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Pharmacokinetics and pharmacodynamics of the aromatase inhibitor 3-ethyl-3-(4-pyridyl)piperidine-2,6-dione in patients with postmenopausal breast cancer*

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Summary. The pyridylglutarimide 3-ethyl-3-(4-pyridyl)-piperidine-2,6-dione (PyG) is a novel inhibitor of aromatase that was shown to cause effective suppression of plasma oestradiol levels in postmenopausal patients. In four patients receiving oral doses of PyG (500 mg) twice daily for 3–4 days, oestradiol levels fell to 31.1% ± 6.3% of baseline values within 48 h and remained suppressed during treatment. Of a further six patients who received oral PyG (1 g) as a single dose, five had quantifiable oestradiol levels. Oestradiol suppression was sustained for 36 h and recovery correlated with a fall of PyG concentrations below a threshold value of ca. 2 μg/ml. The pharmacokinetics of PyG were non-linear and, when fitted to the integrated Michaelis-Menten equation, yielded good parameter estimates for C_o (21.7 ± 1.82 μg/ml), K_m (2.66 ± 0.68 μg/ml) and V_{max} (0.86 ± 0.06 μg ml^{-1} h^{-1}). On subsequent repeated dosing with PyG, both the K_m (4.31 ± 0.48 μg/ml) and the V_{max} (1.83 ± 0.13 μg ml^{-1} h^{-1}) values increased and recovery from oestradiol suppression was more rapid, indicating that PyG induces its own metabolism.

Introduction

Aromatase inhibition is an effective means of treating hormone-dependent advanced breast cancer in postmenopausal patients. Aminoglutethimide (AG) is the only widely used agent having this mechanism of action [15] but it also inhibits an early step in steroidogenesis, cholesterol side-chain cleavage (CSCC), as well as 11β-hydroxylase activity necessitating corticosteroid replacement therapy [5, 25]. More recently, a potent steroidal aromatase inhibitor, 4-hydroxyandrostenedione, has proved to be clinically effective, but it is most effective when given i.m. [31]. A number of non-steroidal aromatase inhibitors are currently being developed as alternatives to AG, and the present report concerns the first studies in humans of one such agent developed in our laboratories, 3-ethyl-3-(4-pyridyl)piperidine-2,6-dione [2-ethyl-2-(4-pyridyl)glutarimide] (PyG).

PyG is an analogue of AG that shows similar inhibitory potency against aromatase but has no effect on CSCC [8]. In experimental studies, PyG showed two additional potential advantages over AG. Firstly, the major metabolite of PyG in the rat and rabbit is PyG N-oxide [29] which is not expected to be toxic. In contrast, one of the two major metabolites of AG in humans, the N-hydroxyderivative [11], belongs to a class of compound known to cause haematologic toxicity and, indeed, a small but significant proportion of patients given AG manifest such toxicity [22]. Secondly, in standard tests of CNS effects in mice, PyG lacked the sedative and other CNS effects caused by AG [9], which are also produced by AG in clinical use [15]. Administration of PyG to mature female rats had no significant effect on plasma oestradiol levels, but luteinizing hormone (LH) levels were significantly elevated, indicating a compensated suppression of ovarian oestrogen synthesis (unpublished results). Although analogues of PyG with far greater potency towards aromatase have been synthesised [13], the most potent such analogues, the C- and N-octyl derivatives, were both extensively metabolised, leading to a half-life for the C-octyl derivative, in rabbits that was about 20 times lower than that of PyG [30]. PyG therefore remained the preferred clinical candidate.

This report relates the results of studies in ten patients receiving oral PyG. The main aim of the studies was to

Abbreviations: PyG, 3-ethyl-3-(4-pyridyl)piperidine-2,6-dione; AG, aminoglutethimide; CSCC, cholesterol side-chain cleavage; HPLC, high-performance liquid chromatography; AUC, area under the concentration versus time curve

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obtain measurements of PyG and oestradiol levels in patients given a dose comparable with that used clinically for AG. Moreover, as it is well established that AG induces its own metabolism on repeated dosing [23], the pharmacokinetics and pharmacodynamics of PyG were studied both before and after repeated dosing.

