



Quantifying adherence to antihypertensive medication for chronic hypertension during pregnancy



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ARTICLE INFO

Keywords:

Pregnancy
Chronic Hypertension
Adherence
Antihypertensive treatment

ABSTRACT

Estimates of adherence to antihypertensive treatment in pregnancy are limited; identifying non-adherence could facilitate intervention and optimise blood pressure control. This study aimed to evaluate adherence to antihypertensive treatment amongst pregnant women with chronic hypertension using high-performance liquid chromatography-tandem mass spectrometry instrumentation. Spot urine samples collected from women who were randomised to labetalol or nifedipine were assessed. Samples from 74 women were included; documented prescribing and urine metabolite detection were concordant in 88% (n = 65). Evidence of self-administration of alternative treatment was observed in 8% (n = 6). Measurement of urinary antihypertensive metabolites in pregnancy provides insight into treatment adherence.

1. Introduction

Non-adherence to medication is considered a key barrier to effective treatment of chronic health conditions such as hypertension [1]. The real and perceived risk of fetal harm impacts adherence to prescription medication in pregnancy [2,3]. Prevalence of non-adherence to antihypertensive medication in pregnancy is estimated to be between 3% and 65% [4]; the wide range of this estimate relates to lack of direct and objective methods of assessing adherence. Indirect methods currently used include interviews and questionnaires (Morisky's scale [5] and the Medication Adherence report scale (MARS)[6]), which can be subject to recollection bias. Other indirect methods include automated monitoring methods such as digitalised records of pharmacy prescription refills or medication event monitoring systems but these measures do not allow for patients engaging in pill dumping [7].

High-performance liquid chromatography-tandem mass spectrometry instrumentation (LC-MS/MS) represents a novel technique that can be utilized as a direct method for assessing adherence to antihypertensive treatment; plasma or urine can be analysed to detect metabolites of a wide range of antihypertensive agents [8]. This study

aimed to evaluate this new technique in assessing adherence amongst pregnant women with chronic hypertension randomised to antihypertensive treatment.

2. Methods

The cohort consisted of women with chronic hypertension randomised to labetalol or nifedipine as first-line antihypertensive treatment within the PANDA study (Pregnancy And chronic hypertension: Nifedipine versus lAbetalol as antihypertensive treatment) between 2014 and 2016. The PANDA study was registered with ISRCTN (DOI <https://doi.org/10.1186/ISRCTN40973936>, www.isrctn.com) and approved by the UK Research Ethics Committee (REC number 13/EE/0390). Women were enrolled at three consultant-led obstetric units in the UK (Guy's and St Thomas' NHS Foundation Trust, Central Manchester University NHS Foundation Trust, and University of Leicester Hospitals NHS Trust). The trial methodology and findings have previously been published [9]. The women who participated in the trial consented to providing urine samples for future research purposes but, as this was a post hoc analysis, they were not aware their

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<https://doi.org/10.1016/j.preghy.2019.05.004>

Received 6 February 2019; Received in revised form 27 March 2019; Accepted 2 May 2019

Available online 03 May 2019

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urine would be tested for antihypertensive metabolites at the time of sampling. Results were therefore not fed back to the clinician or women.

3. Urine analysis—LC-MS/MS

Spot urine samples were collected at routine antenatal clinic appointments following study enrollment. The samples were transferred from the clinic to the laboratory at room temperature and stored at -80°C until further analysis.

LC-MS/MS was performed using an Agilent Technologies 1290 series High Pressure Liquid Chromatograph interfaced with an Agilent Technologies 6460 Triple Quad Mass Spectrometer fitted with a Jetstream electrospray (ESI) source. The nebuliser gas temperature was set at 350°C with a flow of 5 L/min and a pressure of 45 psi. The sheath gas temperature was set at 250°C and a flow of 11 L/min. The LC system was operated in gradient mode using 0.1% acetic acid in water for mobile phase A and 0.1% acetic acid in methanol for mobile phase B. The initial conditions of 5% B/ 95% A were held for 2 min and then ramped to 60% B at 6 min and further 100% B at 9 min. The gradient was held at 100% B for 1 min and then returned to 5% B at 11 min to re-equilibrate. The total run time was 12 min per sample. An Agilent technologies Zorbax Eclipse Plus C18 $2.1 \times 50\text{mm}$ column was used for the LC separation.

