There seems little doubt, however, that the enzyme-inducing activity of rifampicin enables the liver to handle the two drugs adequately within a few weeks. Few of our cases showed abnormalities of function later than the 12th week, and in the series of Lees *et al.* the initial reaction occurred within seven weeks with a mode at three weeks.

Histological data are available from liver biopsy in some patients showing hepatic abnormalities, and these data will be reported in detail elsewhere (Lal *et al.*, 1972), but in the main they support the view that the reactions are mild and non-specific.

We have no experience of the use of rifampicin and isoniazid in alcoholic patients or in those with evidence of liver damage from other causes, and we still feel that rifampicin should be avoided in such cases.

We would like to thank Professor Sheila Sherlock and her colleagues for their advice and help in carrying out this study, and we are also grateful to Ciba Laboratories for generous supplies of rifampicin. We would also like to thank the nursing staff of the chest unit for their precise recording of the results.

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PRELIMINARY COMMUNICATIONS

Prostaglandin-oxytocin Enhancement and Potentiation and their Clinical Applications

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Summary

The pharmacological phenomena of enhancement and potentiation of uterine response occur respectively when combinations of some prostaglandins and oxytocin are given serially and simultaneously to a patient. Employing these phenomena allows small doses of the drugs to achieve the same effects as a large dose given alone. In a pilot study of the use of the combination of prostaglandin and oxytocin for the induction of mid-trimester abortion seven of nine women were aborted within 48 hours. Side effects attributable to prostaglandin were eliminated or reduced in severity.

Introduction

Brummer (1971) demonstrated in this laboratory that after exposure to the E prostaglandins human pregnant myometrial strips in vitro show a greater contractile response to a given dose of oxytocin than before the exposure to the prostaglandin. This phenomenon is termed "enhancement." The enhanced response is seen for about one hour after the prostaglandin has been washed out of the water-bath and is peculiar to the E prostaglandins.

Prostaglandin E or F administered simultaneously with oxytocin exhibits the more usual "potentiation" of effects, in which the total response is greater than that expected by the direct addition of the two separate responses.

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The possibility of applying the phenomena of enhancement and potentiation clinically to induce mid-trimester abortion has been investigated. The aim of the investigation was to decrease the dose of prostaglandin administered and hence minimize the incidence of troublesome side effects.

Material and Methods

Patients in the mid-trimester of pregnancy admitted to hospital for hysterotomy were interviewed and offered the possibility of termination of the pregnancy by the vaginal route. The procedure was explained and only volunteers received the drugs.

The oxytocin (Syntocinon) and prostaglandins were administered into a large superficial arm vein through an indwelling polyethylene cannula (Bardic A catheter, 5·5 cm) by means of a Palmer constant infusion pump. Uterine activity was monitored via a fluid-filled polyethylene catheter (Portex 90 cm 100/380/150) introduced transabdominally into the amniotic sac and connected to a pen recorder (Devices M2) via a semiconductor strain-gauge pressure transducer and appropriate amplifier.

A preliminary investigation was carried out in seven patients. The dose and duration of infusion of prostaglandin E_2 (PGE_2) required to achieve an "enhanced" uterine response to subsequently infused oxytocin was determined. The time after infusion of prostaglandin E_2 during which the enhanced response could still be obtained was also determined. Finally, the doses of oxytocin infused simultaneously with either prostaglandin E_2 or prostaglandin $F_{2\alpha}$ to achieve the maximum potentiation of the drug effects were established. The pregnancies were then terminated by infusion of the previously described dose (Karim and Filshie, 1970a, 1970b; Gillespie *et al.*, 1971) of prostaglandin or by intra-amniotic injection of hypertonic saline.

