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Prevention of fostamatinib-induced blood pressure elevation by antihypertensive agents

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Abstract

Fostamatinib is a tyrosine kinase inhibitor with activity against spleen tyrosine kinase which has completed clinical trials for patients with rheumatoid arthritis. In clinical studies fostamatinib treatment was associated with a small elevation of systemic arterial blood pressure (BP), a similar finding to that seen with other kinase inhibitors, especially those that inhibit VEGFR2 signaling. We have investigated the link between fostamatinib-induced blood pressure elevation and plasma levels of the fostamatinib-active metabolite R940406 in conscious rats and found the time course of the BP effect correlated closely with changes in R940406 plasma concentration, indicating a direct pharmacological relationship. Free plasma levels of R940406 produced in these studies (up to 346 nmol/L) span the clinically observed mean peak free plasma concentration of 49 nmol/L. We have demonstrated that the blood pressure elevation induced by fostamatinib dosing can be successfully controlled by a variety of methods, notably simple drug withdrawal or codosing with a range of standard antihypertensive agents such as atenolol, captopril, and nifedipine. These findings support potential methods of maintaining patient safety while on fostamatinib therapy. Furthermore, we have demonstrated, using nifedipine as an example agent, that this blood pressure control was not achieved by reduction in plasma exposure of R940406, suggesting that potential benefits from the pharmacology of the investigational drug can be maintained while blood pressure control is managed by use of standard comedications.

Abbreviations

ITP, immune thrombocytopenia; RA, rheumatoid arthritis; RTKi, receptor tyrosine kinase inhibitors; SYK, spleen receptor tyrosine kinase; VEGF, vascular endothelial growth factor.

Introduction

Fostamatinib (the prodrug of the active metabolite R940406, also referred to as R406) is a small molecule oral kinase inhibitor with activity for spleen receptor tyrosine kinase (SYK), has completed phase III clinical development for patients with rheumatoid arthritis (RA) (Weinblatt et al. 2013) and is under investigation in phase III clinical studies for patients with immune thrombocytopenia (ITP) (http://www.rigel.com/rigel/pipeline). Fostamatinib inhibits SYK-mediated immune signaling in multiple cell types involved in inflammation and tissue damage and so may inhibit key steps in the progression of autoimmune disease (Wong et al. 2004; Podolanczuk et al. 2009). As is common for receptor tyrosine kinase inhibitors (RTKi), fostamatinib inhibits kinases other than the intended primary target, when assessed in isolated enzyme assays (Davis et al. 2011; Metz et al. 2011), although with lower potency compared to SYK inhibition in assays of cellular function (Braselmann et al. 2006). Recently, fostamatinib has completed phase III clinical studies in patients with RA where it did demonstrate clinical efficacy (Weinblatt et al. 2013).

In both phase II (Weinblatt et al. 2010; Genovese et al. 2011) and phase III (Dawes et al. 2013; Genovese et al. 2013; Weinblatt et al. 2013) clinical studies in patients with rheumatoid arthritis, fostamatinib has been associated with a mean increase in systolic BP of approximately 3 mmHg between baseline and 1 month after treatment initiation, as compared with a decrease of 2 mmHg with placebo. In all cases, BP elevation responded to antihypertensive treatment or a reduction in the dose of fostamatinib. In a study measuring ambulatory blood pressure over 24 h in patients with RA, fostamatinib reproducibly elevated blood pressure to a similar extent as to that observed in the phase II and III trials (Kitas et al. 2014). To date, there have been little or no signals of any associated side effects that may precede hypertensive changes (e.g., inhibition of renal function) leading to the hypothesis that the blood pressure increase may relate directly to the drug pharmacology rather than being a response to another initiating effect.

Development of kinase inhibitors such as R940406 in RA has a high degree of novelty and understanding the emerging efficacy and side effect profiles in particular may benefit from learning from oncology studies where such agents have been most extensively investigated, clinically and preclinically. Learning from these oncology trials and associated preclinical supportive data is that cardiovascular changes are a relatively common observation in patients treated with investigational drugs targeting a variety of kinase signaling pathways (Chen et al. 2008; Mouhayar et al. 2013). Now established agents such as trastuzumab (Herceptin), a monoclonal antibody targeted against mutant forms of the HER2/neu receptor licensed for use against some forms of breast cancer, are associated with cardiac depression and an increase in adverse outcomes when combined with other anticancer agents with known cardiotoxicity risks (Seidman et al. 2002). While agents like trastuzumab have direct cardiotoxic potential, other kinase signaling inhibitor approaches are associated with peripheral vascular effects, in particular, agents that inhibit vascular endothelial growth factor (VEGF) signaling via the VEGFR2 receptor (Sica 2006). This second type of kinase inhibitor-induced cardiovascular side effect appears to offer the best fit with the observations from the fostamatinib trials.

