stant of gentamicin. The K value of gentamicin may therefore be taken as the sum of the mean value of elimination constant of each nephron (k). If we denote the number of functioning nephrons as N, this assumption may be expressed by the following aquation:

$$K = N \times k \quad (2)$$

The present findings indicate that compensatory hypertrophy in adult rats is not attended by an increase in N[5]. If we presume that, in normal conditions, there is a direct relation between KW and N, changes in k after reduction of renal parenchyma may be calculated according to the formula:

$$\frac{k_R}{k_N} = \frac{K_R}{K_N} \times \frac{KW}{KW - E} \quad (3)$$

where K_R and k_N = elimination constant per nephron in reduced and in normal renal parenchyma, respectively. K_R and K_N = elimination constant after reduction of renal parenchyma and under normal conditions, respectively.

Results. The results obtained are summarized in the table. The reduction of the number of nephrons to 50% caused no changes in K of gentamicin, as compared with healthy animals. If the reduction of p was more than 50% of the normal value, the K value decreased in linear relation to p (see figure). Calculated k_R/k_N showed the value of elimination constant per nephron for gentamicin in residual nephrons to be 1.73–1.95 times higher than in normal nephrons. In other words, the elimination constant of gentamicin per nephron under these conditions approximately doubled.

Discussion. The results based on the renal elimination of gentamicin indicate that the reduction of the number of functioning nephrons to 50% of the normal value was fully compensated by the residual nephrons. Calculations of the elimination constant per residual nephron indicate that the increase of gentamicin elimination per nephron can be maximally doubled. The mechanism underlying the increase of gentamicin elimination by residual nephrons cannot be explained on the basis of these experiments. Theoretically, the increase in glomerular filtration rate and the changes in tubular transport of gentamicin should be taken in account.

Pharmacokinetic parameters of gentamicin in rats with reduced renal parenchyma

	(KW–E)× 100/KW[a]	K[b] (h^{-1})	$t_{0.5}$[c] (h)	k_R/k_N[d] –
With both kidneys (normal rats)	100	1.29	0.52	1.00
After unilateral nephrectomy	50	1.26	0.55	1.95
After unilateral nephrectomy and resection of proximal pole of second kidney	37	0.87	0.80	1.81
After unilateral nephrectomy and resection of proximal and distal poles of second kidney	22	0.49	1.41	1.73
After bilateral nephrectomy	0	0.032[e]	22.00[e]	–

[a] See formula 1; [b] elimination constant; [c] half-life; [d] see formula 3; [e] 20 h after bilateral nephrectomy. Number of animals in all groups was not less than 25.

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A tissue-selective prostaglandin E_2 analog with potent antifertility effects

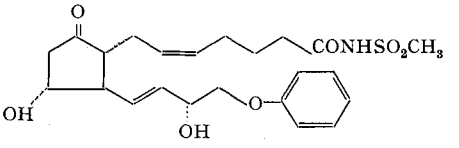
H.-J. Hess, J. S. Bindra, J. W. Constantine, W. Elger, O. Loge, E. Schillinger and W. Losert

Central Research, Pfizer Inc., Groton (Connecticut 06340, USA); and Research Laboratories, Schering A.G., Berlin/Bergkamen, D–1000 Berlin 65 (Germany), 10 January 1977

Summary. N-methanesulfonyl 16-phenoxy-ω-tetranor PGE_2 is a prostaglandin analog which is markedly more tissue selective than PGE_2. This compound is 10–30 times more potent than PGE_2 in animal models which are considered relevant to antifertility effects in humans. In pharmacological tests which are believed to be predictive for side effects in humans, the compound has potency either equal to or less than that of PGE_2.

Achievement of tissue selectivity and metabolic stability are important requirements for the realization of the potential therapeutic usefulness of prostaglandins[1,2]. To this end, one line of research pursued in our laboratories has been the modification of the carboxyl terminus of the prostaglandins. These studies have shown that replacing the carboxyl group in PGE_2 by a methylsulfonyl carboxamido group results in the complete retention of uterine smooth muscle stimulant activity, while other PGE_2-like effects are markedly diminished. Parallel investigations have established that appropriate alterations in the ω-chain of prostaglandins greatly affect potency. This report describes the relevant properties of a PGE_2 analog modified in both the α- and ω-chain, which appears to fulfill the criteria of a potentially useful agent for fertility control in humans, based on its abortifacient potency, metabolic stability, and selectivity of action.

The compound, N-methanesulfonyl 16-phenoxy-ω-tetranor PGE_2 carboxamide, CP-34,089 (ZK 57 671), is a white, crystalline powder, melting at 78.5–80 °C, which is sparingly soluble in water (0.5 mg/ml) and readily soluble in ethanol (> 100 mg/ml).



CP-34,089 (ZK 57 671)

The antifertility effects of CP-34,089 were compared with those of PGE_2 in 3 experimental models (rat, guinea-pig, and rhesus monkey), which distinguish between luteo-

lysis and stimulation of uterine smooth muscle as the mechanism by which pregnancy is interrupted[3,4].

CP-34,089 and PGE_2 were dissolved in castor oil and ethyl benzoate (3:1), and administered s.c. to Wistar rats (weight 200–250 g) daily from the 4th to 7th day of pregnancy. Following sacrifice of the animals on day 9, the implantation sites were counted. Luteolysis was assessed by examination of the corpora lutea at autopsy and determination of serum progesterone levels by radioimmunoassay on day 3, 5, 7 and 9 of pregnancy. The fully effective dose of CP-34,089 was 0.3 mg/animal day (threshold 0.1 mg, 5/12 animals). The threshold dose (3/4 animals of PGE_2 in this test was 1 mg (no effect at 0.3 mg). With both compounds, clearly lowered serum progesterone concentrations were observed only after completion of the treatment phase, which suggests that luteolysis alone cannot account for the observed antifertility effects. This suggestion is supported by the observation that progesterone administration (2 mg/day, s.c.) only partially prevented the antifertility effects of PGE_2.