The presence or absence of metabolites of labetalol and nifedipine was assessed in two samples taken at the same timepoint to ensure concordance of findings. Non-adherence to antihypertensive treatment was defined as complete absence of any prescribed antihypertensive metabolites in a spot urine sample on screening.

4. Results

Urine samples from 74 women (130 samples) randomised to first-line antihypertensive treatment were included in the analysis ($n = 39$ randomised to labetalol and $n = 35$ randomised to nifedipine). Baseline maternal characteristics at enrolment and maternal and perinatal outcomes were similar between treatment groups (Table 1). Among the women prescribed nifedipine as first-line antihypertensive treatment, 5 (14%) required additional treatment with labetalol; no women in the labetalol group were prescribed nifedipine as a second-line agent at the time of sampling.

Documented prescribing and urine metabolite detection were concordant in 88% (65/74) of women. The proportion of women with metabolite of each antihypertensive detected in their urine are provided in Fig. 1.

5. Discussion

To our knowledge, this is the first study to use this novel technique for detection of urinary drug metabolites in the direct assessment of adherence with prescribed antihypertensive medication in pregnancy. We demonstrate good concordance (88%) of antihypertensive agent prescription and detection of urinary drug metabolites in pregnant women with chronic hypertension. The need to explore barriers to adherence with women is highlighted, with some women only taking one of their prescribed treatments and others taking medication that was undocumented.

Outside pregnancy this technique has been used to highlight non-adherence among those referred to secondary care with ‘drug-resistant’ hypertension; [8] Tomaszewski and colleagues (2014) demonstrated non-adherence in 25% of their secondary care cohort and found an association between non-adherence and referral for renal denervation for suspected resistant hypertension. Non-adherence within our cohort was lower (12%); this may reflect that the women were participating in a randomised controlled trial and may therefore be more likely to adhere to their medication. It is also acknowledged that this assessment of

Table 1

Baseline characteristics and maternal and perinatal outcomes.

	Overall cohort (n = 74)	Randomised to Labetalol (n = 39)	Randomised to Nifedipine (n = 35)
Age at study entry ^a , years	35 (5)	35 (5)	35 (5)
Body mass index ^a , kg/m ²	31 (6)	31 (7)	31 (5)
Nulliparous	17 (23%)	9 (23%)	8 (23%)
Ethnicity			
White	21 (28%)	11 (28%)	10 (28%)
Black	39 (53%)	20 (51%)	19 (54%)
Asian	10 (14%)	5 (13%)	5 (14%)
Other	4 (5%)	3 (8%)	1 (3%)
Booking blood pressure ^a , mmHg			
Systolic	136 (21)	138 (19)	137 (14)
Diastolic	87 (16)	88 (15)	87 (11)
Superimposed pre-eclampsia	12 (16%)	3 (8%)	9 (26%)
Mode of delivery			
Spontaneous vaginal	27 (36%)	16 (41%)	11 (31%)
Assisted vaginal	5 (7%)	2 (5%)	3 (9%)
Elective Caesarean section	11 (15%)	6 (15%)	5 (14%)
Emergency Caesarean section	31 (42%)	15 (39%)	16 (46%)
Gestation at delivery ^a , days	260 (25)	265 (20)	256 (28)
Preterm birth < 37 weeks	18 (24%)	5 (13%)	13 (37%)
Livebirth	71 (96%)	38 (97%)	33 (94%)
Birthweight ^a , grams	2790 (840)	2900 (720)	2670 (930)
Birthweight < 10th centile	26 (35%)	14 (36%)	12 (34%)
Neonatal unit admission	14 (19%)	5 (13%)	9 (26%)

^aMean (SD).

adherence does not differentiate a single missed dose from continuous non-adherence and thus adherence rates may have been higher.

The sensitivity of LC-MS/MS to detect urinary drug metabolite in those on lower doses of medication is uncertain but, in our study, urinary metabolites of labetalol and nifedipine were detected in women on the lowest dosing regimens. The timing of last dose of antihypertensive medication may also have impacted the sensitivity of the mass spectrometry and as such this technique might require further prospective studies to assess detection in relation to timing of dose, prior to introduction into clinical practice.