Patients and methods

Patients and treatment. All patients were postmenopausal and had cytologically or histologically diagnosed recurrent metastatic breast cancer. No patient had undergone prior endocrine therapy or chemotherapy within 4 weeks of treatment with PyG. Informed consent was obtained from all patients and the study was approved by the Ethics Committees of the Royal Marsden Hospital and St. George's Hospital. PyG was synthesised by Chemserve (Manchester, UK) by scale-up of a published procedure [13] and was formulated in the Department of Pharmacy, University of Strathclyde (UK), as a crystalline powder into 100 mg ampoules that were stored at 4° C.

Two studies were conducted on a total of ten patients. In the first, preliminary study (study 1), four patients each received oral doses of PyG (500 mg) twice daily for 3 or 4 days. Doses of PyG were given at 1200 and 1800 hours each day. Blood samples for the measurement of oestradiol and PyG were taken shortly (1 h) before administration of each dose of PyG and 2–3 days after the last dose. In the second, more extensive study (study 2), six patients each received a single oral dose of PyG (1 g) on day 0; samples for both PyG and oestradiol assay were obtained prior to and at 0.5, 1, 2, 4, 6, 8, 10, 12, 15, 24, 28, 32, 36, and 48 h after drug administration. Further doses (1 g) were then given daily for 5 days (days 2–6), the first dose being given immediately after the 48 h sample. After the last dose of PyG on day 6, samples were obtained at the same times as those drawn following the first dose of PyG on day 0. Blood samples for PyG and oestradiol measurement were taken into heparinized plastic tubes and plain glass tubes, respectively. Separated plasma (pharmacokinetic studies) and sera (endocrinology) were stored frozen at –20° C until analysis.

The plasma protein binding of PyG was determined by ultrafiltration in eight patients, four from each study. Plasma samples containing approx. 10 μg/ml total PyG were selected for this study. Centrifree micropartition systems (Amicon, Gloucestershire, UK) were used to separate the free PyG from the protein-bound drug. Aliquots (1 ml) of both the plasma filtrates and the plasma from which they were obtained were assayed in parallel for PyG.

Analytical methods. Plasma concentrations of PyG and its principal metabolite, the N-oxide, were measured by reverse-phase HPLC with UV detection at 254 nm [29]. Plasma (1 ml) was applied to a 100 mg C8 Bond Elut® column (Analytichem International, Harboc City, USA) preconditioned with methanol (1 ml) and distilled water (1 ml). The cartridge was washed with distilled water (2 ml) and PyG and its N-oxide were eluted with methanol (1 ml). The methanol was evaporated under N_2 at room temperature and the residue was redissolved in running eluent (200 μl); 14:86 v/v acetronitrile:0.01 M sodium phosphate buffer, pH 6.7). Aliquots (50 μl) were injected onto the column (Apex: 5 μm C18 15 cm ×4.6 mm internal diameter; flow rate, 1.5 ml/min). Recoveries of PyG and its N-oxide by this extraction procedure were 95% and 80%, respectively. The detection limits of the assay were 0.02 μg/ml for PyG and 0.04 μg/ml for the N-oxide metabolite. The intra- and inter-assay coefficients of variation were 3.8% and 6.8%, respectively, for PyG and 4.9% and 8.7%, respectively, for the N-oxide. The plasma concentration-time data obtained after oral dosing were fitted to the integrated Michaelis-Menten equation by a non-linear least-squares regression program (Fox 85). The AUCs were calculated by the trapezoidal rule up to the last time point and, where indicated, were extrapolated to infinity by dividing the last concentration by the terminal slope (λ_z).

