tested over hourly periods from midnight using the chi-square test. Neither was there any evidence of cyclical trend when two-hourly periods from midnight were examined, for both years combined (Figure 1) or separately. The specific time of death was unknown in 28 cases. Of these, 10 patients died between 08.00 and 22.00 hours (four died in the morning, four in the afternoon/evening) and nine died between 22.00 and 08.00 (one died before midnight, two after midnight and four were found dead in bed). In nine cases the time of death was simply not noted.

The results show that for this group of patients, no time of death is predominant, either in the early morning or at any other time of day. It is important to note that the population was a selected one, but this enabled an accurate time of death to be achieved for most patients. It would be useful to widen the scope of this study population and look at non-malignant causes of death. Unfortunately, the actual time of death is frequently unknown and unrecorded.

We are at present studying hospital and general practice records to ascertain whether our findings are representative of deaths from all causes.

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Hypokalaemia with beta-blocker/thiazide combinations

Sir,

I have recently completed an assessment of my hypertensive patients and a total of 174 individuals (123 women, 51 men) were identified as currently taking antihypertensive drug therapy, out of a list size of 2700 from a mainly urban population. Of the patients, 134 (77%) had satisfactory blood pressure control on a single preparation and 87 patients (50%) were controlled with either a beta-blocker alone or beta-blocker/thiazide combination. Only seven patients (4%) required more than two drugs for satisfactory control. Atenolol (either 50 mg or 100 mg) was the sole agent used in 40 patients and when combined with chlorthalidone, a further 38 patients benefited from this combination.

The role of thiazides and related diuretics has come in for criticism recently and there is increasing concern over possible risk factors in this group of drugs. Thiazide diuretics have been available for nearly 30 years and their long term side-effects have been well established — hyperglycaemia, hyperuricaemia, hypokalaemia and increased plasma cholesterol.[1] Indeed the question of thiazide diuretics themselves being implicated in the pathogenesis of atherosclerosis has been raised.[2] My own interest in thiazides centred on the changes in serum potassium in patients taking beta-blocker/thiazide combinations. Table 1 summarizes the results from 53 patients (39 women, 14 men) who were using a beta-blocker/thiazide combination.

Table 1. Hypokalaemia with beta-blocker/thiazide combinations

Preparation	Number (%) of patients		
	Total	Serum potassium <3.4 mM	Serum potassium <3.0 mM
Tenoret 50[a]	16	1	0
Tenoretic[b]	24	8	3
Prestim[c]	13	2	2
Total	53	11 (*21*)	5 (*9*)

[a]Tenoret 50 (Stuart) = atenolol 50 mg/chlorthalidone 12.5 mg. [b]Tenoretic (Stuart) = atenolol 100 mg/chlorthalidone 25 mg. [c]Prestim (Leo) = timolol 10 mg/bendrofluazide 2.5 mg.

All patients had a normal serum potassium before commencing therapy and the readings shown in Table 1 were taken after at least six months treatment on the above regimens. These results confirmed earlier studies showing that the hypokalaemic effect of thiazides is dose related, as no levels of serum potassium less than 3.4 mM were found in patients taking one tablet of timolol 10 mg/bendrofluazide 2.5 mg (Prestim) and only one marginally low level with atenolol 50 mg/chlorthalidone 12.5 mg (Tenoret 50). Increasing the number of fixed-dose combination tablets puts the patient at risk from potentially serious hypokalaemia.

The significance of hypokalaemia induced by thiazide diuretics is still controversial. It seems generally agreed that when serum potassium levels fall below 3.0 mM, then this should be corrected with potassium supplements but there is a grey area within the range 3.0–3.4 mM and treatment in this range is disputed. However, there have been reports recently of mild hypokalaemia (less than 3.5 mM) being associated with cardiac arrythmias in patients suffering an acute myocardial infact.[3] This would be significant from the hypertensive's view point as he is at risk from an infarct. There also appears to be an association between diuretics and an increased death rate in those with underlying heart disease, although the mechanism remains obscure.

Looking at the overall picture in uncomplicated hypertension, there seems little justification for increasing the diuretic component of beta-blocker/thiazide combinations beyond a therapeutic threshold level. Most observers appear to favour a low dose thiazide approach and Breckenridge has recently stated that 'a smaller dose of thiazide diuretic (for example, bendrofluazide 2.5 mg) is recommended'.[4] Perhaps drug manufacturers should be making available preparations which would allow a step-wise increase in beta-blocker dose, while keeping the thiazide component constant. If this were to happen, from this small study it would seem reasonable to deduce that serum potassium levels would remain normal (or only marginally low) and the need for monitoring serum electrolytes in these patients would become unnecessary.

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