Results

In Fig. 1 an intra-amniotic pressure tracing from a woman 16 weeks pregnant shows both enhancement and potentiation. Traces A, B, and C show the response of the uterus to an infusion of oxytocin progressively increasing from 16 mU/

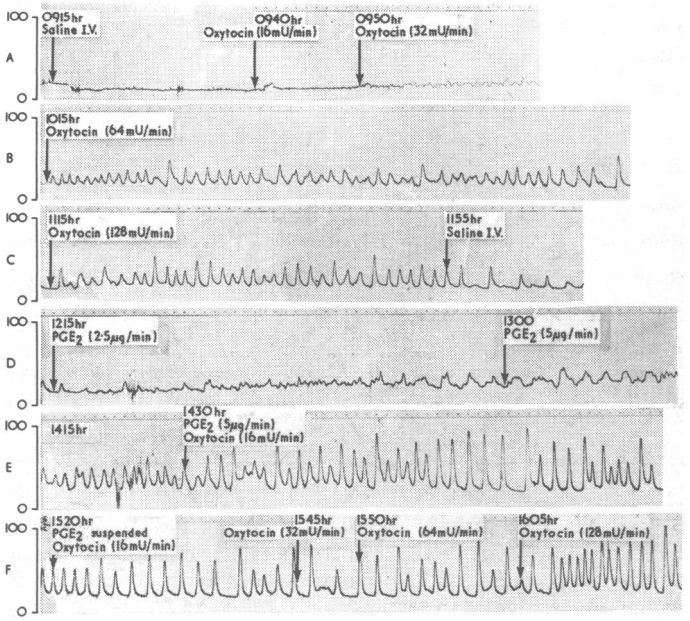

FIG. 1—Sixteen-week pregnancy. Intra-amniotic pressure record. Full-scale vertical deflection 100 mm Hg. Time scale, in minutes, upper margin of trace.

min to 128 mU/min. The rapid fall off in response when the oxytocin infusion was stopped is seen towards the end of trace C.

In trace D there is a progressively increasing response to the infusion of prostaglandin E_2 2·5 μg/min and 5 μg/min. In trace E at 1430 hr oxytocin 16 mU/min was added to the prostaglandin E_2 5 μg/min. The sharply increased amplitude of the uterine contractions (greater than the sum of the amplitudes of contractions achieved with prostaglandin E_2 5 μg/min and oxytocin 16 mU/min separately) in the remainder of trace E can be seen (potentiation).

At the beginning of trace F the prostaglandin E_2 was stopped. The response to oxytocin 16-128 mU/min was then greater than that seen in traces A, B, and C before prostaglandin infusion. Note that the enhancement still persists an hour after stopping the prostaglandin. By 90 minutes the response was decreasing but could be re-established by another short infusion of prostaglandin E_2. Only one patient was aborted with this technique alone. In practice the necessity to repeat the infusion of prostaglandin E_2 every one to one and a half hours proved too tedious to be applicable clinically. Prostaglandin $F_2\alpha$ does not enhance the response to subsequently infused oxytocin in vitro. No attempt was made to confirm this in vivo.

A record of the activity in a 16-weeks pregnant uterus is given in Fig. 2. Traces A, B, C, and D are continuous and each lasts one and a half hours. Basal uterine activity is shown

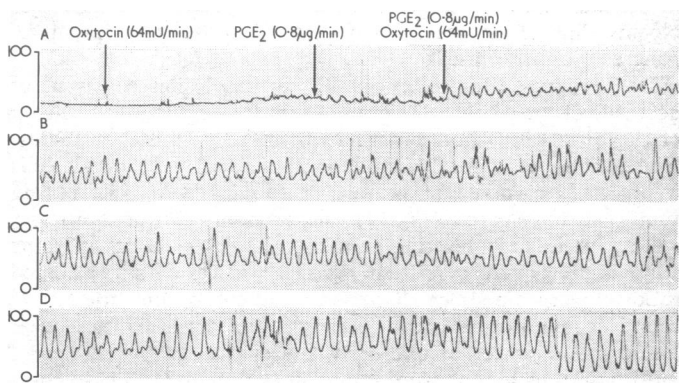

FIG. 2—Sixteen-week pregnancy. Continuous record of intra-amniotic pressure during infusion of prostaglandin E_2 0·8 μg/min and oxytocin 64 mU/min. Full-scale vertical deflection 100 mm Hg. Time scale, in minutes, upper margin of trace. Each trace one and a half hours.