Serum oestradiol levels were measured according to a method previously described [6]. Briefly, 200 μl serum (×2) was extracted with ether and the reconstituted extract was subjected to radioimmunoassay with a highly specific rabbit antiserum (Baxter, UK) that had been raised against an oestradiol-6-carboxymethyl oxime-bovine serum albumin conjugate using oestradiol-6-carboxymethyloxime-[2-^{125}I]-iodohistamine (Amersham International, UK) as the radioactive ligand. The detection limit of the assay was 2.8 pmol/l and the intra- and inter- assay coefficients of variation were 9.4% and 12.8%, respectively, at a plasma concentration of 30 pmol/l.

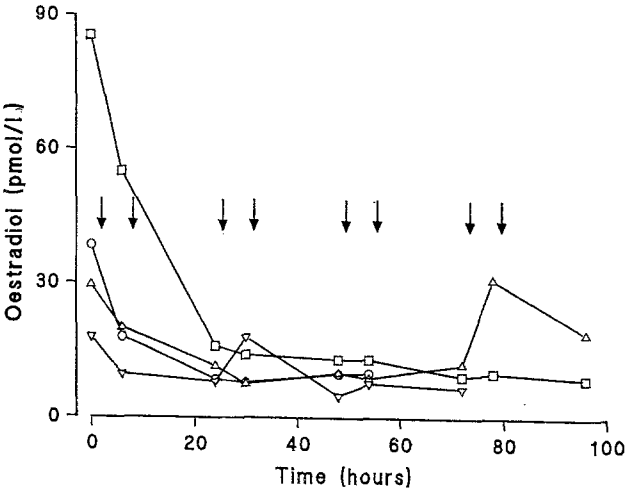

Fig. 1. Serum levels of oestradiol in individual patients receiving oral doses of 500 mg PyG b.i.d. *Arrows*, times of administration; ○, patient A; △, patient B; □, patient C; ▽, patient D

Results

Study 1

The levels of oestradiol found in the four patients who received PyG (500 mg) twice daily are shown in Fig. 1. All patients showed suppression of oestradiol levels within 5 h of the first dose. After 24 h levels had fallen to a mean of 31.1% ± 6.3% of the pretreatment values and this was essentially the maximal suppression seen. The majority of on-treatment values fell within the range of 5–15 pmol/l, the mean pre-treatment value being 43 ± 15 pmol/l. At 2–3 days after the last dose (results not shown), all four patients showed recovery to between 75% and 108% of pre-treatment levels. The pharmacokinetic data obtained in this preliminary study were limited to mesurements of PyG concentrations in plasma samples taken 1 h piror to each dose of the drug and are recorded in Table 1.

The concentrations of PyG measured prior to the 12 noon dose (a.m.) were lower in all cases than those found prior to the 1800 hour dose (p.m.) on the same day, as would be expected from this asymmetric dosing interval. Indeed, the morning concentrations of PyG measured prior to the first dose of the day give a good estimate of the trough drug concentrations occuring with this dosing regimen. In the three patients who received PyG for 4 days, drug concentrations were seen to decline after the 2nd or 3rd day of treatment, indicative of the occurrence of induced metabolism. The large inter-individual variation of PyG concentrations observed in this study (e.g. 5.07–16.09 μg/ml, day 2, p.m.) may thus reflect the variable extent of autoinduction occurring in each patient. However, the finding that the full inducing effect may not be

Table 1. Plasma concentrations of PyG in patients receiving oral doses of 500 mg PyG b. i. d.

Pateint	Concentration of PyG (μg/ml)										
	Day 0		Day 1		Day 2		Day 3		Day 4 a. m. (96 h)	Days post-treatment	
	a. m. (0 h)	p. m. (6 h)	a. m. (24 h)	p. m. (30 h)	a. m. (48 h)	p. m. (54 h)	a. m. (72 h)	p. m. (78 h)		2	3
A	ND	8.22	8.52	13.18	9.68	14.61	–	–	–	–	ND
B	ND	8.02	5.85	8.43	2.05	5.07	0.26	5.22	0.18	ND	–
C	ND	8.82	10.63	16.48	12.34	16.09	10.58	14.94	7.19	ND	–
D	ND	9.82	7.64	14.87	5.25	12.36	3.42	10.09	–	–	ND

ND, Not detected

completely expressed within the treatment period of 3–4 days makes these data difficult to interpret. In one subject (patient B) the nadir concentration (12 noon) on day 3 was probably below the effective therapeutic concentration as a surge in the oestradiol level was seen shortly after this point (72–78 h; Fig. 1). A surge in the oestradiol level of patient D on day 1 (24–30 h) did not correlate with the drug concentration.