These licensed anti-VEGF medicines and investigational drugs are all associated with reports of hypertension driven by increased peripheral resistance due to vascular constriction. This observation occurs regardless of the site or mechanism of signaling inhibition, appearing after use of agents that target the circulating VEGF ligand, for example, bevacizumab (Avastin) (reviewed by Syrigos et al. 2011) or the kinase signaling domain of the receptor such as sunitinib (Sutent) (Zhu et al. 2009) and cedirinib (Recentin) (Drevs et al. 2007). Hypertension is now regarded as an established class effect of the VEGF inhibitor class (Shah et al. 2013), in fact moreover it is increasingly thought to offer potential as a biomarker to predict a positive efficacy outcome for different dose levels of some drugs in the class, for example, bevacizumab (Ryanne Wu et al. 2009; Scartozzi et al. 2009), sunitinib (Bono et al. 2011; George et al. 2012), and axitinib (Rini et al. 2011).

Although a variety of mechanisms have been proposed for the hypertension induced by inhibition of VEGF signaling (reviewed by Bhargava 2009), the most commonly proposed and agreed mechanism is an increase in peripheral vascular resistance following inhibition of the physiological relaxant activities of endothelial nitric oxide synthase (eNOS). Using this understanding, a number of clinical regimes have been established to control hypertension following use of anti-VEGF therapies to maintain patient safety (Langenberg et al. 2009). These safety monitoring and intervention plans involve treatment discontinuation if certain hypertensive levels are observed, dose reduction and use of a range of standard antihypertensive agents.

The aim of the studies described here was to investigate the dynamics and pharmacodynamics of fostamatinib-induced blood pressure elevation in preclinical models and to understand consistency or variance to those observed with anti-VEGF agents. Second, and drawing on learning and management of blood pressure attenuation with VEGF inhibitors in both nonclinical models and in the clinic, the ability of antihypertensive agents representing different mechanisms to control fostamatinib-induced blood pressure changes was tested.

Materials and Methods

In all experiments male Sprague Dawley rats, weighing 250–300 g, were surgically implanted with TL11M2-C50-PXT telemetry transmitters (Data Sciences International, St. Paul, MN) under pentobarbital anesthesia at Charles River Laboratories (Raleigh, NC) or at AstraZeneca Alderley Park (Macclesfield, Cheshire, UK). Male rats were selected to remove the minor blood pressure changes associated with the estrous cycle. The sterile surgical procedure consisted of an abdominal midline incision and peritoneal placement of the transmitter. The pressure cannula was inserted rostral to the aortic bifurcation with the tip resting approximately 1 cm caudal to the emergence of the left renal artery. Studies were classified as acute – >1 week live-phase studies, or chronic, 28 days studies. Rats were exposed to a 12-h light:dark cycle and given full ad libitum access to a standard rat chow (Purina Labdiet 5001) and house potable water at all times. The

vehicle used for fostamatinib for all studies was an aqueous solution containing 0.1% sodium carboxymethylcellulose, 0.1% methyl paraben, and 0.02% propyl paraben and all oral doses were administered in volumes of 10 mL/kg. All telemetry recordings were generated from 30-sec samplings every 5 min using Dataquest A.R.T. software (Data Sciences International).

After a 2-week recovery period at the vendor following telemetry device implantation, rats used on studies with automated blood sampling were again anesthetized with pentobarbital and surgically implanted with a femoral vein cannula, advanced 45 mm into the inferior vena cava. The cannula was used during the experimental phase of the study to obtain blood samples using an automated blood sampler (Culex, BASi, West Lafayette, IN). Rats were then shipped to AstraZeneca where they acclimated to the facility for 1 week before being connected to the Culex automated blood sampler. An additional 16-h acclimatization was allowed before the experimental protocol commenced.

28 days dosing study

To examine the time course and reversibility of fostamatinib-induced blood pressure elevations following 28 days of repeat dosing, 24 male Sprague Dawley rats received two daily oral doses of vehicle or 8.5 or 30 mg/kg of fostamatinib for 28 days. The first daily dose was administered at approximately 8 AM and the second dose at approximately 2 PM. Prior to this regimen these study rats received 3 days of sham vehicle dosing to acclimate them to the procedure. Plasma concentrations of R940406, the active fostamatinib metabolite, were obtained on day 12 of the study. Each rat was bled via a tail vein before the first daily dose and 2 h after the second daily dose in order to obtain steady-state minimum and maximum representative exposures for each rat. Telemetry recording continued for 3 weeks after cessation of dosing to confirm the reversibility of the hypertensive effects.

