Is dosing time important for treating hypertension?

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The TIME study aims to investigate the importance of time of dosing in treating hypertension and reducing the risk of cardiovascular events. Here, Professor Tom MacDonald discusses how the trial will be conducted, patient eligibility and how GP practices can aid recruitment.

Hypertension affects one in four adults in the UK. Having high BP, persistently ≥140/90mmHg, significantly increases the risk of cardiovascular disease including heart attack and stroke. This condition, which is increasingly common with age, poses a significant threat to the health of millions of people but, once diagnosed, can be managed well with drug treatment.

Now, a team of researchers from across the UK, led by Professor Tom MacDonald based at the University of Dundee and Ninewells Hospital, and backed by a British Heart Foundation (BHF) research grant worth more than £1 million, aims to answer an important research question. The Treatment in Morning vs Evening (TIME) study is currently recruiting patients across the UK following a successful pilot that has been ongoing since 2011. TIME is a British Hypertension Society Research Network study. The TIME study looks to substantiate the findings of an earlier study (the MAPEC study), which showed a reduction of cardiovascular events in patients that took their antihypertensive medication in the evening compared with those who took it in the morning. The MAPEC study had several limitations, which is why the TIME study has been designed to definitively answer the hypothesis of whether evening dosing is more cardioprotective than morning dosing.

Figure 1. Patients with BP that lowers during the night tend to experience fewer cardiovascular events, suggesting that the time of antihypertensive dosing may be important.

Antihypertensive medication and time of dosing

We know that taking antihypertensive medication in the morning is beneficial in controlling high BP, but recent findings (enabled by the use of 24 hour BP monitoring) suggest that night-time dosing may be better still. Patients with BP that lowers during the night tend to experience fewer cardiovascular events compared to those whose BP barely dips. Essentially, those with constant high BP day and night do not do so well.

The purpose of our research is to study patients taking once-daily BP medication, aiming to establish whether night-time dosing is better (or worse) than morning treatment in preventing heart attacks, strokes and deaths related to diseases of the heart and circulation. Participants will be randomly allocated into two groups; group one will take their antihypertensives at night, the other in the morning.
Participant recruitment for the TIME study

Recruitment to the study is open to anyone in the UK who is taking tablets for hypertension once daily. We hope to recruit over 10,000 participants of as varied demographics as possible and study them over a period of five years. A study of this size and duration should enable us to know with confidence whether or not the time at which patients take their medication is important. Patients are being invited via GP surgeries and hospitals from all across the UK, and by social media, to participate. Patients who currently take medication for BP twice daily (morning and evening), those who do night shift work or those in other clinical trials at present are unable to take part in this study.

Participants also need to have regular access to the internet, as this study is done entirely through a secure website and all contact is by email. Although this excludes a certain proportion of patients, for practical and financial reasons it would be difficult to conduct a study of this size in the conventional way where participants are seen by a clinician regularly. Previous studies that have used this method found correspondence via social media, to participate. Patients who have an email account and are interested in being part of this study can visit www.timestudy.co.uk, which has detailed information that they should read carefully before deciding whether to sign up. After registering an interest, they will be sent an email to confirm their email address and desire to participate. We will then request explicit consent for us to access and use the information we need. This includes relevant medical records from GP surgeries and hospitals. We also ask for permission to write to their GP or a nominated next of kin in case we are unable to hold of participants, although neither is compulsory for inclusion into the study.

As for all studies, if during the research there is an enormous outcome difference between the morning and the evening group, we may be instructed to discontinue the study as it would be unethical to carry on. All patients will be notified in this instance.

Data security

The TIME study website that has been set up for this study and all associated data are stored securely at the University of Dundee. Personal data will be treated with the strictest confidentiality by the staff working on the study, and publications will not have any identifiable details about participants.

Involvement of GP practices

A mailing to all GP practices in the UK has recently been completed, asking for practices to indicate if they would be interested in taking part in TIME by writing to all of their hypertensive patients currently on once-daily medication. If practices are interested then network support is available to help with patient identification and invitation.

Practices can register their interest by emailing the study at time-gpregistrations@dundee.ac.uk, registering on the website (www.timestudy.co.uk/GPRegistration.aspx) or returning a freepost response slip to the coordinating centre in Dundee. Upon receiving interest, practices will be contacted either by network staff or by Dundee directly to start the recruitment process. Once patients have been invited then no further input is required from practices.

We are also asking if practices can put up posters in their practices even if they do not wish to actively invite patients.

Involvement of hospital clinics

The study is adopted by the British Hypertension Society and members of their network have already been asked if they can directly invite suitable patients from their clinics. We hope that consultants who are not members of the network will also do the same. Anyone who is interested in finding out more about this can email the coordinating centre in Dundee at TIME-study@dundee.ac.uk.

Blood pressure medications

Currently there is no set guidance on when patients should take their BP tablets. The TIME study randomly allocates participants to either morning (06.00 to 10.00) or evening (20.00 to 24.00) dosing. Diuretic tablets could potentially increase urine volume at night. For those randomised to evening dosing we would like them to try taking this tablet in the evening, but if they find it a problem they can move the time forward in two-hour increments (ie 18.00 or earlier) until it is no longer a problem. If participants encounter any problems with their allocated time they are free to change back whenever they wish.

Conclusion

If this study shows that the time of day at which patients take their BP medication can have an effect on events such as strokes and heart attacks, it could provide enormous health benefits. Even demonstrating a modest effect within the TIME study could imply an incredible benefit to the population at large.

Acknowledgement

We’d like to thank the BHF, who have funded this study, and the British Hypertension Society, who are co-ordinating it. The text of this article was based on an interview published in the November/December issue of the BHF Heart Matters magazine.

Declaration of interests

None to declare.

Tom MacDonald is professor of clinical pharmacology and pharmacoepidemiology at Dundee University, consultant physician at Ninewells Hospital and Medical School, and president of the British Hypertension Society