Study 2

This protocol was designed to compare the pharmacokinetics and pharmacodynamics of PyG after a single oral dose of 1 g daily with those observed after repeat dosing. In one of the six patients recruited, the pre-treatment level of oestradiol was too low for suppression to be monitored, and only pharmacokinetic data are reported for this patient. The mean levels of oestradiol in the five evaluable patients for both the single-dose and repeat-dose phases of the study are shown in Fig. 2. All patients showed a fall in oestradiol levels within 2 h of the first dose of PyG. Suppression was progressive for the first 12 h, and this degree of suppression (to a mean nadir of 33.5% ± 2% of pre-treatment levels) was sustained until 36 h after the first dose. By 48 h, levels had recovered to a mean of 72% ± 9.8%. After the last of the repeated doses of PyG, mean oestradiol levels began to fall from 50.8% ± 5.7% to a nadir of 22.5% ± 4.3% of pre-treatment levels between 6 and 15 h. Levels had recovered to a mean of 39.8% ± 5.9% by 24 h and continued to recover during the next 24 h.

Figure 3 shows the mean plasma concentration-time profiles of PyG obtained in the six patients studied. In all patients these profiles were curvilinear and showed excellent fits ($r^2 \geq 0.995$ in all cases) to the integrated Michaelis-Menten equation. These yielded good parameter estimates of C_o, K_m and V_{max} as indicated by the small standard errors of determination obtained (<10% in all but 5 of the 36 parameter estimates). After a single dose of PyG the mean values for C_o, K_m and V_{max} were 21.7 ± 1.82 μg/ml, 2.66 ± 0.68 μg/ml and 0.86 ± 0.06 μg $ml^{-1} h^{-1}$, respectively. After repeated dosing there was no significant change in C_o (21.41 ± 1.28 μg/ml), indicating that the volume of distribution of PyG had not altered. However, significant increases in both the K_m (4.31 ± 0.48 μg/ml; $P < 0.05$) and the V_{max} (1.83 ± 0.13 μg $ml^{-1} h^{-1}$; $P < 0.0005$) values were observed. This was reflected in a significantly lower AUC for PyG on repeated dosing (mean reduction, 39.4% ± 4.9%; Table 2). Calculation of the time-averaged plasma clearance (dose/AUC) gave a significantly higher value after repeated dosing (90 ± 13.6 ml/min) than after a single dose (54.4 ± 9.8 ml/min; $P < 0.0005$). These changes

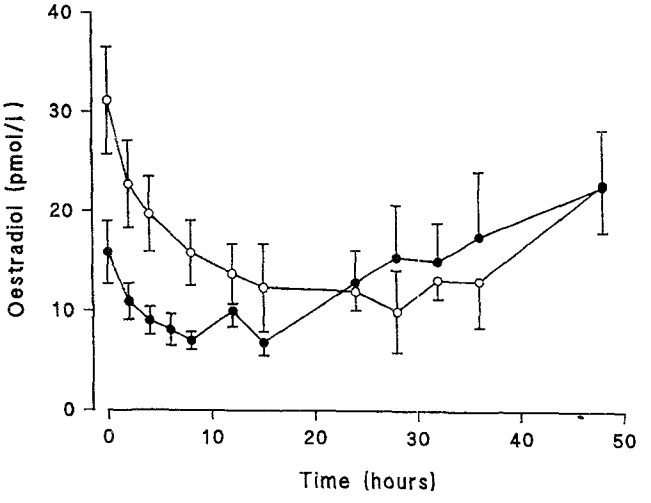

Fig. 2. Serum levels of oestradiol in 5 patients following administration of 1 single dose (○) and 5 single daily doses (●) of 1 g PyG p. o. Values represent the mean ± SE