in the initial 10 minutes of trace A. A slight increase in activity occurred during the 20-minute infusion of oxytocin at 64 mU/min and during the 20-minute infusion of prostaglandin E_2 0·8 μg/min that followed. In the last third of trace A the potentiated myometrial response to the infusion of the drugs together can be seen. Traces B, C, and D show the progressive evolution of uterine activity observed when this combination of drugs is given. The amplitude of contractions and the basal uterine tone can be seen to increase. The recording was "offset" by 30 mm Hg in the final 15 minutes of trace D to show the 100 mm Hg amplitude contractions occurring at that time. These contractions were recorded for a further half-hour till the membranes ruptured. Complete abortion occurred three and a half hours later.

In addition to this patient the combination of prostaglandin and oxytocin was given to a further eight patients and the results are summarized in the Table. The oxytocin was always

Results of Intravenous Infusion of Prostaglandin and Oxytocin to Women in Mid-trimester of Pregnancy

Age	Parity	Gestation (weeks)	Prostaglandin	I.D.I. (hr)
34 ..	2	16	E_2 0·8 μg	10
30 ..	2	18	E_2 1 μg	Stopped at 12
24 ..	0	14	$F_2\alpha$ 10 μg	Stopped at 24
18 ..	0	18	$F_2\alpha$ 10 μg*	45
26 ..	0	18	$F_2\alpha$ 10 μg	20
21 ..	1	16	$F_2\alpha$ 10 μg	18
21 ..	0	17	$F_2\alpha$ 10 μg*	46
20 ..	0	19	E_2 1 μg*	29
19 ..	0	20	$F_2\alpha$ 10 μg*	42

*Doubled at 24 hours.
I.D.I. = Induction-delivery interval.

infused at 64 mU/min; six of the patients received prostaglandin F_2 at 10 μg/min, and two prostaglandin E_2 at 1 μg/min. In most cases the rate of infusion of both drugs was doubled if abortion had not occurred after 24 hours.

Seven of the nine women were aborted within 48 hours. Vomiting occurred immediately before abortion in only two women. Diarrhoea did not occur. All patients experienced pain in the arm at and above the infusion site.

Discussion

The major disadvantage to the termination of mid-trimester pregnancy by prostaglandin infusion is that the dose necessary to produce effective uterine contractions is only moderately less than that which will cause gastrointestinal stimulation. Karim and Filshie (1970a, 1970b) reported vomiting or diarrhoea or both in half the women receiving prostaglandin $F_2\alpha$ and 20% receiving prostaglandin E_2. Wigvist and Bygdeman (1970) also reported a high incidence of diarrhoea during the infusion of prostaglandin $F_2\alpha$. Any technique which decreased the side effects of prostaglandin infusion without significantly decreasing the efficacy would therefore be of advantage. Burnhill *et al.*, (1962) had previously shown that enormous doses of oxytocin alone, though not causing serious side effects, are ineffective in producing abortion.

Enhancement of responses to other agonists is a specific property of the E prostaglandins and has been previously shown in vitro using guinea-pig myometrium by Clegg *et al.* (1966) and lately by Brummer (1971) using human pregnant myometrium. Enhancement can still be demonstrated in depolarizing media. This suggests that the prostaglandin E produces the enhancement by an action at an intracellular site, possibly by facilitation of intracellular excitation-contraction coupling rather than by facilitating cell-to-cell conduction.

This study has shown that the intact pregnant human uterus responds in the same way as the myometrial strips in that it exhibits an enhanced response to oxytocin after previous exposure to prostaglandin E_2. Application of this phenomenon did not prove clinically useful.

A physiological role for the prostaglandins in parturition whereby these substances cause the uterus to contract by enhancing the myometrial response to circulating endogenous oxytocin can at present be only an interesting hypothesis, but the recent development of accurate methods of measuring plasma oxytocin and prostaglandin during labour may allow it to be tested soon.