Test compounds were administered orally. Vehicle (1% polysorbate, p.o.) was administered using a dose volume of 5 mL/kg on day 1. Cardiovascular data were recorded for 24 h. On day 2, fostamatinib (100 mg/kg p.o.) was administered using a dose volume of 5 mL/kg and again cardiovascular data were recorded for up to 48 h (this was to allow monitoring of any recovery phase).

Antihypertensive combination studies

Four individual studies were carried out at Alderley Park, UK, in groups of four Han Wistar rats from a total colony of 16 rats implanted with radiotelemetry devices as described earlier, with at least 2 weeks gap between dose levels for any animals used more than once. Further data were captured for 2 days following this (i.e., on the days following compound dosing) to enable measurement of any recovery phase if required.

In experiments using antihypertensive agents, the timing of their dosing relative to the fostamaitinib administration was rationally selected on the basis their expected pharmacokinetics in the rat. The timing of each administration was designed to test their ability to modulate the expected peak hypertensive effect observed after fostamatinib dosing. Captopril has relatively slow absorption but prolonged duration of plasma cover in the rat and was dosed 2 h prior to the fostamatinib. Atenolol and nifedipine have relatively rapid absorption but shorter duration of action due to more rapid plasma clearance, especially in the case of nifedipine, and were dosed 30 min or 2 h after fostamatinib, respectively. The doses of each compound were selected on the basis of previously demonstrated antihypertensive efficacy following dosing of the VEGFR2 kinase inhibitor cedinarib (Curwen et al. 2008). Nifedipine was dosed at 10 mg/kg, atenolol at 15 mg/kg, and captopril at 30 mg/kg. All dosing of the antihypertensive agents was via oral gavage using 1% polysorbate vehicle at a dose volume of 0.25 mL/100 g.

Intervention studies using nifedipine with automated blood sampling

Twenty-four additional rats were used in this study. On the experimental day rats received one of four possible dosing regimens (see Table 1). All rats received two oral dosings of 10 mL/kg each, with each volume containing an appropriate volume of either the vehicle or the vehicle plus 100 mg/kg of fostamatinib or the vehicle plus 2 mg/kg of nifedipine. The two dosings were separated by a 2-h period. The dose groups were as follows: Group I – fostamatinib at time 0; Group II – fostamatinib and nifedipine at time 0; Group III – nifedipine at time 0; Group IV – fostamatinib at time 0 and nifedipine 2 h later. Plasma concentrations of R940406, the active fostamatinib metabolite, were obtained from each telemetered rat via the automated blood sampler at 1, 3, 4, 8, 9, 10, 11, 12, 16, 24, and 48 h after the first oral dose of the study.

Statistical analyses

In all studies baseline comparisons prior to dosing were made using a two-way *t*-test. The primary measure of effect was selected to be the mean level at each timepoint. Compound effects that produce increases or decreases from vehicle are both possible, leading to a two-sided testing approach. Differences from vehicle are presented (as differences in least squares means) along

Table 1. Treatments.

Treatment group	Treatment * minutes after first oral dose		Oral dosing volume (mL/kg)	Dose (mg/kg)		Concentration of formulated dosing solutions (mg/mL (μmol/L))	
	0 min	120 min		Fostamatinib (Fos)	Nifedipine (Nif)	Fostamatinib (Fos)	Nifedipine (Nif)
I	Fos.	Fos. veh.	5	100	0	20 (27.3)	0
	Nif. veh.	Nif. veh.	5	0	0	0	0
II	Fos.	Fos. veh.	5	100	0	20 (27.3)	0
	Nif.	Nif. veh.	5	0	10	0	2 (5.8)
III	Fos. veh.	Fos. veh.	5	0	0	0	0
	Nif.	Nif. veh.	5	0	10	0	2 (5.8)
IV	Fos.	Fos. veh.	5	100	0	20 (27.3)	0
	Nif. veh.	Nif.	5	0	10	0	2 (5.8)

with associated standard errors. Effects are reported as statistically significant (at the 5% level) if the *P*-value is <0.05. No adjustment for multiple testing was performed; isolated significant differences (e.g., one or two time-points at one dose in a parameter, unsupported by similar differences at other time-points, higher doses or other related parameters) will generally not be considered real effects.