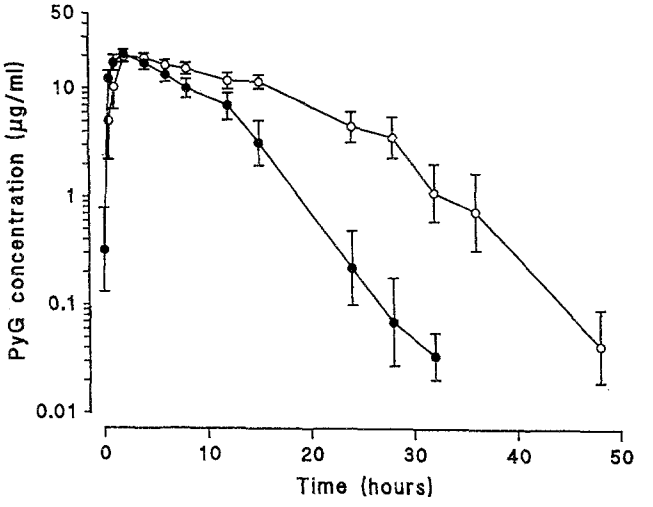

Fig. 3. Plasma concentration-time profile of PyG in 6 patients following administration of 1 single dose (○) and 5 single daily doses (●) of 1 g PyG p. o. Values represent the geometric mean ± SE

Table 2. AUC data for PyG and its N-oxide (NO) after administration of 1 g PyG p. o.

	AUC (μg ml^{-1} h)		AUC_{NO}/AUC_{PyG}
	PyG	NO	
Single dose	$350.2 \pm 49.4_{0-\infty}$	$80.2 \pm 10.2_{0-\infty}$	0.235 ± 0.017
Repeat dose[a]	$208.4 \pm 31.5_{0-24\,h}$*	$106.1 \pm 19_{0-24\,h}$	0.516 ± 0.055**

[a] After repeated dosing, $AUC_{0-24\,h}$ was deemed to be the most appropriate value to determine for comparative purposes, as at steady-state this represents AUCτ and, as such, should be equivalent to $AUC_{0-\infty}$ after a single dose

* $P < 0.002$, ** $P < 0.0001$ (paired t-test)

Values represent means ± SE ($n = 6$)

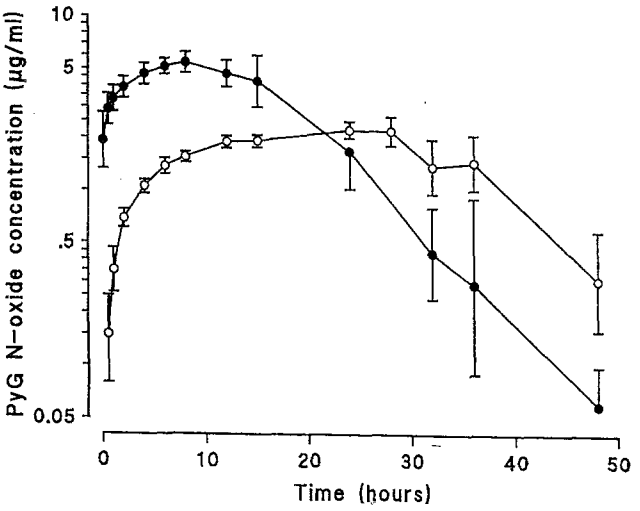

Fig. 4. Plasma concentration-time profile of PyG N-oxide in 6 patients following administration of 1 single dose (○) and 5 single daily doses (●) of 1 g PyG p. o. Values represent the geometric mean ± SE

in K_m, V_{max}, AUC and clearance on repeated dosing are highly indicative of PyG inducing its own metabolism. The terminal half-lives of PyG, as calculated by linear regression of the terminal phase of decline, were 2.4 ± 0.2 and 1.9 ± 0.1 h after a single dose and repeated dosing, respectively. These values are only approximations, as the true first-order rate constant, which is never reached until the concentration is zero, is given by the ratio V_m/K_m. Calculation of the terminal half-lives using this ratio $[0.693/(V_m/K_m)]$ gave values of 2.1 ± 0.4 and 1.6 ± 0.1 h after a single dose and repeated dosing, respectively. The similarity of the half-lives obtained using these two methods of calculation indicates that the kinetics of PyG are approaching first order at these lower concentrations.