Encouraging results have been obtained with the potentiation of the uterine response exhibited when oxytocin and prostaglandin $F_{2\alpha}$ or prostaglandin E_2 are administered simultaneously. This technique enables the prostaglandin to be infused at one-fifth the usual abortifacient dose and virtually eliminates gastrointestinal side effects. The preliminary work suggests that the abortifacient efficiency of this combination is high, probably because the prostaglandin enables the oxytocin to exert its very specific stimulatory action on the myometrium in an efficient manner. A more detailed study of the use of the potentiation of oxytocin and prostaglandin effects to produce mid-trimester abortion is underway.

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Nephrotoxic Lesions from 5-Aminosalicylic Acid

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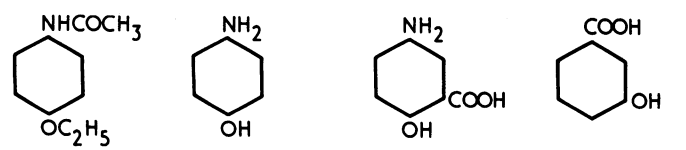
Summary

5-Aminosalicylic acid given to rats as a single intravenous injection led to necrosis of the proximal convoluted tubules and of the renal papilla. These two lesions developed at the same time and the cortical lesions did not appear to be a consequence of the renal papillary necrosis. Since the compound possesses the molecular structure both of a phenacetin derivative and of a salicylate these observations may be relevant to the problem of renal damage incident to abuse of analgesic compounds and suggest the possibility that in this syndrome cortical lesions may develop independently of renal papillary necrosis.

Introduction

5-Aminosalicylic acid has structural similarities to both the *p*-aminophenol-derived phenacetin analgesics and the salicylates (see Formula). In a study of the comparative nephrotoxicity of aspirin and phenacetin derivatives (Calder, Funder, Green, Ham, and Tange, 1971) 5-aminosalicylic acid was found to have the unique property of inducing both necrosis of proximal convoluted tubules and renal papillary necrosis. In this paper we are concerned with the evolution of the renal lesion produced by 5-aminosalicylic acid and its possible relation to renal damage associated with prolonged and excessive intake of compound analgesic preparations.



Phenacetin — *p*-Aminophenol — 5-aminosalicylic acid — Salicylic acid

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Methods

Sixty female hooded rats weighing about 200 g were given water to drink and a pellet diet. Animals were individually marked, anaesthetized with ether, and given a single intravenous injection of the sodium salt of 5-aminosalicylic acid in a dose of 1·4, 2·8, or 5·7 mM/kg. Animals were killed in pairs by bleeding under ether anaesthesia 24, 48, and 96 hours and one and two weeks after injection. Ten animals were used as controls and given a single intravenous injection of 1 ml of normal saline. Twenty animals were killed six hours after a single intravenous injection of 5-aminosalicylic acid 5·7 mM/kg. Tissues were fixed in 10% formalin and processed for paraffin embedding or in glutaraldehyde and osmium tetroxide for embedding in Araldite for thin sections and examined by light microscopy.

Kidney and muscle K^+ was measured by flame photometry in 10 control animals and in 20 experimental animals killed 24 hours after intravenous injections of 5-aminosalicylic acid (5·7 mM/kg).

Results

The animals became cyanosed after the injection of 5-aminosalicylic acid; this effect was transient. All the animals recovered from the effects of injection and anaesthesia and remained apparently well until killed. Lesions were found only in the kidneys, both the cortex and the medulla being affected. No histological changes were found in the heart, lungs, liver, pancreas, or intestine.

By 24 hours after injection the cortical lesion consisted of necrosis of proximal convoluted tubular epithelium, usually of the distal third but sometimes in more proximal segments. The lesions were focal, involving individual cells or all cells in isolated segments or groups of tubules, with intervening tubules being spared (Fig. 1). At 48 hours frequent mitoses were seen in neighbouring tubule cells. At 96 hours in some animals there were persistent signs of cortical damage; dilated tubules were lined by flattened epithelium and interstitial round-cell infiltrates were present. No abnormalities were found in the cortex at one or two weeks.

A variety of lesions were found in the medulla. These comprised necrosis of the tip of the papilla (Fig. 2) or of a portion of the tip or sometimes partial necrosis affecting Henle's loops, vessels, and interstitial cells but sparing the collecting