Regarding the patient selection process, it was stated that the patients were not selected on the basis of previous withdrawal reactions. However, it was not stated how they were selected, and why all of the volunteers were receiving 0.9 mg/day of clonidine. It is possible that the selection process introduced a bias, such that the patients were only representative of the individuals who require a large dose of clonidine.

Also, the authors did not use placebo during the withdrawal phase of their study, and this could have caused anxiety and apprehension to their patients with accentuation of the withdrawal response to clonidine.

More importantly, the study does not represent the majority of patients, who receive clonidine for hypertension. In our experience, most patients with hypertension do not require more than 0.2 to 0.6 mg of clonidine per day. In our study of 20 patients (Whitsett, Chrysant, Dillard & Anton, 1978), the majority were taking less than 0.6 mg/day and none of the individuals had a discontinuation syndrome. Also, for the mean arterial blood pressure to be 110 mmHg on 0.9 mg of clonidine per day, these were most likely not patients with mild to moderate hypertension, but rather individuals with a moderate to severe elevation in blood pressure. Again, the question is raised regarding whether these subjects were representative of the majority of individuals

with hypertension, and it would appear to us they were not.

While research designed to discern the frequency of a particular condition is important, it is crucial that the study design does not introduce bias. Further, the segment of the population the study sample represents should be stated. Otherwise, it is quite possible that invalid conclusions may be drawn by the authors and the readers.

THOMAS L. WHITSETT & STEVEN G. CHRYSANT

Department of Medicine, University of Oklahoma Health Sciences Center, P.O. Box 26901, Oklahoma City, Oklahoma 73190, USA

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CLONIDINE WITHDRAWAL MECHANISM AND FREQUENCY OF REBOUND HYPERTENSION

A reply to the letters of Dr McMahon (1979) and Drs Whitsett & Chrysant (1979)

We agree that the study of any drug should preferably be done double-blind with identical placebo. In our study, not using placebo, the results are a combination of real pharmacological effects and the psychological effect of withdrawing the clonidine tablets.

However, we did not, as Dr McMahon (1979) presumed, tell our patients all the possible symptoms, but, as described under methods, informed them that they might feel uncomfortable, without specification. It is therefore unlikely that these subjective and objective symptoms, which started only 12–24 h after cessation of the medication and were progressive, were the results of the previous interview. Indeed, as the symptoms of our patients were consistent with exaggerated sympathetic tone and identical to those reported by many authors after clonidine withdrawal

(as well as by other patients seen by us who were not aware that withdrawal might cause symptoms) the possibility they were induced by our information seems less probable. The provocation of such a specific syndrome by suggestion has to our knowledge not been documented.

Although the question of rebound or overshoot of the blood pressure remains open to discussion, there is no doubt about an overshoot of urinary noradrenaline excretions, which after clonidine withdrawal increased to abnormally high levels in all but one of our patients.

In their recent prospective study using placebo, Whitsett, Chrysant, Dillard & Anton (1978), also found an overshoot of urinary noradrenaline excretion in the post clonidine period. In their, as in our study, urinary noradrenaline excretion did

correlate with the blood pressure. This indicates that the rise in blood pressure was related to the exaggerated sympathetic nervous system activity.

In their study Whitsett *et al.* (1978) even found a statistical significant elevation of the standing blood pressure above the control values on the second withdrawal day (after 30 days clonidine therapy, dose range 0.2–1.2 mg/day).

About the selection of our patients, it is true that none of our patients had mild hypertension because they were selected from our special hypertension clinic. Independent of their blood pressure they all received the same dose of clonidine (0.9 mg/day) during the days before withdrawal. Lower dosages in patients with mild hypertension were not studied, but in this group of patients on this dose we did find the 50% incidence of subjective symptoms after withdrawal and the 3 of the 14 patient with a rather alarming syndrome as described in the case records.

Even when the incidence of the full blown syndrome will be lower than our 50% (especially when lower dosages are used) there is enough evidence that several patients will have an exaggerated sympathetic activity during some post-

clonidine treatment days, to warn physicians using this otherwise effective hypotensive drug for a hazard which may easily be prevented by appropriate measures.

G.G. GEYSKES, E.J. DORHOUT MEES & P. BOER

Department of Nephrology & Hypertension, University Hospital, Utrecht, The Netherlands

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