After a single dose of PyG, mean plasma concentrations of the N-oxide metabolite of PyG steadily increased during the first 10 h to reach a plateau value of approx. 2 μg/ml at 15 h (Fig. 4). Concentrations remained at this level for about 18 h and started to decline at 28–36 h after PyG administration. After repeated dosing, concentrations were much higher (approx. 5 μg/ml), plateaued earlier (6–8 h) and started to decline much sooner (15–24 h) than after a single dose. The AUC of the N-oxide increased by a mean of 32% ± 13.5% on repeated dosing, although a slight decrease (11%) was observed in one patient, making this difference statistically non-significant (Table 2). The concomitant changes in AUCs for both the parent compound and the metabolite on repeated dosing were characterized overall by a significant increase in the ratio of the AUC of the N-oxide to the AUC of PyG. The terminal half-lives of the N-oxide were similar after both single and repeated doses (4.4 ± 0.4 and 4.5 ± 0.4 h, respectively). The plasma protein binding of PyG was between 12.6% and 20.5% (mean, 17.4% ± 0.8%) in the eight patients studied and was not concentration-dependent in the range tested (8–15 μg/ml). No change in the extent of protein binding was observed on repeated dosing.

Discussion

PyG is a selective inhibitor of the aromatase enzyme complex [8] that lacks experimentally, the CNS side-effects (sedation, ataxia and anticonvulsant activity) associated with its parent compound AG [9]. In the present study the pharmacokinetics and pharmacodynamics (i.e. serum oestrogen suppression) of PyG were studied in postmenopausal patients. The suppression of oestradiol levels was used as an indirect marker of the effectiveness of aromatase inhibition. The degree of oestradiol suppression by PyG observed in this study is comparable with the maximal suppression achieved with other aromatase inhibitors currently being used in clinical trials, such as 4-hydroxyandrostenedione [7] and CGS 16949A [27]; at an equivalent dose (250 mg q.d.), AG suppresses oestradiol levels to a similar extent [26].

The use of parallel samples for pharmacokinetic and endocrine measurements in the present study enabled us to relate the drug concentration to the pharmacological response observed. We can estimate that the minimal plasma concentration of PyG required to inhibit aromatase effectively is approx. 2 μg/ml, as this is the concentration below which oestradiol levels started to recover from suppression in both the single- and repeat-dose phases of the 1 g oral-dose study. Since concentrations of PyG were above this value for approx. 15 h after dosing even in the situation of near maximal induction (1 g × 5), it is conceivable that a lower dose of PyG, which would induce less metabolism, would be equally effective. This has been demonstrated for AG, which achieves maximal oestradiol suppression even after halving of the dose to 250 mg b.i.d. [12]. Thus, it seems likely that an oral dose of 1 g PyG daily is supramaximal, and studies are currently under way to assess the minimal PyG dose that achieves maximal oestradiol suppression.

The pharmacokinetic data generated in this study demonstrate that PyG exhibits Michaelis-Menten kinetics. In this respect, PyG behaves in the same way as do a number of other drugs such as ethanol [34], phenytoin [1], amobarital [10] and salicylate [14]. Indeed, the shape of the plasma concentration-time profile of PyG suggests that a high fraction (f >0.9) of the drug is eliminated via a saturable process when linear conditions operate [32]. The

extent of saturation of this process at a given concentration can be calculated using the following equation [33]:

$$\% \text{ saturation} = \frac{C}{K_m + C} \times 100.$$

After a single dose of PyG (1 g), the initial ($C = C_0$) degree of saturation was 89.1% ± 2.3%. On repeated dosing, both the K_m and the V_{max} values for the elimination process increased approx. 2-fold, with no change occurring in the C_0 (i.e. unaltered V_d) or the plasma protein binding of PyG. Thus, not only was the initial extent of saturation lower (83.1% ± 2%), but the maximal rate of elimination was doubled. As a consequence, the AUC for PyG decreased on average by nearly 40% on repeated dosing. These changes in the pharmacokinetics of PyG after repeated dosing indicate that it induces its own metabolism. The time course of this autoinduction was found to be variable in both studies. Thus, in the 1-g oral-dose study, the extent of autoinduction appeared to be maximal in four of the six patients after the 5-day treatment period, as indicated by the similar PyG concentration observed both on administration of the last repeated dose (O h; mean, 0.08 ± 0.02 μg/ml) and one dosing interval later (24 h; 0.10 ± 0.03 μg/ml). This was in contrast to values obtained in the other two patients, who had much higher PyG concentrations at O h (3.6 and 7 μg/ml, respectively), and in whom maximal induction had not been attained, as indicated by the lower concentrations of PyG observed at 24 h (2.6 and 2.4 μg/ml respectively).

The principal metabolite of PyG in human urine has previously been identified as the N-oxide [29], which is inactive against both the aromatase and the CSCC enzymes [8]. In this study the N-oxide was shown to be the major circulating metabolite of PyG in man. In addition, several minor metabolite peaks were also observed (Cp_{max} < ca. 0.5 μg/ml) and these are currently being characterised. The shape of the plasma concentration-time profile obtained for the N-oxide is highly indicative of dose-dependent metabolite formation [32]. Thus, as one approaches the maximal metabolite formation rate (→ V_{max}), the plasma concentration of the N-oxide approaches a limiting value and tends to plateau (Fig. 4). A similar profile for salicyluric acid, a product of a major and saturable pathway of salicylate metabolism, has been observed following the administration of high doses of acetylsalicylic acid (1.5 g) [2]. After repeated dosing, N-oxide concentrations observed in the present study tended to plateau to a much lesser extent than after a single dose, indicating that enzyme induction had increased the maximal formation rate of the metabolite. Moreover, the increase in the AUC for the N-oxide in this situation can be explained by a decrease in the extent of saturation of the N-oxidation process on autoinduction. These observations suggest that on repeated dosing, PyG induces its own metabolism by induction of the N-oxidation process.

The occurrence of autoinduction is well established for AG [19, 23], which has been shown to induce the formation of its hydroxylaminoglutethimide metabolite while simultaneously reducing the formation of its N-acetyl metabolite [11]. AG has also been shown to stimulate the metabolism of other compounds such as dexamethasone [24], warfarin [18], theophylline [17] and digitoxin [17], indicating possible therapeutic implications. In the rat, both AG [4] and PyG [3] have been characterized as potent phenobarbitone-like inducers of the hepatic mixed-function oxidases. Therefore, analogously to AG, drug interactions should be expected to occur between PyG and any drug that is metabolised by the relevant hepatic microsomal enzymes. The clinical importance of such interactions obviously depend on the therapeutic index of the drug affected, with monitoring of drug concentration being indicated for compounds with narrow limits between their minimal therapeutic and toxic plasma levels.

It has been suggested that the clinical effects of AG may be related not only to its effect on oestrogen production (aromatase inhibition) but also to its effects on oestrogen metabolism caused by the enzyme-inducing properties of the drug [20]. These effects include a stimulation of oestrone 16α-hydroxylase [16], a 100% increase in plasma oestrone sulfate clearance [20] and a 46% decrease in the plasma ratio of oestrone sulfate/oestrone [21] during chronic AG therapy. As oestrone sulfate may quantitatively be a more important source of oestrogen for the tumour cell than are androgens [28], these induced changes could have clinical significance. As a closely related analogue of AG that has similar enzyme-inducing properties, PyG might also be expected to provide such a contribution to its mechanism of action, and studies to ascertain this are under way.

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