In guinea-pigs placental progesterone is sufficient to maintain pregnancy after the 25th day, as shown in ovariectomy studies[5]. After this time, pregnancy can be interrupted by an effect on the uterus but not by luteolysis. This model, therefore, is considered more relevant to antifertility effects in humans, because prostaglandins do not appear to terminate human pregnancy by luteolysis[6].

CP-34,089 and PGE_2 were administered s.c. to guinea-pigs (Wellcome breed; 700–1000 g) on days 43 and 44 of gestation. Autopsy was performed on day 50 and uteri, ovaries and vaginas were inspected. Serum progesterone levels were determined by radioimmunoassay on days 42, 44, 46, 48 and 50. Complete abortion was observed with CP-34,089 at doses of 0.3 mg/animal day (10/10 animals); threshold 0.03 mg (3/10 animals). In most animals, the fetuses and placentas were expelled a few h after the first or second dose. The fully effective dose of PGE_2 was 3 mg (threshold 1 mg, 3/9 animals). With both PGE_2 and CP-34,089, serum progesterone concentrations decreased markedly only after abortion, and progesterone administration (4 mg/day, s.c.) during days 42–49 failed to prevent pregnancy termination (0/7 animals). These data indicate that the abortifacient effect of CP-34,089 in this guinea-pig model is 10–30 times that of PGE_2, and permit the conclusion that the effect is due to direct stimulation of the uterus.

To demonstrate abortifacient activity in the pregnant rhesus monkey[7], 3 animals (weight 5–5.5 kg) between day 20 and 23 of pregnancy received 3 s.c. doses of 1.5 mg of CP-34,089 12 h apart. Marked vaginal bleeding indicating the beginning of abortion occurred in all animals approximately 12 h after the first dose, and generally continued for several days. Termination of pregnancy was confirmed by rectal palpation of the uterus. With PGE_2, pregnancy was terminated in 3 out of 4 animals at doses of 15 mg. There was a moderate decline in serum progesterone only at the time of intensive uterine bleeding. Progesterone (10.0 mg/day, s.c., days 21–24) failed to prevent termination of pregnancy in 2 animals treated with CP-34,089 on days 22 and 23 of gestation. On the basis of these results, abortion in this species also appears to result from direct uterine stimulation, with CP-34,089 again exhibiting at least a 10fold potency advantage over PGE_2.

In spite of the greater abortifacient potency of CP-34,089 in vivo, several lines of evidence suggest that CP-34,089 and PGE_2 have the same intrinsic activity on the uterus. The 2 compounds were equi-potent in vitro in causing isotonic contractions of the isolated rat (natural estrus and estrus induced by diethylstilbestrol) and guinea-pig uterus. Furthermore, no significant difference was observed between the 2 compounds (concentration range 10^{-8}–10^{-4} M) in displacement of ^{3}H-PGE_2 from binding sites of a membrane receptor fraction isolated from human uterine tissue. The greater abortifacient potency may be due to resistance to enzymatic inactivation, since CP-34,089, in contrast to PGE_2, was not a substrate (10^{-8} M) for prostaglandin C_{15}-OH dehydrogenase from monkey lung.

Nausea, vomiting and diarrhea, the principal limiting side effects of the prostaglandins, generally appear to parallel the activity of these compounds as stimulants of the smooth musculature of the gastrointestinal tract and as promoters of fluid accumulation in the small intestine[8]. In contrast to their comparable uterine stimulant effect in vitro, CP-34,089 was only $^1/_{10}$ as potent as PGE_2 as a stimulant of the isolated guinea-pig ileum in vitro. Although in vivo CP-34,089 and PGE_2 were approximately equi-potent in causing diarrhea in mice (ED_{50} 0.48 mg/kg, i.v.) and in increasing intestinal motility in this species, CP-34,089 is 10–30 times more potent than PGE_2 in its abortifacient effects in vivo, as described above.

CP-34,089 was significantly less potent than PGE_2 with respect to 2 other prominent effects, viz. bronchodilation and vasodilation (hypotension). Significant tracheal relaxant activity could not be demonstrated with CP-34,089 in vitro (guinea-pig), and there was no bronchodilator activity in vivo (antagonism of histamine induced bronchoconstriction in conscious guinea-pigs). Unlike PGE_2, CP-34,089 did not antagonize the stimulant effect of norepinephrine on the rabbit vena cava in vitro, and the threshold hypotensive dose in anesthetized dogs was 20 µg/kg i.v., vs. 0.1 µg/kg i.v., for PGE_2. In addition, in anesthetized rabbits, CP-34,089 caused a greater effect on uterine motility, and had a more prolonged effect on intrauterine pressure compared to PGE_2; other organ functions (blood pressure, intestinal pressure, heart rate, respiratory rate and volume) recorded simultaneously were either not affected or less affected than with PGE_2. These results clearly show that CP-34,089 is markedly more tissue selective than PGE_2.

Initial studies in humans have confirmed the greater abortifacient potency and enhanced tissue selectivity (reflected as better toleration) of CP-34,089 compared to PGE_2.

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