A random effects model is fitted with animal fitted as random, a variance-components covariance pattern, and the Kenward–Roger method for calculating degrees of freedom (Kenward and Roger 1997). Group and time-point are fitted as categorical variables. The two-way interaction between these factors is also fitted. Least squares means are reported (Goodnight and Harvey 1978) (these will be identical to arithmetic means when there is no missing data). The method takes advantage of the repeated measures on each animal to derive a more robust estimate of the standard error of the mean changes.

Results

28 days dosing study

A 28 days dosing study was carried out in telemetered rats to determine the effect of fostamatinib on blood pressure with particular focus on the immediate changes induced by initial dosing, the further development of any changes after 28 days of dosing and the resolution of these effects several days after dosing was complete. Twice daily oral dosing of both 8.5 mg/kg and 30 mg/kg fostamatinib to telemetered rats produced an increase in mean arterial blood pressure above a vehicle-controlled comparator group. There was a clear distinction between the outcomes seen with the two dose levels with respect to the degree of change and time to onset, with the more rapid onset and higher elevation of blood pressure produced in the 30 mg/kg group compared to the lower 8.5 mg/kg treated animals.

Mean, systolic, and diastolic arterial pressures increased progressively by degree and duration over the course of the 28 days of bid dosing of both the high dose, 30 mg/kg, as well as the low dose, 8.5 mg/kg, of fostamatinib. Representative data for mean blood pressure are shown in Figure 1. Dosing 30 mg/kg initiated a marked sustained increase in blood pressures following the second dose on day 1. Blood pressures were not elevated to a statistically significant extent following dosing with 8.5 mg/kg until approximately day 14 and this increase was maintained at day 28 with systolic pressure being increased to a greater extent relative to vehicle treatment.

Total minimum plasma concentrations of R940406 obtained on day 12 prior to the first daily fostamatinib dose were 0.067 ± 0.025 and 0.584 ± 0.125 μmol/L for the 8.5 and 30 mg/kg treatment groups, respectively. Maximum values obtained 2 h after the second daily dose were 1.27 ± 0.45 and 5.05 ± 2.96 μmol/L for the 8.5 and 30 mg/kg treatment groups, respectively, demonstrating that the 8.5 and 30 mg/kg doses were producing dose-related peaks and troughs of plasma exposure. These total levels at 2 h indicate free levels of 27 to 106 nmol/L using an estimate of 97.9% plasma protein binding for R940406 in the rat, comparing well to a clinical mean peak free plasma concentration seen in trials of approximately 49 nmol/L. These plasma levels match the previously published in vitro IC_{50} values (33–158 nmol/L) for R940406-induced inhibition of a range of SYK-dependent cellular functions in rodent and human immune cells (Rolf, Curwen, Veldman-Jones, Eberlein, Wang, Harmer, Hellawell and Braddock, in press). Furthermore, these plasma exposures agree well with the range of 10–300 nmol/L across which R940406 has been shown to inhibit of VEGF-driven endothelial tube formation in vitro in a cellular assay (Rolf et al. in prep.).

The increases in blood pressure due to both doses of fostamatinib appeared to have reversed on day 32, that is, 4 days after cessation of dosing (Fig. 1). On this day there were a small number of statistically significant blood pres-