Severe hypertension in pregnancy is associated with an increased risk of adverse maternal and perinatal outcome [10]. Non-adherence with antihypertensive treatment in pregnancy is likely to increase a woman’s risk of severe hypertension and therefore adverse outcome. Direct assessment of urinary antihypertensive metabolites provides insight into adherence patterns in pregnancy but does not improve understanding of why women may be non-adherent. Clinicians caring for women with hypertensive disorders in pregnancy need to consider the health beliefs and potential barriers to medication adherence and ensure consultations harbour an environment where women are empowered to discuss these issues. Urinary antihypertensive metabolite testing, if undertaken appropriately, could be useful for research studies and clinical use, particularly in the context of ‘refractory hypertension’.

6. Sources of funding

King’s Health Partners Research and Development Challenge Fund and Tommy’s Charity provided funding for the study. This is independent research supported by the National Institute for Health Research (NIHR) Professorship of Lucy Chappell RP-2014–05-019. Paul Seed is partly funded CLAHRC South London (NIHR). Dr Jenny Myers is supported by a NIHR Clinician Scientist Fellowship (NIHR-CS-011–020). Paul Seed is partly funded by Tommy’s (Registered charity no. 1060508) and by CLAHRC South London (NIHR). The views expressed in this publication are those of the author(s) and not necessarily

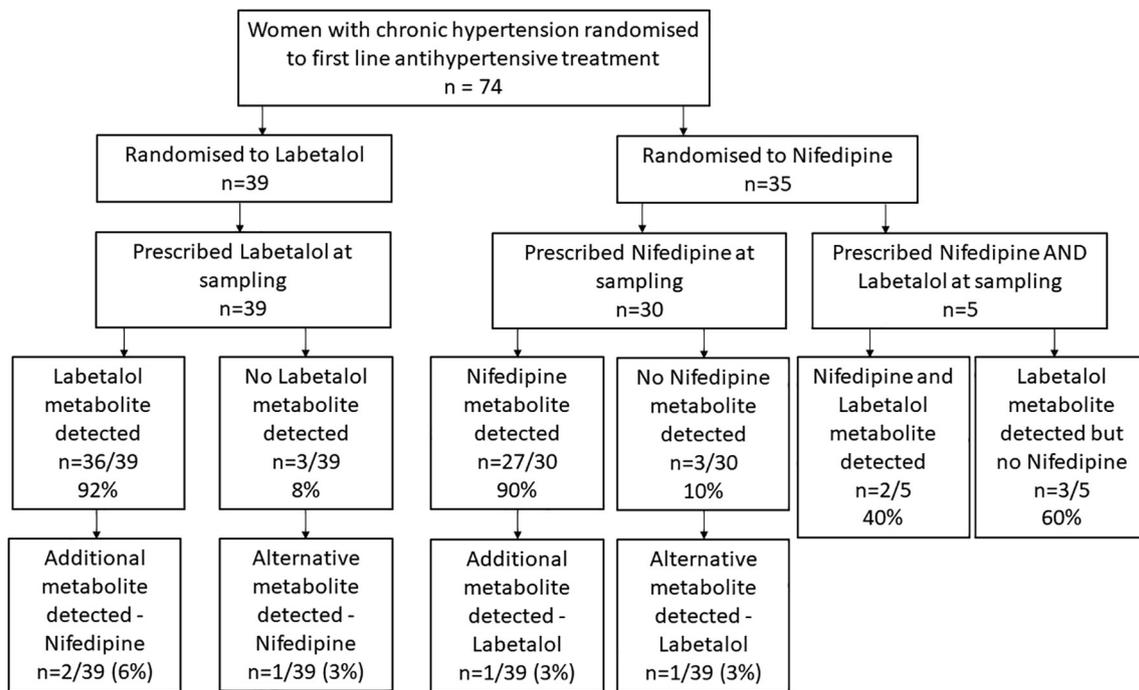


Fig. 1. Overview of study groups and adherence patterns Labetalol doses 200–1200 mg per day and Nifedipine doses 20 to 80 mg per day.

those of the NHS, the NIHR or the Department of Health.

Declaration of interests

Professor Nelson-Piercy reports personal fees from Alliance Pharmaceuticals, UCB Pharmaceuticals, LEO Pharmaceuticals, Sanofi Aventis and Warner Chilcott outside the submitted work. The other investigators have no declarations of interest to report.

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