small bowel motility digoxin absorption may be enhanced due to a longer contact time (Manninen *et al.*, 1973).

While the 20 min level may be influenced principally by absorption the maximum concentration reflects the overall balance between absorption, distribution, metabolism and excretion of paracetamol and alterations at any of these stages may affect the overall situation. The urinary excretion of free or conjugated paracetamol was not altered by giving propranolol in any of the 6 hourly collections over 24 h, but we did not look specifically at the important 0–2 h period. The remaining parameters were not studied.

The results indicate that drugs acting on β-adrenoceptors significantly alter the rate of absorption of paracetamol. In the case of paracetamol these effects may not be of clinical importance, but with drugs such as digoxin, mexiletine and warfarin where the therapeutic or toxic plasma levels are critical (Talbot, Clark, Nimmo, Neilson, Julian & Prescott, 1973) there may be of considerable alteration in the therapeutic response. This has importance in medical practice as agents acting on the adrenergic system are widely used in conjunction with other therapy.

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