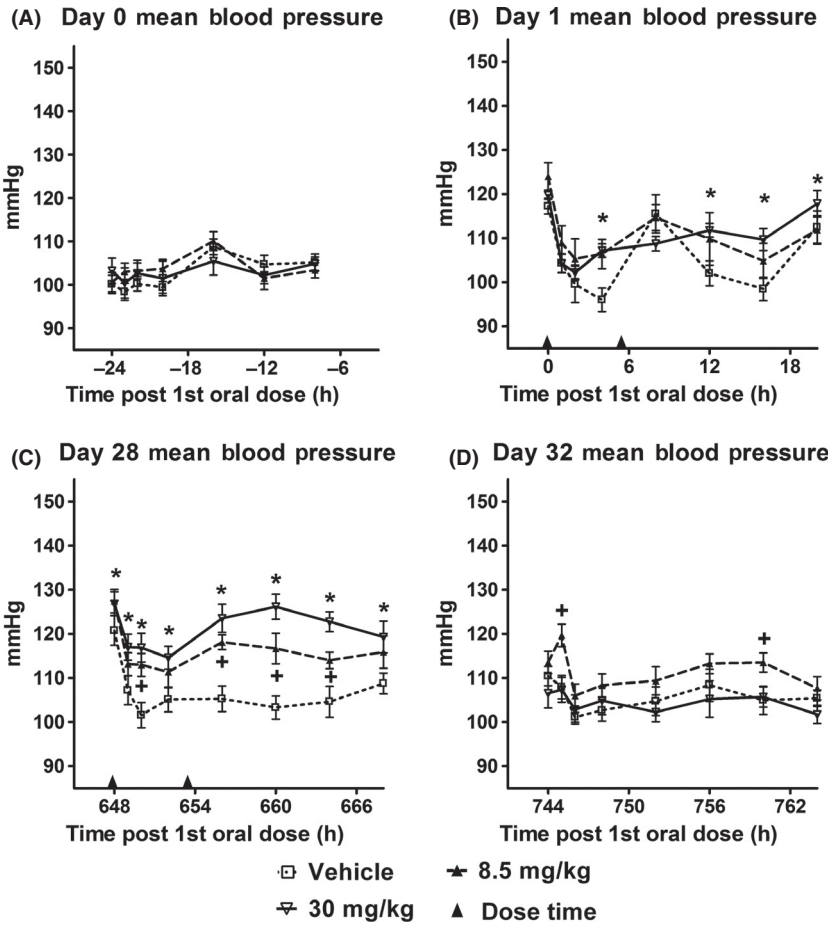

Figure 1. Time courses of fostamatinib-induced elevations in mean arterial blood pressure on select days of the study. After basal blood pressure was measured on day 0 (A), bid dosing began on day 1 (B), and ended on day 28 (C). Significant changes produced by 8.5 mg/kg fostamatinib from time-matched vehicle treatment, $^{+}P < 0.05$. Significant changes produced by 30 mg/kg fostamatinib from time-matched vehicle treatment, $*P < 0.05$. A return to baseline after cessation of dosing was noted (D). All groups contained eight rats.

sure changes relative to time-matched control; however, these were isolated occurrences and were deemed to be within the normal ranges of diurnal variability and possibly due to peaks of occasional animal activity. These effects on day 32 are similar to effects observed on subsequent days out to day 49, 21 days after cessation of dosing. On all days evaluated on or after day 32, basal blood pressures in rats previously dosed with fostamatinib were equivalent to predosed control levels.

Antihypertensive combination studies

A single oral dose of fostamatinib at 100 mg/kg p.o. produced increased systolic and diastolic blood pressure and this effect persisted for more than 24 h after dosing varying between 10 and 15 mmHg when compared to a time-matched vehicle control (Fig. 2A). This increased blood pressure was most obvious during the resting phase of the animal's day–night cycle and was maintained into the next day (data not shown). Blood pressure returned to the predosing baseline during the dark part of the daily light cycle on day 2, the exact time-point obscured by the normal physiological increase in blood pressure during this phase of the normal pattern of activity. The blood pressure elevation induced by fostamatinib dosing was not associated with any changes in heart rate or abnormal animal activity (data not shown), indicating that the finding was not secondary to a behavioral change or stress.

A single oral dose of 15 mg/kg atenolol given 30 min after 100 mg/kg fostamatinib greatly reduced the hypertensive effect observed with an initial 5 mmHg rise returning to the vehicle-dosed baseline within 3–4 h and the hypotensive action lasting for greater than 16 h (Fig. 2B). Predosing 30 mg/kg captopril via oral gavage 2 h prior to 100 mg/kg fostamatinib dosing reduced resting blood pressure by around 10 mmHg, although this

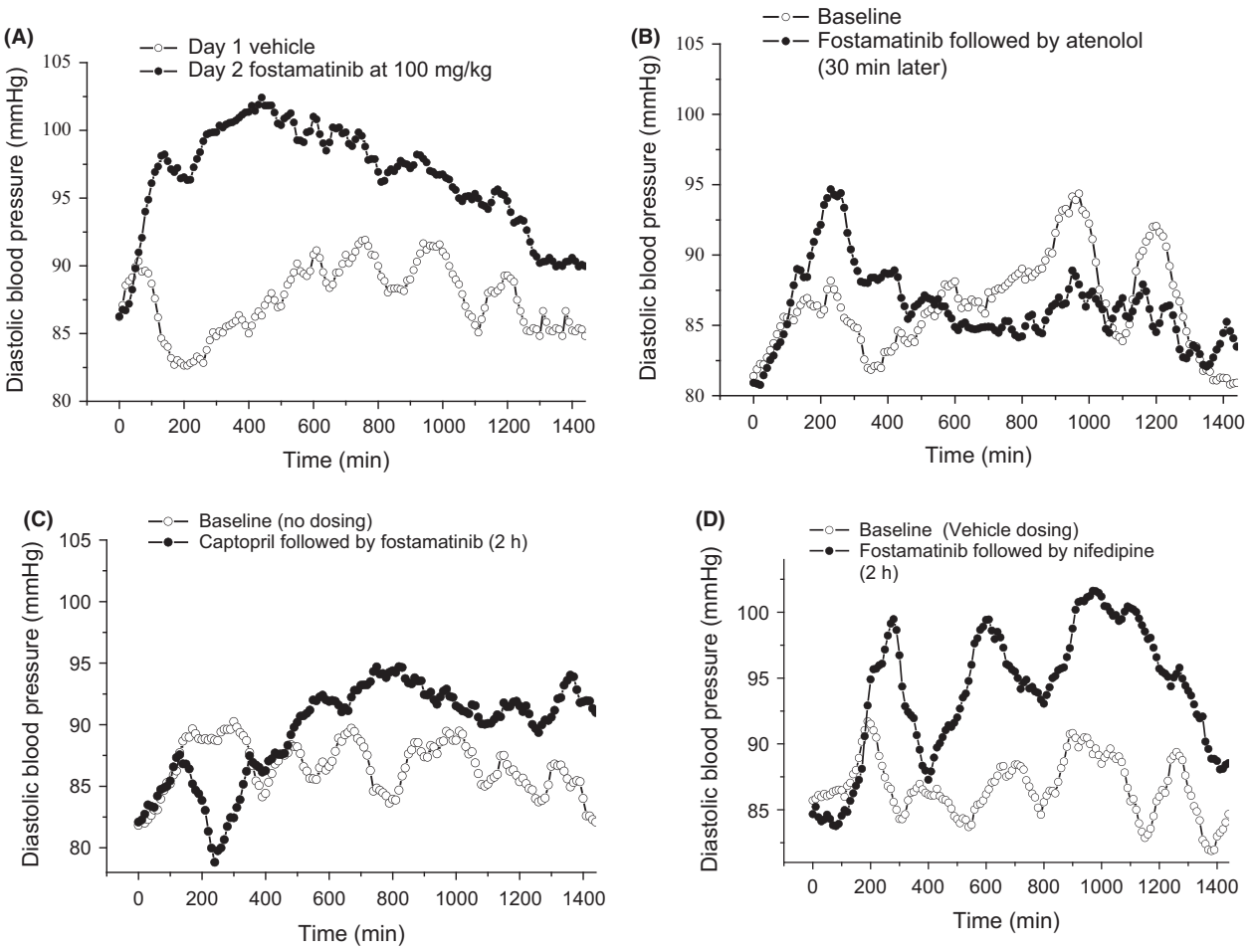

Figure 2. Fostamatinib-induced blood pressure changes in telemetered rats following a single dose of 100 mg/kg either alone (A) or with standard antihypertensive agents atenolol at 15 mg/kg (B), captopril at 10 mg/kg (C), or the short acting agent nifedipine at 30 mg/kg (D). All groups contained four rats.

decrease was mainly seen as an inhibition of the blood pressure change induced by the dosing procedure. This decreased blood pressure was elevated by the later 100 mg/kg fostamatinib dosing, but this hypertensive response was limited to around 5 mmHg above the vehicle-dosed time-matched baseline as opposed to approximately 16–18 mmHg which is produced by 100 mg/kg fostamatinib alone (Fig. 2C). Nifedipine, given orally at 30 mg/kg 2 h post fostamatinib dose, has a very short half-life in the Han Wistar rat and while able to totally reverse a 16 mmHg fostamatinib-induced blood pressure increase, the duration of blood pressure control was short, around 3 h in total (Fig. 2D).

Intervention studies using nifedipine with automated blood sampling

Orally dosed nifedipine treatment prevented on coadministration, and reversed, when dosed 2 h later, the 10–17% increase in mean arterial blood pressure induced by the oral administration of 100 mg/kg of fostamatinib in Sprague Dawley rats (Fig. 3A). Effects of nifedipine began to wane 4 h after fostamatinib treatment, eventually allowing for a re-emergence of the fostamatinib-induced blood pressure elevation by 8 h after the initial fostamatinib dose. The average measured peak plasma levels of R940406 was equivalent across all treatment groups administered fostamatinib (Fig. 3B) and similar in turn to levels obtained during the initial acute single dose study, indicating that nifedipine codosing was not reducing effective R940406 exposure to the rats and that alterations in blood pressure elevation during combination phases of studies were not due to pharmacokinetic changes.

Discussion

We have demonstrated that the blood pressure increases observed in clinical trials of fostamatinib can be replicated

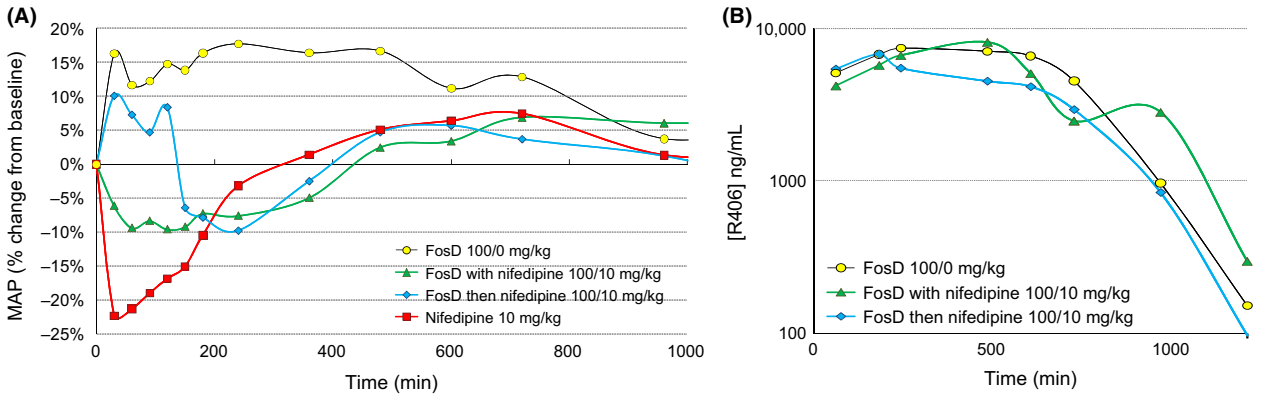

Figure 3. Effect of 10 mg/kg nifedipine, oral coadministration and oral administration 2-h post oral fostamatinib treatment on average mean arterial blood pressure (MAP). (A) Hypertensive effects of 100 mg/kg fostamatinib, alone (●); coadministered with nifedipine (▲); or administered 2 h prior to nifedipine (◊); nifedipine administered alone (■). (B) Comparable total concentrations of fostamatinib in all groups dosed with fostamatinib, 100 mg/kg, p.o. All groups contained six rats.

in preclinical studies in the rat. In previous studies blood pressure has been shown to increase with little or no delay relative to build up of active molecule R940406 in plasma following a single oral dose of fostamatinib in the rat, in particular when using doses above 30 mg/kg, while in a more chronic 28 days of dosing study, lower doses produce a rise in baseline over time, at some point between 1 and 28 days which may be explained by increased plasma exposure with subsequent daily doses.

The acute rise and fall of blood pressure relative to baseline in the studies with pharmacokinetic measures using single doses matched the pattern of R940406 plasma concentrations well, both in terms of onset and resolution, pointing to a direct causal relationship as previously described (Skinner et al. 2013) Our data indicate that a maximum hypertensive effect of approximately 15 mmHg is reached in conscious rats at plasma concentrations of around 6 μmol/L, but blood pressure is not further increased at plasma concentrations up to 16 μmol/L. The probable explanation for this lack of proportional relationship at the higher concentrations is the previous observation in our work that homeostatic control of any greater blood pressure increase in the rat is very efficient, thus there is a physiological limit to the degree of blood pressure change that can be induced and measured due to the onset of reflex compensation (Curwen et al. 2008).

In a similar way to blood pressure rises being related to plasma levels of R940406 in an acute setting after a single dose, resolution of an established blood pressure increase in the chronic study after cessation of dosing on day 28 back to near original baseline on the next measure at day 32 argues against a permanent underlying change in the animal once drug is withdrawn. Taken together, and with rat reflex control aside, the data point to a simple, dynamic relationship between R940406 plasma levels and blood pressure with no induction or lag periods observed.

This direct relationship between circulating active drug level and blood pressure increase offers mechanistic support for a number of clinical findings as well as clinically relevant management and mitigation plans. Given the lack of induction period between drug exposure and initiation of the blood pressure rise in the rat, the relatively early onset of blood pressure increases in the clinic becomes understandable and a consideration of timing alone argues against the need to identify involvement of other causal side effects, for example, the effect is very unlikely to be the result of ongoing renal impairment leading to a blood pressure rise following volume loading over time. Importantly, given the apparently direct relationship between drug and blood pressure, drug withdrawal in patients where a blood pressure rise may need to be controlled should offer a return to pretreatment levels following drug clearance as there does not appear to be lasting hypertensive drive.

Clinical learning from the oncology field suggests that while in healthy inbred rat strains a robust and reproducible relationship between plasma levels of a prohypertensive kinase inhibitor and blood pressure rise can be established, much greater variability are known to exist in patients (Shah et al. 2013). The greater diversity of cardiovascular health and homeostatic capability in patients, in particularly an elderly population with inflammatory autoimmune disease, would mean that for a given plasma level of R940406 patients may display no blood pressure change or a relatively large change depending on the ability of their physiological reflexes to compensate. As such, while an understanding of preclinical pharmacokinetics may be able to provide a useful prediction of a blood

pressure change in any individual rat as demonstrated in the data presented, in patients these relationships may be valid across a large population as variations will average out but there should not be an expectation that drug level in the blood could be used to directly understand the degree of blood pressure change observed on an individual basis.

The plasma levels of R940406 observed in this study that are associated with BP changes are sufficient to match the concentrations that would be expected to inhibit VEGF signaling based on in vitro cell data (Rolf et al. in prep.). In addition, further previous mechanistic work in vivo has shown that the BP increases induced by R940406 in vivo are consistent with those induced by compounds that selectively inhibit VEGF signaling (Skinner et al. 2013). Following the preclinical experience of managing blood pressure rises after use of the potent VEGF receptor kinase inhibitor cediranib (Curwen et al. 2008); in this set of studies, we were able to demonstrate that the blood pressure rise induced by fostamatinib in the rat could be successfully modulated with standard antihypertensive agents of different classes. There was no evidence of resistance to any of the agents tested regardless of antihypertensive mechanism which indicates that the efficacy of the same approaches will most likely translate to the clinic for the majority of patients. These data are consistent with the management of blood pressure elevation in patients with RA who receive fostamatinib and whose blood pressure is managed by a variety of drugs targeting disparate mechanisms (Skinner et al. 2013).

As discussed above in context of the relationship between drug level and blood pressure increase in an individual patient, it should be remembered that there are variations in cardiovascular health and homeostatic capability within a clinical population and in turn this should be considered as part of a safety management plan for blood pressure increases and choice of antihypertensive therapy for an agent like fostamatinib. Some antihypertensive drugs operate via manipulation of homeostatic processes, for example, captopril acts to reduce the formation of vasoconstrictive angiotensin II from angiotensin I by inhibiting the angiotensin-converting enzyme (ACE). In a patient where a pre-existing hypertensive state is present, there may already be physiological down-regulation of angiotensin II via reflex inhibition of renin production. In these patients use of captopril would have less blood pressure lowering effect than expected as there would be less angiotensin II tone for the drug to remove. We have shown previously that some antihypertensive agents do lose efficacy against VEGF inhibitor-induced blood pressure increases at points where the dose level has overcome the reflex capabilities of the rats tested (Curwen et al. 2008). In these situations, however, we demonstrated that using agents that do not rely on normal homeostatic mechanisms, such as the calcium channel blocker nifedipine, retain their ability to normalize blood pressure. The much milder effect on blood pressure seen to date in the clinic with fostamatinib would indicate that the frequency of patients becoming refractory to certain antihypertensive drug classes on therapy, thus requiring switch of agent to a more directly acting drug, would be considerably lower, perhaps seen in only the most physiologically compromised patients, but the pattern of antihypertensive drug effectiveness would be expected to be the same.

Given the potential utility of nifedipine, it was chosen as an example antihypertensive agent in these studies to investigate drug–drug interactions and we demonstrated that the ability of the agent to lower fostamatinib-induced blood pressure increases was not due to altering the levels of R940406 in plasma. These data demonstrated that the blood pressure normalization was due to the desired antihypertensive mechanism of nifedipine and furthermore that use of agents like nifedipine still has potential to maintain baseline blood pressure even in the presence of therapeutically useful levels of R940406.

In summary, we have shown that fostamatinib produces an increase in blood pressure in the rat directly related to its plasma exposure and that simple drug withdrawal is sufficient to restore normotension with time. Furthermore, we have demonstrated that a range of standard antihypertensive drugs are capable of preventing or reversing the blood pressure increase. Given this learning, we propose that the blood pressure management plans in place in oncology trials of VEGF signaling inhibitors would be suitable for use in trials of fostamatinib, despite the much smaller magnitude of the observed effects compared to those reported in the oncology setting, namely a sequential approach involving use of antihypertensive agents of any mechanism followed by switching to an agent such as nifedipine if patients become refractory to the initial therapies, with drug withdrawal as an effective additional option.

Author Contributions

D. L., J. O. C., E. L. B., A. H., J.-P. V., P. D., and M. B. designed and reviewed the experiments. H. B. and H. M. performed pharmacokinetic analysis and telemetry surgery, respectively. K. O. reviewed statistical analyses. All authors contributed to and reviewed the final manuscript.

Disclosures

All authors are employed by AstraZeneca.

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